Children with Anatomical Congenital Anomalies; a Portrait
Follow-up over five years

Kinderen met aangeboren anatomische afwijkingen;
een portret
Vijf jaar nazorg uit voorzorg

The printing of this thesis was financially sponsored by:
Maquet Nederland BV
Zambon Nederland BV
Fresenius Kabi Nederland BV

ISBN: 978-90-78992-07-3

Cover: Vera Terlouw
Lay-out: Margo Terlouw-Willebrand, Nieuwerkerk aan den IJssel
Printed by: Optima Grafische Communicatie, Rotterdam (optima@ogc.nl)

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ter verkrijging van de graad van doctor aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus Prof.dr. S.W.J. Lamberts
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
vrijdag 5 december 2008
om 13.30 uur

door

Petronella Mazer

Geboren te 's-Gravenhage

PROMOTIECOMMISSIE

Promotor:	Prof.dr. D. Tibboel
Co-promotor:	Dr. M. van Dijk
Overige leden:	Prof.dr. J. Passchier Prof.dr. F.C. Verhulst Prof.dr. I.D. de Beaufort

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De openbare verdediging zal plaatsvinden op
vrijdag 5 december 2008
om 15.00 uur

door

Saskia Jacobien Gischler

Geboren te 's-Gravenhage

PROMOTIECOMMISSIE

Promotor:	Prof.dr. D. Tibboel
Co-promotor:	Dr. H. Meijers-IJsselstijn Dr. M. van Dijk
Overige leden:	Prof.dr. N.M.A. Bax Prof.dr. A.J. van der Heijden Prof.dr. F.W.J. Hazebroek

Een droom met een deadline

Het duurt altijd langer dan je denkt,
Ook als je denkt
Het zal wel langer duren dan ik denk
Dan duurt het toch nog langer dan je denkt

Judith Herzberg

CONTENTS

CHAPTERS 1 TO 13 ARE BASED ON THE FOLLOWING ARTICLES:

Chapter 1
Interdisciplinary structural follow-up of surgical newborns: A prospective evaluation.
Saskia J. Gischler, Petra Mazer, Hugo J. Duivenvoorden, Monique van Dijk, Nikolaas M.A. Bax, Frans W.J. Hazebroek, Dick Tibboel.
Journal of Pediatric Surgery (accepted).

Chapter 2
A prospective comparative evaluation of persistent respiratory morbidity after repair of esophageal atresia and congenital diaphragmatic hernia.
Saskia J. Gischler, Monique H.M. van der Cammen-van Zijp, Petra Mazer, Gerard C. Madern, Nikolaas M.A. Bax, Johan C. de Jongste, Monique van Dijk, Dick Tibboel, Hanneke IJsselstijn.
provisionally accepted Journal of Pediatric Surgery.

Chapter 3
Motor function profiles in children with major anatomical congenital anomalies; an evaluation at 5 years of age.
Monique H.M. van der Cammen-van Zijp, Saskia J. Gischler, Petra Mazer, Monique van Dijk, Dick Tibboel, Hanneke IJsselstijn.
submitted.

Chapter 4
Does a structural and proactive approach improve genetic counseling rate for parents of children with congenital anatomical anomalies?
Saskia J. Gischler, Yolande van Bever, Petra Mazer, Nikolaas M.A. Bax, Dick Tibboel, Hanneke IJsselstijn, Monique van Dijk.
submitted.

Chapter 5a
Congenital diaphragmatic hernia in a female patient with craniofrontonasal syndrome.
Alice Brooks, Marieke van Dooren, Jeannette Hoogeboom, Saskia Gischler, Patrick Willems, Dick Tibboel.
Clinical Dysmorphology 2002,11:151-153.

Chapter 5b
Exclusion of a PAX 6, FOXC1, PITX2 and MYCN mutation in another patient with apple peel intestinal atresia, ocular anomalies and microcephaly and review of the literature.
Yolande van Bever, Liselotte van Hest, Roger Wolfs, Dick Tibboel, Thelma L. van den Hoonaard, Saskia J. Gischler.
American Journal of Medical Genetics Part A 146A:500–504 (2008).

Chapter 6
Multidisciplinary management of infantile short bowel syndrome; resource consumption, growth and nutrition.
Joanne F. Olieman, Marten J. Poley, Saskia J. Gischler, Corine Penning, Johanna C. Escher, Thelma L. van den Hoonaard, Nikolaas M.A. Bax, Dick Tibboel, Hanneke IJsselstijn.
submitted.

Chapter 7
Predictive capacity of cognitive and motor development of children with major congenital anomalies at 5 years; an empirical-clinical study.
Petra Mazer, Saskia J. Gischler, Monique H.M. van der Cammen-van Zijp, Dick Tibboel, Nikolaas M.A. Bax, Hanneke IJsselstijn, Monique van Dijk, Hugo J. Duivenvoorden.
submitted.

Chapter 8
Follow-up of newborns treated with extracorporeal membrane oxygenation: a nationwide evaluation at 5 years of age.
Manon N. Hanekamp Petra Mazer, Monique H.M. van der Cammen-van Zijp, Boudien J.M. van Kessel-Feddema, Maria W.G. Nijhuis-van der Sanden, Simone Knuijt, Jessica L.A. Zegers-Verstraeten, Saskia J. Gischler, Dick Tibboel, Louis A.A. Kollée.
Crit Care. 2006; 10: R127.

Chapter 9
Impact of a Child with Congenital Anomalies on Parents (ICCAP) questionnaire; a psychometric analysis.
Petra Mazer, Saskia J. Gischler, Hans M. Koot, Dick Tibboel, Monique van Dijk, Hugo J. Duivenvoorden.
Health and Quality of Life Outcomes (accepted).

Chapter 10
Explorative study on the usefulness of the CBCL/1½-5 for children with major congenital anomalies at age 12 months.

Chapter 11
The impact on parents of having a child with major congenital anomalies: a prospective longitudinal study.

Chapter 12
Telephone helpline for parents of children with congenital anomalies.
Saskia J. Gischler, Petra Mazer, Marten J. Poley, Dick Tibboel, Monique van Dijk.
J Adv Nurs Published Online: Sep 25 2008 DOI: 10.1111/j.1365-2648.2008.04830.x.

Chapter 13
Parents' satisfaction with follow-up care for children with severe birth defects.

Prologue

Proloog

Dal centro della mia vita venne una grande fontana

Louise Glück (1943 -)

Life itself is the most wonderful fairy tale

Hans Christian Andersen (1805 - 1875)

PROLOGUE, A PORTRAIT OF TIM (1994 - 2008)

The story told here – Tim's story – is illustrative of the many tales that motivated us to set up a follow-up program for children with congenital anomalies. It provides a portrait of a boy whose short-lived life was far from uncomplicated.

To start with, Tim's father had a cardiac problem. As both he and Tim's mother wanted to be sure their unborn child would not have the same problem, a second trimester ultrasound was performed. The good news was that Tim did not have a cardiac anomaly. The bad news: it appeared he had a congenital diaphragmatic hernia. This condition is marked by a hole in the diaphragm, or even complete absence of the diaphragm. Organs normally located in the abdomen, such as the intestines, liver, or spleen can therefore protrude into the chest during fetal development and impede lung formation. This is why these newborns at birth often have severe respiratory distress. It can be even life-threatening if not treated right away. Thus, immediately after birth Tim was intubated and resuscitated for over 20 minutes. At the very moment the medical team was about to give up, Tim's cardiac output recovered. Next he was transferred from the delivery room to the ICU. Here after a few hours he was put on ECMO because he showed severe persistent pulmonary hypertension. He could be weaned off ECMO a few days later, upon which his diaphragm was repaired surgically. The postoperative course necessitated several episodes of mechanical ventilation. Once home, Tim deteriorated and was admitted again for a redo of his diaphragmatic repair. It now appeared he had chronic lung disease for which he would need extra oxygen at home. Within the first months, still in hospital, Tim developed an as yet badly understood generalized venous obstructive syndrome, in which almost all large veins were obstructed. No clotting problem was found and no adequate therapy was available. Eventually Tim was discharged home with a lot of medication and on tube feeding and we could only tell his parents that he would probably die within the next few months. Tim's mother apparently only trusted the intensive care physician and brought Tim there unofficially on and off. She did not come to any of the official outpatient departments and turned to complementary therapists – craniosacral therapy, haptonomy, homeopathy, etc. Slowly, and not understood by western medicine, Tim improves, is weaned off tube feeding and against all odds gradually starts to talk and walk although there is psychomotor and mental developmental delay. There is still the problem of venous obstruction, however, on account of which Tim gradually develops a hydrocephaly. For this he needs a ventriculo-peritoneal drain, and many drain revisions are to follow. Nothing ever goes without complications in Tim's life. Eventually, mainly due to his mother's unrelenting efforts in finding the right people to care for Tim (more often in spite of, rather than thanks to the medical system), he is placed in a regular primary school. Physically, though, he is barely able to keep up.

In the meantime, Tim's parents are no longer together. By taking care of Tim, his mother was unable to continue her paid job at a bank and she had no social life left to speak of.

Nine years old, Tim transfers to a school with special attention for children with physical handicaps (Openluchtschool). Here he finally seems to have found his place until gradually in 2007 he develops increasing headaches. In the summer of 2007 Tim is admitted to the Sophia Children's Hospital with a pneumonia. First the headaches are ascribed to his worsening pulmonary function, so supplemental oxygen is started and later nightly non-invasive ventilation. Although he is now slightly less tired, the headaches do not improve. In March 2008 a ventriculo-peritoneal drain dysfunction is diagnosed. The neurosurgeon attempts a drain revision. This is complicated, however, by an intracranial hemorrhage and seizures, due to Tim's major vascular problems. After regaining consciousness Tim (now almost 14 years old), together with his family decides he will have no more surgery. In April he goes home with palliative care. In spite of increasing doses of morphine Tim still manages to direct his life – even such that an unforgettable day can be spent with his favorite dolphins at the Dolfinarium and a final hour at his school, saying goodbye to his classmates. Three days later, on May 25th Tim dies peacefully at home, convinced he will meet his grandfather and his father, who both died in the past years, in heaven.

Over the years Tim, in spite of his many physical limitations and handicaps, has made a very special impact on the many people he came into contact with, including us. His fate, and that of many other children like him, has convinced us that special teams are needed to coordinate care for them and their parents. All efforts should be directed at reducing the burden of disease. This thesis reports on the steps we took to achieve this goal.

PROLOOG, HET PORTRET VAN TIM (1994 - 2008)

Het verhaal dat u hier leest – Tim's verhaal – is tekenend voor de vele gevallen die voor ons aanleiding waren om een follow-up programma te starten voor kinderen met een aangeboren afwijking. Het schetst een portret van het korte en moeilijke leven van een bijzonder kind.

De vader van Tim had een hartafwijking. Om er zeker van te zijn dat hun ongeboren kind niet eenzelfde probleem zou hebben, besloten de ouders een 20-weken echo te laten maken. Het goede nieuws was dat Tim geen hartafwijking had. Het slechte nieuws: hij bleek een congenitale hernia diafragmatica te hebben. Bij deze afwijking zit er een gat in het middenrif, of ontbreekt het middenrif aan één kant helemaal. De organen die normaal in de buikholte liggen, zoals maag, darmen, lever en milt, kunnen hierdoor tijdens de zwangerschap in de borstkas terechtkomen en de longontwikkeling belemmeren. Direct na de geboorte hebben deze kinderen vaak ernstige, levensbedreigende ademhalingsproblemen die directe behandeling vergen. Tim werd dan ook direct na de geboorte geïntubeerd, beademd en meer dan 20 minuten gereanimeerd. Op het moment dat het medische team besloot de reanimatie te staken, kreeg Tim eigen hartactie. Pas toen werd hij van de verloskamer naar de intensive care overgeplaatst. Na een aantal uren bleek gewone beademing onvoldoende te helpen en werd hij aan ECMO (hart-longmachine) gelegd. Enige dagen later kon deze behandeling gestaakt worden. Vervolgens werd het gat in het middenrif operatief gesloten. In de periode daarna bleek Tim nog verschillende malen beademing nodig te hebben zodat hij pas op de leeftijd van 2 maanden naar huis kon. Na enige tijd verslechterde zijn toestand weer en bleek er opnieuw een gat in het middenrif te zitten. Hier was een nieuwe operatie voor nodig gevolgd door een langdurige periode van beademing. Inmiddels waren zijn longen zodanig beschadigd dat hij afhankelijk bleef van extra zuurstof. Bovendien bleken de grote aderen bij Tim steeds meer te verstoppen; zonder duidelijke oorzaak. De bloedstolling was normaal, maar de verstopping van de aderen was zo ernstig dat er niets aan gedaan kon worden. Uiteindelijk werd Tim ontslagen uit het ziekenhuis met sondevoeding, veel medicijnen en extra zuurstof. Met de ouders van Tim werd besproken dat hij naar verwachting binnen enkele weken tot maanden zou overlijden. Ernstig teleurgesteld in de medische wetenschap vertrouwde de moeder van Tim hem niet toe aan de kinderartsen op de polikliniek. Wel kwam zij af en toe officieus langs bij de intensivist, de arts waar zij nog enig vertrouwen in had. Daarnaast zocht zij met Tim haar heil bij de complementaire geneeskunde – craniosacrale therapie, haptonomie, homeopathie, het gebruik van voedingssupplementen, etc. Geleidelijk, en onverklaarbaar voor de westerse geneeskunde, verbetert dan de toestand van Tim. Hij eet steeds meer zelf en tegen alle verwachting in gaat hij niet alleen praten, maar ook lopen, hoewel zijn ontwikkeling duidelijk achterblijft.

Het probleem met de bloedvaten blijft echter; en dit is er de oorzaak van dat er bij Tim een waterhoofd ontstaat. Om het teveel aan vocht in het hoofd af te voeren, wordt een

drain van de hersenholtes naar de buik aangelegd. Na deze ingreep zijn echter steeds weer nieuwe ingrepen nodig voordat de drain goed functioneert. In het leven van Tim verloopt nu eenmaal niets zonder complicaties. Uiteindelijk, met name dankzij de onvermoeibare inzet van Tim's moeder en een aantal, vaak complementair werkende, hulpverleners, kan Tim op een gewone basisschool terecht (meer ondanks, dan dankzij het medische systeem). Dit vergt lichamelijk wel het uiterste van Tim.

Inmiddels zijn de ouders van Tim uit elkaar. Het zorgen voor Tim is zo intensief dat moeder haar baan heeft moeten opzeggen en vrijwel geen sociaal leven meer heeft.

Op de leeftijd van 9 jaar gaat Tim naar het aangepast onderwijs (Openluchtschool). Hier lijkt hij eindelijk zijn draai gevonden te hebben tot hij in 2007 steeds meer hoofdpijn krijgt. In de zomer van 2007 wordt Tim met een longontsteking opgenomen in het Sophia Kinderziekenhuis. Aanvankelijk wordt gedacht dat zijn hoofdpijn het gevolg is van de steeds verder verslechterende longfunctie. Opnieuw wordt ook thuis extra zuurstof gestart en later ook nog neuskapbeademing. Hoewel Tim hierdoor iets meer energie lijkt te krijgen, wordt de hoofdpijn alleen maar erger. In maart 2008 blijkt dat de hersendrain niet meer goed werkt. De neurochirurg probeert de drain te reviseren, maar er treden complicaties op in de vorm van een hersenbloeding en een ernstige epileptische aanval. Nadat hij weer bij kennis is besluit Tim (nu bijna 14 jaar oud), samen met zijn familie, dat hij geen nieuwe operaties meer wil ondergaan. In april wordt hij met een palliatief beleid naar huis ontslagen. Ondanks pijnstilling met steeds hogere doseringen morfine is Tim nog steeds 'in charge'. Via de stichting 'Doe een wens' heeft hij een onvergetelijke dag met de dolfijnen in het Dolfinarium en gaat hij nog een middag naar school om afscheid te nemen van zijn klasgenoten. Drie dagen later, op 25 mei 2008, overlijdt Tim vredig in zijn eigen bed, er van overtuigd dat hij in de hemel zal worden opgewacht door zijn opa en zijn vader die beiden in de afgelopen jaren zijn overleden.

Ondanks zijn vele lichamelijke beperkingen en handicaps heeft Tim op veel mensen, en ook op ons, een onuitwisbare indruk gemaakt en heeft hij een heel speciaal plekje verworven. Tim's verhaal – en dat van vele kinderen met vergelijkbare problemen – heeft ons doen inzien dat er een speciaal team moet zijn dat de zorg voor deze kinderen en hun ouders coördineert en hen langdurig vervolgt. Aan ons is de taak om na de eerste intensieve ziekenhuisopname de ziektelast voor ouders en kind zoveel mogelijk te beperken. Dit proefschrift is een verslag van onze inspanningen om dat doel te bereiken.

General introduction

The very first requirement in a hospital is that it should do the sick no harm

Florence Nightingale (1820- 1910)

CONGENITAL ANOMALIES

Annually some 5.000 newborns (2 - 3% of all births) in the Netherlands present with major anatomical congenital anomalies.[140,395] The causes of most of these are still unknown. So far, genetic or chromosomal causes have been implicated in 13 - 14% of all anomalies,[17,120,214,249,337] and environmental factors, including maternal disease, can explain another 6 - 7%.[149,345,472] Some 20% are known to be multifactorial. Many of these anomalies require immediate surgical correction in order for these children to survive. The pediatric surgeon Ravitch classified six of these anomalies as the so called index diagnoses.[351] These are esophageal atresia/tracheo-esophageal fistula, congenital diaphragmatic hernia, intestinal atresias, Hirschsprung's disease, anorectal malformations, and abdominal wall defects (gastroschisis and omphalocele). They occur either in isolated form or as part of more complex syndromes.[59] Multiple congenital anomalies refers to any combination of two or more major anomalies. As a governmental policy patients presenting with an index diagnosis are to be treated in one of six pediatric surgical centers in the Netherlands.[170] Improved antenatal detection, surgical techniques, and peri-operative care have increased these children's chances of survival.[210] Survivors may show considerable morbidity, however, and many will have to rely on the healthcare system for life.[57,58,165,208,340]

Follow-up

Over the past decades mortality rates in neonates with congenital anomalies have dropped to approximately 10%[210] and increasingly survivors are known to have reached adolescence. Better survival coincides, however, with proportionately more morbidity, which is either the result of the underlying anomaly or a side effect of treatment. This development resulted in an increasing interest in morbidity, both short-term and long-term, from health care professionals. Follow-up in these patients, however, was mostly done by individual specialists and their attention mainly focused on physical issues related to surgery.[19,20,105,116,127]

There are numerous publications on outcome, both physical and developmental, of very low birth weight children. These studies tend to exclude children with congenital anomalies, however, for their relatively small numbers and wide physical heterogeneity.[139,218,457] Even articles on follow-up for high-risk infants in tertiary care centers explicitly exclude this group.[158] Lally and colleagues recently advocated multidisciplinary follow-up programs for children treated for congenital diaphragmatic hernia, supported by the American Association of Pediatrics.[271] Interestingly, such multidisciplinary programs for children with Down's syndrome, meningomyelocele, craniofacial malformations and other complex or chronic diseases have been in place for years.[65,85,100,166,200,212,220,247,303,306,342,362,392] Improved care and outcomes have meanwhile proven the value of the teams involved in these programs. Until recently no multidisciplinary teams were available for children with index diagnoses, in spite of the fact that many different specialists are involved in their care. Consequently, there is

insufficient knowledge of long-term development, psychosocial functioning and quality of life of the child. Equally important, this holds true for knowledge of quality of life of the parents.

The child

According to the attachment theory, infants use their parent as a haven of safety to provide comfort and protection when they are distressed and as a secure base from which they can explore the environment.[61] Whereas secure child–parent attachment relationships in infancy predict positive outcomes in later life,[143,393] an insecure attachment relationship is predictive of less optimal child development.[184,442] Children with congenital anomalies, however, need most of their initial energy merely for surviving in a phase of life that is intended to form a relationship with the world around them. Long hospital admissions in the neonatal phase separate the child from its parents, reducing normal sensory input. Corrective surgical procedures, artificial ventilation, infections and many uncomfortable medical and nursing procedures interrupt the normal flow of life and development. Only in some cases, especially when there are no associated anomalies, like isolated duodenal atresia, the child will be able to lead a normal, healthy life starting in the neonatal period. Regrettably, many will be left with sequelae from the primary anomaly or associated anomalies, or will develop iatrogenic complications. The child might need to use medication for a long time, might be severely disfigured, show organ malfunction or be subjected to invasive therapies. There is every reason, then, to expect a certain degree of motor and mental developmental delay.[54,67,86] Both the primary anomaly itself and its impact on development can influence quality of life. Early signaling of developmental delay is therefore considered crucial.

The parents

These days, with improving ultrasound techniques, more and more anomalies are being detected antenatally. A second trimester ultrasound study has since 2006 become standard procedure in the Netherlands. This implies that parents are faced early on with the fact that the child has a congenital anomaly and its possible serious consequences. This knowledge may induce a process of parental mourning.[320] Abandoning expectations of a healthy child, parents must prepare themselves for raising a child that might be severely ill, sometimes for life.[10,15] Earlier research has shown that antenatal detection of a congenital anomaly can have considerable negative impact on parents during pregnancy.[229,231,232,265,263,264,281] The postnatal impact might be even more pronounced. Parents often face uncertainty about the exact nature of the anomaly, or anomalies, and the implications for the (unborn) child.

All this may severely impair parental quality of life. This has been studied for Down's syndrome, congenital heart disease and meningomyelocele,[14] among other things, but until the start of our study, no structural research had addressed quality of life issues for parents of a child with congenital anomalies.

Multidisciplinary teams

Mortality should no longer be considered the main outcome for children with congenital anomalies. During the past years we have increasingly come across many problems in this group of patients both at the physical and the developmental level. This reflects on quality of life of the affected child, but also on their parents and sibs.[28] Early signaling of such problems is essential. Our responsibility in providing optimal care for these children includes getting parents ready to take care of their own child and to help them face the consequences of their child's anomaly. Streamlining care for children with congenital malformations, both during hospitalization(s) and after discharge home, requires structured multidisciplinary care. Parental uncertainty about the child's future should be kept within the strictest bounds. Thus, pediatric surgeons, pediatric intensive care physicians and organ specialists involved should be consulted, but also a clinical geneticist specialized in congenital malformations and dysmorphology, as well as a psychologist and paramedical specialists like physiotherapists, nurses specialized in stoma care and speech therapists. The parents should get adequate and timely information. Nurses at the bedside should try to involve parents in the care for their child as early as possible and a social worker should be available. Moreover, developmental care teams, backed by a developmental psychologist, are expected to signal early developmental delay and intervene when necessary.

General characteristics

In brief, children with congenital anomalies share a set of characteristics resulting in uncertain perspectives on future physical, developmental and psychosocial functioning:

- The anomalies are rare;
- Individual (para)medical specialists may therefore have insufficient knowledge of the conditions;
- Often more than one organ system is affected;
- One or more surgical interventions are needed;
- There is a high risk of long-term morbidity;
- The high-quality care needed by these children and their parents cannot be delivered in a mono-specialist setting.

The resulting picture is one of insufficient knowledge on quality of life of the child, but also on parental burden and quality of life. Quantifying this burden would seem an essential first step before possibilities to unburden parents can be considered. It could also open the way to determine whether and to which parents support should be offered, and if so, what measures would be most effective in terms of enhancing quality of life. Moreover, there is also lack of knowledge on cost effectiveness.

Genetics

Many congenital anomalies are at first thought to be isolated. A geneticist specializing in dysmorphology may, after careful analysis of physical characteristics, find additional defects or features that enable a genetic or chromosomal diagnosis or at least a syndromal classification. When the genetic basis of disease is unclear, parents cannot

make well-informed decisions on future pregnancies and the risk for other family members remains undefined.[365] Patterns of inheritance often become clear when a genetic diagnosis is made. Careful evaluation of the patient and his or her relatives may sometimes reveal unexpected syndromes or associations. This increases our knowledge on major congenital anomalies, but also creates opportunities to facilitate decision-making and to provide support.[43] In this study we evaluated the impact of a proactive approach to counseling. Moreover, some cases are described in which the careful follow-up by a geneticist revealed unexpected and rare diagnoses.

Over the past years both technical and organizational novelties have been introduced in the Erasmus MC-Sophia. Extracorporeal membrane oxygenation is a very high-tech treatment modality and was introduced in Holland in the early nineties. And in 2004 a multidisciplinary short bowel syndrome team was set up.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass technique for providing life support in acute reversible cardiorespiratory failure when conventional management is insufficient. Most patients receiving ECMO support are neonates suffering from persistent pulmonary hypertension of the newborn, primary or secondary to meconium aspiration syndrome, sepsis, or congenital diaphragmatic hernia. Since 2001 follow-up of patients treated with ECMO was incorporated into our follow-up program. A very invasive therapy such as ECMO needs evaluation by careful follow-up of patients. Morbidity, physical as well as developmental, has been described, both as a result of the underlying disease and the therapy.[34,62,71] In part these patients overlap with the original follow-up population, since a number of ECMO treated patients also has major congenital anomalies. The Erasmus MC Sophia in Rotterdam and the Radboud University Nijmegen are the only two designated centers in the Netherlands providing this therapy. Follow-up in these patients is coordinated between the two centers in the form of a nationwide follow-up program for this population.

Short Bowel team

Short bowel syndrome is a malabsorption syndrome resulting from inadequate bowel length, either anatomical or functional. In children, the most common causes are necrotizing enterocolitis, abdominal wall defects, jejuno-ileal atresia, and mid gut volvulus. Over the past decades there have been significant improvements in nutritional support. Survival rates now range from 80% to 94%, but with a significant length of time on total parenteral nutrition.[383,408,446] Sepsis and parenteral nutrition-related cholestasis are common. Long-term recovery of these children often is remarkable, but there is a 10 to 15% incidence of neurologic and developmental defects.[383] Sometimes children do not recover and small bowel transplant can be considered. Multidisciplinary teams have been advocated for the treatment of patients with short bowel syndrome[312] and since 2004 a short bowel follow-up team is functioning in the Erasmus MC-Sophia. For both child and parents the prolonged hospital stay, home parenteral nutrition and physical

limitations cause a considerable burden. Moreover both ethical and cost considerations play a role in the treatment of these patients.

Economic considerations and cost-effectiveness

Little is known about the cost of caring for children with congenital anomalies. Especially costs after the initial, neonatal admission are often ill defined. It may well be that there is an excess of secondary costs as a result of uncoordinated and unstructured care, leading to redundant hospital visits and diagnostics. Furthermore, the parents' medical consumption and work absenteeism could be high, involving extra costs as well, both for the parents and for society at large. In collaboration with the iBMG, the Erasmus university institute for policy and management in healthcare, several studies were conducted to evaluate cost-effectiveness of surgical treatment of neonates, also taking quality of life after surgery into consideration.[338-341] Following this same model, we tried to evaluate cost effectiveness of the short bowel team. Moreover, we briefly looked at feasibility of a 24-hour telephone helpline for parents of patients with congenital anomalies.

CONCLUSION

Whenever a child with congenital anomalies is born, some universal questions will arise, both in the affected family and in the team treating the child:

- Will the child survive and what is the expected quality of life?
- What is the molecular, chromosomal or genetic basis; or are there other factors influencing abnormal organogenesis?
- What is the expected quality of life of the child and what is the expected burden to the child and the parents?

These questions have led to the studies presented in this thesis, by and large aiming to unravel the consequences of being born with a congenital anomaly both for the child and his or her parents.

AIMS OF THIS THESIS

As the Erasmus MC-Sophia Children's Hospital serves as one of 6 pediatric surgical centers in the Netherlands including a specialized intensive care unit, children with congenital anomalies formed the majority of the patient population. Some ten years ago, departmental staff as well as the Erasmus MC board of directors came to recognize the necessity of long-term follow-up for these patients and their parents. The multidisciplinary team (described above) implemented a follow-up program in which children and their parents were evaluated at 6, 12, 18 and 24 months and at 5, 8, 12 and 16-18 years of age of the child (see figure gi.1). The first 5 years are described in this thesis.

Figure gi.1 Follow-up Schedule

	6 mths	12 mths	18 mths*	24 mths	5 yrs	8 yrs	12 yrs	16 yrs	18 yrs
Child physical functioning	Physical and neurological examination								
					Audiometry **				
	Pulmonary function testing ***				Pulmonary function testing ***				
					Motor function				
Child psychological functioning	Psychomotor assessment								
					Cognitive assessment				
					Social-emotional assessment				
					Quality of life				
Parental functioning	Acceptance								
	General health and Quality of life								
				Parenting stress					

** Optional test moment, indicated by clinical problems,*
*** Only for patients at risk for sensorineural hearing loss,*
**** Only for patients treated with ECMO, CDH and esophageal atresia patients.*

We not only aimed at evaluating children with major congenital anomalies and their parents for the effect the anomaly had on short-term and long-term quality of life, we also aimed at evaluating individual features of the team, as well as the functioning of the team as a whole.

The aims of the research were:

- To study short-term and long-term outcomes of children with (multiple) congenital anomalies, regarding physical, developmental and socio-emotional aspects, and to develop guidelines for predicting risk of unfavorable outcome;
- To study short-term and long-term impact and burden on parents of these children, and to develop guidelines for risk of unfavorable effects;
- To improve both intra- and extramural care for these children and their parents;
- To evaluate the effect of proactive genetic counseling of parents with a child with major anomalies;
- To evaluate follow-up on two subsets of patients, i.e. patients with short bowel syndrome and patients treated with ECMO;
- To develop a mindset reflecting on resource utilization and eventually cost effectiveness;
- To evaluate patient satisfaction with the multidisciplinary team responsible for the long-term follow-up program;
- To develop recommendations on conditions for which multidisciplinary care is thought indispensable;
- To develop future guidelines and a nationwide blueprint for follow-up of patients after intensive care treatment.

Subjects: inclusion and exclusion criteria

All children admitted to the pediatric surgical intensive care unit within the first 6 weeks of life with anatomical congenital anomalies requiring surgical correction were eligible for the study. Excluded were patients with craniofacial malformations and children with meningomyelocele, because these are already participating in separate follow-up programs. Most of the subjects included had one or more of the index diagnoses. For hospital-related logistic reasons patients with complex heart defects were only included when they also had another major congenital anomaly for which they were referred to the pediatric surgical department. Patients were included as from January 1999.

Structure of this thesis

In **Chapter 1** to **6**, the emphasis is on the physical outcome of children with congenital anomalies. **Chapter 1** gives a prospective evaluation of physical characteristics and neurodevelopmental aspects of children with congenital anomalies from birth to age 24 months. **Chapter 2** highlights long-term morbidity in a group of patients with esophageal atresia and congenital diaphragmatic hernia over the first 5 years of life, with a special focus on respiratory morbidity. **Chapter 3** is a detailed study on motor

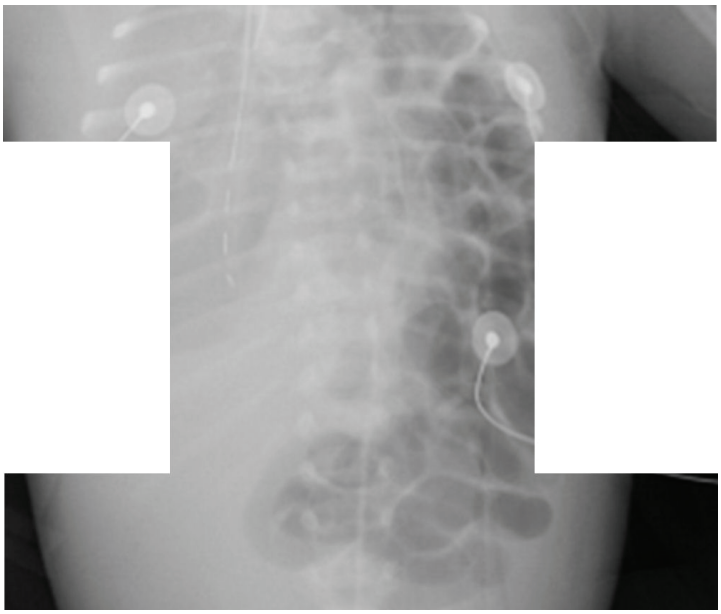
function profiles in children with major anatomical congenital anomalies at 5 years of age. In **Chapter 4** and **5** we describe the input of the geneticist in the multidisciplinary team. **Chapter 6** describes the functioning of our multidisciplinary short bowel team with regards to outcome and cost-effectiveness.

Chapter 7 to **11** highlights the neurodevelopmental and behavioral aspects of long-term follow-up of children with congenital anomalies and psychological impact on parents. In **Chapter 7** we try to predict developmental outcome for children with congenital anomalies at the age of 5 years from developmental scores in the first 2 years. While in **Chapter 8** a 5-year follow-up study of Dutch ECMO patients is described. **Chapter 9** describes the development of a questionnaire to asses impact of giving birth to a child with congenital anomalies on parental quality of life within the first 6 months after birth. **Chapter 10** evaluates the use of the CBCL/1½-5 for 12 months old children. In **Chapter 11** a longitudinal study evaluates the influence of a child with congenital anomalies on parenting stress and parental general health.

In **Chapter 12** and **13** parental support by means of a telephone helpline and parental satisfaction with the long-term follow-up team as a whole are evaluated.

Finally in the general discussion and conclusion the main findings and conclusions of the thesis are discussed. Ethical considerations in the care for children with congenital anomalies are described and implications and recommendations for follow-up are given, not only for this specific group of patients, but for all patients that underwent intensive care treatment.

PART



MEDICAL BACKGROUND OF CONGENITAL ANOMALIES

Interdisciplinary structural follow-up of surgical newborns: A prospective evaluation

Language is the means of getting an idea from my brain into yours without surgery

Mark Amidon (1962 -)

ABSTRACT

Background

Information on physical and developmental outcomes of children with anatomical congenital anomalies (CA) may indicate the need for early intervention and reduce impact on the child's life and parental burden.

Methods

From 1999 to 2003 101 children with CA (76.5% of initial survivors) were seen 6-monthly in a tertiary children's hospital. Growth, neurological outcome, mental and psychomotor development as determined with the Bayley Scales of Infant Development, and categorization of predictive sociodemographic and medical variables of the children were evaluated prospectively and longitudinally.

Results

Congenital diaphragmatic hernia (CDH) and esophageal atresia patients showed impaired growth, i.e. both height for age (-1.5 SDS) and weight for height (-1.0 SDS). Overall neurological outcome was normal, however, suspect or abnormal for 40% of CDH patients. Overall mental development was normal, but psychomotor scores were significantly lower than the norm (95% CI 83.8 to 92.2 at 6 months and 87.9 to 98.5 at 24 months respectively). Sex, maternal age, socioeconomic status, CA, severity-of-disease covariables, and need of medical appliances at home could predict negative outcome significantly ($p < 0.05$).

Conclusions

CA survivors show impaired growth and psychomotor developmental delay up to age 2 years. This warrants specific follow-up programs and infrastructure for these patients.

INTRODUCTION

Annually some 5000 newborns (2.5% of all births) in the Netherlands present with major structural defects or anatomical congenital anomalies (CA), usually requiring timely surgical correction.[396] Ongoing advances in surgical techniques and peri-operative care have increased these children's chances of survival.[210] Survivors may show considerable morbidity, however, and many will have to rely on the healthcare system for life.[57,58,208,340] These effects may have great impact on the children's and parents' quality of life.[439] Structural and interdisciplinary follow-up of children after surgical correction for CA is still lacking in many centers. By contrast, there are numerous publications on outcome of very low birth weight children. Studies on outcome of neonatal intensive care tend to exclude the CA group, however, for its relatively small numbers and wide heterogeneity.[139,187,189,213,457] Neonates with CA, however, are at risk for adverse neurodevelopmental outcome.[158]

A few studies focused on morbidity in the CA group. In a cross-sectional study Bouman evaluated somatic and psychosocial functioning of 139 children aged 8 to 12 years after neonatal surgical correction of CA.[59] Forty-five per cent had suffered from multiple congenital anomalies (MCA). Overall school level was below expectation in 36% of all children; IQ was significantly below the norm and 17% needed special education, versus 4% in the general population. Cortes reported that survivors of congenital diaphragmatic hernia (CDH) showed considerable morbidity, growth failure and adverse neurodevelopmental outcome at ages 1 and 2 years.[105] Moreover, outcome data at varying moments in time on patients with anorectal malformations, Hirschsprung's disease, gastroschisis and esophageal atresia were published showing decreased quality of life in all but the gastroschisis patients, usually related to physical dysfunction.[19,20,116,127]

Apart from research on cardiac malformations there are few longitudinal studies on impact of CA, and longitudinal data on cohorts of children with CA are scarce.[210,243,283] Moreover, in many clinics follow-up is performed on a monospecialistic base.

To narrow the knowledge gap, we conducted a longitudinal cohort study of children with CA treated in our hospital in the years 1999 through 2003. The primary outcome measures were physical, mental and psychomotor development established up to age 24 months. We aimed at examining diagnostic group differences regarding mental and psychomotor development and to evaluate how medical and physical covariables influence outcome.

METHODS

Design

Observational, prospective, longitudinal cohort study consisting of repeated measurements at 6, 12, 18 and 24 months.

Setting

The pediatric surgical department of our institution is a large tertiary facility in which all major surgical specialties are represented. The referral area has 4 million inhabitants with 44,000 newborns annually.

In 1999 a follow-up program was started, run by a team of pediatricians, psychologists, a physiotherapist, nurses, a social worker, a clinical geneticist, and a consultant senior pediatric surgeon. The program aims at monitoring children with CA until the age of 18 years in an attempt to reduce overall morbidity.

Patients

Patients with major anatomical CA in line with Ravitch's so-called surgical index diagnoses of CA[351] admitted to the pediatric surgical intensive care within 7 days after birth were eligible for this study. Eligible for this study were 142 patients with one or more major CA, born and subsequently admitted from January 1999 to May 2001 and followed until May 2003. Eventually parents of 101 children (76.5% of initial survivors) gave written informed consent for their child to participate in the study. Diagnoses were equally distributed between the participating and non-participating groups, except for CDH, due to early deaths from CDH in the non-participating group. (Figure 1.1)

Procedure

The Erasmus MC ethical review board agreed with the study, and written parental informed consent was obtained for all subjects. Medical data were collected prospectively from the first day of admission. A clinical geneticist routinely evaluated major chromosomal, syndromal and cerebral abnormalities during admission. The Therapeutic Intervention Scoring System (TISS)[109,250] was used as a measure of severity of illness during initial admission. Sociodemographic characteristics included parental ages, marital status, ethnicity and family socioeconomic status (SES),[397] earlier presence of congenital anomalies in the family and the child being first born or not.

By protocol the children were seen at ages 6, 12, 18 and 24 months, corrected for gestational age. The same pediatrician, in collaboration with one of the pediatric surgical consultants, performed a full physical examination, including anthropometric measurements.[161] Neurological examination was done according to the method of Touwen.[44,418,420] Neurological outcome was classified as normal, suspect or abnormal. Abnormality was defined as severe abnormality of tone, posture, and movement leading to functional impairment or delay in motor development. A suspect outcome was defined as moderate functional impairment or developmental delay. The same developmental psychologist performed mental and psychomotor assessments, using the Dutch version of the Bayley Scales of Infant Development[31] (BOS 2-30).[434] Mental Developmental Indexes (MDI) and Psychomotor Developmental Indexes (PDI) were determined in relation to Dutch population norms (mean 100, SD 16).

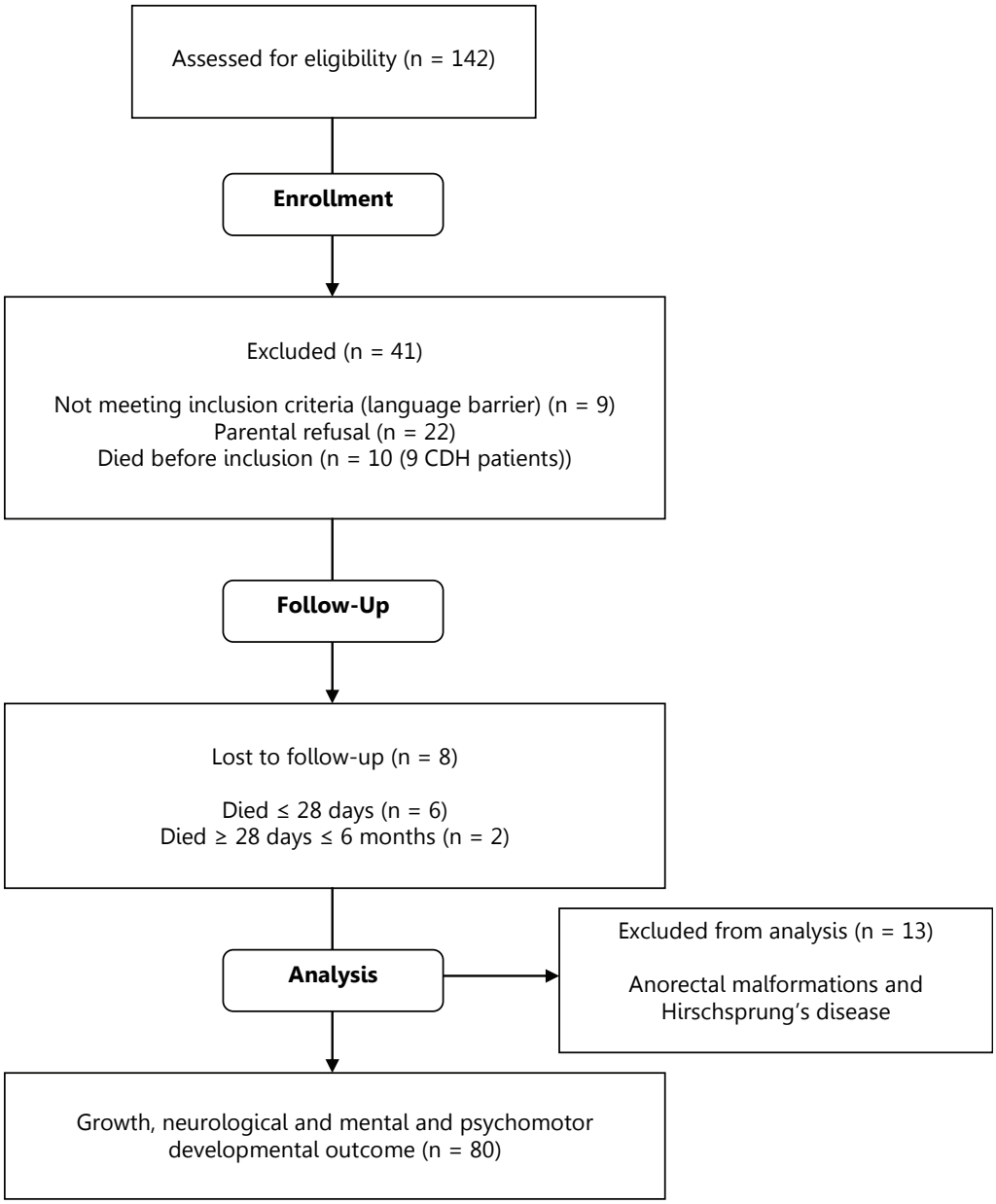


Figure 1.1 *Flowchart showing group composition.*

Outcome variables and time-varying covariables were assessed at all four measurement moments, whereas time-invariant covariables were assessed only once, i.e. at 6 months.

Power analysis

It was assumed that the repeated measurements are substantially correlated (r = 0.80). Therefore, one endpoint (i.c. after 1 year) was used for power analysis. Two psychological outcome variables (i.e. mental and psychomotor development) are highly intercorrelated, implying that basically one principal factor is assessed, the α-error (two tailed) was set at 0.05, while the β-error is fixed at 0.20 (Power is 1- β: 0.80). Power analysis was performed by a 5 (i.e. categories for parents) x 2 (i.e. repeated measurements) ANOVA. For each category the number of parents required equals 18 to detect a change of 0.25 (in terms of Cohen's d) across time.

Statistical analyses

A priori, CA were divided into groups largely in line with Ravitch's so-called surgical index diagnoses of CA.[351] Thus, the following groups were specified: 1) abdominal wall defects (AWD), 2) congenital diaphragmatic hernia (CDH), 3) small intestinal anomalies (SIA), 4) esophageal atresia (EA), and 5) anorectal malformations (ARM) and Hirschsprung's disease (HD) were taken together as one group due to small sample sizes per group. For each group both outcome variables, MDI and PDI, were compared to the Dutch age norm, using ANOVA. Random regression models were used across time to examine relationships between mental and psychomotor development as outcome variables, and on the other hand clinically deemed important time-invariant and time-varying covariables individually. Time trend was identified (i.e. linear, quadratic and cubic trend) using orthogonal polynomials.[52] The error (co)variance matrix was considered to be unstructured. Differences between the five CA subgroups were estimated adjusting for the child's sex, maternal age and SES. It appeared necessary to add the linear time trend as a random effect variable. Finally, modeling was performed by adding the covariables individually, with and without testing of effect modification of the time trend by each covariable. Since these turned out mostly to be insignificant, we have omitted these effect modifications. As measure of importance for the covariables, the unstandardised regression weights (B) are presented. Missing values of the outcome variables were assumed to be missing at random.[287,288,372,450] The mixed modeling analyses were carried out using the SAS software package, version 8.2 (PROC MIXED).

RESULTS

The children's medical and sociodemographic characteristics at first discharge are presented in Table 1.1. We distinguished the six aforementioned categories: AWD (n = 19), CDH (n = 18), SIA, such as duodenal atresia, malrotation and volvulus (n = 34), EA (n = 17), ARM (n = 6) and HD (n = 7). It turned out no statistical analyses could be performed on the combined anorectal malformations and Hirschsprung's disease group due to small numbers. Moreover, their characteristics were such that we felt they were not representative for these diagnoses at large (see Table 1.1).

First admission

Median gestational age was within the norm. Overall birth weight, although below 0SD, was within the norm. Children in the AWD group, however, had a mean birth weight below -1SD, corrected for gestational age. Maximum total number of anomalies per child was 7, with the highest number for EA. In total 7 children had a major chromosomal or syndromal anomaly, mainly Down syndrome in the intestinal atresia group, and 4 children had severe neurological impairment due to intraventricular hemorrhage (n = 2) and cerebral infarction (n = 2).

Table 1.1 Baseline characteristics and sociodemographic characteristics at first discharge, distinguished by CA subgroup

	Total Population	**AWD**	**CDH**	**SIA**	**EA**	**ARM/HD**
	(n = 88)*	**(n = 19)**	**(n = 18)**	**(n = 34)**	**(n = 17)**	**(n = 13)**
Boys, n (%)	47 (53.4)	8 (42.1)	12 (66.7)	19 (55.9)	8 (47.1)	12 (92.3)
Gestational age, median (IQR), wk	38.3 (36.8 - 40.0)	38.1 (36.7 - 41.0)	39.6 (38.3 - 40.3)	37.2 (35.4 - 39.0)	38.6 (36.9 - 40.1)	38.3 (36.7 - 39.2)
Apgar score 1 min, median (IQR)	8 (7.0 - 9.0)	8 (6.3 - 9.0)	7 (5.0 - 7.8)	8 (8.0 - 9.0)	9 (6.0 - 8.0)	9 (8.0 - 9.0)
Apgar score 5 min, median (IQR)	9 (8.0 - 9.3)	9 (7.8 - 10.0)	8 (5.0 - 9.0)	9 (9.0 - 10.0)	10 (8.0 - 9.0)	9 (9.0 - 10.0)
Birth weight, median (IQR), kg	3.0 (2.5 - 3.3)	2.6 (2.4 - 3.2)	3.3 (3.0 - 3.6)	3.0 (2.5 - 3.4)	3.0 (2.6 - 3.2)	3.3 (3.0 - 3.6)
Birth length, median (IQR), cm	48 (47.0 - 50.0)	45 (40.0 - 47.8)	50 (50.0 - 50.0)	48 (47.0 - 50.0)	50 (48.0 - 51.5)	51.5 (48.8 - 53.0)
Birth head circumference, median (IQR), cm	34.0 (32.0 - 36.0)	33.7 (31.6 - 34.8)	36.0 (33.8 - 36.0)	33.0 (32.0 - 34.6)	34.0 (32.8 - 35.3)	33.0 (32.8 - 34.0)
Death, n (%)	8 (9.1)	0 (0.0)	6 (33.3)	1 (2.9)	1 (5.9)	1 (7.7)
Syndromal/chromosomal, n (%)	7 (8.0)	1 (5.3)	0 (0.0)	5 (14.8)	1 (5.9)	3 (23.1)
Severe neurological impairment, n (%)	4 (4.5)	1 (5.3)	0 (0.0)	1 (2.9)	2 (11.8)	0 (0.0)
Major CA, median (IQR)	1 (1.0 - 2.0)	1 (1.0 - 3.0)	2 (1.0 - 2.0)	1 (1.0 - 2.0)	1 (1.0 - 2.5)	2 (1.0 - 3.0)
Total CA, median (IQR)	2 (1.0 - 3.0)	1 (1.0 - 4.0)	2 (2.0 - 2.3)	2 (1.0 - 3.0)	2 (2.0 - 4.0)	3 (1.0 - 4.5)
First admission, median (IQR), days	30 (21.0 - 64.0)	30 (21.0 - 74.0)	40 (25.8 - 68.8)	25 (20.0 - 42.0)	56 (23.5 - 99.0)	19 (14.5 - 26.0)
Admission in 1st 6 months, median (IQR), days	37.5 (27.0 - 81.0)	41.0 (28.0 - 74.0)	35.0 (23.5 - 71.8)	30.5 (23.8 - 81.0)	72.0 (30.5 - 128.0)	31.0 (24.5 - 37.5)
Admission in 24 months, median (IQR), days	42.0 (27.0 - 95.0)	41.0 (28.0 - 94.0)	43.5 (29.0 - 83.3)	33.0 (25.0 - 86.0)	78.0 (30.5 - 130.5)	38.0 (33.0 - 51.0)
ICU admission in 24 months, median (IQR), days	14.0 (8.0 - 38.0)	11.0 (3.0 - 68.0)	32.5 (19.0 - 57.5)	9.0 (6.5 - 13.0)	41.0 (20.5 - 81.0)	8 (5.0 - 12.5)
Tiss ≥ 10, median (IQR), days	8 (3.0 - 19.0)	8 (1.0 - 20.0)	24 (13.8 - 34.5)	4 (2.8 - 7.5)	15 (5.5 - 22.5)	5 (3.0 - 6.5)
Surgical interventions in 24 month, median (IQR)	3 (1 - 4)	3 (1 - 3)	3 (2 - 4)	2 (1 - 3)	4 (2 - 7)	3 (2.0 - 5.0)
O2 at home, n (%)	3 (3.4)	2 (10.5)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)
Tracheostomy at home, n (%)	2 (2.3)	1 (5.3)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)
NG tube at home, n (%)	26 (29.5)	6 (31.6)	6 (33.3)	6 (17.6)	8 (47.1)	3 (23.1)
Enterostomy at home, n (%)	13 (14.8)	1 (5.3)	0 (0.0)	9 (26.5)	3 (17.6)	9 (69.2)
Total medical appliances at home, median (IQR)	1 (0 - 2)	1 (0.0 - 2.0)	1 (0.0 - 2.0)	0 (0.0 - 2.0)	2 (1 - 2)	2 (1.5 - 2.5)
Additional medical problems, n (%)	56 (63.6)	12 (63.2)	12 (66.6)	19 (65.9)	13 (76.5)	9 (69.2)
Septic complications, n (%)	36 (40.9)	9 (47.4)	9 (50.0)	11 (32.4)	7 (41.2)	3 (23.1)
Sedative dependency, n (%)	5 (5.7)	2 (10.5)	3 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Neurological complications, n (%)	5 (5.7)	1 (5.3)	2 (11.1)	2 (5.9)	0 (0.0)	1 (7.7)
First born, n (%)	46 (52.3)	9 (47.4)	8 (44.4)	21 (61.8)	8 (47.1)	5 (38.5)
Non Dutch, n (%)	14 (15.9)	3 (15.8)	4 (22.2)	4 (11.8)	3 (17.6)	4 (30.8)
CA in family, n (%)	21 (23.9)	5 (26.3)	5 (27.8)	8 (23.5)	3 (17.6)	6 (46.2)
Maternal age at delivery, median (range), y	31 (18 - 45)	31 (18 - 39)	32 (24 - 45)	31 (18 - 39)	31.5 (19 - 40)	30 (24 - 36)
Paternal age at delivery, median (range), y	33 (19 - 50)	32 (19 - 41)	33 (29 - 43)	33 (23 - 50)	36.5 (23 - 43)	32 (25 - 39)
Socioeconomic status, n (%)						
Low	22 (25.0)	7 (36.8)	2 (11.1)	7 (48.6)	6 (35.3)	2 (15.4)
Middle	42 (47.7)	7 (36.8)	11 (61.1)	17 (50.0)	7 (41.2)	9 (69.2)
High	24 (27.3)	5 (26.4)	5 (27.8)	10 (29.4)	4 (23.5)	2 (15.4)
Married or living together, n (%)	81 (92.1)	16 (84.2)	18 (100.0)	30 (88.2)	17 (100.0)	13 (100.0)

*IQR, interquartile range, * = excluding ARM/HD.*

Maximum duration of first admission was 314 days. TISS scores for 85 children exceeded 10 (indicating need of intensive care) with a maximum of 128 days. Most of these were in the CDH and EA groups. Numbers of surgical interventions were largest in the EA group.

Maximum number of medical appliances needed at discharge was 7. Over half the patients (63.6%) had additional medical problems. These were mainly related to the primary congenital anomaly, like gastro-esophageal reflux and recurrent respiratory infections. Thirty-six children had septic complications in the first 6 months and 5 children had a sedative dependency and needed weaning off sedatives. Sociodemographic characteristics did not differ per group except for paternal age in the EA group.

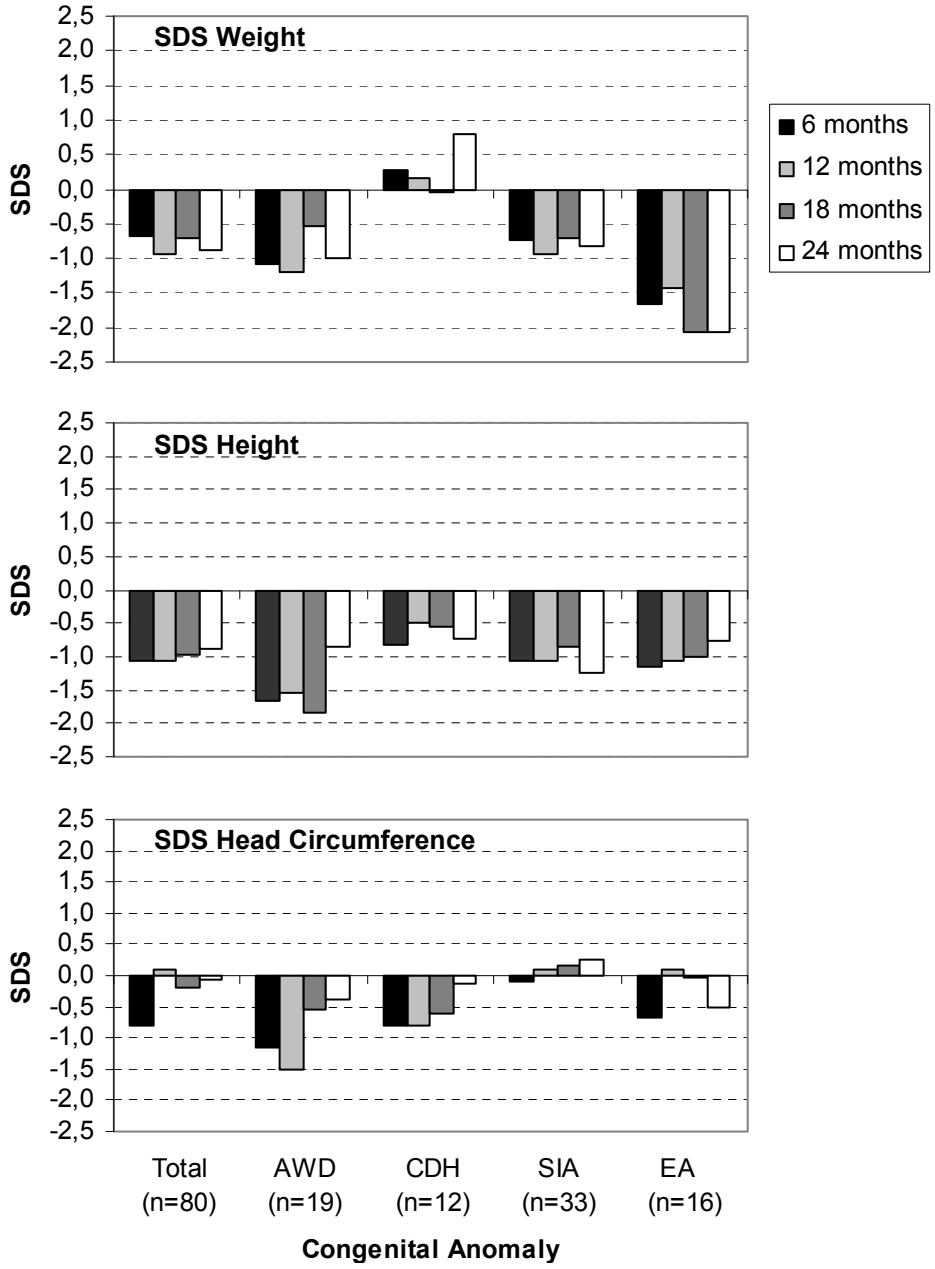


Figure 1.2 *Growth over time.*

Follow-up

Growth over time (Figure 1.2) deviated from the norm in the AWD and EA groups mainly. In the EA group height was significantly below the norm and weight for AWD.[161]

Neurological outcome at 24 months was most notably suspect or abnormal for children in the CDH (24% and 16%) and EA (4% and 33%) groups. In intestinal atresia (18%), this was largely due to chromosomal abnormalities. Overall, neurological outcome was normal in 68.8% of cases. Seventeen patients were neurologically abnormal, of which 6 had a syndromal or chromosomal abnormality and 4 a severe neurological impairment due to brain damage.

Due to the restrictions of range of reliable measurements of the mental and psychomotor development with the BOS 2-30, 11 patients with a major chromosomal or syndromal anomaly or severe neurological impairment had to be eliminated from statistical analysis. Overall mental development of the 69 remaining patients was within the norm. The lowest scores were seen at 18 months, mainly determined by the CDH and AWD groups. Highest scores were seen in the SIA group at all moments. At 24 months these scores were significantly higher than the norm (Table 1.2).

Overall psychomotor scores were significantly lower than mental scores, with lowest scores for CDH (-1SD at 6 and 12 months).

Random regression modeling of mental and psychomotor development on CA subgroup shows a significant linear trend (B: 4.06, 95% Confidence Interval (CI): 0.65 to 7.46) for psychomotor development, whereas mental development shows a significant cubic trend (B: 3.25, 95% CI: 0.78 to 5.71).

Table 1.3 shows covariables influencing mental and psychomotor development. Higher number of major CA and additional medical problems, longer duration of admission, higher TISS scores and higher number of surgical interventions all negatively influence outcome. Certain medical appliances, notably a tracheostomy, have the same effect.

DISCUSSION

This study shows that surgical newborns suffer from impaired growth and developmental delay, mainly with respect to psychomotor development within the first two years of life. Factors indicative for severity of disease have a negative influence on mental and psychomotor developmental outcome. Number of CA as well as duration of admission and number of surgical interventions proved to be significant determinants of mental and psychomotor outcome.

Table 1.2 Mental and psychomotor developmental outcome distinguished by CA subgroup

	Total (n = 69)		**AWD (n = 17)**		**CDH (n = 12)**		**SIA (n = 27)**		**EA (n = 13)**	
months	$\bar{x}$	95%CI	$\bar{x}$	95%CI	$\bar{x}$	95%CI	$\bar{x}$	95%CI	$\bar{x}$	95%CI
MDI										
6	99.4	95.6 to 103.3	100.4	93.4 to 107.5	96.8	84.7 to 109.0	103.1	98.3 to 107.8	98.5	89.3 to 107.7
12	100.0	94.4 to 105.6	98.4	83.6 to 113.1	99.4	82.8 to 115.9	104.0	96.7 to 111.2	98.8	86.8 to 110.8
18	96.6	90.6 to 102.5	89.2	75.5 to 102.9	90.1	72.3 to 107.9	104.6	96.8 to 112.3	99.2	83.0 to 115.4
24	101.7	95.5 to 108.0	95.1	81.5 to 108.8	95.3	76.0 to 114.6	*112.6	105.4 to 119.7	94.8	75.9 to 113.7
PDI										
6	*88.0	83.8 to 92.2	*85.9	79.8 to 92.1	*83.0	71.3 to 94.7	92.2	85.3 to 99.2	91.5	79.0 to 104.0
12	*91.5	85.5 to 97.6	89.8	81.0 to 98.6	82.6	65.0 to 100.3	96.4	86.6 to 106.1	97.2	77.0 to 117.5
18	93.6	87.9 to 99.2	91.3	77.6 to 105.0	84.5	67.0 to 102.0	98.5	90.7 to 106.3	99.6	87.5 to 111.6
24	*93.2	87.9 to 98.5	91.4	82.7 to 100.2	86.1	66.6 to 105.6	96.7	88.5 to 104.9	95.4	80.0 to 110.8

*Abbreviations: $\bar{x}$ = mean, CI, confidence interval; MDI, mental developmental index; PDI, psychomotor developmental index; * Statistically significant at the 0.05 level (2-tailed).*

Table 1.3 Random regression modeling of mental and psychomotor development on medical and physical covariables separately*

	MDI		PDI	
	B‡	95%CI	B‡	95%CI
First born	-0.37	-10.48 to 9.75	-4.81	-14.41 to 4.78
Non Dutch	-11.28	-24.62 to 2.07	-3.25	-16.25 to 9.74
Gestational age	-0.20	-2.13 to 1.72	0.66	-1.18 to 2.49
Birth weight	4.72	-4.76 to 14.20	6.51	-2.34 to 15.36
Birth head circumference	2.20	-0.88 to 5.27	2.33	-0.54 to 5.19
Number of major CA	‡ -9.81	-14.25 to -5.37	‡ -10.60	-14.71 to -6.48
Length of admission in 1st 6 months	‡ -0.19	-0.29 to -0.09	‡ -0.17	-0.26 to -0.07
TISS ≥ 10	‡ -0.44	-0.66 to -0.22	‡ -0.40	-0.62 to -0.18
Surgical interventions in 24 months	‡ -3.64	-5.74 to -1.54	‡ -3.37	-5.40 to -1.34
O_2 at home	‡ -20.14	-33.70 to -6.59	0.69	-12.93 to 14.32
Tracheostomy at home	‡ -43.23	-71.46 to -15.00	‡ -36.01	-63.51 to -8.51
Total medical appliances at home ^	‡ -5.07	-8.52 to -1.62	‡ -5.05	-8.35 to -1.76
Additional medical problems	‡ -4.38	-6.39 to -2.37	‡ -4.27	-6.17 to -2.37
Septic complications	-2.57	-6.42 to 1.28	‡ -3.71	-7.33 to -0.09
Sedative dependency	-18.64	-39.19 to 1.91	-14.92	-34.72 to 4.87
Neurological complications	‡ -23.50	-46.46 to -0.54	-7.06	-29.49 to 15.36

Abbreviations: MDI, mental developmental index; PDI, psychomotor developmental index; B, unstandardized regression coefficient; CI, confidence interval.
** Adjusted for sex, parental age, socioeconomic status, time trend and subgroups*
‡ 95%CI values without 0 signify significance at the ≤ 0.05 level
^ Enterostomy (mainly for Hirschsprung's disease and anorectal malformations) or gastrostomy (CDH and esophageal atresia), central venous catheter (mainly for small intestinal anomalies), nasogastric tube feeding (least for small intestinal anomalies), tracheostomy (mainly for major airway malformations and esophageal atresias), oxygen at discharge and monitoring of vital functions at home (mainly for abdominal wall defect and airway malformations).

Since we aimed at focusing solely on the effect of CA, analysis was adjusted for sex, socioeconomic status and parental ages. Gestational age and initial growth parameters are below average, but still within the norm. Growth over time is below the norm in the AWD and EA subgroups. All groups, however, show below-average weight, which may partially be explained by severity of disease and feeding problems. Yet, other factors like increased work of breathing and recurrent respiratory infections probably also contribute to this phenomenon and persistent surveillance is indicated.

The CA cohort of children is characterized by long and/or frequent admissions in the neonatal period and many surgical interventions under general anesthesia. Interventions are most numerous in the EA group – mainly due to gastro-esophageal reflux (GER) and strictures of the anastomosis. Medical appliances needed at home seemed to impede outcome. This effect is most prominent for tracheostomy, supplemental oxygen and nasogastric tubes as they restrict mobility and interfere with normal explorative activity. On the other hand, one has to take into account that

gastrostomy tubes and nasogastric tubes were sometimes placed because of developmental problems, so no definitive conclusion can be drawn from this factor.

Delayed psychomotor development could be influenced by initial illness and (postoperative) limitation of movement, especially after surgery for large AWD.

CDH has the highest mortality rate. Both CDH survivors and children with EA are most prone to long admissions and high associated morbidity. The high mortality and morbidity in CDH are in accordance with the literature. The duration of first admission in CDH patients is flattered because 6 out of 18 (33.3%) died within the first month. In CDH survivors, morbidity is due to pulmonary sequelae from artificial ventilation, lung hypoplasia and perinatal asphyxia. For this group of patients disease-specific follow-up has recently been advocated by the American Association of Pediatrics.[194] Children with EA have recurrent respiratory tract infections and tracheomalacia. For both groups GER contributes to morbidity.

Neurological outcome was determined for the whole group of survivors (n = 101) and hence affected by major chromosomal or syndromal anomalies, or severe neurological impairment (n = 17). However, in the analysis of mental and psychomotor development this subgroup was excluded because children often could not be scored, but also to straightforwardly evaluate the influence of a CA. Developmental results otherwise would have been worse.

We found developmental recovery to some extent at 2 years of age. One should realize, however, that both mental and psychomotor functions are still relatively undifferentiated at this age and might not be fully representative to predict recovery. Structural and longitudinal evaluation at predetermined time points as will be provided by our follow-up program (6-monthly during the first year two years and then at 5, 8, 12, and 18 years) is essential for further prediction of outcome.

This study has limitations. Literature shows physical, developmental and psychological risks in the group of ARM and HD.[183,194] Due to small numbers and less representative cases of these anomalies in our cohort we were unable to evaluate these risks. Statistical literature[287,372,451] states that the assumption of 'missing at random' is tenable in case of random regression models for repeated measurements. This makes the overall relatively small numbers due to some missing measurements for a number of patients acceptable.

In conclusion, survival alone is no longer a sufficient parameter for successful treatment in surgical newborns. Morbidity, influencing quality of life is equally important. The increased risk for impaired growth and developmental delay warrants a dedicated team of different specialists evaluating morbidity up till adolescence. Scrupulous monitoring of the child for risk factors and early adequate information to parents on what to expect from their child would offer an opportunity for early signaling and intervention and

decrease parental burden. The surgical newborns and their parents deserve an interdisciplinary follow-up team and structured follow-up as a state of the art facility in pediatric surgical centers.

ACKNOWLEDGEMENT

We thank Ko Hagoort for patiently editing the article.

FUNDING AND COMPETING INTERESTS

This study was funded by the Erasmus Medical Centre and the Department of Pediatric Surgery. Funders had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; nor in the decision to submit the paper for publication.

A prospective comparative evaluation of persistent respiratory morbidity after repair of esophageal atresia and congenital diaphragmatic hernia

Freedom is the oxygen without which science cannot breathe

David Sarnoff (1891-1971)

ABSTRACT

Objective

To compare long-term morbidity in children after repair of esophageal atresia (EA) or congenital diaphragmatic hernia (CDH).

Patients and methods

Children were seen at 6, 12, and 24 months and 5 years within the framework of a prospective longitudinal follow-up program in a tertiary children's hospital. Respiratory morbidity and physical condition were evaluated at all moments. At age 5 years, pulmonary function, maximal exercise performance, and motor function were tested.

Results

Three of 23 atresia patients and 10 of 20 hernia patients developed bronchopulmonary dysplasia. Seventeen atresia and 11 hernia patients had recurrent respiratory tract infections mainly in the first years of life. At age 5, 25% of EA and CDH patients measured, showed reduced FEV1 (z-score < -2). Both atresia and hernia patients showed impaired growth, with catch-up growth at 5 years in atresia but not in hernia patients. Maximal exercise performance and motor function development were significantly below normal for both groups.

Conclusions

Esophageal atresia and congenital diaphragmatic hernia are associated with equal risk of long-term respiratory morbidity, growth impairment, disturbed maximal exercise performance and motor function development. Prospective follow-up of EA patients aimed at identifying respiratory problems other than tracheomalacia. Prospective follow-up of CDH patients should be an integral part of interdisciplinary follow-up programs.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) and esophageal atresia (EA) are both severe congenital anatomical anomalies requiring neonatal surgery and intensive care treatment. Follow-up for children with EA tends to focus on gastro-intestinal pathology.[93,284,414] Respiratory pathology, however, seems equally important and is widely described as related to the variable amount of tracheomalacia. Abnormal development of the tracheobronchial tree may contribute to tracheomalacia and recurrent atelectasis.[428]

Tracheomalacia may even lead to cyanotic events and death.[8,90,107,136,280,388,428] Abnormal esophageal motility and epithelial function are likely contributors to respiratory morbidity as well. Data on tracheomalacia-related symptoms seem reliable. However, most other data on pulmonary morbidity have been obtained in cross-sectional long-term follow-up studies. Results, especially regarding respiratory tract infections (RTI), therefore may have been influenced by recall bias. Dudley and Phelan retrospectively evaluated 192 EA survivors and found that 78 children had suffered more than three episodes of bronchitis per year in the first three years of life.[136] More recently Malmström et al showed that 41% of adolescents after repair of EA still had respiratory symptoms, and 52% had ever had pneumonia or wheezing.[298] Pneumonia in the first years of life may give rise to mild lung function abnormalities later in life.[280] Mild lung function abnormalities following EA repair have also been described.[8,90] Several cross-sectional studies report secondary morbidity. Up to 50% of EA patients were found to have associated anomalies like cardiac anomalies, and consequently higher morbidity.[57]

New treatment modalities such as high frequency oscillation (HFO) ventilation, nitric oxide administration and extracorporeal membrane oxygenation (ECMO) have improved survival rates in CDH patients.[105,118,402] Evidence is emerging, however, that better survival coincides with a great deal of morbidity. Data have been mainly obtained from cross-sectional observational studies,[299,422,423,443] but several longitudinal studies are ongoing.[165] Recently the American Association of Pediatrics has published a follow-up guideline for CDH patients[271] and the first retrospective data on multidisciplinary follow-up of CDH patients have become available.[165,315,316] Long-term pulmonary sequelae in CDH survivors seem to result from residual lung hypoplasia with persistent pulmonary hypertension, but also from lung injury induced by ventilatory support.[234] Other risk factors for morbidity are large diaphragmatic defects, ECMO therapy and patch repair.

We hypothesized that children after repair of EA show the same extent of respiratory pathology as CDH survivors, although probably of a different nature, with different causative mechanisms. The aim of the present study was to compare respiratory morbidity in EA and CDH patients with respect to baseline characteristics, respiratory tract infections (RTI), lung function, gastro-intestinal morbidity, physical growth,

maximal exercise performance, and motor development. This is the first study to prospectively evaluate respiratory morbidity in EA patients at the age of 5 years.

METHODS

This longitudinal, observational, prospective, cohort study consists of repeated measurements at 6, 12 and 24 months and at 5 years.

Setting

Pediatric surgical department of the Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands. This is the only tertiary academic facility in the South-Western part of the Netherlands equipped for all major surgical specialties. The referral area has 4 million inhabitants with 44,000 newborns annually.

Since 1999 a multidisciplinary team – consisting of a consultant senior pediatric surgeon pediatricians, psychologists, a pediatric physiotherapist, nurses and a social worker – runs a follow-up program for children born with a major anatomical malformation and their families. A clinical geneticist was added to the team in 2004. The program aims to reduce the overall morbidity associated with these malformations; in particular the index diagnoses as described by Ravitch.[351]

Patients

All 68 patients with EA and CDH admitted to the ICU of our department within 7 days after birth from January 1999 to February 2003 were eligible for this study. For the present study we excluded data from four patients suffering from infections and growth impairment as a result of a major syndromal or chromosomal anomaly itself (EA n = 3, 2 Down syndrome, 1 undefined; CDH n = 1, Wolf-Hirschhorn syndrome). Data of the 16 children who died within 6 months were excluded as well. Five families did not participate in our follow-up program. Thus, 43 children (82.7% of survivors) completed a 5 year follow-up (Figure 2.1).

Procedure

The Erasmus MC ethical review board agreed with the study, and written parental informed consent was obtained for all subjects. Demographic and medical data were collected prospectively from the first day of admission. A clinical geneticist routinely evaluated major chromosomal, syndromal and cerebral abnormalities during admission. By protocol the children were seen at ages 6, 12 and 24 months and 5 years, corrected for gestational age. Age for the final evaluation ranged from 5 to 6.5 years.

General aspects

At each time point a pediatrician performed a full physical examination including neurological examination according to the method of Touwen.[419] A senior pediatric

surgeon evaluated specific pediatric surgical issues. Weight and height were measured, and body mass index (BMI) was calculated. Growth data for the Dutch population served as reference values[53,161] and standard deviation scores (SDS) were calculated using Growth Analyser version 3.5 (Dutch Growth Foundation). Reference values for Dutch children of Moroccan or Turkish origin were used if applicable.[162,163]

Respiratory morbidity

The incidence and severity of bronchopulmonary dysplasia (BPD) were recorded according to the diagnostic criteria of Jobe and Bancalari.[239]

At each time point, therapeutic and prophylactic courses of antibiotic treatment, use of inhaled bronchodilators and steroids, and readmissions for RTI were recorded. We recorded numbers of RTI during the first, the second and the 3rd through 5th years respectively. At the age of 5 years 34 children (EA patients n = 18 and CDH patients n = 16) performed pulmonary function tests (PFT): we obtained flow-volume curves before and after bronchodilation with 400 µg salbutamol and measured the fraction of exhaled NO (FE_{NO}). Flow-volume curves were measured on a Masterscreen electronic spirometer (Jaeger, Würzburg, Germany). FEV_1 was expressed as percentage predicted. FE_{NO} was measured online according to guidelines from the European Respiratory Society (ERS) and American Thoracic Society (ATS) using the NIOX analyzer (Aerocrine, Solna, Sweden).[26]

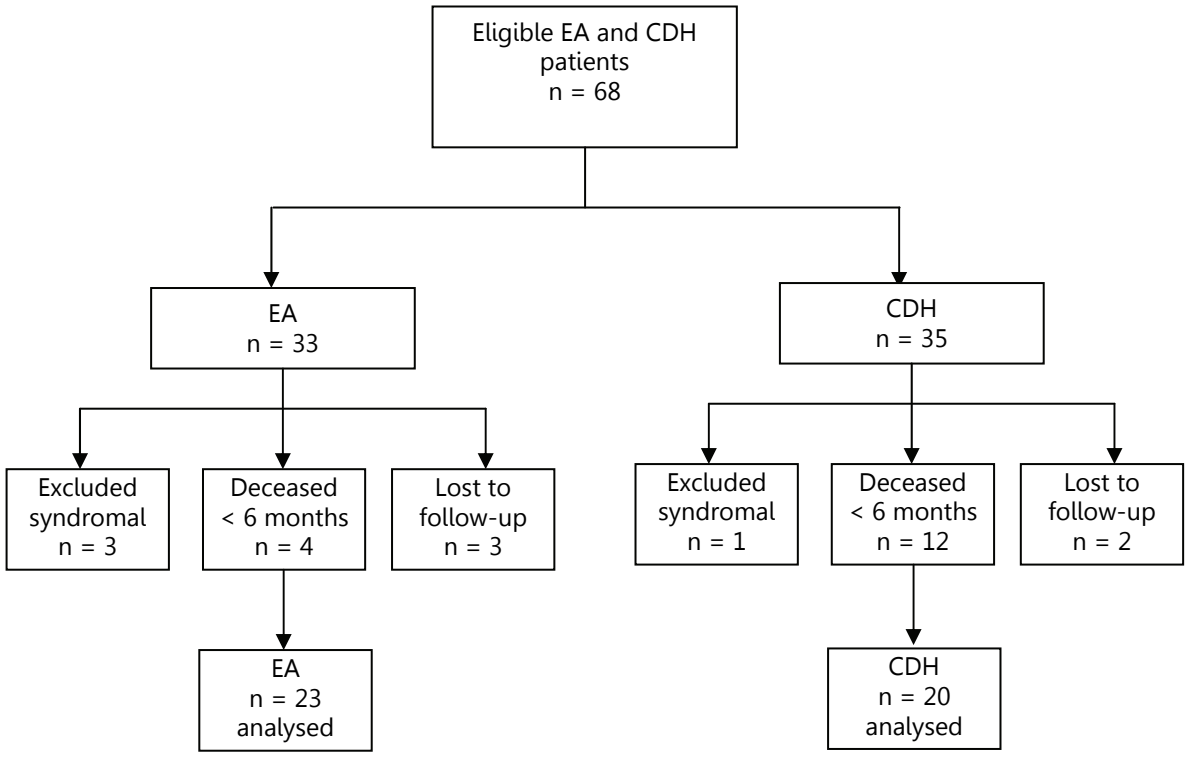


Figure 2.1 *Flowchart showing group composition.*

Gastro-intestinal morbidity
At each time point all children were evaluated for GER by barium swallow X-ray and pH-metry as previously described by Bergmeijer.[39,40] Gastro-intestinal symptoms, use of medication, surgical treatment for reflux, and consultation of a dietician were recorded as well.

Maximal exercise performance
At 5 years the children performed a graded, maximum exercise test using a motor-driven treadmill (En Mill, Enraf Nonius, Rotterdam, the Netherlands) programmed for increases in angle of inclination and speed according to the Bruce protocol.[68]

The children were encouraged to perform to voluntary exhaustion. The maximal endurance time (in minutes, one decimal) served as criterion of exercise capacity, with SD-scores based on recently established reference values for healthy Dutch children (personal communication, van der Cammen-van Zijp). Before, during, and at 2 and 5 minutes after the test, children's heart rate (HR) and transcutaneous oxygen saturation were monitored with a pulse Oximeter (MARS (motion artifact system), type 2001, Respironics Novametrix, Murrysville (PA)). HR of ≥ 185 beats per minute (bpm) or loss of coordination was considered to indicate maximal performance.[246]

Motor function assessment
Motor functioning at the age of 5 years was evaluated by the Movement Assessment Battery for Children (M-ABC). This tool consists of three manual dexterity items (time-related task for each hand separately, bimanual coordination task, and graphical task with the preferred hand), two ball skill items (catching a moving object and aiming at a goal), and three balance items (static balance, dynamic balance while moving fast, and dynamic balance while moving slowly). The total impairment score (TIS), which is the sum of the item scores, was calculated as a percentile score. Scores below or equal to the 5th percentile are indicative of delayed motor function development, scores between the 6th and 15th percentile of borderline performance, and scores above or equal to the 16th percentile are considered normal scores.[215,387]

Data analyses
Descriptive statistics were calculated for baseline characteristics and outcome variables. Data of EA patients and CDH patients were compared with the Mann-Whitney U-test (continuous data) or Chi-square test (categorical data) if appropriate. Growth parameters and SDS maximal endurance time were compared with the reference values using t-tests for independent samples (one tailed). Statistical significance was accepted at the 5% level.
SPSS 15.0 for Windows was used for data analyses.

Table 2.1 Baseline characteristics distinguished by CA subgroup

	EA (n = 23)	**CDH (n = 20)**
Boys, n (%)	15 (65.2)	12 (54.5)
Gestational age, mean (SD), wk	37.2 (3.5)	39.2 (1.5)
Birth weight, mean (SD), kg	2.7 (0.8)	3.4 (0.3)**
Patients without additional (major or minor) CA, n (%)	5 (21.7)	12 (60.0)**
Patients with 1 or more additional major CA, n (%)	6 (26.1)	3 (15.0)
Patients with 1 or more additional minor CA, n (%)	14 (60.9)	5 (25.0)
Patients with cardiac anomaly, n (%) (ASD, VSD, Coarctation of aorta)	4 (17.4)	2 (10.0)
Admission in 1st 24 months, median (range), days	60.0 (11 - 181)	67.5 (15 - 192)
Surgical interventions in 24 months, median (range)	5 (1 - 11)	3 (1 - 6)
Ventilatory support, median (range), days	3.5 (1 - 44)	19.5 (2 - 62)**
Supplemental oxygen, median (range), days	6.0 (1 - 77)	37.5 (3 - 83)*
Patients with additional medical problems at discharge, n (%)	20 (87.0)	18 (90.0)
Patients with additional medical problems at 5 yrs, n (%)	21 (91.3)	18 (90.0)
Additional medical problems per patient at discharge, median (range)	2 (0 - 12)	2 (0 - 6)
Additional medical problems per patient at 5 yrs, median (range)	2 (0 - 7)	2 (0 - 10)

** = significantly less interventions in the CDH group at the 0.5% level as shown by Mann-Whitney test,*
*** = significantly less interventions in the CDH group at the 0.1% level as shown by Mann-Whitney test.*

RESULTS

Baseline characteristics for both groups of children are shown in Table 2.1. All but one EA children underwent primary anastomosis via a lateral thoracotomy within 48 hours. One patient had a type A long gap atresia and underwent delayed primary anastomosis after 3 months. Bronchoscopic evaluation of tracheomalacia during the initial repair was not routinely performed. In 15 of the 20 children with CDH (75%) the diaphragmatic defect was repaired with a Gore-Tex patch. Only one child had a right-sided CDH (5%). Diaphragmatic repair was by subcostal laparotomy in all cases.

A cardiac anomaly was reported for four EA patients (17.4%) and two CDH patients (10%) (NS). These consisted of VSD and clipped open ducts in the EA patients and VSD, large ASD and coarctation of the aorta in the CDH patients. In neither group complex heart defects were found. The frequency of additional major anomalies was higher in EA than in CDH patients without reaching statistical significance (26.1% and 15% respectively, NS). For additional minor anomalies like minor limb, and rib or vertebral anomalies statistical significance was reached (60.9% and 28.6%, respectively, p = 0.001). Overall, significantly more EA patients had additional anomalies (78.3% versus 40%, respectively, p = 0.03). For both groups the major impact of morbidity was during the first year of life: hospital

admissions occurred mainly in the first 6 months and surgical interventions within the first year. EA patients underwent more surgical interventions without reaching statistical significance (Table 2.1). These interventions comprised mainly dilations of anastomotic esophageal strictures (in 70% of EA patients, n = 16, median 2 per patient, range 0 - 9) and Nissen fundoplications (n = 8, 34.8%). Aortopexies had not been performed.

Additional medical problems at discharge were reported in 20 (87%) and 19 (90%) of EA and CDH patients, respectively. These varied from gastro-esophageal reflux (n = 21 EA, n = 18 CDH) to atopic eczema and were mainly (over 80% for each group) related to the primary congenital anomaly. At discharge 21 (87%) of EA patients and all CDH patients received medication. These figures had dropped to 43.5% and 23.8% at the age of 5 years, respectively.

Respiratory morbidity

All EA patients had been ventilated conventionally. Three children (13%) with severe tracheomalacia needed prolonged positive pressure ventilation and developed BPD (Table 2.2). None of the EA patients received ECMO treatment. Bronchoscopy was performed only in the three (13%) patients who required prolonged ventilation.

Eight CDH patients (40%) were primarily ventilated with high-frequency oscillation (HFO) and had been converted to conventional ventilation before surgical closure of the diaphragm. Four (33.3%) of the conventionally ventilated CDH patients were later converted to HFO ventilation. Veno-arterial ECMO was performed in 11 CDH patients (55%), starting at a median age of 13 (range 5 - 265) hours. ECMO was discontinued after a median of 168 (72 - 459) hours.
Routine vaccination against RS virus and/or influenza was not performed.

Table 2.2 gives details of the respiratory morbidity encountered during the 5 years follow-up. Hospitalizations for RTI were rare. Median numbers of RTI are relatively low, but show wide ranges in both groups. Only one of the four EA patients with a cardiac anomaly developed BPD. This child, prematurely born after 28.6 weeks, had no RTI. One other EA patient with a cardiac anomaly, without BPD, suffered from recurrent RTI (over five episodes). The two CDH patients with a cardiac anomaly both developed BPD but did not suffer from RTI. Nine (81.1%) of 11 ECMO-treated CDH patients and one other developed moderate or severe BPD. Five of these 10 (50%) had recurrent RTI, versus six of CDH patients (60%) without or with only mild BPD.

Spirometry before and after bronchodilation was initiated in 34 patients at 5 years. Most patients, however, failed to perform reproducible flow-volume curves. FEV_1 and FE_{NO} were the only two reliably obtained lung function parameters (Table 2.2). In both groups 25% (n = 12 EA, 13 CDH) of patients had abnormally low % predicted of FEV_1. The median FE_{NO} was within the predicted range for (n = 9) EA patients (9.0 ppb), and in the lower range of normal for (n = 9) CDH patients (5.2 ppb).[297]

Table 2.2 Respiratory morbidity in EA and CDH patients during the first 5 years of life

		Esophageal Atresia (n = 23)	**CDH (n = 20)**
Patients with BPD, n (%)	none	19 (82.6)	8 (40.0)
	mild	1 (4.3)	2 (10.0)
	moderate	1 (4.3)	2 (10.0)
	severe	2 (8.7)	8 (40.0)
Total number of RTI in 5 yrs, median (range)		9 (0 - 27)	7 (0 - 17)
Patients with > 5 RTI in 5 years, n (%)		17 (73.9)	11 (55)
Number of patients admitted for RTI in 5 years, median (range)		0 (0 - 4)	0 (0 - 1)
Number of therapeutic courses of antibiotics for RTI, median (range)		3.0 (0 - 17)	3.0 (0 - 8)
	1st year	1.0 (0 - 6)	1.0 (0 - 4)
	2nd year	1.0 (0 - 4)	1.0 (0 - 3)
	3 - 5 years	0.0 (0 - 10)	0.0 (0 - 3)
Patients treated with prophylactic antibiotics for RTI, n (%)			
	1st year	3 (13.0)	0
	2nd year	5 (21.7)	3 (14.3)
	3 - 5 years	6 (26.1)	0
Use of bronchodilators, n (%)		6 (26.1)	5 (25)
Use of inhaled steroids, n (%)		2 (8.7)	2 (10)
FEV1 before bronchodilation, mean % predicted (range)		85 (69 - 118) n = 12	91 (72 - 122) n = 8
Patients with abnormal FEV1 (Z-score < -2), n (%)		3 (25)	2 (25)
FeNO, median ppb (range)		9.0 (5.0 - 20.4)	5.2 (2.8 - 10.0)

Gastro-intestinal morbidity

In both groups 20 children were treated conservatively with antacids and prokinetic drugs initially. Thirteen EA patients and 11 CDH patients also received an acid secretion inhibitor. Eight EA patients (34.8%) and seven CDH patients (35%), respectively, underwent a Nissen fundoplication. For those patients who were treated conservatively the median (range) duration of treatment for GER was 23.11 (0 - 71.7) and 8.0 (0 - 64.9) months in EA and CDH, respectively. EA patients who underwent a Nissen fundoplication had a median number of 9.5 RTI in 5 years (range 0 - 23) versus 7 (3 - 24) for those treated conservatively (NS). Corresponding figures for the CDH patients are 9 (1 - 17) versus 7 (0 - 14) (NS). There was no significant difference in RTI before or after the Nissen fundoplication.

A dietician was consulted for 8 patients in each group (NS).

Physical growth

Data at 6, 12, 24, and 60 months for both groups are shown in Figure 2.2. At 5 years of age EA patients seemed to catch up in weight, concomitant with an increase in height (Figures 2.2b and 2.2a). The BMI SDS was constant after the first year of life for both groups, but reached a higher level for EA patients (Figure 2.2c).

ECMO-treated CDH patients had a significantly lower height at 6, 12 months and 5 years ($p = 0.02$, 0.04 and 0.04, respectively), lower weight at 12 months and 5 years ($p = 0.02$ and 0.02, respectively) and lower BMI at 12 months of age ($p = 0.05$) than non-ECMO-treated CDH patients.

Maximal exercise performance

One EA patient and 2 CDH patients could not perform the maximal exercise test because of neurological underlying disease such as cerebral palsy. Thus, 22 EA patients and 18 CDH patients performed the exercise test. Reliable results could not be obtained for six EA patients for the following reasons: no maximal exercise performance reached n = 3, balance problems n = 2, and poor concentration n = 1. Results for two of the CDH patients were unreliable due to unwillingness to perform maximally or balance problems (n = 1 for each reason).

Both in EA (n = 16) and CDH (n = 16) patients the maximal exercise tolerance was significantly below the norm (mean SDS endurance time -0.60; $p = 0.02$, and -0.84; $p = 0.012$, respectively). One EA patient (6.3%) and two CDH patients (12.5%) had an abnormally low maximal exercise tolerance (i.e. maximal endurance time SDS < -2; NS). The median (range) heart rate at maximal exercise was 181 (194 - 148) and 191 (207 - 146) beats per minute for the EA and CDH group, respectively. Two EA patients (12.5%) had a decreased oxygen saturation (i.e. ≤ 94%) at maximal exercise (94 and 93% respectively). This phenomenon was not observed in any of the CDH patients.

Fig. 2.2a

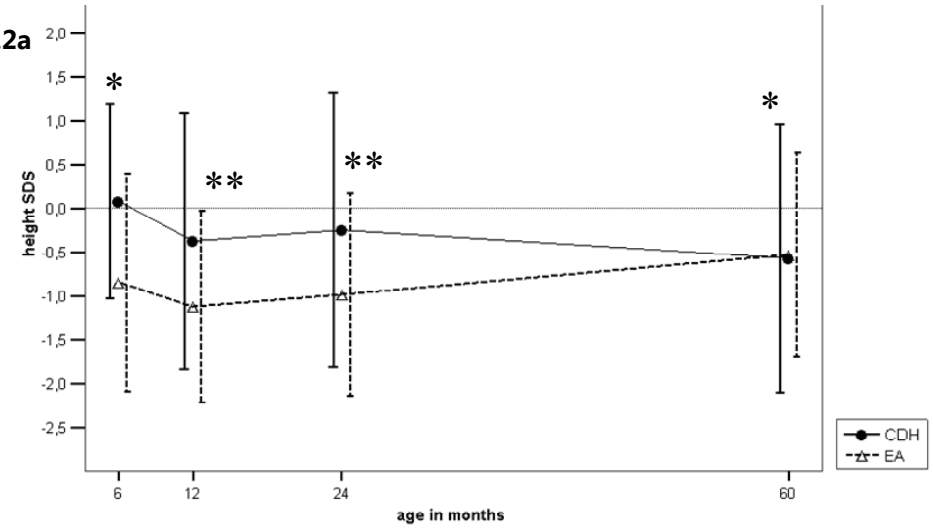


Fig. 2.2b

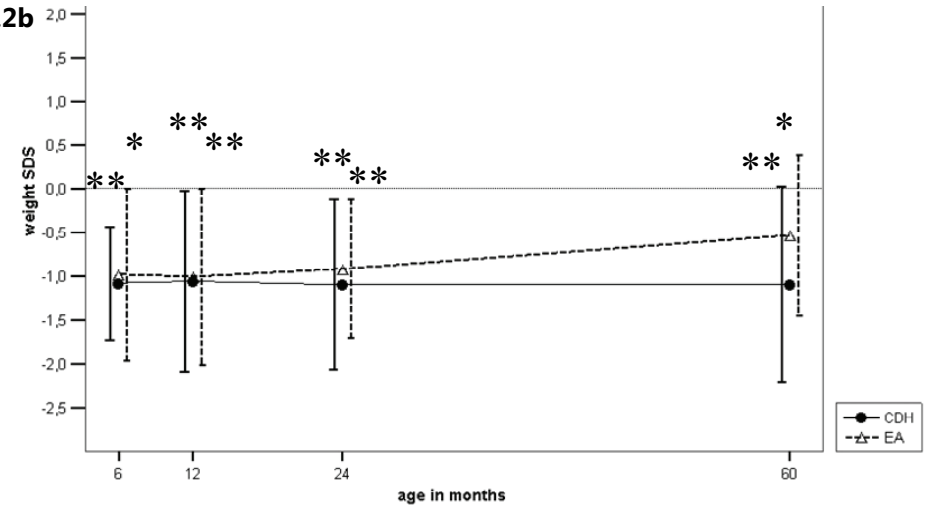


Fig. 2.2c

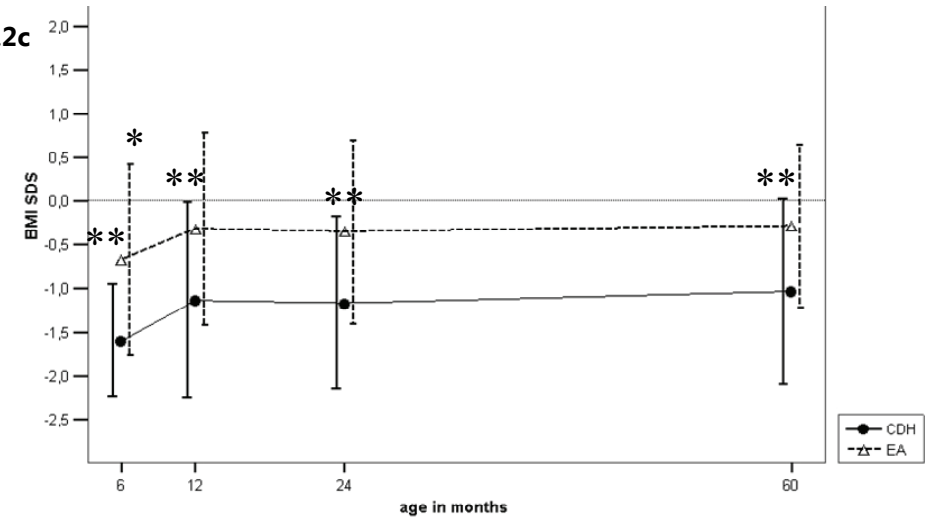


Figure 2.2 *Diagram representing the mean (SDS) for height (a), weight (b), and BMi (c) across time in CDH and EA patients. Circles and solid lines represent CDH, open triangles and dashes lines represent EA. * signals significant deviation from the Dutch norm at the 5% level ($p \leq 0.05$), ** signals significant deviation from this norm at the 0.1% level ($p \leq 0.001$).*

Motor function assessment

Again, the M-ABC could not be applied to one EA patient and two CDH patients because of underlying neurological disease such as cerebral palsy. Thus 22 EA patients and 18 CDH patients were studied. The total percentile scores were indicative of delayed motor function in 13.6% of EA patients and 16.7% of CDH patients (NS). Problems occurred especially in ball skills and static and dynamic balance. Fourteen EA patients (63.6%) and 11 CDH patients (61.1%) showed normal motor function performance, the remaining 22.8% and 22.2% of EA and CDH patients showed borderline motor performance, i.e. were at risk for impaired motor function. These proportions are significantly different from the expected proportions ($p = 0.02$ and $p = 0.01$ for EA and CDH, respectively).

DISCUSSION

We prospectively evaluated respiratory morbidity and factors interrelating with pulmonary disease during the first 5 years in two groups of children born with major congenital anatomical malformations of the respiratory tract: EA and CDH. Both groups showed recurrent respiratory tract infections, a high incidence of GER, impaired physical growth, and decreased maximal exercise tolerance. A little over 60% of patients had a normal total score of motor function development.

Tracheomalacia associated with EA occurs frequently and may lead to respiratory insults. Less frequent are respiratory tract infections (RTI), wheezing and cough; these findings mainly are derived from studies using a cross sectional design.[388,298,106,268] Our prospectively collected data are consistent with these findings. In addition we showed that these problems might negatively affect maximal exercise tolerance. Only three EA patients with severe tracheomalacia required prolonged ventilation and developed BPD, whereas 10 (50%) CDH patients, mainly those treated with ECMO, suffered from moderate to severe BPD according to criteria of Jobe and Bacalari.[239] We assume, therefore, that different mechanisms are involved in persisting respiratory morbidity. In CDH patients the susceptibility of the hypoplastic lungs for artificial ventilatory support is well documented.[54,56,422]

In both groups, the frequency of RTI at any measurement moment did not differ between children who underwent a Nissen fundoplication for gastro-esophageal reflux or those who were treated conservatively. We assume that reflux in these patients is not a major contributor to RTI.

As sample sizes were limited and numbers of possible contributing factors large, we did not perform regression analysis to predict respiratory morbidity. Still, we evaluated several factors that might have contributed to RTI. Being rare in either group, cardiac anomalies did not seem to influence incidences of RTI within the first 5 years. Since

50 - 60% of CDH patients showed recurrent RTI irrespective of BPD we assume that extra-pulmonary factors may be involved as well. Most patients in either group had gastrointestinal problems and impaired physical growth. These factors may well contribute to increased susceptibility for RTI. Nevertheless, the impact of gastrointestinal problems on RTI in EA patients remains inconclusive so far.[136,280,298]

Pulmonary function testing proved problematic. For no more than half of the patients we could interpret FEV_1 before bronchodilation. This revealed airflow obstruction in 25% of them. From the literature it appears that pulmonary function testing was successful in 40 to 83% of five-year-old children.[394]

FE_{NO} is known to be associated with eosinophilic airway inflammation.[297,411] Almost all patients in the present study had normal FE_{NO} levels, in line with findings by Malmström et al.[298] FE_{NO} level was increased in only one CDH patient, who showed an atopic constitution. Low or normal FE_{NO} levels have also been described in children with bronchopulmonary dysplasia,[239] which might explain the lower median FE_{NO} in the CDH patients.

In spite of gastrointestinal and nutritional morbidity, especially in the first year for EA patients, only 13% of parents consulted with a dietician during the child's first year of life. For the CDH patients, failure to thrive remained a problem over time. Attempts should be undertaken to improve caloric intake as work of breathing may require a higher caloric intake in CDH and, to a lesser extent, EA patients.

Both EA and CDH patients showed lower maximal exercise tolerance compared with recently established reference values for healthy Dutch children (personal communication, van der Cammen-van Zijp). Persistent respiratory morbidity, impaired growth, and abnormal motor function development may all contribute to this phenomenon. Proportions of EA and CDH patients with normal motor function were significantly lower than expected: about 60% of patients had a percentile score above P15, whereas a proportion of 85% could be expected.

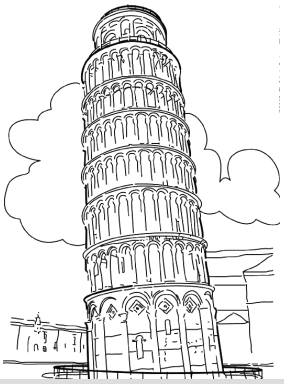
Multidisciplinary follow-up of surgical newborns has hardly been performed so far, but has recently been advocated by the American Association of Pediatrics for CDH patients.[315] The groups of Muratore and Friedman, however, have reported retrospectively collected data on pulmonary, gastro-intestinal, and neurodevelopmental morbidity in CDH patients up to 3 years of age in a multidisciplinary follow-up clinic.[165,315,316] It appeared that these showed continued pulmonary and gastrointestinal morbidity over the years, like the CDH patients in the present study, who show the same pathology up to the age of 5 years.

In conclusion, both EA and CDH patients are at risk for long-term respiratory morbidity, growth impairment, and disturbed maximal exercise performance and motor function

development. Prospective evaluation of EA patients aimed at identifying other respiratory problems than tracheomalacia and prospective evaluation of CDH patients should be an integral part of postoperative disciplinary follow-up programs.

3

Motor function profiles in children with major anatomical congenital anomalies; an evaluation at 5 years of age



The whole imposing edifice of modern medicine is like the celebrated tower of Pisa - slightly off balance

Charles, Prince Of Wales (1948 -)

ABSTRACT

Objective
To investigate motor function profiles at 5 years of age in children with major congenital anomalies (CA).

Design
Descriptive study.

Setting
Outpatient clinic of the pediatric surgery department of a tertiary university hospital.

Participants
Survivors born between January 1999 and March 2003 with the following major anatomical CA were eligible (n = 149): small intestinal anomalies (SIA), congenital diaphragmatic hernia (CDH), esophageal atresia (EA), and abdominal wall defects (AWD). Exclusion criteria: severe psychomotor delay, neurological impairments, and inability to understand instructions (n = 26). Lost to follow-up n = 44. Thus, 79 children were included: SIA n = 17, CDH n = 18, EA n = 24, and AWD n = 20.

Main outcome measure
Total impairment score and subtest scores of the Movement Assessment Battery for Children (M-ABC).

Results
Fifty-eight children (73.4%) had a total impairment score (TIS) within the normal range, 13 (16.5%) were classified as borderline and another 8 (10.1%) as having a motor problem. This distribution is significantly different from the distribution in the norm population (Chi square p = 0.01). Ball skills were impaired in CDH and EA patients, both EA and SIA patients had more problems with balance. The total percentile score of M-ABC correlated negatively with the total number of major CA (r_s = -0.35, p < 0.01), and positively with the number of dynamic sit-ups (r_s = 0.44; p < 0.01, n = 71) and the maximal endurance time from the Bruce test (r_s = 0.31; p = 0.01, n = 62).

Conclusions
Children with CA are at risk for delayed motor function performance. Risk groups are: children with additional anomalies, those with increased long-term morbidity, and decreased abdominal muscle strength following abdominal surgery.

INTRODUCTION

Children with major anatomical congenital anomalies (CA) often need prolonged hospitalization with (multiple) surgical interventions in the neonatal period and thereafter. Improvement of intensive care treatment has reduced mortality rates, but at the cost of more morbidity. Multidisciplinary follow-up is important to detect developmental and physical problems at an early stage and to provide adequate intervention if necessary. The use of validated standardized assessment instruments would be of great help in this respect.

In our hospital motor function in these children is tested at fixed time points, up from the age of 6 months onwards. The instrument used from the age of 5 years is the Movement Assessment Battery for Children (M-ABC).

The M-ABC is a worldwide used test for children up from 4 - 12 years and consists of appropriate items for different age bands.[215] It is organized into three domains of motor performance: fine motor skills (manual dexterity; 3 items), ball skills (2 items), and static and dynamic balance (1 item and 2 items, respectively). Smits-Engelsman showed that the original norm scores and cut-off points are also applicable to Dutch children.[387] This test evaluates motor function in daily life and is suitable for children without neurological impairments who can understand instructions adequately.[215] Physical fitness correlates positively with motor competence assessed by the M-ABC in healthy 9 - 10 year old children.[191]

The M-ABC has been used to evaluate motor function in children with a variety of disorders: developmental speech language disorder (DSLD),[455,464] several neonatal problems like prematurity, small for gestational age (SGA), and asphyxia,[102,121,141,221,245,468] executive function problems such as attention deficit hyperactivity disorder (ADHD),[289] congenital heart disease[47,224] and Turner Syndrome.[322] To our knowledge, standardized assessment of motor function has not been published in children with major CA, other than with cardiac malformations.[47,398]

We hypothesized that children suffering from major CA are at risk for impaired motor function. Different profiles with respect to impairment scores on manual dexterity, ball skills and balance can be expected depending on diagnosis. The more energy resources will be needed to sustain normal cardiorespiratory function and physical growth, the more gross motor function disorders will occur with preservation of the fine motor function. Therefore, we evaluated M-ABC total impairment score (TIS) and subtests scores in different groups of CA patients at the age of five years. In addition we evaluated abdominal muscle strength, hypermobility, maximal exercise capacity, and other underlying causes of previously reported factors that may influence M-ABC scores.

PATIENTS AND METHODS

Patients

Between January 1999 and March 2003, 171 patients with small intestinal anomalies (SIA), congenital diaphragmatic hernia (CDH), esophageal atresia (EA), or abdominal wall defects (AWD) were admitted to the pediatric surgical intensive care unit within 7 days after birth. Twenty-two patients died within the first months after birth (SIA n = 3; CDH n = 14; EA n = 5). Thus, 149 patients were eligible for follow-up. Parents of 27 children declined to participate in the follow-up program. For 17 children, assessment has not been performed (yet) for logistical reasons. Twenty-six patients had to be excluded: children with syndromal or chromosomal disorders suffering from severe psychomotor delay, children with neurological impairments such as cerebral palsy, and those who were unable to understand instructions adequately for other reasons, e.g. insufficient command of the Dutch language. Finally, 79 of 149 eligible patients (53%) were included (Figure 3.1).

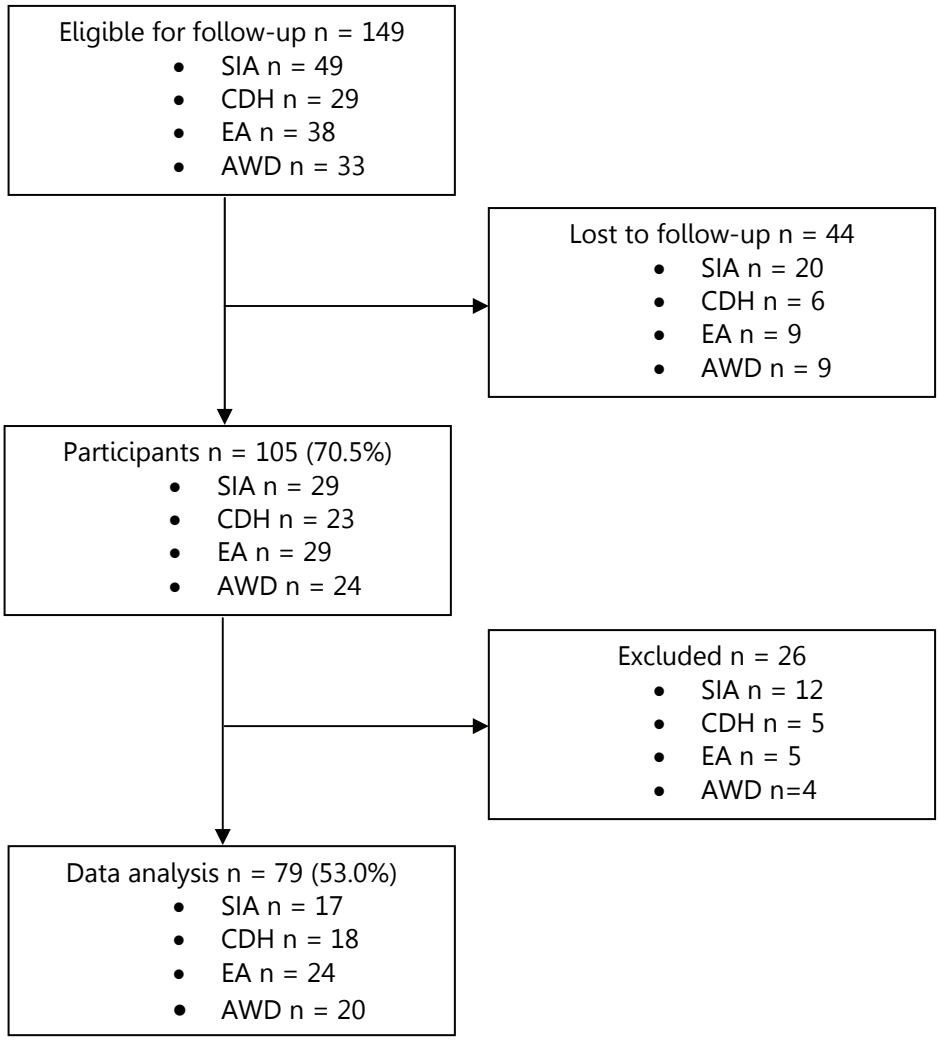


Figure 3.1 *Flowchart*

Procedure

Since 1999, a multidisciplinary team presently consisting of pediatricians, a consultant senior pediatric surgeon, developmental psychologists, a pediatric physical therapist, a social worker, nursing staff, and a clinical geneticist has been involved in the prospective follow-up program of neonates with major CA treated in the pediatric surgical department of our tertiary children's hospital.

The Medical Ethical Review Board of our hospital approved the follow-up program and written parental informed consent for participation in this program was obtained for all subjects. The following data were collected prospectively from the first day of admission: gestational age, birth weight, socioeconomic status (SES),[398] major CA, duration of artificial ventilation during initial hospitalization, treatment with extracorporeal membrane oxygenation (ECMO) in CDH patients, number and duration of hospital admissions and surgical interventions. Small for gestational age (SGA) was defined as birth weight < -2SD for gestational age. Cardiac malformations were recorded if follow-up by a pediatric cardiologist was deemed necessary. Above-mentioned data on baseline characteristics had also been retrieved for 44 children who were lost to follow-up.

Major chromosomal, syndromal and cerebral abnormalities were routinely evaluated as a clinical geneticist saw all children during admission. By protocol the children were seen at ages 6, 12, and 24 months and at 5 years, corrected for gestational age. The evaluation at age 5 years refers to evaluation between 5 and 6.5 years of age. The pediatrician performed a full physical examination, including neurological examination and measurement of height and weight. Previously published data on growth for the Dutch population[161,164] served as reference values and we calculated standard deviation scores (SDS) for height, weight, and body mass index (BMI) using Growth Analyzer version 3.5 (Dutch Growth Foundation). We used reference values for Dutch children of Moroccan or Turkish origin if applicable.[162,163] The following data were recorded: presence of visual impairment, physical abnormalities interfering with motor function, history of or treatment for ADHD (reported by parents), treatment by physical therapist or speech therapist.

Motor function assessment

The M-ABC was used to evaluate the children's motor skills. An experienced pediatric physical therapist guided all tests. Because all patients were younger than 7 years tasks from age band I (4 - 6 years) were used. The M-ABC consists of eight items: three manual dexterity items (a time-related task for each hand separately, a bimanual coordination task, and a graphical task with the preferred hand), two ball skill items (a task of catching a moving object and a task of aiming at a goal), and three balance items (static balance, dynamic balance while moving fast, and dynamic balance while moving slowly). Scaled interval scores for each item were provided varying from good (0) to very poor (5). For items performed by both hands or feet, the scores for each hand

or foot were summed and then divided by 2. A profile of the child's motor performance for each domain of the test was obtained by summing the item scores. The TIS, which is the sum of the item scores, was calculated. Thus, high scores on the M-ABC represent poor performance. Using percentile normative data tables the three subtest scores and the TIS were transformed into percentile scores. The range between the 100th and 16th percentile is regarded as 'normal', 15th to 6th percentile as 'borderline', and the 5th percentile and below as 'definite motor problem'.[215,387]

Muscle strength

We evaluated the strength of the abdominal muscles and hip flexors by dynamic sit-ups. In short, the child was in supine position with the knees bent at right angles, with the feet flat on the floor. The fingers were to be interlocked behind the head. The examiner supported the child's feet to remain on the underground. On command the chest was supposed to curl from supine position till the upper body was vertical, then returned to touch the floor. This complete maneuver was considered as a sit-up. The maximum number of correctly performed sit-ups in 20 seconds was recorded. The sit-up was not counted if the subject failed to reach the vertical position, failed to keep the fingers interlocked behind the head, arched or bowed the back and raised his buttocks off the ground to raise the upper body, or let the knees exceed a 90-degree angle. Reference values for Dutch children (from 6 years onwards) were used.[467]

Evaluation of hypermobility

Hypermobility was assessed as described by Beighton (1989):

1. passive dorsiflexion of the fifth finger beyond 90°;
2. passive apposition of the thumb to the flexor aspect of the forearm;
3. hyperextension of the elbow beyond 10°;
4. hyperextension of the knee beyond 10°; and
5. forward flexion of the trunk with knees fully extended and the palms of the hands being able to rest flat on the floor.

For items 1 - 4 each side is scored separately; item 5 provides one point. Thus, the maximum possible score is 9. Generalized joint hypermobility was defined as a Beighton score ≥ 5.[432]

Maximal exercise performance

At 5 years the children performed a graded, maximum exercise test using a motor-driven treadmill (En Mill, Enraf Nonius, Rotterdam, the Netherlands) programmed for increases in angle of inclination and speed according to the Bruce protocol.[68]

We encouraged the children to perform to voluntary exhaustion. The maximal endurance time (in minutes, one decimal) served as criterion of exercise capacity. Before and during the test and at 2 and 5 minutes thereafter, we monitored heart rate (HR) and transcutaneous oxygen saturation with a pulse Oximeter (MARS (motion artifact system), type 2001, Respironics Novametrix, Murrysville (PA)). HR of ≥ 185 beats per

minute (bpm)[246] or loss of coordination indicated maximal performance. For the maximal endurance time, SDS were calculated using recently established reference values for healthy Dutch children (unpublished observations, van der Cammen-van Zijp).

Language development

Receptive language development was tested by the Reynell Test, a standardized test for Dutch speaking children between 1 and 6 years of age.[436] Expressive language is not required since the children can answer non-verbally. Language expression was tested by two subtests of the Schlichting Test: one testing knowledge of grammatical structure (syntactical development), the other measuring active vocabulary (lexical development).[374] The numbers of correct answers resulting from both the Reynell and the Schlichting tests were transformed into standard quotient scores with a mean of 100 and a standard deviation of 15. A score of < 85 (< 1 SD below the norm) was considered abnormal and indicative of a language developmental disorder.

Data analysis

Data are presented for each diagnosis group separately as median (range) unless stated otherwise. We used One sample t-tests to test the null hypothesis that the SDS of growth parameters and the maximal endurance time were not different from those of the norm population. The Kruskal-Wallis test served to test differences between the diagnosis groups. We used the Mann-Whitney U-test to test differences in baseline characteristics between participants and those who were lost to follow-up and to compare TIS in children with and without treatment by a pediatric physical therapist. A Chi-square test was performed to test if the distribution of motor performance scores in our population differed significantly from that in the normal population. Spearman Rank correlation coefficients (r_s) were calculated to evaluate the association between motor performance scores and baseline variables, growth data, additional major congenital anomalies, hospital admission in the first 6 months, surgical interventions, ECMO treatment, and SES. Statistical significance is accepted at a 5% level. Analyses were performed using SPSS 15.0.

RESULTS

The baseline characteristics are shown in Table 3.1. Most SIA and CDH patients had an isolated CA; multiple major congenital anomalies were mainly found in EA and AWD patients. The primary diagnoses in the SIA group were: duodenal obstruction from annular pancreas (n = 5), duodenal atresia (n = 3), solitary jejunal or ileal atresia (n = 5), multiple small intestinal atresias (n = 2), malrotation (n = 1), and meconium peritonitis without cystic fibrosis (n = 1). Children with AWD had omphalocele (n = 9), gastroschisis (n = 8), or bladder exstrophy (n = 3). Cardiac anomalies were present in only seven patients (11.3%), predominantly with EA or SIA. Concomitant with the nature of the primary CA, prolonged artificial ventilation was necessary in CDH patients, in three EA

patients with severe tracheobronchomalacia, and in two patients with giant omphalocele and lung hypoplasia. Extracorporeal membrane oxygenation (ECMO) had only been applied in 9 CDH patients. Cerebral ultrasound examinations performed within the first weeks of life were abnormal in 2 patients: one CDH patient showed a hyperdense thalamic lesion for 3 weeks as a result of perinatal asphyxia, one EA patient had benign hydrocephalus. The patients who were lost to follow-up differed from the participants with respect to: ethnicity in SIA and EA patients (significantly more parents of non-Dutch origin in the missing group; $p = 0.03$ and 0.02, respectively); and hospital admission within the first 6 months and number of surgical interventions within the first 24 months in CDH patients. Participating CDH patients were hospitalized longer ($p = 0.03$; hospital admission in lost CDH patients was 33 (11 - 51) days) and underwent significantly more surgical interventions ($p = 0.04$; number of interventions was 2 (1 - 3) in lost CDH patients) than children who were lost to follow-up. All other baseline characteristics in participants and missing patients were not significantly different (data not shown).

At age 5 only SIA patients showed normal physical growth (Table 3.2). Weight of CDH, EA, and AWD patients was significantly below the norm; and so was height for the EA and AWD groups. The BMI was lowest in the CDH group. Language testing pointed at problems for five patients only; one of them and 4 other patients had seen a speech therapist at time of assessment or earlier in life. Parents of eight children, mainly in the AWD group, reported ADHD. Two patients suffered from seizures after the neonatal period; subsequent MR-imaging of the brain did not show any abnormalities. Physical problems that might interfere with motor function performance consisted of visual impairment in four children, and scoliosis in six children. Major limb deformities were not observed in this group.

Table 3.3 shows the results of the M-ABC, the dynamic sit-ups, the Beighton score and the Bruce treadmill test of the different groups.

Motor function assessment

All 79 children were tested with the M-ABC. Fifty-eight children (73.4%) had a total impairment score within the normal range, thirteen (16.5%) were classified as borderline and another eight (10.1%) as having a motor problem. This distribution is significantly different from norm values (Chi square $p = 0.01$). Most problems were encountered with ball skills (Chi square $p < 0.001$) and balance (Chi square $p = 0.001$) but not with manual dexterity. Figure 3.2 shows the M-ABC scores for the different groups. The total impairment scores of the children with CDH and EA differed significantly from the norm population ($p = 0.02$ and 0.04, respectively). Ball skills were impaired in CDH patients and EA patients, whereas children with EA and SIA had more problems with balance.

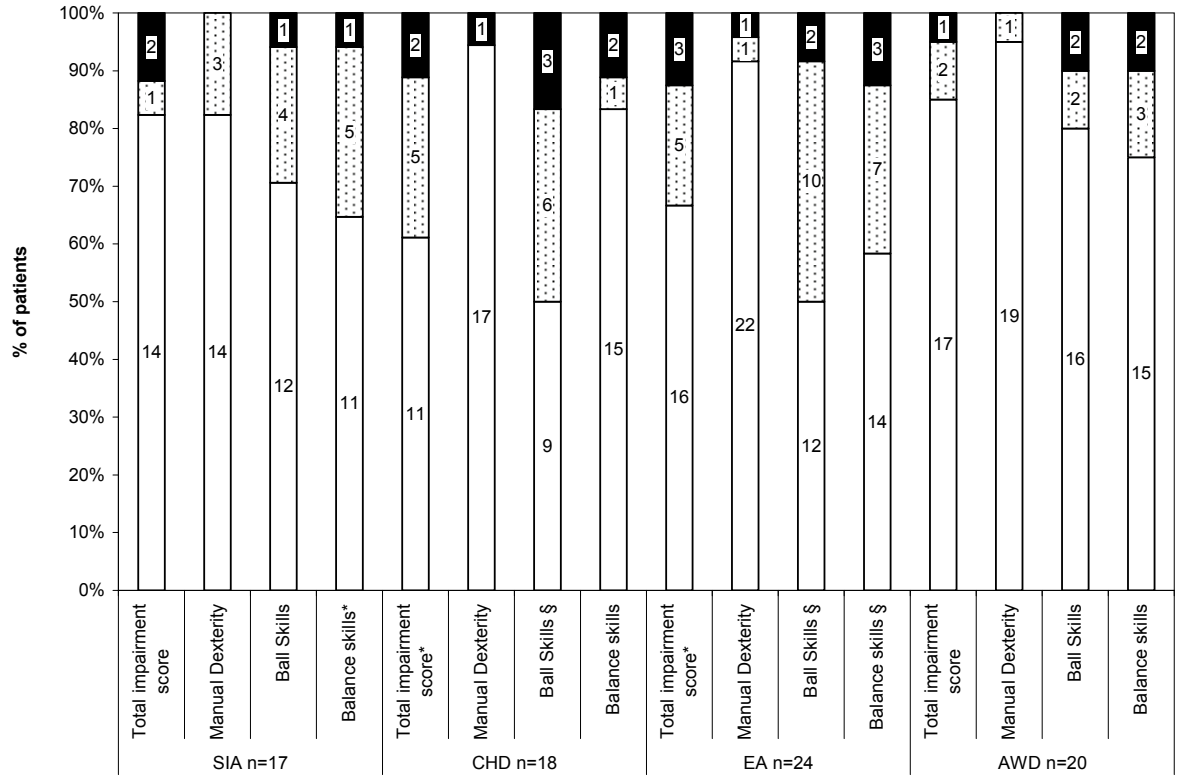


Figure 3.2 *M-ABC scores for different groups,*
** p < 0.05 chi square (difference from norm values),*
§ p < 0.01 chi square (difference from norm values),
for each patient group TIS and subscores are shown normal range (> P15, open bar), borderline range (P6 - P15, stippled bar), definite motor problem (≤ P5, black bar).

Dynamic sit-ups

Data from seven children were missing because they failed to cooperate: SIA (n = 2), EA (n = 3), AWD (n = 2). Children who were not able to perform any proper sit-up obtained a normative score < -1SD. The median number of sit-ups and the number of patients who obtained a score < -1SD are shown in Table 3.3.

Hypermobility

None of the children with SIA showed generalized joint hypermobility. Differences between the groups were not statistically significant (Table 3.3).

Maximum exercise performance

Data of 62 children were analyzed because 17 children did not reach maximal performance according to our pre-defined criteria (SIA n = 3, CDH n = 2, EA n = 6, AWD n = 6). Overall, these 62 children performed worse than the norm population: mean SDS endurance time = -0.3; p = 0.048). Nevertheless, children with SIA and AWD reached a normal mean SDS endurance time. On the other hand, mean SDS endurance time for both CDH and EA patients was significantly below zero (Table 3.3).

Table 3.1 Baseline characteristics

	SIA (n = 17)	**CDH (n = 18)**	**EA (n = 24)**	**AWD (n = 20)**
Boys, n (%)	10 (58.8)	10 (55.6)	16 (66.7)	8 (40)
Gestational age, median (range), wk	36.7 (29.6 - 41.7)	39.4 (36 - 41)	38 (28.6 - 42)	38.1 (33.6 - 41.4)
Birth weight, median (range), kg	2.8 (1.6 - 3.6)	3.3 (2.7 - 3.7)	2.8 (0.8 - 4.5)	2.5 (2.1 - 4.4)
SGA, n (%)	0 (0)	0 (0)	3 (12.5)	4 (20)
Patients with ≥ 1 additional major CA, n (%)	2 (11.8)	3 (16.7)	7 (29.2)	5 (25)
Cardiac malformation, n (%)	2 (11.8)	1 (5.6)	3 (12.5)	1 (5)
Ventilatory support, median (range), days*	2 (0 - 18)	19.5 (2 - 62)	3.5 (1 - 44)	2 (0 - 192)
Hospital admission first 6 months, median (range), days	29 (14 - 151)	58 (14 - 167)	47 (11 - 168)	32 (7 - 182)
Hospital admission between 6 and 24 months, median (range), days	0 (0 - 23)	1.5 (0 - 31)	2 (0 - 35)	0 (0 - 29)
Hospital admission 24 months to 5 years*, median (range), days	0 (0)	0.5 (0 - 18)	0.5 (0 - 31)	0 (0 - 47)
Surgical interventions in 24 months*, median (range)	2 (1 - 5)	3 (1 - 6)	5 (1 - 11)	1 (1 - 6)
ECMO, n (%)*	0 (0)	9 (50)	0 (0)	0 (0)

Presented are the baseline characteristics of the group of 79 children available for analysis. SGA = small for gestational age.
Data given are median (range) or number (n) of infants (%).
** p < 0.01 Kruskal Wallis (differences between groups).*

Table 3.2 Characteristics of the study group at 5 years of age

		SIA (n = 17)	**CDH (n = 18)**	**EA (n = 24)**	**AWD (n = 20)**
Age, mean (SD), years		5.7 (0.4)	5.9 (0.5)	5.9 (0.4)	5.6 (0.3)
Weight SD score, mean (range)		-0.4 (1.1)	-1.3 (0.9)*	-0.5 (0.9)*	-1 (1.4)*
Height SD score, mean (range)		-0.1 (1.1)	-0.7 (1.5)	-0.6 (1.2)§	-0.7 (1.3)§
BMI SD score, mean (range)#		-0.4 (1.0)	-1.1 (1.1)*	-0.2 (0.9)	-0.6 (1.1)§
SES	High, n (%)	8 (47.1)	8 (44.4)	11 (45.8)	5 (25.0)
	Middle, n (%)	7 (41.1)	7 (38.9)	8 (33.4)	8 (40.0)
	Low, n (%)	2 (11.8)	1 (5.6)	5 (20.8)	6 (30.0)
	Unknown, n (%)	-	2 (11.1)	-	1 (5.0)
Dutch parents, n (%)		16 (94.1)	15 (83.3)	22 (91.7)	18 (90.0)
Language problems, n (%)		1 (5.9)	2 (11.1)	1 (4.2)	1 (5.0)
Speech therapy at age 5 or earlier, n (%)		1 (5.9)	1 (5.6)	1 (4.2)	2 (10.0)
Behavioral problems, n (%)		1 (5.9)	2 (11.1)	1 (4.2)	4 (20.0)
Scoliosis, n (%)		-	2 (11.1)	2 (8.3)	2 (10.0)
Visual impairment, n (%)		1 (5.9)	1 (5.6)	2 (8.3)	-
Physical therapy at age 5, n (%)		3 (17.6)	2 (11.1)	6 (25)	-

Data are presented as number (%) of patients or mean (SD).
** p < 0.01 one sample t test (SDS significant below zero),*
§ p < 0.05 one sample t test (SDS significant below zero),
 # p < 0.05 Kruskal Wallis (differences between groups).

Table 3.3 Overall results of motor function performance and maximal exercise capacity per group

	SIA (n = 17)	**CDH (n = 18)**	**EA (n = 24)**	**AWD (n = 20)**
M-ABC overall percentile score, n (%)				
≥ P16 normal	14 (82.4)	11 (61.1)*	16 (66.7)*	17 (85)
P6-P 15 borderline	1 (5.9)	5 (27.8)	5 (20.8)	2 (10)
≤ P5 motor problem	2 (11.8)	2 (11.1)	3 (12.5)	1 (5)
M-ABC TIS (0 - 40), median (range)	5 (0 - 24)	6 (0 - 24.5)	6.8 (1 - 32.5)	5 (0 - 29.5)
Manual dexterity score (0 - 15)	0 (0 - 8)	0.8 (0 - 9.5)	1 (0 - 11.5)	1 (0 - 8.5)
Ball skills score (0 - 10)	1 (0 - 7)	2.5 (0 - 10)	3 (0 - 8)	2 (0 - 8)
Balance score (0 - 15)	3.5 (0 - 15)	1.8 (0 - 12)	2.8 (0 - 15)	1.8 (0 - 14)
Dynamic sit-ups, median (range)	(n = 14) 0 (0 - 8)	(n = 18) 1.5 (0 - 12)	(n = 21) 4 (0 - 13)	(n = 18) 3.5 (0 - 13)
Dynamic sit-ups, < -1SD, n (%)	9 (60)	8 (44.4)	7 (33.3)	6 (33.3)
Hypermobility, n (%)	(n = 16) -	(n = 18) 3 (16.7)	(n = 22) 1 (4.5)	(n = 18) 1 (5.6)
Bruce, SDS endurance time, mean (range) §	(n = 14) 0.22 (-2.8 - 1.8)	(n = 16) -0.71 (-3.5 - 0.9)#	(n = 18) -0.60 (-2.6 - 0.7)#	(n = 14) -0.06 (-2.6 - 1.7)

** Chi Square: p < 0.05 (comparison to the percentage expected),*
§ Kruskal Wallis: p < 0.05 (difference between groups),
 # One sample Test : p < 0.05 (SDS significantly below zero).

Correlations between total percentile score of M-ABC and baseline variables, outcome variables at 5 years, and other motor function or fitness variables

The total percentile score of M-ABC correlated negatively with the total number of major CA (r_s = -0.35, p < 0.01), and positively with the number of dynamic sit-ups (r_s = 0.44; p < 0.01) and the SDS of the maximal endurance time from the Bruce test (r_s = 0.31; p = 0.01).

We also found a significant negative correlation with duration of hospitalization and number of surgical interventions (data not shown). No significant correlation was found between the M-ABC score and other baseline variables, ECMO-treatment, growth parameters, SES, and the Beighton score at 5 years.

Factors influencing motor function performance

Only one of the seven children with a cardiac anomaly was classified as having a definite motor problem on the basis of TIS. The maximal exercise capacity was below normal (SDS < -2) in two of these seven children.

Two of the five children with a language problem showed definite motor problems, two scored between P5 and P15; and only one child had a TIS within the normal range. Three of the five children with a language problem had parents of non-Dutch origin.

Five of the eight children for whom the parents reported ADHD scored within the normal range on M-ABC. The four children with visual impairment all scored abnormally on the M-ABC; three even scored < P5.

Eleven of the 79 tested children (14%) received treatment from a pediatric physical therapist (SIA n = 3, CDH n = 2, EA n = 6). Four of them scored < P5, one between P5 and P15, and TIS ratings for the other six were within normal range. For 14 patients it was thought advisable to start (n = 5) or to continue (n = 9) pediatric physical therapy at home. These 14 children scored significantly worse on the M-ABC than did the other 65 children (p < 0.001).

DISCUSSION

This is the first study describing standardized motor function assessment in 5 - 6 year old children born with major congenital anatomical anomalies other than primary cardiac malformations.[13,14] Motor function was found normal for no more than 58 of the 79 tested children (73.4%). This proportion is significantly lower than that for the reference population. The number of additional congenital anomalies negatively influenced motor function performance. Both abdominal muscle strength and maximal exercise capacity correlated positively with motor function.

Children with developmental speech and language disorder (DSLD), a possible comorbidity in children with major anatomical CA, were found to have abnormal M-ABC scores, both in total impairment score (TIS)[455,464] and particularly in ball skills.[455] In 2007 Visscher and colleagues described the motor profile of 125 children with DSLD: 51% had borderline or definitive motor problems (TIS 15th percentile and below). The authors argue that the basal ganglia are involved in the types of motor activity examined by the M-ABC and in language production and speech initiation as well.[455] Since lesions in the basal ganglia have also been described in perinatal asphyxia[38] – which occurs to some extent in many CA patients with respiratory distress after birth – we evaluated the incidence of brain damage on neonatal ultrasound examination and of speech and language disorders and showed that both of them were very low. Therefore, we assume that our results cannot be explained by any of these problems, although early lesions are not always picked up on neonatal ultrasound.

M-ABC scores were found to be abnormal as well in adolescents born small for gestational age (SGA) and very low birth weight (VLBW) children, but mainly at a different domain: manual dexterity.[141] Children with executive function problems such as ADHD have motor problems with respect to manual dexterity and ball skills, but score normally on balance items.[289] We evaluated the occurrences of the above-mentioned disorders but the small numbers of patients suffering from these problems do not allow for any conclusions at this point.

Eight-year-olds born with complex congenital heart disease have lower M-ABC TIS and subscores than their healthy age- and sex-matched controls.[224] The proportion of children with cardiac malformations in the present study was low, and these malformations were not complex. This may explain that we found higher scores than in Holm's paper.

Apart from TIS and subtest scores of the M-ABC, we also looked at other factors reflecting physical fitness that may influence motor function performance: physical growth, abdominal muscle strength, hypermobility, and maximal exercise performance. Abdominal muscle strength was impaired mainly in SIA patients who underwent neonatal abdominal surgery. Surprisingly, 66.7% of AWD patients were able to perform dynamic sit-ups. The abdominal wall muscles play a vital role in stabilizing the lumbar spine. The transverse abdominal muscle for example resists rotational and translatory forces in the joints of the spine. Impairment of this resistive muscle activity has been associated with low back pain in adults.[470] It is possible that surgery involving the abdominal wall may interfere with the function of the transverse abdominal muscle, and its ability to stabilize the lumbar spine, resulting in low back pain at any age. Therefore, we feel that longitudinal follow-up of abdominal muscle strength and early intervention to improve muscle strength is important for children who underwent abdominal surgery.

The fact that a substantial number of patients in our study were able to perform dynamic sit-ups within the normal range does not necessarily imply strong abdominal musculature. Curled-trunk-sit-up consists of flexion of the spine performed by abdominal muscles, followed by further flexion of the hip joints performed by hip flexors. With strong hip flexors, the entire trunk-raising movement can be performed.[251] However, to our knowledge, no other standardized tests are available for evaluation of abdominal muscle strength in young children.

We found impaired maximal exercise capacity in patients with CDH and EA. These findings are in line with previous studies by Zaccara et al. in CDH patients and in patients operated on for tracheoesophageal fistulas.[474,475] Several authors report on the relationship between physical fitness and motor competence. Haga[191] used different tests to establish physical fitness in 9 - 10 year old children and showed high and significant correlations between the TIS of the M-ABC and physical fitness. Blair[48] argued that physical activity levels can potentially explain the relatively high correlation between physical fitness and motor competence. He concluded that physical fitness results from the degree and intensity of a child's physical activity over time. In the same way, one can also argue that motor competence is a consequence of the level of physical activity, e.g. the more time spent practicing motor skills the more opportunity there is for improved motor performance. We assume that CDH and EA patients with high morbidity, mainly of respiratory and gastrointestinal origin[298,315,316] have little physical activity in the first years of life and hence less opportunity to practice gross motor skills. This may explain the lower percentile scores in these groups and the differences in motor function profiles (less ball skills and balance, but good performance at manual dexterity). Concomitant with less physical activity and impaired gross motor function they are at risk for decreased maximal exercise tolerance. Most children with SIA and AWD have few problems beyond the first few months of life[259,285] and we assume that they have more opportunities for physical activity and hence improvement of motor competence.

Another factor that may contribute to decreased physical activity is parental reluctance to stimulate their children too much out of fear for physical problems. Both CDH and EA patients suffer from pulmonary morbidity, and respiratory distress following physical activity may occur easily as a result of lung hypoplasia and tracheomalacia. Holm and Bjarnason[47,224] reported a similar observation in children with cardiac malformations.

Early identification of children at risk of developmental problems is generally deemed of great importance, and this would seem to be even more urgent for children with motor problems. Studies in prematurely born children have shown that assessment of motor development by a pediatrician alone is insufficient and that standardized tests are needed. Since motor problems do not disappear spontaneously[336] intervention and long-term follow-up are necessary. Therefore, we perform standardized longitudinal follow-up in all patients with major anatomical CA up till the age of 18 years.

The present study has the following limitations:

1. The numbers of subjects studied per diagnosis subgroup were small, which makes it difficult to draw hard conclusions. Comparison of the baseline characteristics of patients who were lost to follow-up with those of the participants revealed that only for CDH patients a possible selection bias might have occurred because participants were hospitalized longer and underwent more surgical interventions. On the other hand, the need for ECMO or duration of ventilatory support did not differ between these groups. Therefore, we feel that the results for CDH patients have not been influenced seriously;
2. The pediatric physical therapist who performed the tests was not blinded to the underlying diagnosis as the evaluations took place within the framework of a longitudinal follow-up program and not primarily as clinical research. The same physical therapist also performed physical examination (e.g. evaluation of scoliosis) so blinding for scars was not possible. Nevertheless, as all tests were performed in a standardized way, and previous data on motor function development in CA patients have not been published, there is good reason to think that the examiner's awareness of the diagnosis has not seriously influenced the results;
3. The normative data on abdominal muscle strength from Wiegersma,[467] which we used in the absence of normative data for children younger than 6 years, refer to ages 6 years and higher. We feel this is justified, as the mean testing age in the present study was 5.8 years, getting close to 6 years. Nevertheless, as Lefkof reported that children can perform dynamic sit-ups consistently up from the age of 6 years onwards,[278] our findings should be interpreted with some caution.

In conclusion, children with CA are at risk for delayed motor function performance, especially those with additional anomalies who have extended hospital length of stay and undergo multiple surgical interventions. Moreover, high comorbidity and decreased abdominal muscle strength negatively affect motor function.

Does a structural and proactive approach improve genetic counseling rate for parents of children with congenital anatomical anomalies?

Iedere vlieg lijkt wel iets op een andere
Maar is toch weer anders

vrij naar Judith Herzberg (1939 -)

ABSTRACT

We hypothesized that a structural, proactive approach would change parents' attitude towards genetic counseling after birth of a child with major congenital anomalies.

We evaluated two cohorts: parents of patients born from 1999 – mid 2001 and parents of patients born from mid 2004 - end 2006, with proactive counseling in the latter cohort. Both cohorts participated in a prospective, longitudinal follow-up program.

The proactive approach significantly increased genetic counseling rate The second cohort comprised significantly fewer children with three or more anomalies; more anomalies fully diagnosed antenatally. Logistic regression analysis revealed a higher chance of seeking counseling for the second cohort, Dutch parents, children with three or more anomalies, antenatally incomplete diagnosis, and familial malformations.

Conclusion
Structural, proactive genetic counseling by a geneticist assigned to a multidisciplinary team increased the counseling rate in parents of malformed children. Parents with different cultural backgrounds and/or antenatally incompletely diagnosed children warrant more attention.

INTRODUCTION

In the Netherlands annually some 5000 newborns (2.5% of all births) present with major congenital anatomical anomalies (CA), either in isolated form or as part of more complex syndromes. Both genetic and environmental sources have been implicated as causative factors in many cases. Genetic research has indeed revealed several causative genetic traits. For example, mutations in MYCN and CHD7 genes are associated with esophageal atresia as part of Feingold or CHARGE syndrome.[152,169,329,369] Chromosomes 15, 22 and 11 have been found associated with congenital diaphragmatic hernia (CDH).[222,253,375] For many CA, however, the etiology is still unexplained. Many centers offer genetic counseling to parents of a child diagnosed with a CA, either prenatally or after birth. Not all parents make use of it, especially when the anomaly is 'simple' and occurs isolated. Various other factors, however, will prompt parents to seek genetic counseling:

1. diagnosis of multiple major birth defects, chromosomal abnormalities, and malformation syndromes;[160]
2. a family history of congenital anomalies or a previous child with CA;[57,210]
3. death of an infant or autopsy on a malformed child, often revealing new anomalies;[147,175]
4. parental knowledge on, and attitude towards genetic counseling,[219] as well as religious aspects.[11,353,405]

Parents may not know, however, that counseling can be offered, or that it is even recommended before a next pregnancy.[1] In the parents' view, a clinical geneticist is best suited to provide information on genetic aspects of their child's disease;[311] and also the one to facilitate psychological adjustment to the child's diagnosis.[115]

We hypothesized that a proactive approach will prompt more parents to seek counseling. To test this hypothesis, we compared aspects of genetic counseling in two cohorts of parents of a malformed child. The first cohort was offered 'standard' counseling, the second cohort had easy access to a geneticist assigned to the ward, with genetic consultations and counseling being offered proactively. In addition, we analyzed factors that might have influenced parents to seek counseling.

METHODS

Setting

Pediatric surgical department of the Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands. This is the only tertiary academic facility in the South-Western part of the Netherlands equipped for all major surgical specialties. The referral area has 4 million inhabitants with 44,000 newborns annually.

Since 1999 a multidisciplinary team consisting of pediatricians, psychologists, a physiotherapist, nurses, a social worker, and a consultant senior pediatric surgeon runs a follow-up program for CA patients and their families until the age of 18 years. A clinical geneticist was added to the team in 2004. The program aims to reduce overall morbidity associated with severe congenital anomalies. Both cohorts studied take part in this program.

Genetic counseling process

The first cohort (1999 - mid 2001) was offered 'standard' genetic counseling. This implies that one of several available clinical geneticists will examine the child during the first admission (often in absence of the parents). If deemed necessary by the geneticist, the pediatric intensivist or pediatric surgeon will recommend the parents to seek genetic counseling, for which they must make an appointment themselves. The possibility of referral for counseling is pointed out again during follow-up visits.

The second cohort (mid 2004 to end 2006) had easy access to one clinical geneticist assigned to the department. One of two geneticists routinely examined all children with CA during first admission, with one or both parents present. Depending on the diagnosis, the assigned geneticist would then consider the advisability of being present at the 6-months follow-up assessment. If so, the geneticist again evaluated and confirmed accurate clinical and genetic diagnosis and if necessary explained the implications and usefulness of counseling. At this time again, the geneticist proactively offered parents the possibility of genetic counseling. Thus, both during admission and after 6 months the clinical geneticist in person offered genetic counseling to the parents. These inpatient and outpatient consultations were not registered as official genetic counseling.

Procedures

As part of the ongoing longitudinal follow-up program data were collected prospectively from medical records, parental questionnaires and clinical geneticist's reports. The following child-related variables were recorded: antenatal screening (was it performed?; was the antenatal diagnosis concomitant with the postnatal diagnosis?), type and number of anomalies, CA in family, first born, level of risk of CA recurrence. Parent-related variables collected were: parental ages, ethnicity, and new pregnancies. Information on new pregnancies was recorded for the first cohort only, because we felt that no reliable figures could be obtained from the second cohort with inclusion until end 2006.

Participants

Eligible for this study were parents participating in the follow-up program. The first cohort included parents of patients born from January 1999 through the first half of 2001. The second cohort included parents of patients born from mid 2004 to the end of 2006. Parents who had insufficient command of the Dutch language were excluded

from the study. In addition, parents of children with meningomyelocele were excluded since they already participated in another multidisciplinary follow-up program. We distinguished six categories of CA – or: index diagnoses[351] – i.e. esophageal atresia, intestinal atresia, congenital diaphragmatic hernia, abdominal wall defects, Hirschsprung's disease and anorectal malformations, and a group of miscellaneous malformations (e.g. cardiovascular, pulmonary and urogenital malformations).

Data analysis

The influences of predictor variables on yes/no genetic counseling were determined with both univariate analyses using the Chi-square test or Fisher Exact test and logistic regression analysis. Nominal predictor variables with multiple levels (e.g. index diagnoses) were recoded into so-called dummy variables (0 and 1 coded). For the six index diagnoses, five dummy variables are needed. Differences between the two cohorts were analyzed using the Chi-square test or Fisher Exact test for nominal variables and the Mann-Whitney U-test for nonparametric continuous variables.

The clinical geneticist estimated the recurrence risk of the same CA for the non-counseled children to include this variable in the logistic regression analysis. Risk was classified as low (between 1 and 5%), high (between 10 and 50%) and unspecified (recurrence risk could not reliably be estimated yet) similar to the levels in the counseled group.
Statistical significance was accepted at a 5% level.

RESULTS

The total sample included parents of 327 patients, 136 in the first cohort and 191 in the second cohort. Table 4.1 gives characteristics for the total sample and the cohorts. Overall, parents of 132 (40.4%) patients opted for genetic counseling, i.e. 38 (27.9%) in the first cohort vs. 94 (49.2%) in the second (Chi-square test $p < 0.001$). Counseling in the second cohort took place later than in the first (child's median age 9 vs. 5 months, respectively Mann-Whitney U-test, $p = 0.001$).

More than half of the patients had multiple anomalies. The second cohort included significantly fewer children with three or more anomalies (Chi-square test $p < 0.001$). Significantly more anomalies were diagnosed antenatally in the second cohort, 36% vs. 46.6% respectively (Chi-square test $p = 0.005$) and almost twice as many anomalies were fully diagnosed antenatally in the second cohort. Seventy-five mothers or couples (22.9%) were of non-Dutch origin: Thirty-seven couples were Turkish or Moroccan, the other 38 included 25 nationalities from four continents. Within the non-Dutch group 45 couples were of the Muslim faith, of whom only 24.4% received counseling as compared with 42.9% of non-Muslim parents (Fisher's exact test, $p = 0.022$); without significant difference between cohorts. A high risk of recurrence was found in 31 (9.5%), a low risk

in 236 (72.2%) and as yet unspecified risk in 60 (18.3%), without significant difference between cohorts. Parental age was comparable to Dutch norms: median maternal age was 31 years (SD = 5.0, range 18 - 46), paternal age 34.1 years (SD = 5.6, range 19 - 61) (CBS, 2007).

Table 4.1 Background characteristics total sample and cohorts

	Total group (n = 327)	**Cohort 1 (n = 136)**	**Cohort 2 (n = 191)**	**p-value**
Index diagnosis				
Intestinal atresia, n (%)	67 (20.5)	39 (28.7)	28 (14.7)	
Congenital Diaphragmatic Hernia, n (%)	59 (18.0)	20 (14.7)	39 (20.4)	
Miscellaneous, n (%)	56 (17.1)	19 (14.0)	37 (19.4)	0.04
Esophageal atresia, n (%)	51 (15.6)	22 (16.2)	29 (15.2)	
Hirschsprung/anorectal malformations, n (%)	47 (14.4)	16 (11.8)	31 (16.2)	
Abdominal wall defects, n (%)	47 (14.4)	20 (14.7)	27 (14.1)	
Antenatal screening				
Diagnosis complete, n (%)	88 (26.9)	24 (17.6)	64 (33.5)	
Diagnosis incomplete, n (%)	50 (15.3)	25 (18.4)	25 (13.1)	0.005
Congenital Anomaly unknown, n (%)	189 (57.8)	87 (64.0)	102 (53.4)	
Genetic counseling, n (%)	132 (40.4)	38 (27.9)	94 (49.2)	< 0.001
Child's age at counseling, median (IQR[a]), months	8 (5 to 12)	5 (2 to 10)	9 (7 to 12)	0.001
Child's Number of anomalies				
One, n (%)	146 (44.6)	42 (30.9)	104 (54.4)	
Two, n (%)	99 (30.3)	48 (35.3)	51 (26.7)	< 0.001
Three or more, n (%)	82 (25.1)	46 (33.8)	36 (18.8)	
Congenital Anomaly in family, n (%)[b]	89 (30.4)	39 (28.9)	50 (31.6)	0.62
Deceased in first year of life, n (%)[c]	32 (9.8)	13 (9.6)	19 (9.9)	1.00
Ethnicity mother				
Dutch, n (%)	252 (77.1)	110 (80.9)	144 (75.4)	0.24
Muslim faith, n (%)	45 (13.8)	15 (11.0)	30 (15.7)	0.26
Consanguinity, n (%)	9 (2.8)	5 (3.7)	4 (2.1)	
Risk of recurrent Congenital Anomaly				
1 to 5%, n (%)[d]	236 (72.2)	99 (72.8)	137 (71.7)	
10 to 50%, n (%)[d]	31 (9.5)	12 (8.8)	19 (9.9)	0.94
Unspecified, n (%)[d]	60 (18.3)	25 (18.4)	35 (18.3)	
First child, n (%)	145 (44.3)	50 (36.8)	95 (49.7)	0.02

[a] *interquartile range,*
[b] *n = 34 no information available (n = 33 in 2nd cohort),*
[c] *50% Congenital Diaphragmatic Hernia,*
[d] *including estimated risk for non-counseled group.*

Table 4.2 Results of logistic regression analysis with yes/no genetic counseling as outcome variable

		95% CI[1] for OR[2]		
Logistic Regression analyses[a]	**OR**	**Lower**	**Upper**	**p-value**
Group (0 = 1st cohort, 1 = 2nd cohort)	5.679	2.929	11.012	< 0.001
Dutch nationality (0 = non-Dutch, 1 = Dutch)	2.615	1.284	5.327	0.008
Three or more anomalies per child (0 = one or two anomalies, 1 = three or more)	5.599	2.776	11.293	< 0.001
Antenatally incomplete diagnosis (0 = antenatally complete or unknown, 1 = antenatally incomplete)	4.485	1.604	12.539	0.004
Antenatally complete diagnosis (0 = partially known or unknown, 1 = antenatally complete)	0.343	0.163	0.720	0.005
Family CA[3] (1 = CA[3] in the family, 0 = no CA[3] or unknown)	3.789	2.020	7.106	< 0.001
First child (0 = not first child, 1 = first child)	1.706	0.984	2.960	0.07
Constant	0.054			< 0.001

Abbreviations: 1 = confidence interval; 2 = odds ratio; 3 = congenital anomaly;
[a] variables in the analysis with a non-significant contribution; the 5 dummy variables for the index diagnoses, deceased/alive, risk for recurrent CA.

Univariate analyses showed that parents of children in whom intestinal atresia was diagnosed significantly less often received counseling (Chi-square test p = 0.05). Parents more often received counseling when antenatal screening yielded incomplete diagnosis compared with those whose child's anomaly was either not diagnosed or fully diagnosed (Chi-square test p = 0.014). A family history of CA was associated with parents receiving counseling more often (Chi-square test p < 0.001). Dutch parents more often received counseling than did non-Dutch parents (Chi-square test p = 0.022). Counseling rates did not differ significantly for parents of a deceased vs. non-deceased child. Level of risk of recurrence influenced counseling rates: 68% in case of high risk versus 53% and 33% in case of unspecified and low risk, respectively (Chi-square test p < 0.001). More first-born children were seen in the second cohort. Within the last 6 to 8 years, the frequency of pregnancies in the first cohort was 38.4%.

The results of a logistic regression analysis are given in Table 4.2 with yes/no genetic counseling as outcome variable. The counseling rate significantly increased in the second cohort (OR = 5.7). Furthermore, parents of children with three or more anomalies have a 5.6 times higher chance to want counseling. While parents of children in whom the antenatal diagnosis was incomplete also are more likely to seek counseling (OR = 4.4), this likelihood is lower when the antenatal screening was correct (OR = 0.3). A family history of CA also increases the chance that parents will seek counseling (OR = 3.8). Parents of a first child are more likely to seek counseling, though not

significantly (p = 0.057). Variables that were included but non-significant were (next to first child) the index diagnosis, deceased/alive, and risk for recurrent CA.
The Nagelkerke R-square is 0.41, Hosmer and Lemeshow test Chi-square = 3.03, p = 0.93 suggesting a good fit.

DISCUSSION

Forty percent of parents of the total sample of 327 received counseling encompassing information on patterns of inheritance, recurrence risk and likelihood of other family members being affected. The prognosis and possible associated anomalies are reviewed as well. As early diagnostics are available for quite a few associated anomalies,[410] the parents are also alerted to the possibilities and/or limitations of different prenatal procedures. The proactive approach applied in the latter period resulted in a significantly higher proportion of parents being counseled, i.e. almost 50% versus 27.2% in the earlier period. Counseling rates from 50 to 75% have been reported for CF patients.[168] The rates found in this study therefore seem quite reasonable, the more so as causes of many CA are still unknown.

Most parents in the second cohort met the geneticist at first admission for immediate consultation. Parents of children with certain isolated anomalies, such as intestinal atresia, received sufficient information on this occasion, and thus did not require extensive counseling. This at least partially explains the lower rate of official counseling by a geneticist for this index diagnosis.

Parents in the second cohort received counseling significantly later in time. Parents' motivation for counseling probably increased over time due to the easy access to the assigned geneticist, who already provided valuable information before the actual counseling process. Furthermore, the child's medical condition often has stabilized after 6 months so that parents will have re-established some measure of emotional balance in their lives at that time. They may then be inclined to consider future offspring, recurrence risk, and implications for other family members.[311] Moreover, the time interval enables the geneticist to re-evaluate the child and to confirm or reconsider different diagnoses as the phenotype may become transparent over time.

Fewer incomplete antenatal diagnoses were shown for the second cohort. This would seem to be due to improved routine antenatal ultrasound practices in the Netherlands. Routine second trimester ultrasound studies were implemented only recently. Early diagnosis of severe congenital anomalies has several advantages. Parents may opt to terminate a pregnancy, but on the other hand this is an opportunity to arrange the best possible postnatal care, aimed at reducing secondary morbidity and optimizing postnatal chances of survival. Parents may experience stress and insecurity, however, during the remaining time of the pregnancy.[229] It is too early to fully evaluate the results

of the nation-wide change in pregnancy screening routine. Still, the fact that there are significantly fewer children with three or more anomalies in the second cohort could reflect the gradual change in attitude towards termination of pregnancy after finding multiple anomalies in the unborn child.

A relatively large group of parents were non-Dutch and from a large variety of cultures. CA in the family is considered shameful in some cultures and thus parents might withhold or not know this information. Also, all nine consanguineous marriages in the total study sample, known to increase the risk of CA, were in the non-Dutch group. The fact that significantly fewer Muslim parents were counseled – in both cohorts – may be due to language barrier, culture and religion. Religious differences alone do not explain the difference since Islam does not reject genetic counseling,[12] although parents may think otherwise. Considering all this, we feel we must pay more attention to this relatively large group, while still remaining non-directive.

Other predictors for counseling are incomplete antenatal diagnosis, a larger number of CA, family history of CA, and the malformed child being the first-born. Understandably, all these factors increase initial parental stress and insecurity, and parents would want to know the recurrence risk for CA before deciding on future pregnancies. In the first cohort as many as 38.4% of parents conceived a second child, but not enough time has passed to evaluate this aspect for the second cohort reliably. Antenatal diagnostics in a next pregnancy and decisions for termination of pregnancy were not evaluated for the first cohort.

In spite of the unraveling of the human genome, the proportion of cases in which the recurrence risk could not yet be reliably estimated, was not significantly lower in the second cohort. This is not only a matter of gaps in the knowledge on causative genetic factors: parents may also lack reliable information on (minor) anomalies in the family. The definite risk of recurrence being unspecified (yet), as experienced by 22.7% of all 327 couples, can be seen as a possible drawback of counseling. Usually, however, parents value information on possibilities and limitations of prenatal diagnosis. This is of special interest for parents with a high risk of recurrence, and might explain why more parents in this risk group sought counseling.

Regrettably, we could not yet incorporate emotional and psychosocial factors that may have been decisive for parents to seek counseling or not. These are still being studied. A possible limitation is using the first cohort as a historical control group to evaluate the effects of a proactive approach after addition of a clinical geneticist to our follow-up team. A randomized controlled study comparing the proactive approach with the conventional approach was considered not feasible, however, as all patients are treated in one ward where parents can share experiences. Therefore, we cannot completely rule out that changes over time may have occurred that are not attributable to the proactive approach.

In conclusion, both antenatal diagnostics and postnatal genetic counseling have clear benefits as described above. A proactive approach to counseling is likely to increase the number of parents seeking counseling. Parents with different cultural backgrounds warrant more attention. Recurrent contacts with a clinical geneticist – as an identifiable member of an interdisciplinary team – over a longer time considerably improve the care for children with major congenital anomalies and their parents.

ACKNOWLEDGEMENTS

We thank our in-house editor, Ko Hagoort, for reviewing this article.

5a

Congenital diaphragmatic hernia in a female patient with craniofrontonasal syndrome

Avevo la forma di uscire e sono nata
I had the right shape for coming out, so I was born

I cento linguaggi di bambini/the hundred languages of children (1996)

Craniofrontonasal syndrome or dysplasia (CFNS, OMIM 304110) is characterized by craniosynostosis of the coronal sutures, hypertelorism, longitudinal grooves of the nails and various skeletal abnormalities (e.g. syndactyly of toes).[97,313] Pedigree analysis is consistent with an X-linked dominant mode of inheritance, whereby all daughters but none of the sons of male patients are affected. Remarkably, females are more severely affected than males. Affected males usually only show hypertelorism.
Recently linkage analysis in 14 unrelated families has mapped the CFNS gene to Xp22,[150,343] but the gene has not yet been isolated.

We recently observed a girl with clinical features consistent with CFNS and a posterolateral defect of the diaphragm (type Bochdalek); a life-threatening congenital anomaly often associated with a variable degree of lung hypoplasia and therapy resistant pulmonary hypertension. Congenital diaphragmatic hernia (CDH) has been reported in only two CFNS patients (two out of six affected males in a fourgeneration family reported by Morris et al.[313] To our knowledge no females with the combination of CFNS and CDH have been reported so far. It is well known that CDH is often associated with other major congenital abnormalities, predominantly of the heart and limbs. In a minority of cases CDH may be part of a syndrome caused by a chromosomal anomaly (e.g. Pallister Killian syndrome due to a partial tetrasomy 12p, and partial trisomy 22) or a monogenic disorder (e.g. Fryns syndrome and Simpson-Golabi-Behmel syndrome).[138] CFNS is one of a growing number of monogenic syndromes associated with CDH.

Our patient is at present a 21-month-old girl. She was born to healthy, non-consanguineous Caucasian parents, after an uncomplicated pregnancy. Birth weight was 4050 g (97th centile), head circumference 33.5 cm (50th centile). Hypertelorism and a broad nasal tip were noted shortly after birth. She was admitted to our hospital on day 2 with respiratory distress. Clinical examination showed hypertelorism with evident facial asymmetry (Figure 5a.1), a broad nose, and grooved nails of the hallux and thumb, syndactyly of the third and fourth toes. The nipples were widely spaced.

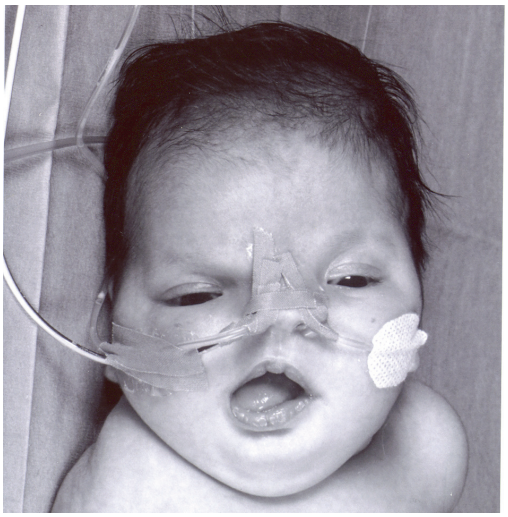


Figure 5a.1 *Frontal view of the patient showing asymmetry of the skull and hypertelorism.*

Radiology of the thorax showed a left-sided diaphragmatic defect with herniation of the intestines into the thorax. Skull X-rays showed craniosynostosis of the coronal suture at the left, which was confirmed with a three-dimensional CT scan (Figure 5a.2). MRI showed an agenesis of the corpus callosum. Cytogenetic analysis was normal.

At operation, a posterolateral diaphragmatic defect (type Bochdalek) was surgically closed with a Goretex patch. At the age of 11 months, the craniosynostosis was operated on.

The most likely diagnosis in our patient is CFNS based on the facial features, the grooved nails and the unilateral coronal synostosis. To our knowledge CDH has only been reported twice in CFNS and never in a female patient, which is remarkable since the CFNS phenotype is more pronounced in female patients. The presence of CDH in three cases of CFNS, a rare syndrome which has only been reported in ± 100 cases, is probably not a coincidental co-occurrence as the frequency of CDH is estimated 1 in 3000 - 4000 live births.[415]
Therefore this case report confirms that CFNS should be added to the expanding list of syndromes that include CDH as an infrequent feature.

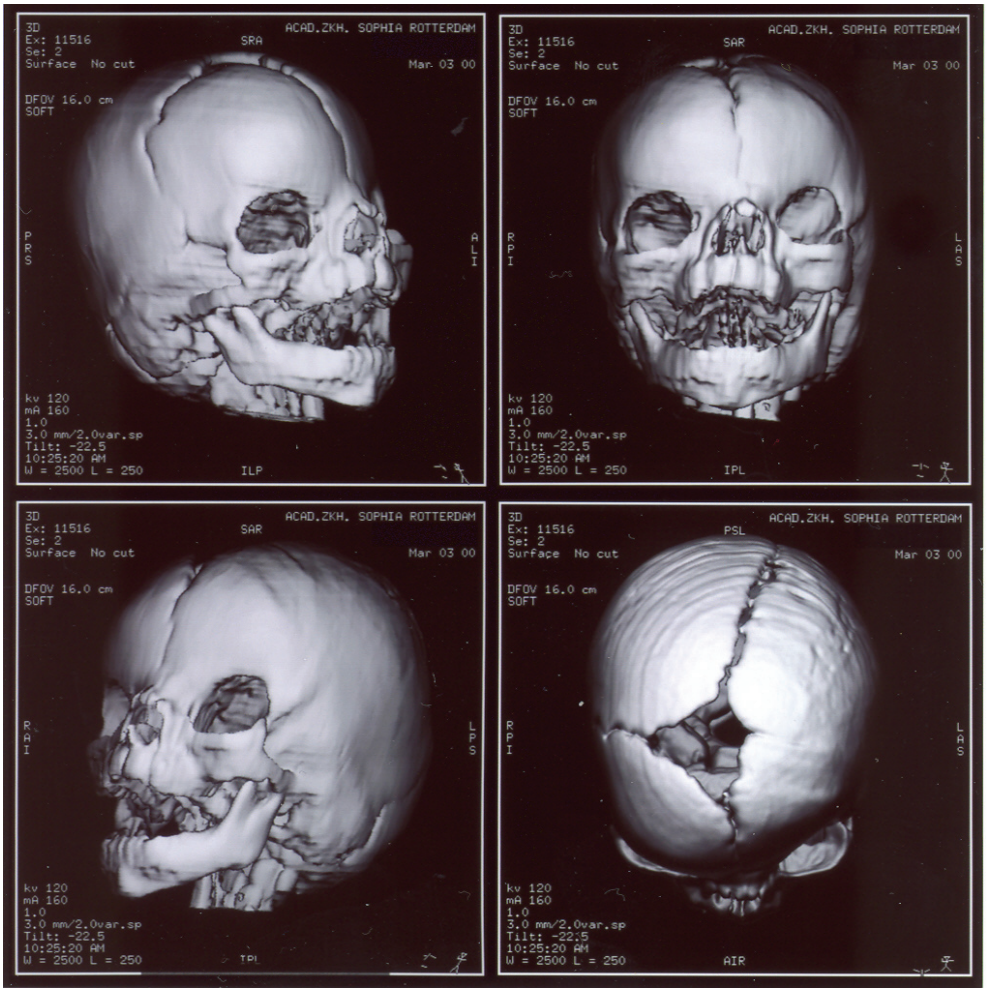


Figure 5a.2 *Three-dimensional CT scan at the age of 3 months showing synostosis of the left coronal suture.*

Exclusion of a PAX6, FOXC1, PITX2, and MYCN mutation in another patient with apple peel intestinal atresia, ocular anomalies and microcephaly and review of the literature

Medizinstudium: Sie lernten Organe, und es kamen Menschen

Uit: Vorsicht, Medizin!, Gerhard Kocher (1939 -)

ABSTRACT

We describe another patient with the combination of apple peel intestinal atresia, microcephaly, microphthalmia, and anterior eye chamber anomalies. Development so far seems to be normal, although there is major visual impairment due to the corneal clouding. Mutation analysis of the PAX6, FOX1, PITX2, and MYNC genes was normal as was MLPA for these genes. Autosomal recessive inheritance is possible as recurrence in sibs was described, although germ line mosaicism or a microdeletion due to a very small parental translocation cannot be ruled out.

INTRODUCTION

Apple peel intestinal atresia is a rare form of jejunal atresia, accounting for only 5 - 10% of small bowel atresias. It is characterized by a significant loss of bowel length, a defect in the mesentery and atresia of the small intestine, which curls around the superior mesenteric artery, giving the impression of an apple peel. Long-term follow-up in the survivors is good.[154] About 15% of patients have additional anomalies.[101,377] ASD, vesicoureteral reflux, imperforate anus, CNS, and limb anomalies have all been described. Neither primary microcephaly nor ocular anomalies are a common finding in nonchromosomal intestinal atresia. The combination of microcephaly and intestinal atresia is found in Feingold syndrome, although this is not described to be an apple peel type of atresia. Anterior segment anomalies of the eye are also quite rare, although the exact incidence is not known. They comprise a group of very heterogeneous anomalies. Cornea opacities, iris hypoplasia, adhesions between iris and cornea, Peters anomaly and Axenfeld-Rieger malformation all fall into this category. A significant proportion of these patients with anterior segment anomalies also have non-ocular symptoms, thus constituting several highly variable syndromes. However, intestinal obstruction or atresia is not among these associated anomalies. Stromme et al.[404] described two sibs with the unusual combination of apple peel intestinal atresia, microcephaly, and eye anomalies consisting of corneal clouding and microphthalmia. Other cases were reported subsequently.[33,60,382,385]

METHODS

Standard karyotyping using GTG banding was performed on metaphase spreads from peripheral blood samples following standard procedures. MLPA (multiplex ligation-dependant probe amplification) was carried out using the MCR-Holland kit. DNA analysis was performed on DNA extracted from a peripheral blood sample, using standard protocols. Informed consent was obtained from the parents prior to analysis.

CLINICAL REPORT

The proband was a Caucasian girl born from healthy, non-consanguineous parents. She had two paternal half brothers. As one of them was born with a bilateral double system of the ureters, an ultrasound was made during pregnancy showing a double bubble sign. After amniocentesis a normal, 46,XX karyotype was found. The proband was born at a gestational age of 34 weeks and 3 days with birth weight (BW) 1,890 g (-1 SD), birth length (BL) 42 cm (-2 SD), occipitofrontal circumference (OFC) 30 cm (-1.5 SD), Apgar scores were 7 and 9 at 1 and 5 minutes, respectively. She had a hematoma at the left occipito-temporal region due to the forceps assisted extraction. The face was narrow with an upslant of the narrow, arched, and short palpebral fissures (Figure 5b.1 a,b), and

a somewhat square left ear. The double bubble seen prenatally was caused by apple peel type jejunal atresia for which a side-to-side anastomosis was made at day 2. She was ventilated artificially until 2 days postoperatively and a sepsis resulted in another 3 days. She was discharged from the hospital at age 5 weeks.

TORCH studies were negative; there was a thrombocytopenia possibly due to the large hematoma of the occipito-temporal region. Ultrasounds of kidneys, brain and heart were normal, as was an early hearing test. The ophthalmologist noted a clinically evident bilateral microcornea and a congenital corneal clouding, with a localization extending to the center, leaving only a small part of the left cornea clear. Gonioscopy was not performed due to the severe clouding. This also made detailed evaluation of the fundus impossible. Slit-lamp examination confirmed the congenital corneal clouding and bilateral adhesions between iris and cornea. Subsequently corectopia developed. As the pupillary opening was situated behind the corneal clouding, a peripheral iridectomy was performed to create a new pupillary opening behind the clear part of the left cornea in an effort to save some vision. Eye pressure remained within normal limits. It is hard to estimate her actual visual acuity, but corneal clouding with amblyopia and the roving eye movements make a poor vision likely. At age 1 year corrected for prematurity she grasps toys when given in her hands and brings them close to her eyes. Motor and mental development are estimated to be within normal limits as sitting, standing and crawling were within the normal age range and she understands simple spoken commands. Weight (8.43 kg) and length (71.5 cm) at 1 year continued at -1 SD and -2 SD, respectively, but OFC (42 cm) dropped to -2.5 SD at 1 year. Because she is doing well, the parents choose not to have a MRI scan. Recently a healthy sister was born.

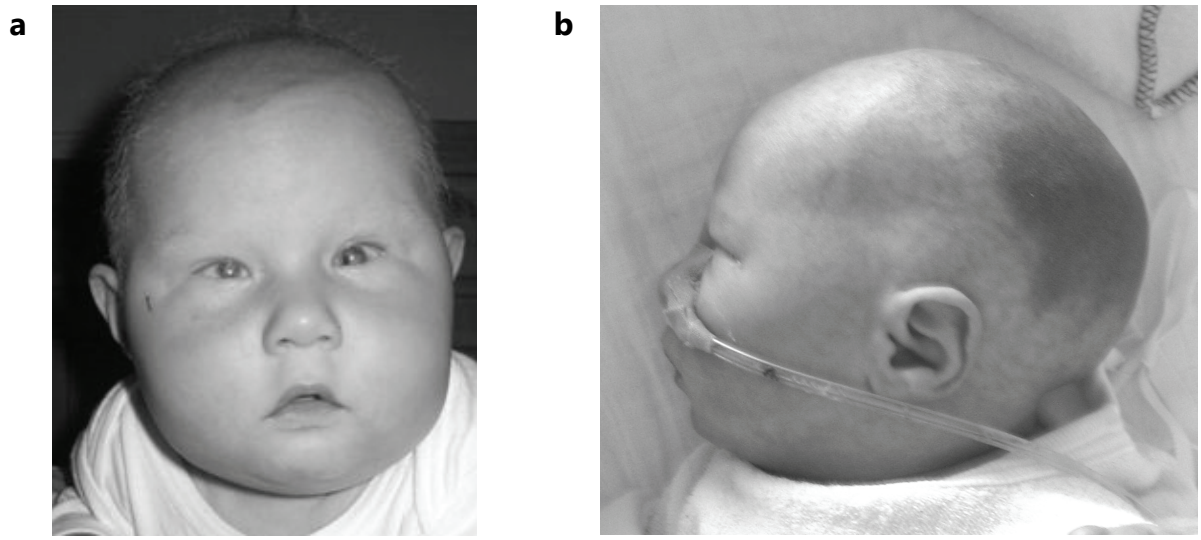


Figure 5b.1 *Proband as newborn, note hematoma, no obvious microcephaly (a) at age 7 months. Note upslant, corneal clouding and small cornea (b).*

GENETIC ANALYSIS

Routine chromosome analysis showed a normal, 46,XX karyotype. The PITX2, FOXC1, PAX6, and MYCN genes were all analyzed for intragenic mutations by PCR and sequencing of all coding exons and splice sites. No mutation was found in any of the genes. MLPA (multiplex ligation-dependent probe amplification, MRC-Holland, Amsterdam, The Netherlands) of the above mentioned genes showed no deletions or duplications, nor did MLPA for the subtelomeric region.

DISCUSSION

Apple peel intestinal atresia is a rare form of intestinal atresia that has been described in sibs, possibly due to an autosomal recessive inheritance in at least some families.[13,145.146,377] Table 5b.1 summarizes the clinical details of the six previously described patients with apple peel intestinal atresia and anterior eye chamber anomalies and the present case. The two sibs described by Stromme et al.[404] developed quite well initially, but micro-cephaly became more pronounced in the elder sib who also seemed more retarded than her younger sister.[403] The patient described by Slee and Goltblatt[385] had severe mental retardation and developed a hydrocephaly and spastic paraplegia. The fourth patient had a slightly increased muscle tone at age 4 months but otherwise seemed to develop well.[33] A patient with multiple intestinal atresias, Peters anomaly, microcephaly and cortical migration defects was described in 2002.[382] Although the term apple peel atresia is not mentioned, the multiple intestinal atresias were all located in the jejunum supplied by the superior mesenteric artery which is also involved in apple peel atresia. As their patient had Peters anomaly, also an anterior chamber anomaly, this patient may have the same syndrome with additional migration defects. Bower at al.[60] described a case with anterior chamber anomalies, apple peel type intestinal atresia who was normocephalic at birth. This child died at age 9 days. She was found to have a mosaic variegated aneuploidy, a condition not described in combination with apple peel intestinal atresia before. It is unclear if the patient with apple peel intestinal atresia, coloboma of the optic nerves, but without anterior chamber anomalies and with a normal head circumference has the same condition.[463] We therefore did not include this patient in Table 5b.1.

All patients have an ocular phenotype in the Axenfeld-Rieger malformation/Peters anomaly spectrum with goniodysgenesis, corneal anomalies and iridocorneal adhesions. Microphthalmia and glaucoma can occur in these entities. Non-ocular manifestations are common and may form recognizable syndromes such as Peters plus syndrome, Rieger syndrome, and SHORT syndrome. As mutations for these malformation syndromes, and the isolated ocular groups have been described in PAX 6, PITX2, FOXC1[199,286,381] and diagnostic tests for these genes are available, we examined these genes in our patient. Microcephaly and intestinal atresia are found in Feingold syndrome, caused by mutations in the MYCN gene.[55] By mutation analysis of the MYCN gene we were able to exclude this gene as disease causing in this patient.

Table 5b.1 Comparison of the 6 patients from the literature to present patient

Feature	Present case	Case 1 and 2[a]		Case 3[a]	Case 4[a]	Case 5[a]	Case 6[a]
sex	female	female	Female	male	male	male	female
age at diagnosis	2 days	2 weeks	Birth	5.5 years	birth	birth	birth
duration of pregnancy	34 + 3 weeks	35 weeks	36 weeks	34 weeks	37 weeks	36 weeks	35 weeks
BW (g)	1890 (-1 SD)	2390 (0 SD)	2800 (0 SD)	1810 (-1 SD)	1890 (< -2 SD)	2350 (-1 SD)	2235 (-1 SD)
BL (cm)	42 (-2 SD)	43 (-2 SD)	46 (-1 SD)	43 (-1 SD)	44 (< -2 SD)		
OFC at birth (cm)	30 (-1.5 SD)	30 (-2 SD)	30 (< -2 SD)	28 (< -2 SD)	27 (< -2 SD)		32 (0 SD)
development	normal	IQ70	IQ83	delayed	normal	delayed	
Apple peel atresia	+	+	+	+	+	multiple jeunal atresias	+
cerebral anomalies	ultrasound age 4 days normal	CT normal	CT normal	CT at birth normal at 9 months: hydrocephalus, atresia foramina Luschka/Magendie	MRI normal	cortical migration defect on MRI	ultrasound age 3 days normal
ocular anomalies	bilateral	right	left	bilateral	bilateral	bilateral	bilateral
corneal clouding	bilateral	right	sclerocornea	bilateral	bilateral l > r	bilateral	bilateral
adhesions	+					+/+	
other ocular anomalies	microcornea	microcornea, shallow anterior chamber, esotropia, irregular, and dilated pupil		peripheral vascularisation, no anterior chamber, descemetocoele, (staphyloma/scleroconea), left buphthalmus			microphthalmia
other congenital anomalies	-			sparse dry hair, slightly dysmorphic	pre auricular tag		abnormal karyotype
age at last follow-up	1 year	6.6 years	4.8 years	5.1 years	4 months	21 months	
weight	8430 (-1 SD)	-1 SD W/L	-1.5 SD	12.1 (-1 SD W/L)	5150 (-2.5 SD)		
length	71.5 (-2 SD)	< -2.5 SD	-2 SD	90 (<< -2.5 SD)	58 (-2.5 SD)		
OFC	42 (-2.5 SD)	<< -2.5 SD	-2.5 SD	50.2 (-1 SD)	36.5 (<-2 SD)	microcephaly	

SD, standard deviation; W/L , weight for length; +, present.
[a] *Cases 1 and 2: Stromme et al.[405]; case 3: Slee and Goldblatt[385]; case 4: Bellini et al.[33]; case: 5 Shanske et al.[382]; case 6: Bower et al.[60]*

FUTURE STUDIES

There are currently two mouse models known for multiple intestinal atresia in humans, $Fgf10^{tm1Ska.}$ and $Fgfr2^{tm1.1Dsn}$. Both mice show abnormal development in many organs.[123,378] FGF10 signaling plays a role in colonic atresia. *FGF10* is expressed in the distal colon; *FGFR2* is expressed throughout the epithelium of the entire gastrointestinal tract. Fairbanks et al.[144] showed that mesenteric occlusion did not occur in the $Fgf10^{-/-}$ and $Fgfr2b^{-/-}$ mice, which show a very proximal colonic atresia. They concluded that the genes have an effect on early organogenesis. The Fgfr2 and Fgf10 mutated mice also show microphthalmia and anophthalmia rather than anterior eye chamber anomalies. *FOXE3* is one of the genes in the Fgfr pathway. It plays a role in anterior segment morphogenesis and its function is *PAX6* dosage dependant.[51] Mutations in *FOXE3* were described in patients with Peters anomaly.[380] *FOXE3* is also expressed in the brain. Further studies of *FGFR2, FGF10*, and genes in this pathway, like *FOXE3* could be a starting point for future research aimed at finding a molecular cause for this syndrome for which we suggest the name Stromme syndrome.

CONCLUSION

We suggest that apple peel intestinal atresia, microcephaly, and anterior segment anomalies of the eye form an entity for which early recognition is important because of the serious visual impairment patients may present. Careful assessments of head circumference, genetic, and ophthalmologic evaluation are recommended in any child with apple peel intestinal atresia. Ultrasound, CT or MRI studies of the brain are useful as hydrocephaly and migration defects have been described. Early monitoring and if necessary treatment of glaucoma is important, as is genetic counseling and a close follow-up to detect psychomotor and neurodevelopmental delay at an early stage. Autosomal recessive inheritance is possible as recurrence in sibs has occurred. We would suggest the name Stromme syndrome to refer to this entity. Future studies are needed to elucidate the molecular cause of this syndrome. The mouse models for multiple intestinal atresia and the genes in the Fgfr signaling pathway could be possible starting points.

ACKNOWLEDGMENTS

The authors wish to thank the family for their cooperation and Dr. M. Mannens, Dr. E. De Baere, and Dr. H. Scheffer for the DNA analysis.

Multidisciplinary management of infantile short bowel syndrome; resource consumption, growth and nutrition

There are three subjects on which the knowledge of the medical profession in general is woefully weak; they are manners, morals, and medicine

Gerald F. Lieberman (1923 - 1986)

ABSTRACT

Objective

The aim of this study is to prospectively evaluate a case series of patients treated by a multidisciplinary short bowel team, with a focus on resource consumption.

Methods

Children with infantile short bowel syndrome (≤ 1 year of age) born between January 2002 and January 2007 and treated by our multidisciplinary team between August 2003 and December 31, 2007. Demographic and medical data of the first admission and total follow-up were recorded. Resource consumption, growth and type of nutrition were assessed.

Results

Ten patients were treated by the multidisciplinary team. Seven patients were discharged with home parenteral nutrition. Duration of total follow-up varied between 9 months and 5.5 years (median 1.5 years). Six patients could be weaned off parenteral nutrition and 5 patients off enteral tube feeding, resulting in full oral intake. Seven patients had normal growth. Median duration of initial hospital admission was 174 days, and average costs of initial admission amounted to 166,045 euros. Total admission days varied from 84 to 478 days with a median of 409 days. Average total costs were 269,700 euro reaching to maximum of 455,400 euros. These costs mainly comprised hospital admissions (82%).

Conclusions

Treatment of short bowel syndrome requires considerable resource consumption, especially when patients depend on parenteral nutrition. As the costs mainly comprise those of hospital admissions, early home parenteral nutrition could contribute to costs reduction. Multidisciplinary teams have the potential to facilitate home parenteral nutrition and thus reduce health care costs, while at the same time benefiting patients' health.

INTRODUCTION

Short bowel syndrome (SBS) is a condition characterized by fast intestinal transit, and thus malabsorption of nutrients and eventually growth retardation. It is often the result of massive resection of the small intestine,[69,182,258,445] but has also been associated with dysfunction of a large segment of bowel. The most frequent underlying diagnoses in neonates are necrotizing enterocolitis, volvulus and congenital anomalies such as intestinal atresia and gastroschisis.[182,258,383] Intestinal adaptation after resection of the small bowel, with gradually increasing fluid and nutrients may last several years during which absorption is inadequate.[130,181] During this period parenteral nutrition (PN) is indispensable. Enteral tube feeding or oral feeding may be introduced in the course of time, and patients can be weaned off PN.

Having considerably improved over the years, survival rates of patients with SBS range from 53% to 94%.[70,180,248,325,346,460] Major predictors of mortality in pediatric SBS are PN-associated cholestasis and age-adjusted small bowel length. Moreover, age-adjusted small bowel length and the presence of the ileocecal valve (ICV) are major predictors of weaning from PN.[391] The fact that more and more patients survive can be attributed to improving care and advancing technology. For example, PN is no longer exclusively given in the hospital, but is gradually giving way to home parenteral nutrition (HPN). Furthermore, patients with SBS are typically treated by several individual professionals, who will see the patients in their own outpatient clinics. However, there is much to say for introducing some type of integrated care that facilitates early discharge home and streamlines redundant procedures, bearing in mind that treatment for SBS can be very costly.[79] Indeed, several reports in the literature emphasize the importance of an integrated, multidisciplinary approach for optimal long-term management of SBS.[182,302,406]

The aim of this study is to prospectively evaluate a case series of patients treated by a multidisciplinary short bowel team, particularly resource consumption, together with information on nutrition and growth.

METHODS

This is a longitudinal observational evaluation of a case series.

Setting

The Erasmus MC-Sophia Children's hospital is a tertiary academic facility equipped with all major pediatric and surgical specialities. It runs the only pediatric surgical service (including ICU) in the Southwestern part of the Netherlands. The referral area has 4 million inhabitants with 44,000 infants born annually.

Following on the recommendations in the literature,[182,302,406] a multidisciplinary SBS team was formed in August 2003. Consisting of a pediatrician, a pediatric surgeon, a pediatric gastroenterologist and a dietician, the team is responsible for the clinical assessment and management of children with SBS. Other specialists are available for consultation; such as a neonatologist, a pediatric intensive care physician, a pharmacist, a nurse specialized in caring for enterostomies, and a social worker.

Patients

This case series includes ten children with infantile SBS (i.e. SBS resulting from intestinal problems ≤ 1 year of age) born between January 2002 and January 2007, and treated by the multidisciplinary SBS team between August 2003 and December 31, 2007. They were either PN dependent or could not be easily weaned off PN. We adhered to the definition by the Dutch national committee on SBS, which includes representatives of the section of gastroenterology of the Dutch Pediatric Association and the Dutch Society of Pediatric Surgery, and dieticians of academic medical centers. The definition is based on consensus on literature data and own experience. The committee defined SBS as:

- 70% resection of the small bowel,[258,412] and/or
- parenteral nutrition needed for longer than 42 days after bowel resection,[248,346,389,460] and/or
- residual small bowel length distal to the ligament of Treitz less than 50 cm for a premature (gestational age 27 - 36 weeks), < 75 cm for term born neonates and < 100 cm for children aged > 12 months.[417]

Patient characteristics and outcome measures first hospital admission

Demographic and medical data including sex, gestational age, birth weight and underlying diagnosis were collected. Date of primary surgery (leading to SBS) was recorded as well as residual small bowel length, measured distal to the ligament of Treitz and post-operative presence of the ileocecal valve (ICV). Complications such as sepsis episodes, PN-related cholestasis and central venous catheter (CVC) (re)placements as a consequence of occlusion, thrombosis or sepsis were recorded. Cholestasis is defined as serum conjugated bilirubin level ≥ 2.5 mg/dl (≥ 43 μmol/l).[391] Furthermore it was recorded whether HPN was initiated.

Follow-up

The total follow-up period was defined as the time (in years) elapsed after discharge from the first hospital admission until either the date of study closure (December 31, 2007) or the date of last evaluation (applicable to patients not followed by the SBS team anymore at study closure). Duration of follow-up by the SBS team was defined as the time (in years) elapsed after the patient's first treatment by the multidisciplinary SBS team until either the date of study closure (December 31, 2007) or the date of last evaluation. Age at start of treatment by the SBS team was recorded, as well as number and main reason for hospital re-admissions, sepsis episodes and CVC's after the first admission.

Weight (kg) and height (cm) were recorded every 3 months in the first year of SBS and every 6 months thereafter. Body weight (kg) was uniformly measured on a calibrated scale (Digital baby scale, Kubota, Japan) to the nearest 0.01 kg, after having removed the child's diaper and clothes. Recumbent height (cm) was measured to the nearest 0.1 cm using a rigid length board with a moveable foot piece. The parent's height was measured in the outpatient clinic or by their general practitioners. Target Height (TH) was calculated as [(fathers height + mothers height ± 13) / 2] + 4.5 centimetres. Target height range (THR) was defined as TH-SDS ± 1.3 sds. Values were compared to national standards[161] and expressed in standard deviation scores (SDS), depending on sex and age and corrected for prematurity (until the age of 2 years) and race (Growth Analyser version 3, Dutch Growth Foundation, Rotterdam, the Netherlands).

Nutrition

Dates on which minimal enteral feeding (MEF) and enteral nutrition started or stopped were recorded. MEF was defined as ≤ 25 kcal/kg/day feeding and its start was defined as the first day after the date of primary surgery leading to SBS. Clinical practice shows that MEF starts as low as 6 ml/day. Enteral nutrition is a way to provide food through a tube to the gastrointestinal tract, and is further referred to as enteral tube nutrition (ETN). Type of nutrition was classified as polymeric, breastfeeding, or semi-elemental. Interruption of ETN, necessitated by inadequate passage through the intestinal tract, was recorded. Furthermore duration of PN was recorded, distinguished into PN during admission and HPN.

Resource consumption and costs

The resource consumption and direct medical costs related to the treatment of SBS were evaluated. Length of stay (LOS; in days) was determined, regarding both the initial admission and all readmissions, broken down for length of stay in intensive care units and medium care/high care units. Stays in referring hospitals preceding the initial admission to our hospital were included. All surgical interventions related to the diagnosis of SBS were recorded. Mean PN and ETN intakes were calculated. Finally, outpatient visits to the SBS team and previous visits to individual specialists were regarded.

Following established methods[326] we proceeded to calculate real economic costs. There are basically two approaches i.e. "top down" and "bottom up." The former allocates total hospital costs down to the level of a unit (e.g., a nursing ward or operating room), resulting in average costs per patient. The latter measures the resource items specific to individual patients.[225,238,409] In this study, a combination of these two methods was adopted. The cost price of a hospitalization day was largely calculated using the top down method and, therefore, mainly referred to all patients of the pediatric surgery department. The integral cost price included personnel costs, costs of materials and medications, and overhead costs (eg, housing, utilities, cleaning, management, etc.). The cost prices of surgical interventions (combination of top down and bottom up)

consisted of both fixed costs per surgical intervention (e.g., costs for materials, sterilization, and the recovery room) and variable costs depending on the duration of the intervention (e.g., costs for equipment, operating room assistants, anesthesia nurses, surgeons, and anesthetists). Costs of parenteral and enteral nutrition were calculated separately. Finally, cost prices of the initial visit to the outpatient clinic and revisits were calculated from personnel costs, costs of material, and indirect costs (top-down method), as well as from costs of medical specialists, a nurse, and a dietician (bottom-up method). All costs were calculated for the year 2006 and reported in Euro (€).

Data Analysis

Due to the descriptive character of this study, no statistical analyses were performed other than reporting frequencies expressed as median and ranges unless stated otherwise.

RESULTS

Patient characteristics and outcomes of the first hospital admission

The underlying diagnoses for the ten patients with infantile SBS reported here are shown in Table 6.1. Patient 7 had a completely necrotic small bowel with only the duodenum and 10 cm of colon in situ. Patients 8 and 10 underwent a Bianchi procedure a few weeks after the diagnosis of SBS, in which the remaining small bowel was doubled in length. Seven patients were discharged with HPN. Patient 10 was still in the hospital at the end of the study period. Two patients (1 and 9) did not have an anatomical SBS, but received PN > 42 days. All characteristics of the first admission are shown in Table 6.1.

Follow-up

The total follow-up period varied between 9 months and 5.5 years (median 1.5 years). Three patients were lost to follow-up. Two of them (patients 2 and 4) recovered very well and were discharged from treatment by the SBS team; patient 7 was put on the waiting list for combined liver and small bowel transplantation and further care was transferred to Belgium. Four patients were discharged home before the SBS team was established and had previously been seen several times by individual specialists. All follow-up data are shown in Table 6.2.

Figures 6.1 and 6.2 show the growth charts of all patients. All grew according to their growth line, except patient 6, whose height declined from -1 SD to -2 SD. This patient had only 10 cm remaining small bowel and is still dependent on HPN. Still, patients 3, 5 and 6 grew below the limits of the THR. Patients 3 and 5 were both born prematurely. Patient 5 with gestational age of 24 weeks has always been under THR even after correction. And patient 3 dropped below THR after the correction for gestational age stopped.

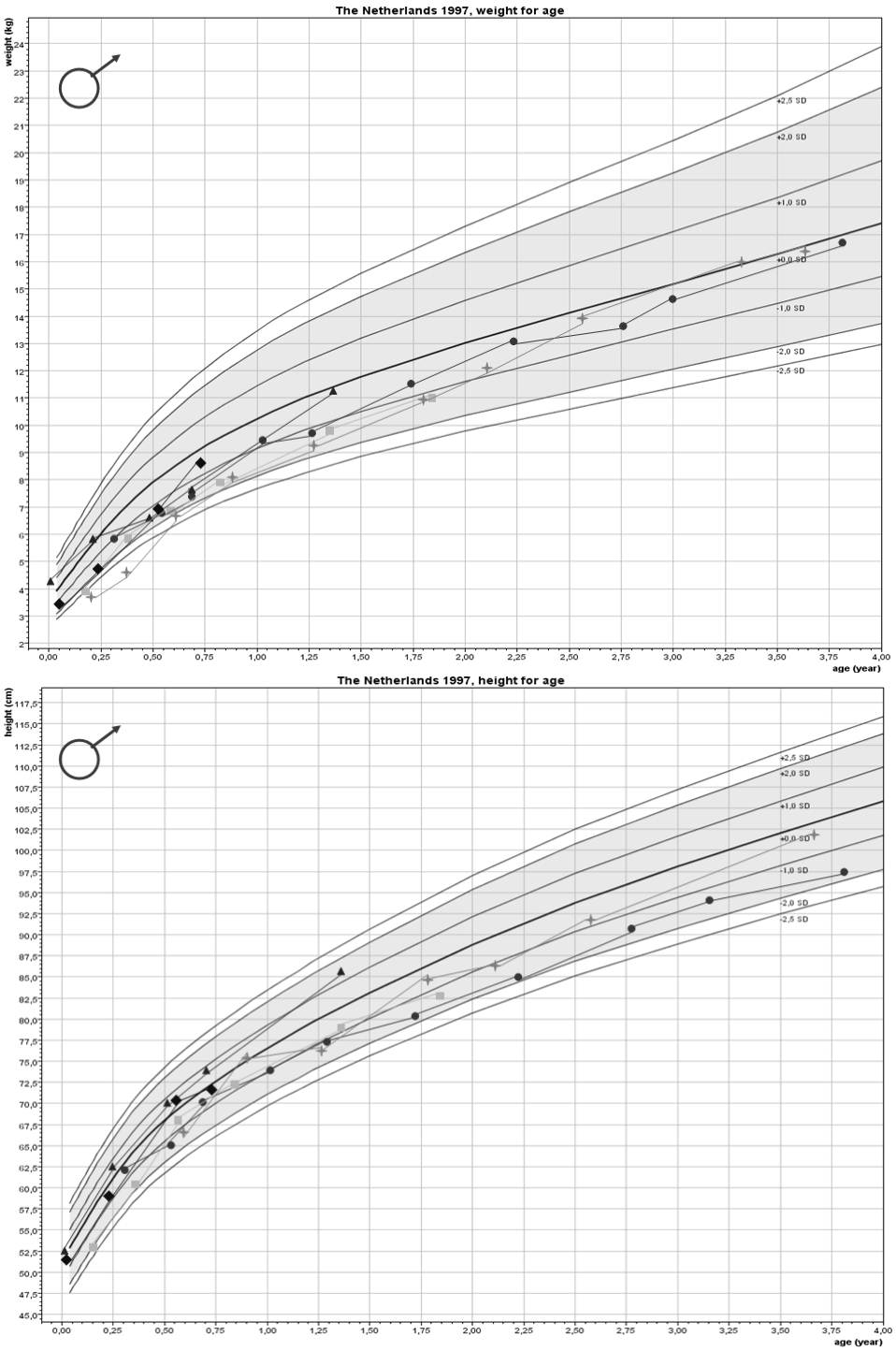


Figure 6.1 *Growth charts males*

- ✦ *Patient 1*
- ● *Patient 6*
- ■ *Patient 7*
- ▲ *Patient 8*
- ◆ *Patient 10.*

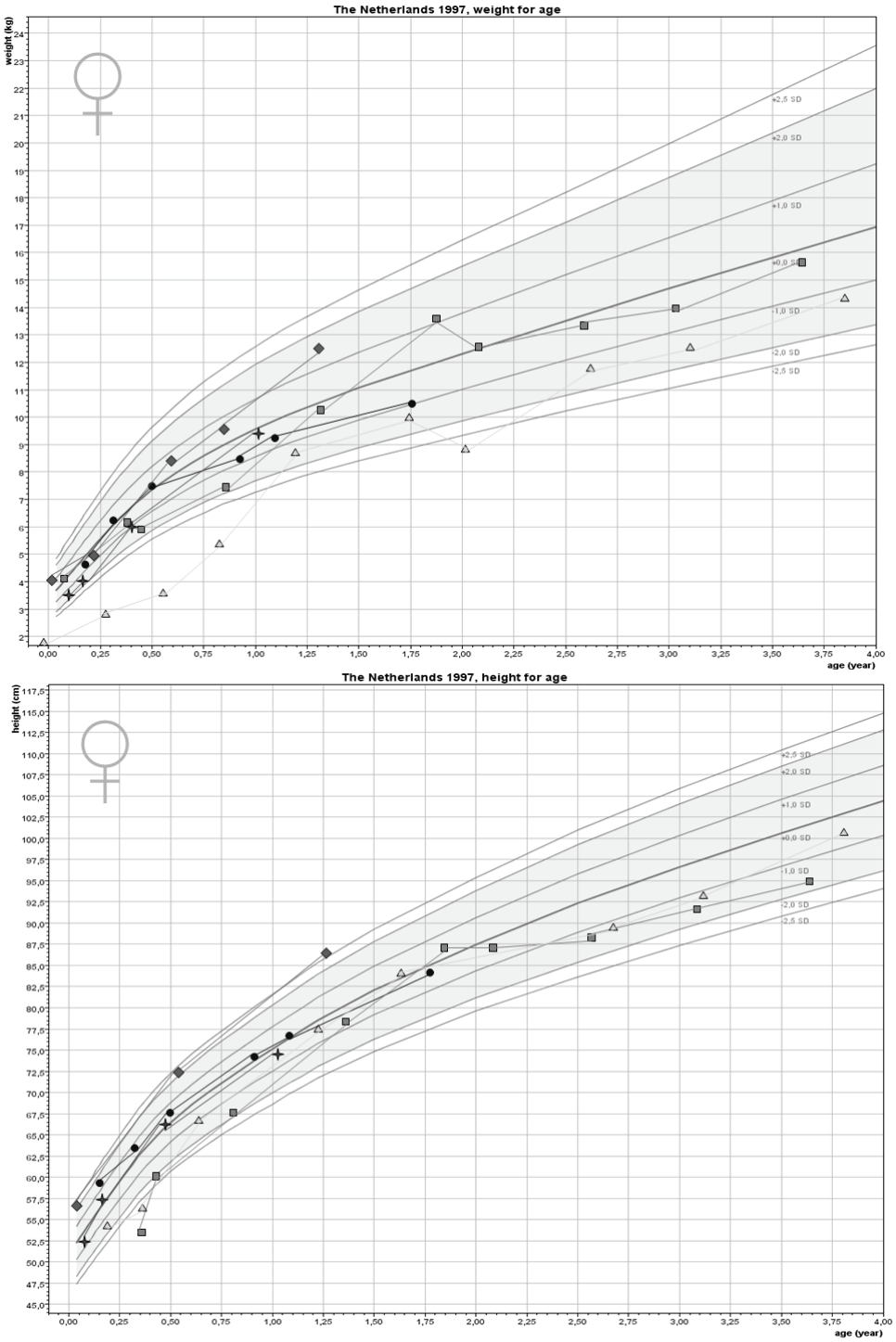


Figure 6.2 *Growth charts female*

- ● *Patient 2*
- ■ *Patient 3*
- ◆ *Patient 4*
- ▲ *Patient 5*
- ✦ *Patient 9.*

Nutrition

MEF was started as early as two days and as late as 83 days after the initial operation. Table 6.3 provides details of PN and ETN intakes. Most patients started MEF with either breast milk or semi-elemental nutrition. Six patients could be weaned off PN after 77 - 477 days (median 218 days) and five patients could be weaned off ETN after 86 - 429 days (median 359 days). Patient 3 is still ETN dependent as a result of oral food aversion. Patients 1 and 6 still need EN to obtain as many calories as possible enterally to sustain optimal growth.

Resource consumption and costs

As shown in Table 6.1, initial length of stay (LOS) varied between 84 days and 350 days. Median LOS was 174 days (mean 182 days): 83 ICU days, 98 HC/MC days. A median of 5 surgical interventions (range 2 - 9) was performed during initial admission. The median number of re-admissions was 2 (range 0 to 52; 0 - 386 hospital days) (Table 6.2). The outlying value for patient 1 was mostly due to recurrent central line sepsis, that for patient 6 to diarrhea and sepsis. Overall, sepsis was the main reason for readmission. The number of outpatient visits was strongly related to duration of follow-up by the SBS team: the three patients who had been followed for more than 4 years were seen 26, 31, and 53 times, respectively, and had been admitted for a median of 409 days (total of all admissions). Median LOS for all ten patients was 239 days (range 84 to 478 days).

Table 6.4 lists the cost prices. Multiplying these prices by the respective volumes gave total costs of hospital admissions, surgical interventions, nutrition, and outpatient visits for each patient (Table 6.5). The average cost of the first hospital admission is € 166,045 (for hospital days only). Total costs (first admission and follow-up) reached a maximum of € 455,400 for patient 6 (average € 269,700; median, € 250,500). On average, the total costs mainly comprise costs of hospital admissions (82%), followed by nutrition (12%), surgical interventions (5%), and outpatient visits (1%). Obviously, the costs are related to duration of follow-up. Therefore, we plotted the cumulative costs against the patient's ages (Figure 6.3). The average costs at the age of 3 years are € 321,000 (median, € 327,000).

DISCUSSION

So far, the multidisciplinary SBS team in our department followed 10 children with infantile short bowel syndrome. To our knowledge this is the first study describing resource consumption. Management of these children makes a substantial claim on health care resources, with an average total cost of € 269,700. The costs comprised mainly of hospital admissions (82%). Furthermore seven patients had normal growth. Six patients could be weaned off PN and 5 patients could be weaned off ETN, resulting in full oral intake.

Table 6.1 Patient characteristics and characteristics of the first admission

Pt	Sex	GA (wks)	BW (sds)	Age SBS (days)	Diagnosis	Bowel length (cm)	ICV	Surgical interventions (n)*	LOS in days (IC/HC, MC)	HPN	Sepsis/month PN (n)	CVCs (n)	PN related Cholestasis
1	M	39.3	-0.4	3	M.Hirschsprung[b]	100	No	5	137 (22/115)	Yes	0.22	2	Yes
2	F	38.3	0.7	3	Volvulus	32	Yes	9[‡]	182 (155/27)	Yes	0.87	7	Yes
3	F	34	3.0[a]	4	Meconium peritonitis	30	Yes	6	218 (218/0)	No	0.8	6	Yes
4	F	33.3	2.5	15	NEC	86	No	5	229 (91/138)	Yes	0.28	2	Yes
5	F	24.9	-1.1	46	NEC	26	Yes	5	223 (147/76)	Yes	0.27	3	Yes
6	M	40		47	Volvulus	10	Yes	5	92 (92/0)	Yes	0	2	No
7	M	37.4	-1.4	2	Gastroschisis	0	No	3	165 (28/137)	Yes	0	1	Yes
8	M	35.1	2.0	1	SIA	21	No	5	136 (45/91)	Yes	0.45	4	Yes
9	F	34.6	0	1	Volvulus	58	Yes	2	84 (17/67)	No	0.40	1	No
10	M	35.3	0.3	3	SIA	8	Yes	7[‡]	>350 (19/331)[§]	n.a.	0.26	4	Yes

Abbreviations: BW, birth weight; SDS, standard deviation score; SBS, short bowel syndrome; CVC, central venous catheter; EN, enteral feeding; F, female; GA, gestational age; HC/MC, high care/medium care; HPN, home parenteral nutrition; IC, intensive care; ICV, ileocecal valve; LOS, length of hospital stay; M, male; PN, parenteral nutrition; NEC, necrotizing enterocolitis; SIA, small intestinal atresia.

[a] *sds BW is skewed, because patient was born with fetal hydrops.*

[b] *Long segment Hirschsprung's disease.*

* *Including insertion and/or removal central venous catheters.*

[‡] *One of these interventions was performed in another hospital prior to admission to our hospital and thus had to be omitted from the cost calculations.*

[§] *Patient was still admitted on December 31, 2007.*

Table 6.2 Results follow-up

Patient	Year of diagnosis*	Total follow-up (years)	Length of follow-up by SBS team (years)	Age at start treatment by SBS team (years)	Hospital re-admissions (n)	Main indication readmission	Total LOS in days (IC/HC, MC)	Surgical interventions (n)†	Sepsis/ month PN (n)	CVCs (n)	Previous outpatient visits (n)	Outpatient visits SBS team (n)
1	2002	5.48	4.18	1.54	37	Sepsis	272 (7/265)	27	0.30	18	22	31
2	2002	1.26	0.17	1.75	1	Sepsis	14 (14/0)	0	2	0	15	2
3	2002	4.64	2.72	0.93	2	PEG insertion	6 (0/6)	1	0	0	1	6
4	2002	0.77	0.35	1.05	2	Sepsis/pneumonia	10 (0/10)	0	0.36	0	11	4
5	2003	4.29	4.14	0.63	9	Sepsis	128 (1/127)	3	0.24	2	0	26
6	2003	4.26	4.22	0.39	52	Diarrhea/sepsis	>386 (6/380)‡	22	0.28	14	0	53
7	2005	1.49	1.45	0.49	11	Sepsis/cholangitis	74 (2/72)	8	0.17	5	0	10
8	2006	1.18	1.05	0.38	2	Sepsis/pneumonia	11 (0/11)	0	0.27	0	0	12
9	2006	1.17	0.88	0.28	0	-	0	0	0	0	0	4
10‡	2007	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

Abbreviations: SBS, short bowel syndrome; CVC, central venous catheter; IC, intensive care; HC/MC, high care/medium care; LOS, length of hospital stay; PN, parenteral nutrition; PEG, Percutaneous endoscopic gastrostomy; n.a., not applicable.

** For all patients, this is also the year of birth.*

† Including inserting and/or removing central venous catheters.

‡ Patient was still admitted at 31/12/2007.

Table 6.3 Nutrition

					Total Nutrition					
	Enteral Nutrition during first admission				Parenteral Nutrition			Enteral Nutrition		
Patient	Start MEF (days)	Start ETN (days)	Type of Nutrition	Interruptions[†] (n)	Mean Intake[‡] (ml/day)	Duration (days)	HPN (days)	Mean Intake[‡] (ml/day)	Duration (days)	Mean Type ETN
1	3	6	Polymeric	3	559 ml	> 1,985[*]	> 1,682[*]	649	> 2,131[*]	50% semi-elemental / 50% polymeric
2	6	10	Semi-elemental	3	285 ml	190	1	699	359	semi-elemental
3	6	27	Semi-elemental	7	285 ml	189	-	848	> 1,879[*]	35% semi-elemental / 65% polymeric
4	13	23	Breastmilk	6	290 ml	300	77	537	345	semi-elemental
5	18	49	Semi-elemental	1	206 ml	477	162	398	429	semi-elemental
6	24	51	Semi-elemental	1	413 ml	> 1,508[*]	> 1,036[*]	455	> 1,595[*]	70% semi-elemental / 30% polymeric
7	-	-	-	-	920 ml	> 706[**]	> 465[**]	-	-	-
8	2	64	Breastmilk	4	412 ml	247	106	297	425	polymeric
9	3	6	Breastmilk	0	273 ml	77	-	301	86	polymeric
10	83	162	Breastmilk	5	740 ml	> 347[*]	n.a.	102	> 185[*]	11% semi-elemental/ 89% polymeric

Abbreviations: MEF, minimal enteral feeding; ETN, Enteral Tube Nutrition; HPN, home parenteral nutrition.
** Patient was still on total parenteral/enteral nutrition at December 31, 2007, ** Patient was still on HPN when lost to follow-up.*
† Number of interruptions in enteral feeding.
‡ Mean intake/day for the total period they received PN and or ETN.

Table 6.4 Costs of units pertaining to the direct medical costs of treating patients with SBS

Hospital days	
Intensive care	€ 1,359
Medium care/high care	€ 538
Surgical interventions*	
Bowel	€ 1,772
Inserting and/or removing a CVC	€ 939
Other (e.g., endoscopies, biopsies)	€ 821
Nutrition	
Parenteral nutrition (per day)	€ 37 - € 73†
Enteral tube nutrition (per day)	€ 0.19 - € 14†
Outpatient visits	
SBS team	
First visit	€ 175
Revisit	€ 162
Regular visit	
First visit	€ 60
Revisit	€ 48

** Not all surgery performed on the patients can be enumerated here. To give an impression of the costs, interventions were organized into three categories, of which the table gives the average prices.*
† Depending on the quantity and type of nutrition.

The literature contains several studies on multidisciplinary SBS teams.[156,256,129,312,324,416] The picture emerging from these studies is that such teams have great merits and that early referral is important for successful management.[156,182,324,416] A study by Modi et al., using a historical comparison group, indeed indicated that a multidisciplinary SBS program, coordinating both inpatient and outpatient management, was associated with a higher survival rate.[312] Diamond et al. used a similar methodology, but their study did not confirm these findings: the effects of a SBS program did not show better overall survival and nutritional outcomes. Still, mortality from liver failure had decreased, and fewer septic periods were noted.[129] Torres et al. showed that under the management of a multidisciplinary team, liver function and nutritional parameters had improved even in patients with < 40 cm intestinal length or < 10% of normal bowel length; they could be weaned off PN while maintaining growth.[416] In addition, multidisciplinary SBS teams may deliver other more intangible benefits to the patients and their parents, such as integration of expert management, better continuity of care and improved communication with and satisfaction of parents.[256,324] None of the above mentioned studies described the costs of such teams nor costs of treatment.

Table 6.5 Costs of Hospital Admissions, Surgery, Nutrition, and Outpatient Visits

Patient	Hospital admissions			Surgical interventions	Nutrition	Outpatient visits	Total costs
	First admission	Readmissions	Total				
1	€ 91,900	€ 151,700	€ 243,600	€ 37,000	€ 117,000	€ 6,100	€ 403,700
2	€ 225,700	€ 19,400	€ 245,100	€ 7,500	€ 10,300	€ 1,100	€ 264,000
3	€ 295,700	€ 3,400	€ 299,100	€ 9,700	€ 34,000	€ 1,000	€ 343,800
4	€ 197,800	€ 5,600	€ 203,300	€ 7,700	€ 14,000	€ 1,200	€ 226,200
5	€ 240,600	€ 69,800	€ 310,400	€ 9,900	€ 20,000	€ 4,200	€ 344,500
6	€ 124,600	€ 212,700	€ 337,300	€ 26,600	€ 82,900	€ 8,600	€ 455,400
7	€ 111,600	€ 41,400	€ 153,000	€ 11,100	€ 46,900	€ 1,600	€ 212,600
8	€ 109,600	€ 5,700	€ 115,200	€ 11,500	€ 14,500	€ 2,000	€ 143,200
9	€ 58,700	-	€ 58,700	€ 4,000	€ 3,100	€ 700	€ 66,500
10	€ 204,100	n.a.	€ 204,100	€ 7,500	€ 25,300	n.a.	€ 237,000

Figures are rounded to the nearest € 100.
Abbreviation: n.a., not applicable.

There are only a few earlier studies into resource consumption and costs of SBS treatment, mostly limited to the initial hospitalization and some of which are rather dated by now. For example, in the 1989 study of Caniano and co-workers, the average cost of the initial hospitalization was $ 315,000 – equivalent to € 389,000 in 2006 –, with an average stay of 450 days in 10 patients.[79] Recently, Longworth et al. showed that the average costs of 24 stable SBS patients (not requiring transplantation) were £ 159,000 based on 1998/1999 prices – equivalent to € 266,000 in 2006 – over 30 months with a mean hospital stay of 50 (± 74SD) days.[291] To compare costing studies from different countries is a perilous exercise, because of differences in the range of health care facilities available, in incentives to health care professionals and institutions, and in absolute and relative prices of health care resources.[133,367] Still, the findings by Longworth seem roughly in line with the costs calculated in our study (average total costs of € 321,000 at the age of 3 years). It seems that the costs in our study (initial hospitalization costs of € 166,045 for hospital days only) are clearly lower than the costs reported by Caniano et al. This may be explained by the 2.5 times longer initial hospitalization in the patient group described by Caniano.

A growing interest in evidence-based and cost-effective medicine has emerged.[223,338] It is increasingly required to provide insight into whether the effects of treatment are large enough to justify its costs. The present study calculated considerable direct medical costs of treatment for SBS. From the perspective of a decision maker faced with scarcity of resources, the question is whether the outcomes in terms of length and quality of survival are worth these high costs. Mental and motor development and health-related quality of life of patients with SBS as described in the literature are generally satisfying.[179,226,279] The design of our study did not provide for an evaluation of

the (cost-) effectiveness of the multidisciplinary SBS team. Such evaluations, using a controlled design, are not easy to achieve, because it is difficult to create a genuinely comparable control group. Nevertheless, we feel that the multidisciplinary team has important merits, in terms of efficiency and quality of care. The SBS team was launched with the explicit aim of facilitating patients' transition from inpatient PN to HPN and therefore reduction of costs can be expected. As early as 1993, Schalamon and co-workers had calculated that the annual cost for PN in hospital is approximately $ 205,000 compared to $ 90,000 for HPN.[373] Other authors also showed that HPN is about 50 - 75% percent more "economical" than in-patient hospital care.[99,344,356]

It can be concluded from Figure 6.3 that the costs for most patients seem to reach a plateau within a couple of years, probably reflecting completion of intestinal adaptation and thus less need for PN. Costs for two patients (1 and 6) steadily increased, however, as they could not be weaned from PN and its complications.

There are some points to bear in mind when interpreting the results of our study regarding the costs of treatment. First, the number of patients was rather small. Second, we did not calculate costs of laboratory tests, diagnostic radiology, intercollegial consultations and medications of outpatients. It is plausible however that these costs make up only a minor proportion of the total costs, and therefore that this omission did not bias the results. Third, we adopted a combination of top down and bottom up calculations, which is common practice. Applying bottom up techniques for all cost items would have resulted in more precise calculations, but is very labor intensive and is unlikely to have substantial effects on the overall outcomes of the calculations. Despite these reservations, we have confidence in the results, as we applied established methods, for example calculating real economic costs and not relying on charges, which do not provide a true representation of the real costs incurred.

Previously we have shown shorter LOS, shorter duration of PN and significantly higher z-scores for weight for age for SBS patients in the years 1990 - 1999 as compared with the preceding decade.[325] We concluded that there was still room for improvement, notably with regard to stimulating early nutritional intake.[325] Comparison cannot be extended however, to present case series, as these 10 patients have much shorter bowel lengths than the ones in decade 1990 (median 28 cm [0 - 100 cm (range)] versus 74 cm [30 - 120 cm (range)]).

For none of the 10 patient's z-scores on weight for age declined in the first year of life. All patients but one grew according to their growth curve. This is consistent with a study performed by Torres et al.[416] Our observation that three out of the ten children grew below their target height range is more in line with other studies reporting higher percentages of growth failure.[256,324,27] Two of the three patients with impaired growth were premature born. Few studies showed that premature children even after catch-up growth will have suboptimal growth attainment.[188,190,332] Two patients needed no longer

be followed after 2-4 outpatient visits. Bowel adaptation occurred under the management of the SBS-team and they grew properly on oral nutrition without the support of PN nor ETN.

Minimal enteral feeding was started as early as 2 days to as late as 83 days after surgery. Early MEF seemed to shorten PN dependency, except for the patient diagnosed with long segment Hirschsprung's disease. However, it is possible that a sicker bowel might be associated with a later start of MEF. Duration of ETN lasted between 86 to over 2131 days. Duration of ETN did not differ between five patients who received polymeric nutrition (of whom four breastmilk) and the four who received semi-elemental nutrition. Likewise Ksiazyk et al. did not find any difference in absorption between polymeric and semi-elemental nutrition.[270] Moreover Koehler et al. also did not find an association between the type of formula used and successful weaning from ETN.[256] These studies are in line with our previous findings on protein absorption in preterm neonates after bowel resection.[371] This study demonstrated that protein absorption capacity of the small intestine is intact and that these results do not support the use of semi-elemental formula to improve the amino acid uptake.[371] Since semi-elemental formula is much more expensive than polymeric formula, the latter would therefore be the preferred formula. Nevertheless, we studied a small and heterogeneous group of patients with different bowel lengths and underlying diagnoses.

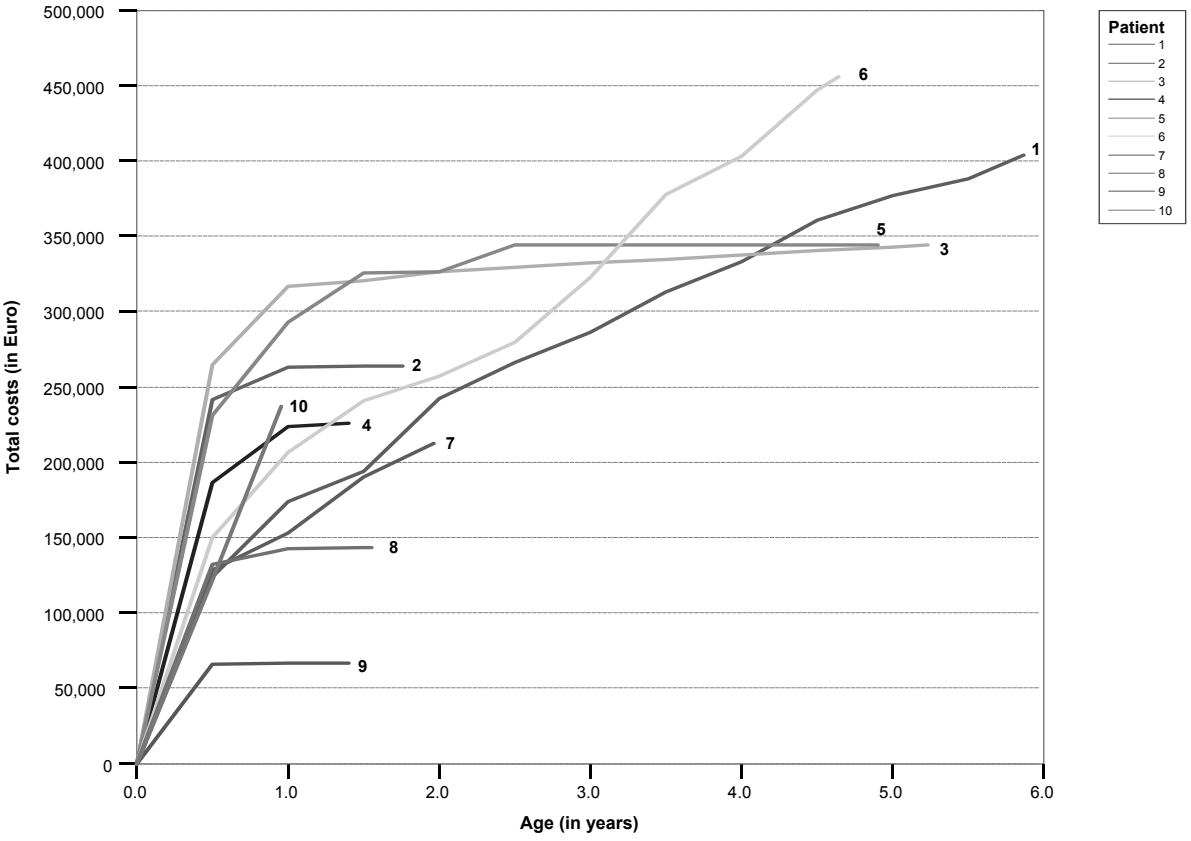


Figure 6.3 *Total cumulative costs by age during follow-up.*

In conclusion, treatment of infantile SBS requires considerable resource consumption, especially when patients depend on PN. As the costs mainly comprise hospital admissions, early HPN could contribute to cost reduction. Systematic nutritional strategies are essential to wean SBS patients off PN as soon as possible and thus prevent, delay or reverse complications such as PN-induced liver disease. The ultimate goal is to optimize intestinal adaptation while preserving adequate growth and development. Multidisciplinary teams have the potential to facilitate early HPN, and to optimize growth by tailor made treatment. Thus, they may be instrumental in reducing health care costs, while at the same time benefiting patients' health and quality of life of both patients and parents.

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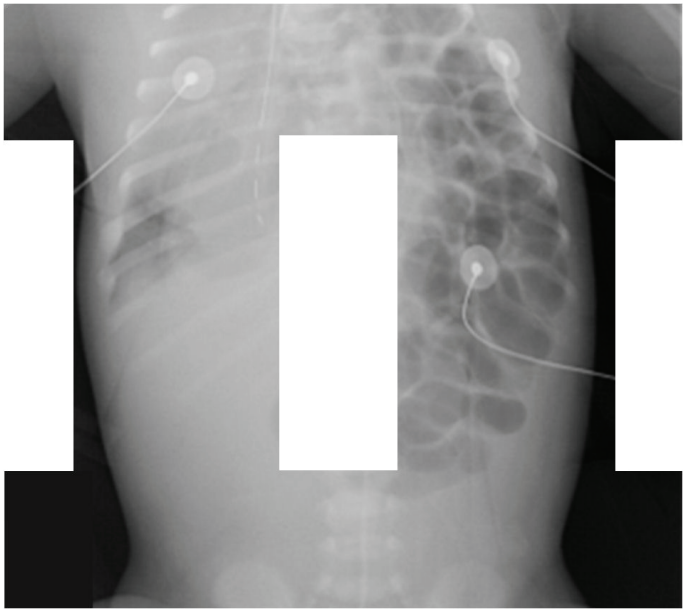


DEVELOPMENTAL PSYCHOLOGICAL BACKGROUND OF CONGENITAL ANOMALIES

Predictive capacity of cognitive and motor development of children with major congenital anomalies at 5 years; an empirical-clinical study

Each child is born with four invisible brothers protecting it
These are intelligence, friendship, strength and poetry

Balinese Hindu wisdom

ABSTRACT

Aim

To determine whether early development of children with major congenital anomalies will predict development at age 5 years.

Method

Bayley Scales of Infant Development -Mental Developmental Indexes (MDI) and Psychomotor Developmental Indexes (PDI)- were administered at ages 6, 12 and 24 months; the Revised Amsterdam Children's Intelligence Test -intelligence quotient (IQ)- and Movement Assessment Battery for Children -Total Impairment Score (TIS)- at age 5 years. Logistic regression analysis served to determine MDI and PDI prediction potential of IQ and TIS at 5 years of age.

Results

At 5 years, 87 of 116 children (75.0%) had an IQ ≥ 85 and 29 (25.0%) an IQ < 85. Sixty-two of 87 children (71.3%) had a normal TIS, 15 (17.2%) showed a borderline score and 10 (11.5%) presented with a definite motor problem. MDI and PDI scores at 6, 12 and 24 months were equally sensitive to significantly predict the discretized IQ and TIS.

Conclusions

Mental and motor development in the first 24 months were positively related with cognitive and motor outcome at 5 years of age and TIS was positively related with IQ. Early developmental assessment of children with major congenital anomalies predicts impaired development at the age of five years.

INTRODUCTION

About 2 - 3% of newborn children in the Netherlands are born with major anatomical congenital anomalies (CA). Most of these are life-threatening unless surgically corrected.[396] Examples are intestinal atresias, abdominal wall defects, congenital diaphragmatic hernia (CDH), anorectal malformations and Hirschsprung's disease. These conditions are to be treated in specialized centers for pediatric surgery. Presentation may be isolated or as part of a spectrum of anomalies. Advances in surgery and peri-operative care have reduced mortality rates (apart from CDH) to approximately 10%.[210] This reduction, however, has led to more morbidity, possibly extending into adulthood.[59,208,340] Thus, there is often uncertainty about future quality of life, also in view of the risk of developmental problems.[59,210] Bouman and colleagues evaluated in a cross-sectional design 115 children's somatic and psychosocial functioning 8 to 12 years after surgical correction of an anatomical CA. For 36% of children overall school level was below the average of normal population: IQ (mean = 91) was significantly ($p < 0.001$) below the norm of 100. Seventeen percent of the children needed special education, four times more frequent than in the general population.

Follow-up data, especially prospective longitudinal data, on the impact of CA on cognitive and motor development at pre-school age are lacking. Still, early identification of cognitive and motor developmental problems could enable early intervention and thus reduce potential later morbidity.

The main focus of the present observational, prospective, longitudinal cohort study was to determine whether cognitive and motor development at ages 6, 12 and 24 months might predict development at 5 years of age.

METHOD

Setting

The Erasmus MC-Sophia Children's Hospital is a university hospital with a pediatric surgical department in which all surgical specialties except open-heart surgery are represented. As the traditional monospecialistic approach of children with CA was felt inadequate, a multidisciplinary treatment, support and evaluation team for these children and their parents was instituted in 1999.

Participants

From January 1999 to November 2002 a total of 205 children with CA were admitted to the pediatric surgical intensive care and eligible for inclusion. Parents of 33 children did not participate in the follow-up program, 26 children died before the age of 6 months and 2 children died respectively at 14 and 20 months of age. Parents of 27 children

refused consent for evaluation at 5 years of age. Thus, 117 children participated in the study (see Figure 7.1). Eighty-eight children were seen at all four time points.

Largely in line with Ravitch's so-called surgical index diagnoses of CA,[351] the following categories were distinguished:

1. abdominal wall defects (AWD);
2. congenital diaphragmatic hernia (CDH);
3. esophageal atresia (EA);
4. small intestinal anomalies (SIA);
5. anorectal malformations (ARM);
6. Hirschsprung's disease (HD) and
7. a group of miscellaneous diagnoses.

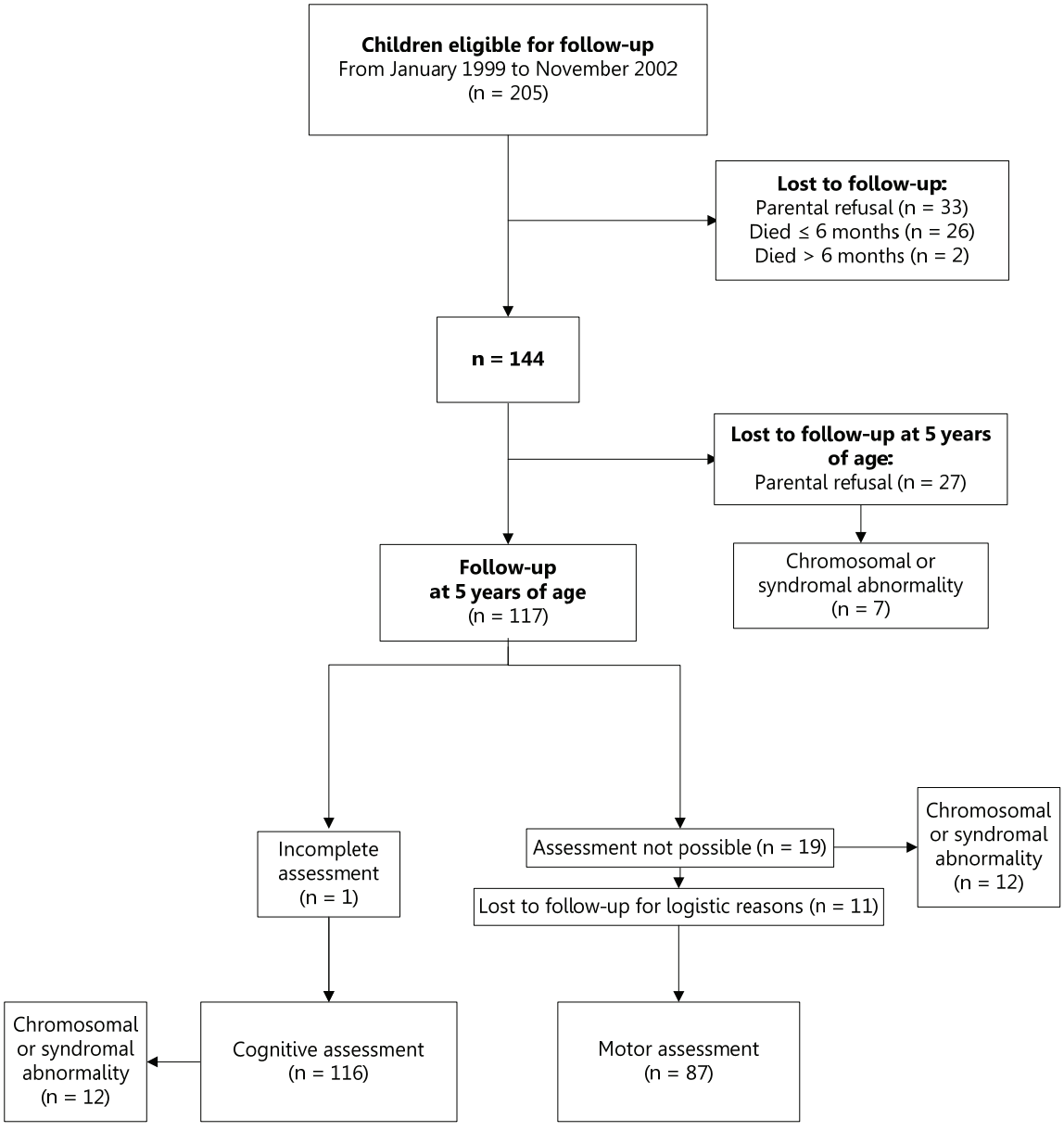


Figure 7.1 *Flowchart*

Design

This is an observational prospective, longitudinal cohort study comprising four assessments: at 6, 12 and 24 months and 5 years after the birth of the child.

Procedure

The Erasmus MC ethical review board agreed with the study, and written parental informed consent was obtained for all subjects. At all time points the participants were seen by a developmental psychologist, a pediatrician and a consultant pediatric surgeon; at age 5 years also by a pediatric physical therapist. Results of the first three assessments were corrected for gestational age. A clinical geneticist evaluated all children for major chromosomal, syndromal and cerebral abnormalities during first admission.

Demographic and medical data were collected prospectively from the first day of admission. Demographic characteristics included ethnicity, i.e. parents being native Dutch or non-native Dutch and socioeconomic status (SES).[397] Medical characteristics included type of CA, total number of minor and major anomalies, duration of admission in the first 6 months, number of medical appliances at discharge, number of surgical interventions and number of additional medical problems in the first 24 months (Table 7.1).

Table 7.1 Demographic and medical characteristics

	Total population (n = 117)		**Missing (n = 27)**	
	n	**%**	**n**	**%**
Female	54	46.2	9	33.3
One or both parent(s) non-native Dutch	20	17.1	7	25.9
Socioeconomic status				
Low	19	16.3	11	40.7
Medium	61	52.1	12	44.5
High	37	31.6	4	14.8
Primary Congenital Anomaly				
Small intestinal anomaly	39	33.3	8	29.6
Abdominal wall defect	18	15.4	3	11.1
Congenital diaphragmatic hernia	16	13.7	3	11.1
Esophageal atresia	15	12.8	5	18.5
Miscellaneous	13	11.1	3	11.1
Hirschsprung's disease	10	8.5	3	11.1
Anorectal malformation	6	5.1	2	7.4
Chromosomal or syndromal abnormality	12	10.3	7	25.9
	median	**IQR**	**median**	**IQR**
Congenital anomalies per patient (number)	2	1 to 3	2	1 to 3
Total admission in first 6 months (days)	42	27 to 76	34	27 to 52
Medical appliances at discharge (number)[a]	1	0 to 2	1	0 to 2
Surgical interventions in first 24 months (number)	3	2 to 5	2	1 to 4
Additional medical problems in first 24 months (number)	2	1 to 4	1	0 to 4

[a] *Medical appliances includes: O2, tracheostomy, nasogastric tube and enterostomy*

Cognitive and motor development

Children's mental and psychomotor development at ages 6, 12 and 24 months were assessed by the Bayley Scales of Infant Development.[31,434] This test has been designed to evaluate developmental status in the first 30 months of life. Mental Developmental Indexes (MDI) and Psychomotor Developmental Indexes (PDI) were determined in relation to Dutch population norms with a mean score of 100 and a standard deviation (SD) of 16. Scores of all three assessments were corrected for gestational age.

At age five years the short version of the Revised Amsterdam Children's Intelligence Test (RAKIT) for children aged 4 to 11 years was administered. The RAKIT is a Dutch standardized instrument with good psychometric properties.[49,50] The short version comprises six subtests and refers to logical reasoning, word knowledge, word fluency, visual-motor integration, memory, and visual synthesis. The raw subtest scores were transformed into a short RAKIT intelligence quotient (IQ) (mean 100, SD 15).

Motor development at age five years was assessed with the Movement Assessment Battery for Children (M-ABC).[215,387] It consists of three manual dexterity items, two ball skill items, and three balance items, each to be scored on a 6-point scale ranging from good (0) to very poor (5). Thus, high scores on the M-ABC represent poor performance. Total impairment score (TIS) and subscores for each of the three domains were calculated. Using percentile normative data tables, TIS and the three domain scores were interpreted as a percentile score. TIS at or below the 5^{th} percentile is indicative of a motor problem, TIS between the 6^{th} and 15^{th} percentile of a borderline motor problem, TIS above the 15^{th} percentile is considered normal. As the M-ABC is not suitable to test children with neurological impairment or severe motor retardation, it was not applied to children with syndromal or chromosomal disorders suffering from potential severe psychomotor delay and children with neurological impairments such as cerebral palsy.

Statistical analyses

As measures of central tendency the means and medians were estimated, including the 95% confidence intervals (95%CI) when the data were continuous. The standard deviation (normal distribution) and interquartile range (non-normal distribution) served as measures of dispersion. In case of categorical data the numbers and percentages were presented. The intra- and intercorrelations of the cognitive and motor developments were estimated by the method of Spearman Rank correlation including the pertinent p-values (two-sided).

The values of candidate-determinant predictor variables (MDI and PDI) and medical covariables in differentiating the dichotomized outcome variable IQ and trichotomized outcome variable TIS measured at 5 years were estimated by the method of logistic regression analysis. Concerning the outcome variable IQ, analyses were performed both with inclusion and exclusion of children with syndromal or chromosomal disorders to correct for the potentially large impact of suffering from severe psychomotor delay.

Outcome variable IQ was dichotomized into two categories: 1. IQ ≥ 85 (corresponding to less than 1*SD below the mean of the population) and 2. IQ < 85 (corresponding to more than 1*SD below the mean of the population).

Outcome variable TIS was trichotomized into three categories: 1. normal (> 15^{th} percentile), 2. borderline (corresponding to > 5^{th} and ≤ 15^{th} percentile) and 3. definite motor problem (≤ 5^{th} percentile).

The higher the Odds Ratio (OR), the higher the score on the determinants for the first outcome category (coded 1). The other way round, the lower the OR, the lower the score on the determinants for the first outcome category. The same line of reasoning applies to the trichotomized logistic regression analysis (also called multiple nominal analysis): only a high OR indicates higher score on the determinants for the first and second outcome categories (coded 1 and coded 2) compared to the reference category (coded 0). All analyses were adjusted for gender. Duration of hospital stay in the first 6 months of life, number of surgical interventions in the first 24 months, number of medical appliances at discharge, number of additional medical problems, and number of congenital anomalies were entered in the logistic regression analyses and kept when their contribution was statistically significant.

To evaluate if earlier assessments might have missed risk of cognitive problems at 5 years we checked which children with an IQ < 70 at 5 years had MDI scores ≥ 85 at 6, 12 or 24 months. Conversely, we identified those children who seemed at risk at 6, 12 or 24 months (MDI scores < 70) but who had an IQ ≥ 85 at 5 years. To evaluate if earlier assessments might have missed risk of motor problems at 5 years (TIS ≤ 5^{th} percentile), we checked which children had PDI scores ≥ 85 at 6, 12 or 24 months. Conversely, we identified those children who seemed at risk at 6, 12 or 24 months (PDI scores < 70) but who had a TIS > 15^{th} percentile at 5 years.
All statistical testing was performed at the 0.05 level of significance.

RESULTS

General characteristics

Characteristics of the 117 children seen at the age of five years (Figure 7.1) are presented in Table 7.1. The most frequent diagnosis was SIA (33%), followed by AWD, CDH and EA. Total number of minor and major anomalies per child ranged from one to three (IQR) with a median of two. Median duration of admission in the first 6 months was 42 days. Children underwent a median of three surgical interventions in the first 24 months. Twelve children with a major chromosomal or syndromal abnormality (Down's syndrome in 41.7%) were at risk of severe psychomotor delay. The group of 27 children for whom parents refused consent for evaluation at age 5 years was characterized by

low SES (11/27) and high frequency of major chromosomal or syndromal abnormality (7/27), over twice that in the children that were seen at 5 years.

Cognitive development

One of the 117 children tested at 5 years of age could not complete the cognitive assessment because of insufficient command of the Dutch language and behavioral problems. Of the remaining 116 children, 87 children (75.0%) had an IQ ≥ 85 and 29 children (25.0%) an IQ < 85. Table 7.2a presents these children's cognitive outcomes at 6, 12 and 24 months as well as those for the 28 who were lost to follow-up at age 5 years, including the one who was not able to complete the tests at age 5. The last three columns present these outcomes for the population excluding those with syndromal or chromosomal disorders.

Mean scores for the group 'IQ ≥ 85' increased over the years, and were all within the age-specific norm. Means scores for the group 'IQ < 85' decreased over the years, and were all > 1 SD below the norm. For the group 'lost to follow-up at 5 years' the mean scores peaked to 89.7 at 12 months.

One hundred and four of the 116 children (89.6%) tested at age 5 years had no syndromal or chromosomal disorders. Twenty-two children of the 28 (78.6%) of the 'lost to follow-up at 5 years' group had no syndromal or chromosomal disorders. Here, too, mean scores for the 'IQ ≥ 85' group increased over the years. Scores for the two other groups decreased over the years.

Motor development

At 5 years, 87 children were assessed with the M-ABC. Sixty-two of those (71.3%) had a percentile score within the normal range, 15 (17.2%) a percentile score indicative of a borderline motor problem and in 10 (11.5%) children the percentile score represented a definite motor problem. Table 7.2b presents the motor outcomes at 6, 12, and 24 months for the patients classified by the three TIS categories and the group for whom M-ABC assessment was not possible. Twelve children were not tested because of syndromal or chromosomal disorders and risk of severe psychomotor delay and seven children because of neurological impairments such as cerebral palsy. The last column gives the results at 6, 12 and 24 months for thirty-eight 'lost to follow-up' patients at the 5 year-visit. Eleven children were lost to follow-up for logistic reasons and for twenty-seven children the parents refused consent. Differences between the 3 TIS categories are primarily between normal vs. borderline and definite motor problem. PDI scores improve over time for all three TIS categories.

Table 7.2a Cognitive assessment results, mean (SD)

	Total population n = 144			Population without patients with syndromal/chromosomal abnormalities n = 126		
	IQ ≥ 85 n = 87	**IQ < 85 n = 29**	**Lost to follow-up at 5 years n = 28**	**IQ ≥ 85 n = 87**	**IQ < 85 n = 17**	**Lost to follow-up at 5 years n = 22**
MDI 6 months	99.8 (13.3)	76.4 (22.5)	86.4 (24.1)	99.8 (13.3)	88.1 (18.3)	93.6 (21.2)
MDI 12 months	105.7 (20.0)	72.2 (23.8)	89.7 (26.8)	105.7 (20.0)	85.7 (21.4)	97.6 (21.7)
MDI 24 months	107.0 (18.4)	64.4 (20.4)	79.9 (27.0)	107.0 (18.4)	73.4 (21.6)	88.1 (24.6)
IQ 60 months	108.3 (12.4)	63.1 (13.1)	-	108.3 (12.4)	71.7 (10.2)	-

Table 7.2b M-ABC assessment results, mean (SD) (n = 144)

	Normal n = 62	**Borderline n = 15**	**Definite motor problem n = 10**	**M-ABC not possible n = 19**	**Lost to follow-up at 5 years* n = 38**
PDI 6 months	91.1 (15.8)	79.9 (14.8)	66.8 (18.0)	64.8 (16.0)	87.7 (24.3)
PDI 12 months	101.8 (17.3)	74.2 (17.6)	77.8 (25.8)	56.1 (13.1)	91.1 (25.6)
PDI 24 months	103.3 (13.5)	87.8 (20.2)	85.3 (19.9)	53.6 (14.6)	86.6 (23.0)
IQ 60 months	106.9 (15.3)	100.7 (14.1)	87.3 (22.4)	64.2 (23.5)	102.7 (17.7)

* Lost to follow-up included eleven for logistic reasons, twenty-seven parental refusal

Predictability of cognitive outcome

For cognitive outcome, two sets of analyses were performed, i.e. for the total group and for the group excluding those with syndromal or chromosomal disorders. Table 7.3a presents the results of the logistic regression analyses with MDI, SES, being non-native Dutch and number of anomalies as predictor variables. MDI at all three measurement moments significantly predicted the IQ outcome category.

For the total population, SES, being non-native Dutch and number of congenital anomalies were of added value for predicting the IQ outcome category. A high SES at 6 months significantly predicted the IQ outcome category at 5 years. At 6 and 12 months, being non-native Dutch was significantly predictive of an IQ < 85. Also, a higher number of congenital anomalies was significantly predictive of an IQ < 85 for almost all measurement moments in both sets of analyses.

Seventeen children with low IQ at 5 years (IQ < 70) should have been considered at risk for cognitive problems at earlier assessments. All had been seen at least once either at 6, 12 or 24 months. MDI scores at 6 months were available for 16 of them; four children showed MDI scores ≥ 85. At 12 and 24 months, all seventeen children scored MDI < 85. Seven out of 87 (8%) children with normal cognitive development (IQ ≥ 85) at 5 years of age had one or two MDI scores < 70 at 6, 12 or 24 months. Only two children showed MDI scores < 70 twice.

Predictability of motor outcome

Concerning motor outcome, Table 7.3b presents the results of the logistic regression analyses with PDI, SES, being non-native Dutch and number of anomalies as predictor variables. PDI was predictive for the trichotomised outcome variable M-ABC. The higher the PDI score, the higher the probability of 'normal' motor outcome, at all three measurement moments.

The variables SES, being non-native Dutch and number of congenital anomalies were not of added value for predicting motor outcome at 5 years of age.

Of the ten children with a definite motor problem (TIS ≤ 5th percentile) at 5 years of age, six showed PDI ≥ 85 once or twice at 12 and 24 months. Only one child showed PDI ≥ 85 at 6 months. Five children at 12 months and four children at 24 months showed PDI ≥ 85.

Six out of 62 (9.7%) children with a normal motor development (TISS > 15th percentile) at 5 years of age showed PDI < 70 at 6 months. At 12 months two children showed PDI < 70 and at 24 months none of the children showed PDI < 70.

Table 7.3a Prediction of IQ < 85 versus IQ ≥ 85 at 5 years from information at 6, 12 and 24 months and relevant background variables

	Total population			Non-syndromal/chromosomal abnormalities		
Predictors[1]	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
6 months (n_6 = 106 [2], 93 [3])						
SES[4] medium	2.04	0.43 to 9.80	0.37	2.08	0.42 to 10.27	0.37
SES[4] high	10.88	1.29 to 91.64	0.03	13.47	1.07 to 169.69	0.04
Non-Dutch	0.15	0.03 to 0.74	0.02	0.16	0.03 to 0.79	0.02
Number of congenital anomalies	0.68	0.48 to 0.96	0.03	0.75	0.52 to 1.07	0.11
MDI 6 months	1.09	1.05 to 1.13	0.00	1.07	1.02 to 1.12	0.00
12 months (n_{12} = 102 [2], 91 [3])						
SES[4] medium	0.97	0.17 to 5.49	0.97	1.00	0.19 to 5.3	1.00
SES[4] high	4.91	0.63 to 38.42	0.13	8.38	0.69 to 106.7	0.10
Non-Dutch	0.11	0.02 to 0.71	0.02	0.14	0.02 to 0.85	0.03
Number of congenital anomalies	0.60	0.40 to 0.89	0.01	0.63	0.41 to 0.96	0.03
MDI 12 months	1.07	1.04 to 1.10	0.00	1.05	1.02 to 1.09	0.00
24 months (n_{24} = 102 [2], 92 [3])						
SES[4] medium	0.77	0.10 to 6.07	0.80	0.91	0.13 to 6.28	0.92
SES[4] high	3.61	0.25 to 53.11	0.35	8.33	0.30 to 230.67	0.21
Non-Dutch	0.47	0.06 to 3.59	0.47	0.48	0.07 to 3.19	0.45
Number of congenital anomalies	0.56	0.35 to 0.90	0.02	0.58	0.36 to 0.94	0.03
MDI 24 months	1.10	1.05 to 1.15	0.00	1.08	1.03 to 1.13	0.00

[1] Adjusted for gender, [2] Total population, [3] Non-syndromal/chromosomal abnormalities,
[4] SES = Socioeconomic status

Relationship between cognitive and motor functioning

On average high correlations were found for MDI and PDI scores across time. For MDI correlation coefficients ranged from 0.51 to 0.71; for PDI from 0.50 to 0.72. Lowest correlations were seen between 6 and 24 months for both outcomes (see Appendix). MDI and PDI scores also correlated across the same measurement times from 0.56 (24 months) to 0.76 (at 6 months). Correlation between MDI and PDI across measurement times vary from 0.59 to 0.64. Furthermore, moderate significant correlations were found between the predictor variables MDI and PDI and the non-dichotomized outcome variables IQ and TIS across time, with coefficients ranging from 0.21 to 0.58. Thus, mental and motor development in the first 24 months were positively related with cognitive and motor outcome at 5 years of age and TIS was positively related with IQ.

Table 7.3b Prediction of M-ABC[1] at 5 years from information at 6, 12 and 24 months and relevant background variables

	'Borderline' versus 'Normal'			'Definite motor problem' versus 'Normal'		
Predictors[2]	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
6 months (n_6 = 77)						
SES[3] medium	1.67	0.14 to 19.74	0.68	1.60	0.08 to 30.80	0.75
SES[3] high	0.75	0.06 to 10.29	0.83	0.36	0.01 to 8.76	0.53
Non-Dutch	0.85	0.11 to 6.50	0.87	1.21	0.12 to 12.68	0.87
Number of congenital anomalies	1.41	0.91 to 2.14	0.13	1.42	0.81 to 2.51	0.23
PDI 6 months	0.94	0.90 to 0.98	0.00	0.90	0.84 to 0.96	0.00
12 months (n_{12} = 73)						
SES[3] medium	2.27	0.17 to 30.74	0.54	4.18	0.31 to 56.58	0.28
SES[3] high	1.22	0.09 to 17.09	0.88	0.64	0.04 to 10.32	0.76
Non-Dutch	2.85	0.21 to 38.13	0.43	5.38	0.53 to 54.79	0.16
Number of congenital anomalies	0.91	0.44 to 1.91	0.81	1.35	0.81 to 2.24	0.25
PDI 12 months	0.92	0.88 to 0.97	0.00	0.93	0.89 to 0.97	0.00
24 months (n_{24} = 76)						
SES[3] medium	-[4]	-[4]	-[4]	-[4]	-[4]	-[4]
SES[3] high	0.64	0.15 to 2.71	0.54	0.59	0.09 to 3.76	0.58
Non-Dutch	0.57	0.05 to 6.62	0.65	2.18	0.24 to 20.09	0.49
Number of congenital anomalies	1.01	0.62 to 1.64	0.98	0.83	0.45 to 1.56	0.57
PDI 24 months	0.94	0.89 to 0.98	0.01	0.92	0.87 to 0.98	0.01

[1] Outcome categories 'Borderline' (coded 1) and 'Definite motor problem' (coded 2) compared to the reference category 'Normal' (coded 0).
[2] Adjusted for gender, [3] SES = Socioeconomic status, [4] Eliminated due to multicollinearity (high interdependency) of the predicted variables

DISCUSSION

This empirical-clinical study shows that cognitive and motor development of children after repair of anatomical malformations assessed at 6, 12 and 24 months predicted cognitive and motor development at 5 years. Low MDI and PDI scores over the first 24 months are equally predictive for unfavorable cognitive and motor outcomes at 5 years of age. Even the separate scores obtained as early as at 6 months are predictive for cognitive development at 5 years. Only in a few cases developmental outcomes in the first 24 months proved false positive or false negative resulting in faulty risk stratification. Almost all children with cognitive and motor problems at 5 years of age and normal performances at 6 months, showed developmental problems at 12 and 24 months. On the other hand, only few children with normal cognitive and motor performances at 5 years, showed poor performances once or twice at 6, 12 or 24

months. These children probably still showed adverse consequences of treatment and initial illness, from which they recovered later.

Findings from this study are primarily based on a population including a substantial proportion of children with additional syndromal or chromosomal disorders, conditions which may give rise to severe psychomotor delay. The rationale for inclusion is that these disorders in general occur frequently in children with CA. Subanalysis in the group excluding these children revealed, however, that mental developmental scores at an early stage are still predictive for cognitive development at 5 years. So, all in all it is possible to make a reasonably precise prediction of cognitive development of children with CA.

Studies on outcome of neonatal intensive care and articles on follow-up for high-risk infants[158] in tertiary care centers explicitly exclude the CA group, for its relatively small numbers and heterogeneity.[139,187,189,456,457] Still, our findings are in line with findings from studies in prematurely born children, whose neurodevelopmental status at 12 months of age was closely related to cognitive and motor skills at 4 years[128,401] and 8.[366] In addition to MDI and PDI scores, also socioeconomic status, being (non-native) Dutch and number of congenital anomalies were predictive of outcome. Probably the number of anomalies is the most objective measure to predict severity of illness. Duration of hospital admission, number of surgical interventions, number of medical appliances at discharge or number of additional medical problems did not have the power to predict cognitive outcome at 5 years. This finding is in line with findings of a cross-sectional study by Bouman et al.[57] performed about one decade ago in our clinic, that failed to reveal significant correlations between duration of neonatal hospitalization and number of operations on the one hand, and IQ on the other hand. Comparable studies have reported that the neurological score together with the nature of the home environment and the child's family background (SES)[128] are important determinants of cognitive development for very low birth weight children.[128,465] The study of Weisglas-Kuperus and colleagues compares well to the present study, because it was conducted in a similar demographic context (i.e. same hospital).

Furthermore, cognitive and motor developmental outcomes in the present study are comparable with neurodevelopmental outcomes at 5 years in a nationwide Dutch study in neonates treated with veno-arterial ECMO (extracorporeal membrane oxygenation).[196] Twenty percent of those neonates had CDH, the other patients did not have an anatomical congenital anomaly. In the present study, 16% of the children without syndromal or chromosomal abnormalities showed cognitive delay at 5 years, versus 14% in the ECMO study. In the present study 28.7% had an actual motor problem or were at risk for a motor problem versus 26.1% in the ECMO study.

Our study has a possible limitation in that the group of children who did not undergo assessment at five years of age differed from the group that was assessed (i.e. more

than twice as many children with low SES and major chromosomal or syndromal abnormalities). The children with major chromosomal or syndromal abnormalities who did not visit the follow-up clinic, were all cared for by specialized organizations, for example Down teams and rehabilitation centers. So it seems that for these children the focus should be on smooth transition to those organizations.

Extended studies are needed to ascertain the predictability of cognitive and motor development at the longer term. Attention deficit, concentration disorders and learning problems, for example, are known not to emerge until after the age of 5 years.[457] Thus, concentration and memory should be part of neuropsychological assessment at 8 and 12 years follow-up. Further data collection at ages 8 and 12 years is ongoing in our institute.

Conclusion

This study is the first to show that developmental assessment over the first two years after correction of a major anatomic malformation is highly predictive of cognitive and motor outcomes at five years of age. It helps to identify patients at risk of impaired cognitive and motor development, who then may be offered interventions aimed at reducing flawed development later in life.

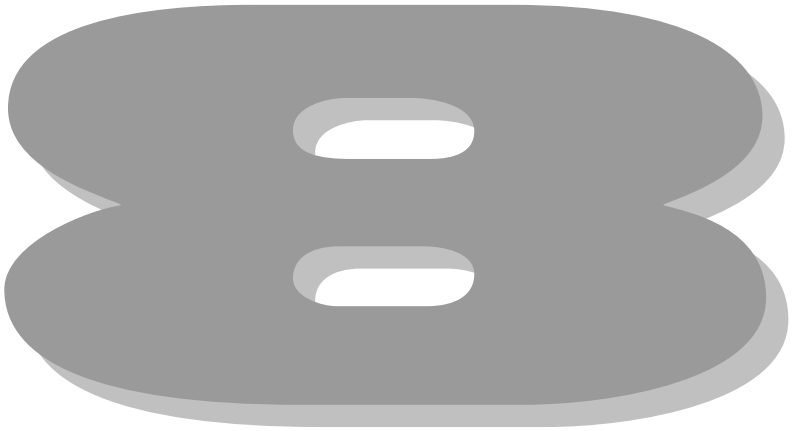
Acknowledgements

We gratefully acknowledge the co-operation of all patients and their parents who participated in the study; without them this study would not have been possible. Also, we thank Ko Hagoort for editing, and Marjan de Jong for her priceless help in data retrieval.

Appendix Matrix of cognitive and motor intra- & intercorrelations across time

		6 months		12 months		24 months		60 months	
		MDI	**PDI**	**MDI**	**PDI**	**MDI**	**PDI**	**IQ**	**TIS[1]**
6 months	**MDI**		0.00	0.00	0.00	0.00	0.00	0.00	0.00
	PDI	0.76		0.00	0.00	0.00	0.00	0.00	0.00
12 months	**MDI**	0.71	0.68		0.00	0.00	0.00	0.00	0.00
	PDI	0.64	0.68	0.72		0.00	0.00	0.00	0.00
24 months	**MDI**	0.51	0.48	0.67	0.50		0.00	0.00	0.07
	PDI	0.59	0.50	0.61	0.72	0.56		0.00	0.00
60 months	**IQ**	0.38	0.27	0.41	0.39	0.58	0.53		0.01
	TIS[1]	0.44	0.45	0.41	0.56	0.21	0.42	0.28	

Upper triangle: p-values
Lower triangle: Spearman's rho correlations
[1] *TIS = Total Impairment Score*



Follow-up of newborns treated with extracorporeal membrane oxygenation: a nationwide evaluation at 5 years of age

Medicine knows no limits, especially not its own

Gerhard Kocher (1939 -)

ABSTRACT

Introduction

Extracorporeal membrane oxygenation (ECMO) is a supportive cardiopulmonary bypass technique for babies with acute reversible cardiorespiratory failure. We assessed morbidity in ECMO survivors at the age of five years, when they start primary school and major decisions for school careers must be made.

Methods

Five-year-old neonatal veno-arterial ECMO survivors from the two designated ECMO centers in the Netherlands (Erasmus MC-Sophia Children's Hospital in Rotterdam, and University Medical Center Nijmegen) were assessed within the framework of an extensive follow-up program. The protocol included medical assessment, neuromotor assessment, and psychological assessment by means of parent and teacher questionnaires.

Results

Seventeen of the 98 children included in the analysis (17%) were found to have neurological deficits. Six of those 17 (6% of the total) showed major disability. Two of those six children had a chromosomal abnormality. Three had mental retardation and were profoundly impaired. The sixth child had a right-sided hemiplegia. These six children did not undergo neuromotor assessment. Twenty-four of the remaining 92 children (26%) showed motor difficulties: 15% actually had a motor problem and 11% were at risk for this. Cognitive delay was identified in 11 children (14%). The mean IQ score was within the normal range (IQ = 100.5).

Conclusion

Neonatal ECMO in the Netherlands was found to be associated with considerable morbidity at five years of age. It appeared feasible to have as many as 87% of survivors participate in follow-up assessment, due to cooperation between two centers and small traveling distances. Objective evaluation of the long-term morbidity associated with the application of this highly invasive technology in the immediate neonatal period requires an interdisciplinary follow-up program with nationwide consensus on timing and actual testing protocol.

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass technique for providing life support in acute reversible cardiorespiratory failure when conventional management is not successful. Most patients receiving ECMO support are neonates suffering from persistent pulmonary hypertension of the newborn, primary or secondary to meconium aspiration syndrome, sepsis, or congenital diaphragmatic hernia. Worldwide, over 18,700 neonates have been treated with ECMO for respiratory problems, and the overall survival rate was 77%.[142]

The UK Collaborative ECMO Trial Group in 1996 presented the results of a randomized controlled clinical trial, showing a significant survival benefit of ECMO, without a concomitant rise in severe disability at one year of age.[426,427] Even for the 35 neonates with congenital diaphragmatic hernia (CDH) the risk of death was reduced (relative risk, 0.72; 95% confidence interval, 0.54 - 0.06; p = 0.03). Of the 18 neonates with CDH allocated to ECMO, however, 14 died (one after discharge) and only three children survived to age 4 years. All 17 infants in the conventional management arm died before discharge.[137] No other therapeutic intervention (that is to say, high-frequency oscillatory ventilation, surfactant, and inhaled nitric oxide) for neonatal acute respiratory failure has such a positive impact on mortality and morbidity.[197]

Nevertheless, the severity of illness of potential candidates for ECMO, as well as the risks associated with the procedure itself, places the ECMO survivor at high risk of developing brain injury and subsequent function deficits. All patients receiving ECMO support have suffered from severe respiratory failure prior to treatment. Prolonged episodes of severe hypoxemia may occur, despite the administration of 100% oxygen. The inevitable high ventilatory pressures and hyperventilation may cause alterations in cerebral blood flow.[198,292] In veno-arterial ECMO the right common carotid artery and right internal jugular vein are cannulated and subsequently ligated after bypass is finished. Finally, the heparin that is administered to prevent the blood from clotting might cause intracranial hemorrhage as a confounder for long-term morbidity. It is not easy, therefore, to predict the long-term outcome of neonates treated with ECMO.

The few reports on structural follow-up of ECMO survivors either describe infants up to age 2 or patients from a single centre with wide age distribution.[7,9,42,173,195,237,360,421,426] The reports point out that logistic problems may prevent patients from being available for predetermined, structural evaluation. Major disabilities in terms of severe developmental delay or neuromotor disabilities were reported in some 20% of ECMO survivors.[173,237,360,426,] The range of morbidity widens with evaluation after age one, when assessment of cognitive skills, coordination, behavioral difficulties, and sensory loss can be more precise.[34] Long-term longitudinal follow-up of these children therefore seems essential for placing ECMO results in perspective. Only two studies describe longitudinal neurodevelopmental evaluation at school age.[34,174] Although surviving children treated

for severe life-threatening respiratory failure soon after birth show considerable long-term morbidity, the results of the UK ECMO trial point to a favorable profile of long-term morbidity in the group assigned to ECMO.[34]

Glass and colleagues reported a 61% response rate; 25% did not participate because of long traveling distances in the USA.[174] Neonatal ECMO in the Netherlands is provided in two designated centers only, authorized by the Dutch government. All parents of ECMO survivors are invited to enter their child into a follow-up program. High response rates are feasible because traveling distances are short in the Netherlands and regionalized high-risk perinatal care, including ECMO, is available. The children are scheduled to undergo assessment at ages 6, 12, 18 and 24 months and 5, 8 and 12 years. In the present paper we present the follow-up findings at age 5 years, when children are in the first or second year of primary school and major decisions for their future school careers must be made.

MATERIALS AND METHODS

Patients

The study population included five-year-old neonatal veno-arterial ECMO survivors from both ECMO centers in the Netherlands (the Erasmus MC-Sophia Children's Hospital Rotterdam and University Medical Center Nijmegen). The patients were seen either between May 2001 and December 2003 (Rotterdam) or between March 1998 and December 2003 (Nijmegen). According to national consensus on neonatal follow-up and the obligation to provide these data based on reports of the Dutch Ministry of Health, the assessment protocol is the standard of care in the Netherlands following ECMO. As a consequence IRB approval was waived, while all parents were routinely informed about the long-term follow-up program in the neonatal period of life of their child.

Assessment protocol

Complete assessment included a one hour medical assessment by a pediatrician/neonatologist experienced in the follow-up evaluation, a 1.5-hour neuromotor assessment by a pediatric physiotherapist, and a three hour neuropsychological assessment by a psychologist or psychological test assistant (Table 8.1). In Nijmegen a speech therapist assessed speech and language development, and in Rotterdam the psychologist performed the neuropsychological assessment. The complete assessment took place in one day. The sequence of the different assessments could vary for logistic reasons.

In addition, one month before assessment, the parents were invited to complete questionnaires on parental socioeconomic status and the child's current general health and behavior.

Table 8.1 Assessment protocol at 5 years of age

	Time (hours)	**Instrument**	**Nijmegen**	**Rotterdam**
Medical assessment (pediatrician)	1	Physical and neurological examination	X	X
Neuromotor assessment (pediatric physiotherapist)	1.5	Movement Assessment Battery for Children	X	X
		Exercise test		X
Neuropsychological assessment (psychologist and speech therapist)	3			
Intelligence		Revised Amsterdam Intelligence Test	X	X
Visual-motor integration		Beery		X
Receptive language development		Reynell	X	X
Expressive language development		Schlichting	X	X
Behavior		Child Behavior Checklist/ Teacher's Report Form	X	X

Perinatal characteristics such as birth weight, gestational age, age at start of ECMO, duration of ECMO, primary diagnosis, and possible intracranial abnormalities were obtained from each center's ECMO registry and are included in the Extracorporeal Life Support Organization Registry Report.[142]

Medical assessment

Medical assessment consisted of taking the child's medical history, the measurement of growth parameters, and a standard physical examination followed by a standard neurological examination. Length and weight were expressed as the standard deviation (SD) score using the Dutch Growth Analyser, version 2.0 (Dutch Growth Foundation, Rotterdam, Netherlands). The results of the neurological examination were categorized into normal (no neurological abnormalities), minor neurological dysfunction (neurological abnormalities without influence on normal posture or movement), and major neurological dysfunction (neurological abnormalities with abnormal posture or movements, including seizure disorders).

Neuromotor assessment

The Movement Assessment Battery for Children (M-ABC) was used to measure motor functioning.[215] A Dutch standardization study has shown that the original norm scores and cut off points can also be applied to Dutch children. Good validity and reliability have been demonstrated.[215,387]

The M-ABC was developed for children aged 4 - 12 years. The measure has four age-related item sets, each consisting of eight items: three manual dexterity items (a time-related task for each hand separately, a bimanual coordination task, and a graphical task with the preferred hand), two ball skill items (a task of catching a moving object and a task of aiming at a goal), and three balance items (static balance, dynamic balance while moving fast, and dynamic balance while moving slowly). Scores may range from 0 to 5 for each item. A high score on the M-ABC indicates poor performance. The total impairment score, which is the sum of the item scores, was calculated as a percentile score. A score below the 5th percentile is indicative of a motor problem, a score between the 5th and 15th percentile means borderline performance, and a score above the 15th percentile is a normal score.[215]

Exercise test

The children seen in Rotterdam performed a graded, maximum exercise test using a motor-driven treadmill. The treadmill was programmed for increases in angle of inclination and speed every three minutes according to the Bruce protocol.[68,110] The Bruce protocol starts with a speed of 2.7 km/hour at an incline of 10%. The children are encouraged to perform to voluntary exhaustion. The maximal endurance time was used as criterion of exercise capacity and compared with data reported previously.[46,110]

Neuropsychological assessment

Cognitive development

A short version of the Revised Amsterdam Intelligence Test (RAKIT) for children was used to evaluate cognitive development. The RAKIT is a well-known standardized instrument in the Netherlands for children aged 4 - 11 years. Good reliability and validity have been demonstrated.[48,50] The short version contains six subtests. The raw subtest scores are converted into standardized scores, which are then transformed into a short RAKIT intelligence quotient (IQ) with a mean of 100 and a SD of 15. Cognitive delay was defined by a test result more than -1 SD below the norm (that is to say, IQ ≤ 85).

Visual–motor integration

The Developmental Test of Visual–Motor Integration for children aged from 3 to 18 years measures the integration of visual perceptual and motor abilities.[32] Children are asked to copy figures of increasing geometric complexity. The computed raw item scores are transformed into a visual–motor integration standard score with a mean of 100 and a SD of 15.

Behavior

The Dutch versions of the Child Behavior Checklist and the Teacher's Report Form were completed by parents and teachers, respectively.[4,5] Both have been standardized for the Dutch population from 4 to 18 years old, and rate 120 problem behavior items on a three-point scale (0 = not true, 1 = somewhat true or sometimes true, 2 = very true or often true).[451,452] A total problem score is computed by summing the scores of all items. Two broadband scales were constructed: an internalizing scale including withdrawn behavior, somatic complaints without physical cause, and anxious-depressive feelings; and an externalizing scale including aggressive and delinquent behavior. Total scores ≥ 60 classify children in the borderline/clinical range.

Language development

Language development was assessed with the Reynell Test and the Schlichting Test. The Reynell test assesses receptive language development of Dutch-speaking children between ages 1 and 6 years.[436] Expressive language is not required since the children may respond nonverbally.

The Schlichting Test assesses language expression of Dutch-speaking children between ages 1 and 6 years.[374] Two subtests were applied: one testing knowledge of grammatical structure (syntactical development), and the other subtest measuring active vocabulary (lexical development).

The numbers of correct answers in the tests were transformed into standard quotient scores with a mean of 100 and a SD of 15. The following categories were discerned:

delayed/abnormal development (score less than -2 SD), at risk (score from -1 SD to -2 SD), and normal (score greater than -1 SD).

Data analysis
Data are presented for the entire group and also by diagnosis. An independent-sample Student *t* test was performed when appropriate to analyze differences between the study group and general population norms. $p < 0.05$ represented statistical significance. A chi-square test was performed to test whether the motor performance scores in this ECMO population differed significantly from the distribution in the normal population. $p < 0.05$ was considered statistically significant.

RESULTS

A total of 144 neonates received veno-arterial ECMO support from January 1996 up to and including December 1998. Thirty-one of them (22%) died before age 5 years, all during first admission at median age 21 days (interquartile range, 11 - 35 days; range, 2 - 120 days). Fourteen infants were lost to follow-up for various reasons. The present addresses of two children could not be traced, the families of three children moved abroad, and parental consent was withheld for five children. Four other children failed to appear, even after repeated invitations. Ninety-nine infants therefore participated in the follow-up program (Figure 8.1). The parents of one child, however, withheld consent to use data for publication purposes, so eventually we present data of 98 children (35 children in Rotterdam, 63 children in Nijmegen) (87% of all survivors).

The perinatal characteristics and ECMO-treatment characteristics of the participants are presented in Table 8.2. The children's basic characteristics at time of follow-up are presented in Table 8.3.

Outcome medical assessment
Seventeen children (17%) were found to have a neurological disorder. Six of those (6%) showed major neurodevelopmental disability, including two children with a chromosomal abnormality. Of the latter, one child was known to have Down syndrome and the second child (diagnosed with CDH) showed unbalanced translocation of chromosome 11 - 22 (unknown at the time of ECMO). This boy was severely impaired and mentally retarded, and is known to have died at age six years.

Of the other four children with major neurological disorder, one had a right-sided hemiplegia caused by nonhemorrhagic infarction during ECMO. He walked with an orthesis and attended special education. The second child had developed a right-sided hemiplegia as a result of left-sided cerebral hemiatrophy. He was confined to a wheelchair and was mentally retarded. The third child with major neurological disorder (diagnosed with meconium aspiration syndrome) had severe asphyxia and had been

resuscitated in the immediate postnatal period. Still suffering from a seizure disorder, she used a walking frame, and she was mentally retarded. The fourth child suffered from seizures, used a wheelchair, and was mentally retarded.

Table 8.2 Perinatal and extracorporeal membrane oxygenation (ECMO) characteristics

Male/Female	60/38
Birth weight (kg)	3.3 (2.9 - 3.8)
Gestational age (weeks)	40 (38 - 41)
Apgar score at 1 minute/5 minutes	5/7
Primary diagnosis	
Meconium aspiration syndrome	51
Congenital diaphragmatic hernia	20
Sepsis	11
Persistent pulmonary hypertension of the newborn	15
Congenital cystic adenomatoid malformation of the lung	1
Outborn (n)	
Home	10
> 20 km from ECMO centre	51
< 20 km from ECMO centre	30
Oxygenation index prior to ECMO[a]	39 (24 - 58)
Alveolar arterial oxygen distention gradient[b]	622 (606 - 637)
Age at start of ECMO (hours)	28 (17 - 43)
Duration of ECMO support (hours)	155 (127 - 188)
Duration of mechanical ventilation (days)	16 (13 - 22)
Supplemental oxygen after ECMO (days)	8 (4 - 16)
Duration of first admission (days)	38 (30 - 55)
Haemorrhagic intracranial abnormalities (n)	
Minor: intraventricular hemorrhage grade 1 and grade 2	8
Major: intraventricular hemorrhage grade 3 and grade 4	0
Nonhaemorrhagic intracranial abnormalities (n)	
Minor: ventricular dilatation and focal atrophy	17
Major: general atrophy and infarcts	4
Observed infants with epileptic insults (n)	27
Patients treated with Phenobarbital as prophylaxis (n)	37
Duration of Phenobarbital treatment in infants with epileptic insults (days)	49 (21 - 90)

Perinatal characteristics of the 98 children available for analysis, presented as n *(%) of infants or median (interquartile range).* [a] *Calculated as* $[(\text{mean airway pressure} \times FiO_2)/PaO_2] \times 100$. [b] *Calculated as* $P_{atm} - P_{H2O} - PaO_2 - PaCO_2$ *(*PaO_2 *and* $PaCO_2$ *in mmHg).*

Table 8.3 Basic characteristics of the study group at 5 years of age

	Total group (n = 98)
Males/females	60/38
Age (months)	62 (3.0)
Weight SD score	-0.5 (1.5)*
Height SD score	-0.4 (1.2)**
Weight for height SD score	-0.4 (1.4)***
Socioeconomic status (%)	
High	26 (27)
Normal	49 (50)
Low	19 (19)
Unknown	4 (4)
Ethnic group (%)	
White	85 (87)
African	3 (3)
Asian	1 (1)
Turkish or Moroccan	9 (9)

*Data presented as n (%) of patients or mean (standard deviation (SD)). The mean weight, height and weight for height (SD scores) for the entire population were all significantly below zero: * p = 0.001, ** p = 0.002, *** p = 0.008. Children with congenital diaphragmatic hernia had significantly lower height and weight than children with meconium aspiration syndrome (p < 0.001).*

Eleven children (11%) showed minor neurological dysfunction, varying from strength differences in the upper and lower extremities to very mild hemiplegia and a mild form of West syndrome (one child).

The mean (SD score) weight and height for the entire population were -0.5 (1.5) and -0.4 (1.2), respectively (Table 8.3). Both parameters were significantly below zero (p = 0.001 and p = 0.002, respectively).

Eighteen children (18%) had respiratory complaints. Twelve of them regularly used a combination of β-sympathicomimetic drugs and inhalation steroids. None of the children needed supplemental oxygen. Two of the total population were followed because of a muscular ventricular septal defect, without hemodynamic consequences; one because of atrial septal defect. One of the 20 children diagnosed with CDH was still on (nightly) tube feeding because of low weight (-3.4 SD) and pulmonary problems, and a second child had received tube feeding until his fourth birthday. The child who was known with unbalanced translocation of chromosome 11 - 22 was fed through a gastrostomy drain and had undergone a Nissen fundoplication because of gastro-esophageal reflux. Another child, not diagnosed with CDH, was also fed via a gastrostomy drain.

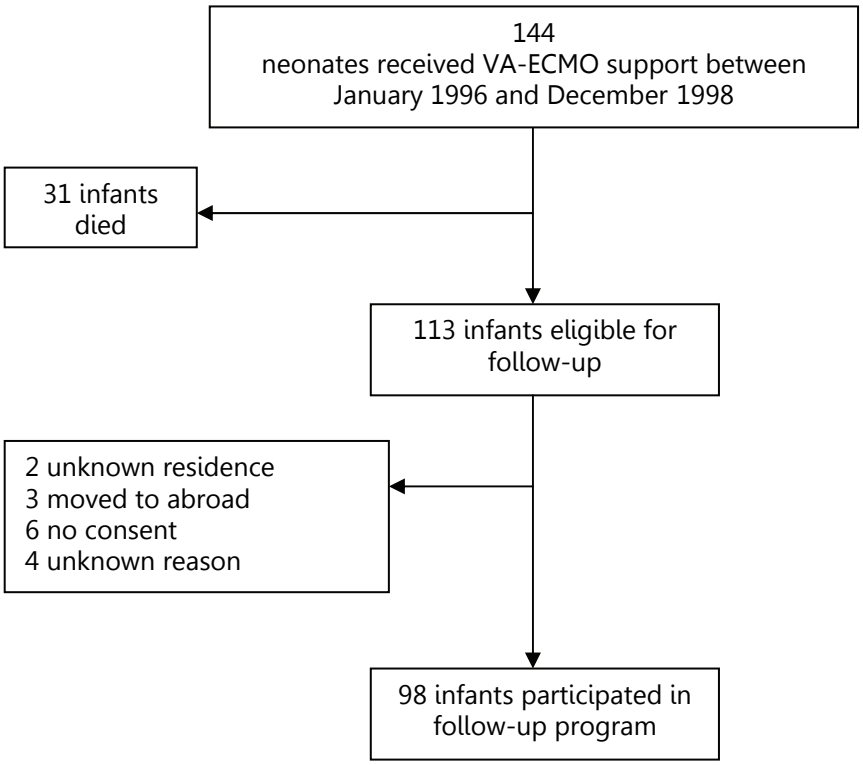


Figure 8.1 *Flowsheet of infants included in the follow-up program. VA-ECMO, veno-arterial extracorporeal membrane oxygenation.*

Outcome neuromotor assessment

Excluding the six children with major neurodevelopmental disability, 92 of the 98 children were tested using the M-ABC. Twenty-four children (26.1%) were classified as having some kind of motor difficulty (percentile score < P15), which represents a significantly higher proportion than expected (chi-square test, $p < 0.005$).

Fourteen children (15.2%) had scores indicative of a motor problem (percentile score < P5) (chi-square test, $p < 0.001$), 10 children (10.9%) had borderline performance (percentile score < P15 but > P5), and 68 children (73.9%) performed normally (percentile score > P15) (Table 8.4).

Table 8.4 Movement assessment battery for children results

	Total group (n = 92)^	**MAS (n = 49)**	**CDH (n = 19)**	**Sepsis (n = 11)**	**PPHN (n = 12)**
Total impairment score (mean (SD))	8.4 (8.1)*	6.8 (6.6)	13.4 (10.3)	7.5 (7.5)	7 (7.1)
Score < P5, motor problem (n (%))	14 (15.2%)**	3 (6.1)	7 (36.8)	1 (9.1)	2 (16.7)
Score P5 - P15, borderline (n (%))	10 (10.9%)	3 (6.1)	4 (21.1)	2 (18.2)	1 (8.3)
Score > P15, normal (n (%))	68 (73.9%)***	43 (87.8)	8 (42.1)	8 (72.7)	9 (75.0)

*^Including congenital cystic adenomatoid malformation of the lung (n = 1) with score < P5, *t-test: significant, p < 0.001, **Chi-square test: significant, p < 0.001, *** Chi-square test: significant, p < 0.005, MAS = Meconium aspiration syndrome, CDH = Congenital diaphragmatic hernia, PPHN = Persistent pulmonary hypertension of the newborn, SD = standard deviation.*

A comparison with population norms revealed that the mean (SD) M-ABC score of the total group was significantly below the reference value: 8.4 (8.1) versus 5.2 (5.6) ($p < 0.001$).[18]

Twenty-nine of the 35 children seen in Rotterdam performed the exercise test according to the Bruce protocol (Table 8.5). Five children with major neurological impairment could not perform the test. One child (diagnosed with CDH) was too anxious to use the treadmill and performed a six-minute walking test instead. The height and weight of the 29 children (15 boys) were expressed as SD scores. These did not differ significantly from the reference value (SD = 0) and there were no significant differences between boys and girls. Comparison of endurance times with the Canadian norms reported by Cumming and colleagues[215] revealed a significantly lower mean (SD) endurance time for the boys: 9.0 (1.2) versus 10.4 (1.9) ($p < 0.005$). The mean endurance time for the girls was not significantly different: 9.2 (1.8) versus 9.5 (1.8) ($p = 0.6$).

Outcome neuropsychological assessment

To create a mutually comparable group, three children with chromosomal or syndromal abnormalities as well as 11 children who did not speak Dutch as their native language and one child with severe hearing problems were excluded from data analysis. In 1 child no neuropsychological tests could be performed, leaving 82 children for analysis. For three children all data on cognitive development were missing. Three children could not be successfully tested on expressive language, and one child could not be tested either on expressive or on receptive language. Visual-motor integration in Rotterdam was tested in 28 out of 35 children. Major neurological impairment precluded testing in five children and the data of two other children were missing. The neuropsychological outcome data are presented in Table 8.6.

Cognitive development

Eleven children (14.1%) showed cognitive delay. The mean RAKIT score of the total group (IQ = 100.5) did not differ significantly from the Dutch norm.

Table 8.5 Exercise test

	Total group (n = 29)	**Boys (n = 15)**	**Girls (n = 14)**
Endurance time (minutes) (mean (standard deviation))		9.0 (1.2)*	9.2 (1.8)
Less than -2 SD, abnormal (n (%))	1 (3.4%)	0	1
-1 SD to -2 SD, suspect (n (%))	8 (27.6%)	7	1
Greater than -1 SD, normal (n (%))	20 (69.0%)	8	12

*Score according to Cumming and colleagues.[21] *t test: significant, p < 0.001.*

Table 8.6 Neuropsychological outcome

	Total group (n = 82)
Intelligence quotient (n = 79)	100.5 (19.7)
70 – 85	4 (5.1)
51 – 70	3 (3.9)
≤ 50	4 (5.1)
Expressive language (n = 78)	
Grammar	104.2[a] (17.9)
70 – 85	11 (14.1)
51 – 70	2 (2.6)
≤ 50	--
Vocabulary	103.2 (19.6)
70 – 85	6 (7.8)
51 – 70	5 (6.5)
≤ 50	2 (2.6)
Receptive language (n = 81)	104.3[a] (15.3)
70 – 85	1 (1.2)
51 – 70	5 (6.1)
≤ 50	--
Visual - motor integration (n = 28)	96.6 (13.7)
70 – 85	7 (25)
51 – 70	--
≤ 50	--

Data presented as the mean (standard deviation) or as n *(% of total number).* [a] *Significant difference (p < 0.05) from the Dutch population norm.*

Language development

In the expressive language test, 13 children (16.7%) scored ≥ 1 SD below the norm on grammar and vocabulary. In the receptive language test, six children (7.3%) scored ≥ 1 SD below the norm. The mean scores on grammar and receptive language were significantly above the Dutch norm.

Visual-motor integration

Seven children (25%) scored ≥ 1 SD below the norm. The mean score of the total group did not differ significantly from the Dutch norm.

Behavior

The results of the Child Behavior Checklist are presented in Table 8.7. Of all children, 10.5% had a total problem score above 63, indicating behavioral problems. Internalizing problems occurred slightly more than did externalizing problems.

Table 8.7 Child Behavior Checklist (n = 86)

Total problem score	
< 60	72 (83.5)
60 - 63	5 (5.9)
> 63	9 (10.5)
Internal problem score	
< 60	72 (83.7)
60 - 63	7 (8.1)
> 63	7 (8.1)
External problem score	
< 60	76 (88.4)
60 - 63	6 (7.0)
> 63	4 (4.7)

Data presented as number of patients (%). The internal scale includes withdrawn behavior, somatic complaints without physical cause, and anxious-depressive feelings. The external scale includes aggressive and delinquent behavior. Scores ≥ 60 but < 63 are in the borderline range. Scores ≥ 63 are in the clinical range.

Discussion

The present report presents nationwide neurodevelopmental sequelae of 98 veno-arterial ECMO-treated neonates at age 5 years (87% of all survivors). Seventeen children (17%) presented with major or minor neurological disorders. Another 24 children (26.1%) of the children who participated in the neuromotor assessment presented with some kind of motor difficulty, 14 of whom (15.2%) had an actual motor problem and 10 of whom (10.9%) were at risk for a motor problem. Cognitive delays were identified in 11 children (14% of 82 analyzed children).

Two of the 17 children with neurological disability had a chromosomal disorder accounting for neurological impairment, and one child had West syndrome associated with mental retardation and seizures. Four of the remaining 14 patients (14%) had major neurological impairment and 10 children had minor neurological impairment without an underlying disorder. Our findings seem not completely consistent with findings reported by Glass and colleagues[174] in 103 children: 17% of children in that study had one or more major disability versus 14% in our group. Glass and colleagues, however, ranked mental disability, as well as motor disability and seizure disorders, also under major disability. Had we included children who scored abnormal in the medical assessment, motor assessment, or mental assessment as well, we would have found a similar proportion (17%).

The UK ECMO Trial Group has reported on the outcome of ECMO-treated neonates at age 4 years.[34] A consistent comparison is hampered by the fact that methods were

different. In the United Kingdom one pediatrician assessed the children in six clinical domains, including cognitive ability, neuromotor skills, general health, behavior, vision, and hearing. Nineteen per cent of the children had test scores outside the normal range. With regard to 'disability', 13% of the children were moderately to severely disabled, which is consistent with the 14% we report.

The rate of motor difficulties in our cohort was 26% (score < P15); 15% of the children had an abnormal motor score (score < P5). This 15% we found exceeds the 6% reported by Glass and colleagues.[174] Unfortunately, few follow-up studies have used standardized tests such as the M-ABC to assess neuromotor outcome. Even in our study some of the children with minor motor difficulties were assessed normal at neurological examination. In the M-ABC assessment, however, the children are stressed to move under velocity or accuracy demands. Such circumstances are more sensitive to detect motor performance problems. It is essential, therefore, that professionals with specific experience should assess the developmental domains in the context of a structured follow-up program.

In our study 29 children performed a maximum exercise test. The maximal endurance time was used as the criterion of exercise capacity, and we compared outcomes with the data presented by Cumming and colleagues.[110] Binkhorst and colleagues in 1992 published references values for normal exercise performance in Dutch boys and girls aged 4 - 18 years using the Bruce treadmill protocol.[46] The authors included few 4 year olds and the number of 6 year olds is unclear, however, and they did not provide means and SDs for these ages. This is why we did not use these Dutch reference values. Nevertheless, 41% of the children in our study would score below the 5th percentile according to these Dutch reference values. The question is whether this can be explained by impaired physical condition of ECMO-treated patients or by the fact that the reference values established by Binkhorst and colleagues insufficiently reflect the exercise performance of contemporary healthy Dutch children. Future studies are needed and will be performed in Erasmus MC-Sophia Children's Hospital in the near future.

Follow-up at age 5 is important because children are in their first year or second year of primary school, at the start of their further school career. Eleven children (14%) showed cognitive delay, a proportion comparable with that reported by Glass and colleagues (13%). The IQ summary scores are comparable as well: 100 in our cohort versus 96 in their study. Although in the UK ECMO trial cognitive ability at age 4 did not show evidence of a difference between the two trial groups, 23% of ECMO-treated children showed cognitive delay (defined as IQ greater than -1 SD).[34]

Behavioral problems beyond the clinical cutoff point were identified in 11 children in our cohort. These problems might contribute to school failure, even in the absence of cognitive delay.[459]

Language development scores were all above population norms. Children without Dutch as their native language who had difficulty understanding and speaking Dutch were, however, excluded from these tests. Still, language development seems unaffected.

In the absence of a matched control group it remains difficult to establish to what extent ECMO treatment contributes to the outcome. The UK ECMO trial did show a benefit of ECMO based on the primary outcome of death or severe disability. Children were assessed at age 4 in six different domains (cognitive ability, neuromotor skills, general health, behavior, vision, and hearing). The trial defined outcome as normal, impaired, or disabled on the basis of the degree of functional loss in any of the domains. There was no evidence of significant difference regarding cognitive ability and motor disability between the conventional treatment and ECMO groups. The overall rate of moderate disability in the conventional group was 11% versus 13% in the ECMO group. Severe disability was only reported in the ECMO group (that is to say, 3%).[34] The rate of disability (that is to say, cerebral palsy) reported in a study of 89 surviving children with moderate to severe perinatal asphyxia at age 8 years was 15%. Ten per cent of children had profound cognitive delay.[361] The intelligence quotient in a group of non-disabled children with mild and moderate perinatal asphyxia was 106 (± 14).[361] These proportions are in the same range as the proportions reported in the present study.

Since all infants received veno-arterial ECMO, would veno-venous ECMO improve cognitive or neuromotor outcome? When using the Extracorporeal Life Support Organization Registry,[142] no significant difference in primary outcome between veno-venous ECMO and venoarterial ECMO has been reported.[384]

Conclusion

The outcome figures of ECMO-treated neonates at follow-up at age 5 years presented in the present study show considerable morbidity, but they do not greatly differ from those reported in previous publications on ECMO-treated neonates.[34,174] The high response rate of 87% (versus 61% by Glass and colleagues[174]) was feasible for various reasons: cooperation between two centers, small traveling distances, as well as the quality of the health care system in the Netherlands. We believe that a successful follow-up program of severely ill neonates should be structured in consultation with representatives from different disciplines, such as a pediatrician, a psychologist, a pediatric physiotherapist, and a speech therapist. Further longitudinal follow-up studies will focus on the relationship between neonatal status and test results at 5 years and on detailed analysis of the different domains. Within the framework of the nationwide follow-up program, longitudinal data at ages 8 and 12 years are expected to become available in due time.

Impact of a child with congenital anomalies on parents (ICCAP) questionnaire; a psychometric analysis

There will come a time when a diseased condition of the soul life will not be described as it is today by the psychologists,
But it will be spoken of in musical terms,
As one would speak, for instance, of a piano that was out of tune

Rudolph Steiner (1861 -1925)

ABSTRACT

Background

The objective of this study was to validate the Impact of a Child with Congenital Anomalies on Parents (ICCAP) questionnaire. ICCAP was newly designed to assess the impact of giving birth to a child with severe anatomical congenital anomalies (CA) on parental quality of life as a result of early stress.

Methods

At 6 weeks and 6 months after birth, mothers and fathers of 100 children with severe CA were asked to complete the ICCAP questionnaire and the SF36. The ICCAP questionnaire measures six domains: contact with caregivers, social network, partner relationship, state of mind, child acceptance, and fears and anxiety. Reliability (i.e. internal consistency and test-retest) and validity were tested and the ICCAP was compared to the SF-36.

Results

Confirmatory factor analysis resulted in 6 six a priori constructed subscales covering different psychological and social domains of parental quality of life as a result of early stress. Reliability estimates (congeneric approach) ranged from 0.49 to 0.92. Positive correlations with SF-36 scales ranging from 0.34 to 0.77 confirmed congruent validity. Correlations between ICCAP subscales and children's biographic characteristics, primary CA, and medical care as well as parental biographic and demographic variables ranged from -0.23 to 0.58 and thus indicated known-group validity of the instrument. Over time both mothers and fathers showed changes on subscales (Cohen's d varied from 0.07 to 0.49), while the test-retest reliability estimates varied from 0.42 to 0.91.

Conclusions

The ICCAP is a reliable and valid instrument for clinical practice. It enables early signaling of parental quality of life as a result of early stress, and thus early intervention.

INTRODUCTION

About 2 - 3% of newborn children exhibit major anatomical congenital anomalies (CA). Most of these are life-threatening unless surgically corrected.[396] Presentation may be isolated or as part of a spectrum of multiple congenital anomalies (MCA). Examples are intestinal atresia, abdominal wall defects, congenital diaphragmatic hernia (CDH), anorectal malformations and Hirschsprung's disease. Advances in surgery and peri-operative care have reduced mortality (apart from CDH) to approximately 10%.[210] This, however, has caused much more morbidity, with effects possibly extending into adulthood and placing a heavy burden on patients and parents, as well as on healthcare.[59,208,340] Earlier research by our group and others has shown that prenatal identification of CA can have considerable impact.[229,231,265,281] Therefore, it is presumed that postnatal impact of a child with CA may be even more striking and longer lasting.

Thinking about the serious consequences of (M)CA may induce a process of parental mourning. Abandoning expectations of a healthy child, parents must prepare themselves for raising a child being severely ill, either temporarily or life-long.[320] Children with CA face many problems, including multiple surgical interventions, long neonatal hospitalization, and often uncertainty about future quality of life. Delay in establishing the definitive picture of associated anomalies or the diagnosis of a syndromal pattern of malformation may even heighten parental insecurity, notably in the case of MCA.

While empirical research has evaluated parental burden experienced one year after the birth of a child with CA,[228] little is known of parental adaptation during the first six months. The early stage is likely to be the most stressful period for parents. Many studies employed structured interviews and generic questionnaires at a later stage, not specifically geared to the particular situation of parents of a child with MCA.[63,76,117,228,293,365] An example of a generic questionnaire is the General Health Questionnaire.[176,257] The Perinatal Grief Scale[230,413] on the other hand is an example of a questionnaire developed for a specific condition, in this case grief. Nevertheless, none of the available instruments is specifically geared to the particular situation of parents with a malformed child. The more so because generic questionnaires lack specific domains of impact on parental burden, such as 'social support' and 'contact with caregivers'. In other words, parents will not recognize their specific situation in these generic questionnaires. Therefore, we constructed a new questionnaire designed to evaluate parental early stress and quality of life in the first 6 months after the birth of a child with (M)CA, the Impact of a Child with Congenital Anomalies on Parents (ICCAP) questionnaire. The intended use of the ICCAP is as an alert system to signal parents at risk of threatened quality of life.

We consider MCA patients and their parents to be a group that shares many characteristics. The ICCAP is specially targeted for this group because they are usually excluded from studies on outcome of neonatal intensive care.[139,187,457]

The aim of the study was the psychometric analysis of the ICCAP questionnaire as a potential tool for early intervention. It could be used in a clinical setting for early identification of parent-child couples who are most at risk for early stress.

METHODS

Study population

The Erasmus MC-Sophia Children's Hospital is a university hospital with a 15-bedded tertiary pediatric surgical intensive care unit (PSICU) in which all surgical specialties except open-heart surgery are represented. A multidisciplinary treatment, support and evaluation team is available for the management of children with MCA and their parents. Consecutive children with CA admitted to this PSICU from January 1999 to May 2001 were eligible for this study. Patients with meningomyelocele were excluded, because they already participated in the follow-up program of the multidisciplinary meningomyelocele team in our institution.

Assessments

Instrument to be psychometrically tested: ICCAP

The ICCAP questionnaire was constructed as a self-report questionnaire for parents of children with any kind of CA. As an initial step we reviewed relevant questionnaires on psychological and social functioning to identify applicable domains for assessing early parental stress and quality of life. The General Health Questionnaire[176,257] and Perinatal Grief Scale[230,413] were most relevant in identifying divergent theoretical domains. Subsequently, items were formulated fitting these theoretical domains and representing aspects insufficiently covered by existing questionnaires.

In order to ensure adequate content validity, four experienced pediatric intensivists involved in the management of MCA patients independently identified indicators associated with MCA-related parental early stress. Indicators were classified into six domains:

1. contact with caregivers, signifying contact with medical and paramedical personnel and psychosocial support services;
2. social network, signifying contact with friends and family;
3. partner relationship, signifying the relationship with the co-parent of the child;
4. state of mind, signifying the state of mind parents find themselves in as a result of the birth of the child;
5. child acceptance, signifying the way the child can be accepted as a part of the family, and
6. fears and anxiety, containing items describing fears, worries and anxiety about the immediate and long-term future of the child and the burden as experienced by both child and parent (see Table 9.3 for the contents of the items selected for each domain separately).

If required, items were rephrased to meet style criteria: unambiguous, concise, easily understandable and void of double negations. The original questionnaire comprised 82 items to be rated on a 5-point scale ranging from:

1. strong agreement;
2. agreement;
3. disagreement;
4. strongly disagreement, and
5. non applicable.

Non applicable was scored when for instance contact with caregivers had not taken place (at 6 months). Positively phrased items were recoded as follows: 1 = 5, 2 = 4, 3 = 2, 4 = 1, and non-applicability was recoded as '3'. Thus, higher scores indicate a higher quality of life.

Subsequently, the items which were formulated fitting the theoretical domains parental stress and quality of life were allocated to these six domains: an item pool of multiple-choice questions was constructed into a prototype questionnaire. Then, the prototype questionnaire was reviewed for comprehensibility by a panel composed of two psychologists (one is a methodologist and one wrote a thesis on parental burden and grief);[11] clinicians; selected PSICU nursing staff of the unit; and selected parents. Interviewing an additional group of 20 parents, our social worker then evaluated the questionnaire for face validity and comprehension. A number of questions were modified in the light of advice and comments from these quarters.

Instrument for validation: Short Form 36

The SF-36 is a generic health status questionnaire.[103,435,462] It consists of 36 questions organized into 8 domains:

1. physical functioning;
2. social functioning;
3. role limitations because of physical health problems;
4. role limitations because of emotional problems;
5. general mental health;
6. vitality;
7. bodily pain, and
8. general health.

It also contains two summary measures: physical health (including domains 1, 3, 7 and 8) and mental health (including domains 2, 4, 5 and 6). Total scores are linearly transformed to range from 0 to 100, with higher scores indicating a better-perceived health status. A generic measure, the SF-36 has proven useful in surveys of general and specific populations.

Background and medical variables

Table 9.1 lists the children's biographic characteristics, primary CA, and medical care as well as parental biographic and demographic variables used in the data analysis. Severity of disease was derived from the TISS (Therapeutic Intervention Scoring System) scores. The TISS is a well-known method of measuring factual intensity of nursing care in a hospital setting.[109,250] In our department TISS is used as a standard assessment score. (see Table 9.1)

Table 9.1 General characteristics of patients and parents

	n = 100	
Patients		
Female/male	41/59	
Gestational age (wks)	38 3/7*	(28 - 42 6/7)**
Birth weight (kg)	3.0*	(0.75 - 4.51)**
Primary anomalies		
Abdominal wall defect	17	
Congenital diaphragmatic hernia	13	
Small intestinal anomaly	32	
Esophageal atresia	15	
Anorectal malformation	4	
Hirschsprung's disease	5	
Miscellaneous	14	
Congenital anomalies (CA) per patient	2*	(1 - 7)**
Medical care		
Duration of first admission (days)	27.5*	(4 - 314)**
Total admission in first 6 months (days)	37*	(4 - 182)**
Period until complete diagnosis (days)	4*	(0 - 205)**
Medical appliances at discharge (number)	0*	(0 - 7)**
TISS ≥10 in first 6 months (days)	6*	(0 - 128)**
Parents		
Age mothers (yrs)	31*	(19 - 45)**
Age fathers (yrs)	33*	(23 - 50)**
Socioeconomic status		
Low	22	
Medium	55	
High	23	
CA in family	28	
Duration of parental relationship (yrs)	5*	(0.50 - 20)**
Single parents (mothers)	4	
Sibs at time of birth (number)	1*	(0 - 5)**

** = median, ** = range, TISS = Therapeutic Intervention Scoring System.*

Design

This is a prospective, longitudinal study comprising two measurement moments: 6 weeks and 6 months after the birth of the child.

Procedure

The Erasmus MC medical ethical review board approved the study. Parental written and signed informed consent was sought within the first week after an eligible child's birth. At both measurement moments parents were asked to complete two questionnaires: ICCAP and SF-36. Parent couples were explicitly instructed to complete the questionnaires independently. The questionnaires were either handed to parents on the ward or mailed to them after discharge of the child. Usually they were completed at home. When the questionnaires were not returned within two weeks, parents were telephoned once to remind them. Children's background and medical variables for assessing the child's condition and severity of disease were collected prospectively during admission and follow-up.

Data analysis

A priori we postulated six theoretical domains. As the sample size was relatively small, we attempted to identify the dimensional structure for each separate empirically operationalised domain. To that end we applied the model generating strategy, after first having performed exploratory factor analysis to get an impression of the dimensionality of the data structure. This provided a far from clear structure. The model generating strategy, however, pointed to a confirmatory factor analysis solution. The main advantages of the latter approach are:

1. identifying and testing for model fit;
2. flexibility of estimating the factor intercorrelations;
3. enabling to fix parameters to certain values;
4. relaxing parameter values to be free, and
5. enabling comparison of factor structures (in this study comparison of the two measurement moments).

Confirmatory factor analysis was applied for both measurement moments separately.
The following measures of model performance were used:

1. χ^2 –tests for model fit in addition to the p-value corresponding to the χ^2 –value (preferably p-value > 0.05);
2. χ^2 divided by the degrees of freedom (preferably < 2.0);
3. comparative fit index (CFI preferably > 0.95);
4. Tucker-Lewis index (TLI preferably > 0.95);
5. Root Mean Square Error of Approximation (RMSEA preferably < 0.05), and
6. Weighted Root Mean Square Residual (WRMR preferably < 1.00).

The standardized regression coefficient was used as a measure of relative importance for the individual variables. Variables used in the analysis were considered to be ordinal. Values were estimated using the weighted least square approach, applying a diagonal

weight matrix with robust standard errors and mean- and variance-adjusted χ^2 -tests. For items to be selected, they had to load substantially (≥ 0.50) on preferably one factor. Also, all items loading onto the same factor had to be conceptually homogeneous.

For all subscales reliability was investigated using:

1. parallel estimates;
2. tau-equivalent estimates, and
3. congeneric estimates.[186,242]

If the squared loadings and the residual variances were equal, parallel estimates were allowed. If only the squared loadings are equal, tau-equivalence was allowed. If neither squared loadings nor the residual variances were equal, congeneric reliability was indicated. With congeneric measures, the reliability coefficient of the scale score equaled the summation of squared factor loadings for that scale, divided by the summation of squared factor loadings plus the summation of error variances.[352,355] For stability of the instrument test-retest reliabilities of the six empirically constructed scales were estimated.

To evaluate congruent validity of ICCAP, the two summary measures of the SF-36 were correlated with the domains of ICCAP using Spearman's rank order correlation coefficient (r_s).

Likewise, to evaluate known-group validity, the background variables were correlated with the ICCAP domains. Confidence intervals (95%) were calculated for the correlation coefficients. No correlation was expected with background variables, except with those associated with severity of illness.

Concerning change over time (sensitivity to change and parental (dis)congruence): a measure for the probability of difference is presented, symbolized by the p-value (two-tailed), as well as a measure of the magnitude of change, symbolized by (Cohen's) d-measure of discrimination. A p-value below 0.05 indicates that the change is beyond chance level. In other words, in case of $p < 0.05$ the change is at least 1.96 x the standard error, signifying real change and not measurement instability. Cohen's d (rule of thumb: small = 0.20, moderate = 0.50 and high = 0.80) was used to indicate the magnitude of the differences between mothers and fathers at both measurement moments.[96]

For correlations the rule of thumb for effect size provided by Cohen[96] was used: low = 0.10, moderate = 0.24 or high = 0.37.
Wilcoxon signed ranks test was used to determine significance for paired samples for ICCAP.
All statistical testing was performed at the 0.05 level of significance (two-tailed).
The software programs SPSS 14.0 for Windows and Mplus version 4.1[317] were used.

RESULTS

General characteristics

From January 1999 to May 2001 a total of 159 eligible consecutive patients were admitted. Parents of 59 children did not participate for the following reasons: 13 children (8%) died before or shortly after study inclusion; in 16 cases (11%) parents lacked sufficient command of the Dutch language; and in 30 cases (19%) parents refused to participate for various reasons. Thus, parents of 100 children participated in the study, i.e. returned both questionnaires for at least one of the two measurement moments. This resulted in notably less than 100 repeated measurements as shown in Figure 9.1. Four children had single mothers.

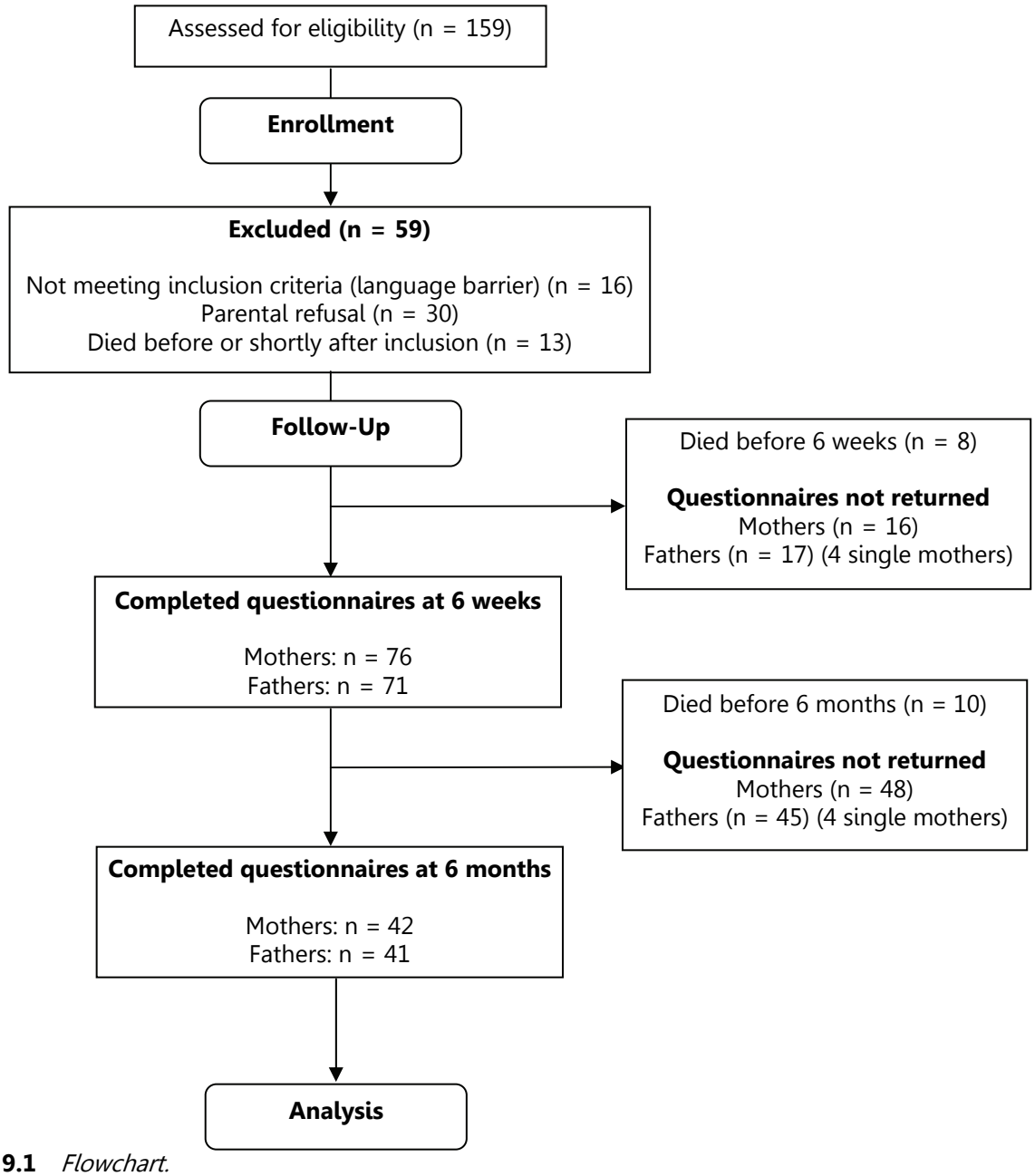


Figure 9.1 *Flowchart.*

Characteristics of children and parents are presented in Table 9.1. Diagnoses were equally distributed between the participating and non-participating groups, except for CDH, which was overrepresented in the non-participating group due to early deaths (10 out of 13 deaths).

Gestational age and birth weight were mostly within the lower range of normal. Forty percent of the children were still hospitalized at 6 weeks. Median duration of the first admission was 27.5 days; and median number of days on which TISS scores were ≥ 10 was 6. Most children (80%) were discharged before the age of 6 months.

ICCAP structure determination

Confirmatory factor analysis was used to test the à priori assumption of a 6-factor model and expectations about which variables load onto which factors were tested likewise. The four factor analyses across time for both parents individually turned out to be similar within random fluctuation and resulted in a 6-factor solution with a total of 36 items contributing significantly to the empirical solutions. The remaining 46 items were deleted: some items overlapped; others did not fit any of the 6 factors; and some items with ambivalent phrasing were removed. The model performances for both parents across time appeared to be clinically satisfactory. Although the χ^2 -values turned out to be significant, yet the values of χ^2 divided by the degrees of freedom were adequate (see Table 9.2). Also, CFI and TLI values were adequate, whereas RMSEA values were less satisfactory. The performance measure WRMR, most important performance measure for ordinal data, was clinically acceptable (see Table 9.2).

Table 9.3 presents standardized factor loadings of the models identified for both parents for 6 weeks and 6 months respectively: most of these loadings exceeded the value of 0.70.

Scores were linearly transformed to range from 0 to 100 with higher scores indicating a better-perceived status, analogous to the transformation as applied to SF-36 scales.

Scale reliability

Congeneric scale reliability estimates were used, since factor loadings as well as the residual variances differed. Table 9.4 shows these reliability estimates for the six ICCAP domains at both measurement moments for both parents. Reliability estimates ranged from 0.49 to 0.92. On average reliability estimates did not show major differences across time for mothers or fathers. However, reliability estimates did differ for the different domains. The reliability estimate of the domain partner relationship was highest (mean: 0.87), with lower reliabilities of social network, fears and anxiety and state of mind (mean: around 0.58) (see Table 9.4). Test-retest reliabilities for the six scales turned out to be satisfactory, with values varying from 0.42 (contact with caregivers) to 0.91 (fears and anxiety).

Table 9.2 Performance measures of model fit

	6 weeks		6 months	
	Mothers	**Fathers**	**Mothers**	**Fathers**
χ^{2} [I]	96.51	101.93	51.11	59.01
df [II]	41	39	27	26
p [III]	0.001	0.001	0.003	0.001
χ^{2}/df	2.35	2.61	1.89	2.27
CFI [IV]	0.92	0.92	0.94	0.94
TLI [V]	0.94	0.94	0.94	0.94
RMSEA [VI]	0.13	0.15	0.15	0.18
WRMR [VII]	1.07	1.15	1.00	1.07

I χ^{2}*-test is a measure of model fit,*
II df indicates degrees of freedom of χ^{2}*-test,*
III p-values of the χ^{2}*-test,*
IV CFI = Comparative Fit Index,
V TLI = Tucker – Lewis Index,
VI RMSEA = Root Mean Square Error of Approximation,
VII WRMR = Weighted Root Mean square Residual.

Congruent validity

Moderate to high correlations, ranging from 0.34 to 0.77, were found between state of mind and the SF-36 summary measures for both mothers and fathers, at 6 weeks and, more outspoken, at 6 months. In addition, fears and anxiety for both parents appeared to be substantially related to the SF-36 mental component scale, with correlations ranging from 0.30 to 0.43.

Known-group validity

Moderate to high correlations with mostly child-related background variables were found for fears and anxiety for both parents at 6 weeks and 6 months, with coefficients ranging from -0.30 to -0.58 and to a lesser extent for state of mind for mothers at 6 weeks, ranging from -0.23 to -0.41. These significantly correlated background variables were mainly related to severity of illness of the child, and included duration of admission and number of medical appliances at discharge.

A significant negative correlation (r_s) was found between parental age and partner relationship (-0.35 to -0.45) at 6 months for both parents. Acceptance of the child at 6 months turned out to be negatively correlated with duration of parental relationship for both parents (-0.35 and -0.40). For fathers, contact with caregivers showed significant positive correlations with gestational age at both measurement moments (0.29 for 6 weeks and 0.53 for 6 months).

Table 9.3 Standardized factor loadings

ICCAP dimensions	Item	6 weeks		6 months	
		Mothers (n = 76)	**Fathers** (n = 71)	**Mothers** (n = 42)	**Fathers** (n = 41)
Contact with caregivers					
Doctors clearly explain things	17	0.94	0.77	0.94	0.99
I have good interaction with nurses	18	0.74	0.95	0.70	0.60
Doctors take enough time to listen to me	20	0.74	0.95	0.94	0.99
I am satisfied about my contacts with doctors	32	0.74	0.95	0.86	0.97
Social network					
My friends support me	2	0.78	0.82	0.79	0.90
My colleagues are understanding	11	0.68	0.54	0.68	0.49
People around me support me	19	0.82	0.90	0.72	0.95
My friends help me with practical things	21	0.62	0.81	0.75	0.67
I can share worries with my family	29	0.76	0.61	0.59	0.69
I can share worries with good friends	33	0.91	0.98	0.84	0.63
Partner relationship					
I feel my partner sympathizes with me	1	0.94	0.86	0.89	0.87
On important issues I agree with my partner	7	0.98	0.93	0.96	0.86
My partner is someone I can talk to	8	0.98	0.81	0.93	0.99
Generally I am happy with my partner	12	0.96	0.99	0.94	0.96
My relationship with my partner is good	14	0.94	0.99	0.91	0.93
State of mind					
I feel sad	3	0.99	0.89	0.78	0.86
I feel angry	16	0.87	0.89	0.94	0.74
I wonder whether I am to blame for my child's CA	22	0.46	0.70	0.35	0.42
I feel guilty	34	0.61	0.89	0.57	0.88
Child acceptance					
My child fits into my life	26	0.87	0.81	0.99	0.85
My child is welcome in our family as it is	31	0.69	0.79	0.90	0.89
I am happy with my child	35	0.99	0.87	0.96	0.84
I wish my child was never born	36	0.70	0.63	0.80	0.14
Fears and anxiety					
My child faces a difficult life	4	0.62	0.57	0.70	0.89
I expect my child will be able to function well	5	0.85	0.74	0.96	0.79
The CA is/are a heavy burden on my child	6	0.76	0.87	0.73	0.59
I wonder whether my child will ever be healthy	9	0.80	0.85	0.61	0.77
I am very anxious about all the tests on my child	10	0.73	0.46	0.37	0.59
My child is facing a difficult period	13	0.86	0.82	0.86	0.91
My child is the same as other children	15	0.61	0.84	0.65	0.70
I worry a great deal about my child's health	23	0.79	0.74	0.87	0.79
I doubt whether my child will be happy later	24	0.72	0.91	0.90	0.88
I fear about my child's expectations for the future	25	0.85	0.90	0.90	0.83
My child is handicapped	27	0.72	0.69	0.68	0.80
I feel I can't do enough for my child	28	0.74	0.59	0.75	0.74
My child will be able to have a normal life later	30	0.80	0.87	0.76	0.91

Sensitivity to change

Over time ICCAP showed change for mothers and fathers, mainly on the parental relationship domain, with Cohen's d of -0.47 and -0.49, respectively (see Table 9.5). Significant positive change over time was found for fears and anxiety, in paired measurements, for both parents (mothers: Wilcoxon test, z = -1.99, p = 0.04, n = 34, fathers: z = -2.37, p = 0.02, n = 34). Negative change was found for partner relationship (mothers: z = 1.90, p = 0.03, n = 33, fathers: z = 1.92, p = 0.03, n = 34) (see Table 9.5).

Parental (dis)congruence

Table 9.5 shows comparable ICCAP scores for fathers and mothers, indicated by low Cohen's d (< 0.20), both at 6 weeks and at 6 months, with the exception of state of mind (d = 0.27 and 0.37, respectively). The higher levels of agreement for both parents were reached on acceptance of the child and partner relationship, with lower agreement between parental levels on fears and anxiety, contact with caregivers and social network.

At 6 weeks paired measurements showed significant differences between parents for two domains: contact with caregivers (Wilcoxon test: z = 1.55, p = 0.04, n = 65) and fears and anxiety (z = -2.01 p = 0.04, n = 69), and at 6 months for state of mind only (z = -2.53, p = 0.04, n = 41).

Both fathers and mothers clearly perceived lower quality of life than the norm group, particularly on the SF-36 mental component scale (see Table 9.5). At 6 weeks fathers of children with CA had higher scores than the norm group on the physical component scale although at 6 months scores had decreased to slightly below the norm.

Mothers perceived lower quality of life than did fathers, both at 6 weeks and 6 months. The physical component scale shows the greatest discrepancy between parents at 6 weeks.

Table 9.4 Reliabilities i.e. congeneric estimates of the six subscales of the ICCAP

		6 weeks		6 months	
ICCAP dimensions	**n° of items**	**Mothers**	**Fathers**	**Mothers**	**Fathers**
Contact with caregivers	4	0.63	0.83	0.75	0.82
Social network	6	0.59	0.63	0.54	0.55
Partner relationship	5	0.92	0.84	0.86	0.85
State of mind	4	0.58	0.72	0.49	0.56
Child acceptance	4	0.68	0.60	0.84	0.56
Fears and anxiety	13	0.58	0.59	0.58	0.63

Table 9.5 SF-36 and ICCAP distinguished by parent across time

	6 weeks							6 months							6 weeks - 6 months	
	Mothers			**Fathers**				**Mothers**			**Fathers**				**Mothers**	**Fathers**
ICCAP	$\bar{x}$	sd	n	$\bar{x}$	sd	n	d*	$\bar{x}$	sd	n	$\bar{x}$	sd	n	d*	d*	d*
Contact with caregivers	78.63	15.94	72	75.57	21.15	68	-0.16	75.39	15.81	36	76.97	15.39	38	0.10	-0.20	0.07
Social network	76.39	16.38	73	73.75	19.71	69	-0.15	73.30	14.99	38	71.36	17.53	38	-0.12	-0.19	-0.13
Partner relationship	89.88	13.53	72	89.58	13.27	71	-0.02	83.00	16.33	40	82.11	17.92	41	-0.05	-0.47	-0.49
State of mind	68.15	22.49	75	74.29	23.86	70	0.27	71.76	21.08	42	79.20	18.79	41	0.37	0.16	0.22
Child acceptance	92.00	12.65	76	90.77	11.80	71	-0.10	89.35	15.59	42	88.96	13.66	40	-0.03	-0.19	-0.14
Fears and anxiety	61.74	22.98	74	64.37	21.44	70	0.12	66.70	23.06	42	67.08	22.99	41	0.02	0.22	0.12
SF36																
PCS ($\bar{x}$ = 83.4; sd = 24.1)‡	76.67	19.90	68	85.24	14.81	64	0.49	76.69	20.59	79	83.18	22.03	71	0.30	0.00	-0.11
MCS ($\bar{x}$ = 81.4; sd = 21.3)‡	62.68	20.76	68	67.02	23.74	64	0.20	64.56	21.93	79	72.27	23.99	71	0.34	0.09	0.22

*$\bar{x}$ = Mean, sd = standard deviation, * Cohen's d was used where the standard deviation was pooled, PCS = Physical Component Scale, MCS = Mental Component Scale, ‡ Population norms: n = 221, age 25 - 34 (24).*

DISCUSSION

The purpose of this study was to validate a new questionnaire designed to measure the impact of early stress on quality of life of parents confronted with a newborn baby showing severe birth defects. From confirmatory factor analysis it appeared feasible to reduce a first 82-item version to 36 items in a 6-domain model. The number of items per domain range from 4 to 6, except for fears and anxiety, which contains 13 items. We felt this domain is best geared to detect impact in this specific group of parents, and may therefore carry heavier weight.

In this study we established three kinds of validity, i.e. congruent validity, known-group validity, and sensitivity to change. First, concerning congruent validity, the ICCAP domain state of mind positively correlated with the SF-36 mental and physical component scales at both measurement moments and for both parents. The domain fears and anxiety similarly correlated with the mental component scale for both parents. For the other ICCAP domains correlations are less outspoken, implying that ICCAP and SF-36 measure different aspects of parental functioning. The theoretical and empirical constructs clearly differ. ICCAP aims to measure quality of life as a result of parental stress and is more differentiated than SF-36, whereas the latter aims to measure general quality of life. In conclusion, ICCAP gives additional specific information when used next to the SF-36.

Second, known-group validity is supported by the fact that severity-of-illness variables showed considerable correlations with state of mind and fears and anxiety. These correlations are consistent at both measurement moments with a slight decrease in magnitude at 6 months.

High parental age and longer duration of parental relationship were risk factors for parental relationship and child acceptance, respectively, for both parents.

Concerning sensitivity to change as a third measure of validation, the level of fears and anxiety felt for the child and its future appeared to decrease significantly over time for both parents. Two possible explanations present themselves. On the one hand, parents may have gained better understanding of what to expect in the future. On the other hand, the acute severity of disease and the child's discomfort will usually have abated over time. This sensitivity to change in ICCAP makes the instrument useful in a clinical setting, the more so as it could alert to changes in risk for early stress.

We also looked at parental (dis)congruence. On most domains there was parental congruence, increasing over time. This may be partly due to maternal physical recovery. Only on state of mind we observed parental discongruence increasing over time. Parental discongruence in parents of the same child on contact with caregivers and fears and anxiety disappears over time. This is replaced by discongruence in state of

mind. Discrepancies in reported impact by parents of the same child might be an indicator of impact, suggesting lack of communication, unequal burden and other possible disturbances in parental relationship.

ICCAP fits clinical practice very well, especially since the questions are easy to understand and completion takes only 10 minutes. It may also serve as a screening tool to identify parents in need of support from a psychologist or a social worker. Furthermore, we are in the process of developing a user-manual, presenting norms of larger CA population samples.

Our study has a limitation in that data assessed at 6 months are based on a relatively small sample size (n = 41 - 42). Larger sample sizes are needed to show whether these correlations might be of clinical significance. Further data collection and analysis of data are, however, part of ongoing investigation in our institute.

CONCLUSIONS

The ICCAP is a reliable and valid instrument for clinical practice. It enables early signaling of parental quality of life as a result of early stress. After cross validation of ICCAP in a new, larger, study group we will be able to determine ICCAP cut-off scores that signal high risk for early stress. Tailored interventions to ease the parental adaptation process can thus be evaluated.

Explorative study on the usefulness of the CBCL/1½-5 for children with major congenital anomalies at age 12 months

When the father actively compensates for limitations in the depressed mother's functioning, the child's risk of problem behaviors may be reduced

Jen Jen Chang et al. Arch Pediatr Adolesc Med. 2007

ABSTRACT

Objective
This study aims to assess the usefulness of the Child Behavior Checklist/1½-5 (CBCL/1½-5) for twelve-month-old children with major anatomical congenital anomalies.

Method
Mothers and fathers of 120 twelve-month-old children with congenital anomalies completed the Dutch version of the CBCL/1½-5. Experts gave their opinions on suitability of each of the items of the CBCL/1½-5 for twelve-month-olds. Mental and motor development was assessed with the Dutch edition of the Bayley Scales of Infant Development II (BSID-II-NL).

Results
Experts judged 21 of the 99 items unsuitable. Parents reported little problem behavior and inter-parent agreement was high. Mental development was correlated with problem behavior. Children with lower mental development showed more internalizing problem behavior.

Conclusion
The results of this study show that the CBCL/1½-5 is not suitable to assess problem behavior in these children at age twelve months.

INTRODUCTION

In the Netherlands 2 to 3% of infants are born with a major congenital anomaly (CA).[395] This condition typically involves hospitalization and surgical intervention at neonatal age, sometimes for extended periods. This may affect these children's development, quality of life and behavior.[340] As the traditional monospecialist approach was felt inadequate, a multidisciplinary follow-up team for these children – and their parents – was instituted in our department in 1999. Follow-up visits are scheduled at 6, 12 and 24 months and at 5 years. At all time points, parents complete questionnaires, and a pediatrician, a developmental psychologist and a consultant pediatric surgeon examine the children. Evaluation at age 5 years also includes assessment by a pediatric physiotherapist. One aspect of evaluation at 12 and 24 months is the child's behavioral development.

Young children develop at different rates, which is also reflected in their behavior.[41] Deviant behavior can be assessed by the American Psychiatric Association's Diagnostic and Statistical Manual (DSM),[16] or the Zero to Three Diagnostic Classification of Early Mental Disorders (DC: 0-3).[476] These assessments need to be performed by clinicians. Another instrument, the Child Behavior Checklist 1½-5 (CBCL/1½-5) does not require professional involvement but is based on proxy report by parents. It provides norm scores on a wide array of behavioral and emotional problem scales in children from 18 to 60 months of age.[354] The CBCL/1½-5 is an internationally well-accepted validated instrument to evaluate behavior in children of different cultural backgrounds. The CBCL manual advises against the use of the CBCL/1½-5 in children younger than 15 months.[3] Nevertheless, several researchers have aimed to extend the use of this instrument across the advised age limits, particularly because no validated instruments are available to assess behavior of younger children. For one, Van Zeijl et al evaluated the externalizing scale of the CBCL in a general population sample of 638 12-month-old infants.[441] They found a factorial structure that was comparable to the one found in 2 - 3 year old children. Furthermore, Briggs-Gowan et al. applied the CBCL/1½-5 in 12-month-old infants, but failed to comment on its feasibility in this age group.[64] Neither of these two studies evaluated the usefulness of the individual items.

In the current study we used the CBCL/1½-5 to evaluate children at 12 and 24 months of age and set out to evaluate its usefulness at ages 12 months. To this aim we compared scores for the same children at 12 and 24 months, and analyzed possible differences between fathers' and mothers' scores. Furthermore, we asked developmental psychologists to identify those items that, in their view, are not applicable to 12-month-old children. Finally, scores on the CBCL/1½-5 were compared with mental and psychomotor developmental scores collected within the context of our multidisciplinary follow-up program.

METHODS

Setting

The Erasmus MC-Sophia Children's Hospital is a university hospital with a pediatric surgical department in which all surgical specialties except open-heart surgery are represented. The long-term, multidisciplinary follow-up program as described above was initiated from this department in 1999.

Participants

From June 2003 to 15th of October 2006 a total of 258 children with a major congenital anomaly were eligible for inclusion in the follow-up program. Twenty-eight children died before the age of 12 months (corrected for prematurity). Parents of 123 children completed the CBCL/1½-5 at the child's age of 12 months. Three questionnaires were incomplete and excluded from analysis. Sixty-one of 120 parents also completed the CBCL/1½-5 at 24 months (corrected for prematurity). Figure 10.1 gives information about the sample size.

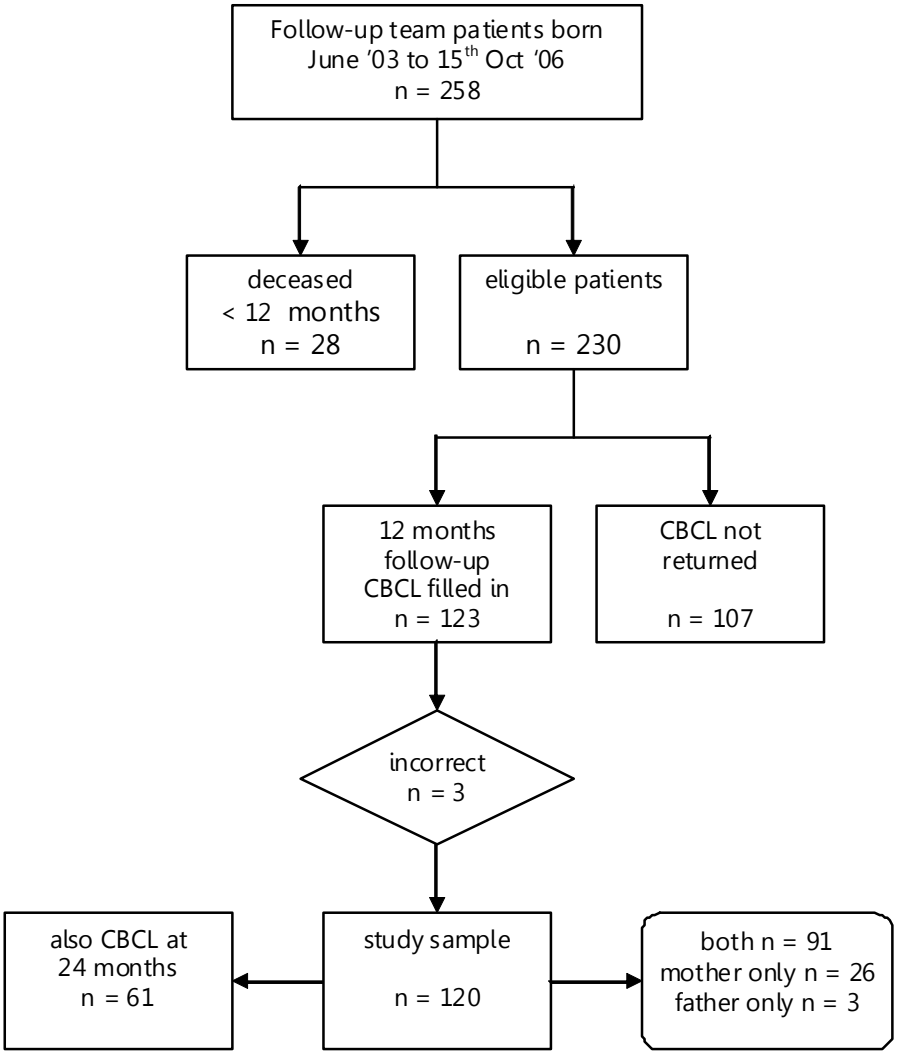


Figure 10.1 *Flowchart showing patient inclusion and response rate.*

The following categories of anomalies were distinguished:

1. small intestinal anomalies;
2. abdominal wall defects;
3. congenital diaphragmatic hernia;
4. esophageal atresia;
5. Hirschsprung's disease;
6. anorectal malformations, and
7. miscellaneous diagnoses (see Table 10.1).

Table 10.1 Background characteristics (n = 120)

	n	**%**
Sex (boy/girl)	68 / 52	56.7 / 43.3
Primary Congenital Anomaly		
Congenital diaphragmatic hernia	27	22.5
Small Intestinal atresia	22	18.3
Esophageal atresia	20	16.7
Miscellaneous	19	15.8
Hirschsprung's disease/anorectal malformation	17	14.2
Abdominal wall defect	15	12.5
Chromosomal or syndromal abnormality	9	7.5
Number of congenital anomalies per patient, median (range)	1 (1 - 8)	
Gestational age, median (range)	39.2 (28 - 42)	
Hospital stay in first 6 months in days, median (range)	26 (2 to 173)	
Social economic status		
Low	30	25.0
Middle	46	38.3
High	43	35.8
Unknown	1	0.8

Measures

CBCL/1½-5

The CBCL/1½-5 consists of 99 closed questions about emotional and behavioral problems and one open question informing after other problems. The closed questions have been classified into seven subscales. The four subscales Emotionally reactive, Anxious/depressed, Somatic complaints and Withdrawn form the 'Internalizing' scale. The two subscales Attention Problems and Aggressive behavior form the 'Externalizing' scale. The seventh scale is the Sleep problems scale. Summation of the scores on the seven subscales including any additional problems entered by the respondent for the open-ended item yields the Total Problems score. Raw scores are to be transformed into T-scores with a mean of 50 and a standard deviation (SD) of 10. Higher T-scores imply more problem behavior. For all scales, scores are classified into normal, subclinical

and clinical ranges. For the Internalizing and Externalizing scales: T-score < 60 is normal; T-score ≥ 60 and < 63 classifies children in the subclinical range; and a T-score ≥ 63 classifies children in the clinical range. Scores in the subclinical or clinical range may be reason to consider additional assessments or interventions.

Bayley Scales of Infant Development-Second Edition
The infants' mental and psychomotor development was assessed by the Bayley Scales of Infant Development–Second Edition–Dutch version (BSID-II-NL).[30,433] This test has been designed to evaluate developmental status in the first 42 months of life. Mental Developmental Indexes (MDI) and Psychomotor Developmental Indexes (PDI) were determined in relation to Dutch population norms with a mean score of 100 and a SD of 15. Scores were corrected for prematurity.

Procedure
Parents received two copies of the CBCL/1½-5 by mail some time before the scheduled evaluations at ages 12 and 24 months, corrected for prematurity. Parent couples were explicitly instructed to complete the questionnaires independently. Usually the questionnaires were completed at home and handed in at the follow-up visits. The developmental psychologist administered the BSID-II-NL during these visits.

Demographic and medical characteristics were collected prospectively from the first day of admission. Medical characteristics included total length of stay in the first 12 months and type of anomaly. Socioeconomic status (SES) was assessed according to Dutch classifications. It included 9 levels and was transformed into 3 ranges (low, middle and high SES).[397]

An expert team was composed consisting of 19 developmental psychologists with a minimum experience of 5 years, and known to use the CBCL/1½-5 on a regular basis. They are active either in the Erasmus MC-Sophia Children's Hospital or the department of medical psychology of the Reinier de Graaf hospital (Delft, the Netherlands). The experts were asked by mail to participate. At the same time, they were sent the CBCL/1½-5 scale and were asked to indicate the usefulness of the individual items for 12-month-old children. A return envelope was included to enhance compliance.

Data analysis
Scores on the CBCL/1½-5 questionnaires were entered in the Assessment Data Manager program of the Achenbach System of Empirically Based Assessment (ASEBA, Burlington, USA) and next exported to SPSS 15.0. Normally distributed variables are presented as mean and standard deviation (SD). Variables that deviate from normality are presented as median and minimum and maximum values. We created the following decision rule with regard to the expert opinions on usefulness of items: for an item to be not applicable, 50% or more experts should agree on its non-usefulness. This rule was

compared to the experts' individual opinions using Cohen's kappa. A kappa value of 0.61 or higher was considered to be acceptable.

Parental agreement was determined by calculating the standardized mean difference (Cohen's d). When this value is 0.2 or lower, the difference in level is considered minor.[95] If low, the parental mean score is used for further exploration. The Intra Class Correlation Coefficient is used to calculate the association between parental scale scores; alternatively, the quadratic weighted Cohen's kappa is used when CBCL/1½-5 scale values lack variation. CBCL/1½-5 scores at 12 and 24 months are compared by the Spearman's rank order correlation coefficient (r_s).

Pearson's product moment correlation coefficient served to estimate the linear association between Internalizing and Externalizing on the one hand and background and medical characteristics on the other hand

RESULTS

General characteristics

Table 10.1 gives the background characteristics of the 120 children included in the analysis. Nine children (7.5%) had a major chromosomal or syndromal abnormality and were at risk of severe psychomotor delay. Children's factual age at the 12-month evaluation varied between 12 and 15 months, 70% was exactly 12 months old. Factual age at the 24-month evaluation varied between 23 and 27 months, and 77% was aged between 23 and 25 months.

The group of 107 parents who did not complete the CBCL at 12 months included significantly more parents (one or both parents) who were non-native Dutch ($p < 0.001$, $n = 222$) and who tended to have a lower SES ($p = 0.061$, $n = 185$) compared to those who completed the CBCL. The distribution of diagnoses was significantly different for the responding and non-responding parents ($p = 0.03$). Among participating parents, those of a child with congenital diaphragmatic hernia were overrepresented (27 out of 39; 69.2%); those with a child with Hirschsprung's disease or an anorectal malformation were underrepresented (17 out of 49; 34.7%).

Behavioral outcome

Table 10.2 gives the mean scores on the CBCL/1½-5 scales and the BSID-II-NL for the 12- and 24-month-olds. At 12 months, 96% of the children have a normal score on the Internalizing scale; only two children were in the subclinical range and another two in the clinical range. Scores for all but one child on the Externalizing scale were in the normal range. The one child who scored in the clinical range on the Externalizing scale, also scored in the clinical range on the Internalizing scale. Three of the four children with behavioral problems (in the subclinical or clinical range) were characterized by

physical problems or eating problems, and received physiotherapy or speech therapy. At 24 months one child scored still in the clinical range on the internalizing scale and another child had clinical scores on both scales.

Parental agreement at 12 months

Parent couples of 82 children completed the CBCL/1½-5 at 12 months. As scores were predominantly in the normal range, the quadratic kappa was used to compare the three ranges (normal, subclinical and clinical) between fathers and mothers. Agreement ranged from 91%, $\kappa = 0.28$ for Somatic complaints to 100%, $\kappa = 0.74$ for subscales Anxious/Depressed and Aggressive behavior.

Comparison of scores at 12 months versus scores at 24 months

The differences between the mean scores on the Internalizing and Externalizing scales at 12 and 24 months are small (Cohen's d respectively 0.10 and 0.46.) The mean score on the total scale increased from 40 (SD 8) to 45 (SD 8) with a Cohen's d of 0.26.

For scores on the Externalizing and Internalizing scales, correlations between 12 and 24 months were 0.44 (95% CI 0.21 to 0.62, $p < 0.001$) and 0.39 (95% CI 0.15 to 0.58, $p = 0.002$) respectively. The Spearman's rank order correlation coefficient for scores at 12 and 24 months varied from 0.17 (95% CI -0.09 to 0.41, $p = 0.20$) for subscale Physical complaints to 0.59 (95% CI 0.40 to 0.73, $p < 0.001$) for Attention problems.

Factors predicting behavior

SES, sex, congenital anomaly and PDI score did not significantly influence scores on the Internalizing, Externalizing and Total Problems scales. Total length of stay in the first 12 months was moderately but significantly correlated with Internalizing and Total Problems scale, both $r = 0.20$ (95% CI 0.02 to 0.37, $p = 0.03$). The correlation between the CBCL Internalizing scale and the MDI mental developmental index score is -0.36 (95% CI = -0.52 tot -0.18, $p < 0.001$). Thus, children with a lower mental developmental index score show more internalizing problems. Only one child with a chromosomal abnormality scored in the clinical range for internalizing problems and in the subclinical range for total problems.

Clinical usefulness of the CBCL/1½-5 at 12 months

Sixteen of the nineteen developmental psychologists (84.2 %) returned the CBCL/1½-5 after having marked non-applicable items for 12-month-old children. On average the experts considered 23 items not applicable (minimum = 9 and maximum of 51). Twenty-one of the ninety-nine items (21.2%) were considered not applicable by eight or more psychologists, thus fulfilling the criterion of non-usefulness. Each expert's opinion was compared to the group consensus, and kappa varied between 0.24 and 0.68. Kappa was below 0.61 for nine of the 16 experts. Table 10.3 shows the least appropriate items for this age group for the various scales. Overall, 94% qualified item 65 'Resists toilet training' as the least applicable item, followed by item 33 'Feelings easily hurt'.

Table 10.2 Behavioral and mental and psychomotor developmental outcome

	12 months n = 120	**24 months n = 61**
	Mean (SD)	Mean (SD)
CBCL/1½-5		
Internalizing scale	43.1 (10.1)	42.5 (8.0)
Externalizing scale	40.3 (7.4)	45.6 (7.5)
Total scale	40.3 (7.9)	43.2 (7.7)
BSID-II-NL		
Mental developmental index	106.0 (20.5)	99.6 (20.8)
Psycho-motor developmental index	89.3 (18.2)	91.0 (13.2)

Table 10.3 Items judged 'not applicable' by ≥ 50% of the respondents for 12-month-olds

Itemnr	**Item**	**Subscale**	**% respondents**
65	Resists toilet training	Other problems	94
14	Cruel to animals	Other problems	69
17	Destroys own things	Other problems	69
76	Speech problem	Other problems	69
55	Plays with sex parts	Other problems	63
26	No fun	Other problems	50
36	Gets into things	Other problems	50
33	Feelings easily hurt	Anxious/depressed	88
68	Self-conscious	Anxious/depressed	69
86	Too concerned with neatness	Somatic complaints	75
39	Headaches	Somatic complaints	56
95	Wanders away	Attention problems	75
5	Can't concentrate	Attention problems	50
99	Worries	Emotionally reactive	75
83	Sulks a lot	Emotionally reactive	50
35	Gets in fights	Aggressive behavior	69
27	Lacks guilt	Aggressive behavior	69
18	Destroys others' things	Aggressive behavior	69
69	Selfish	Aggressive behavior	56
53	Attacks people	Aggressive behavior	56
23	Doesn't answer	Withdrawn	69

DISCUSSION

We performed this explorative study to evaluate the usefulness of the CBCL/1½-5 as an instrument for early identification of problem behavior, i.e. at 12 months of age. Experts judged twenty-one of the 99 items not applicable at this age. The team that developed the instrument advises against interpretation of the CBCL/1½-5 results when eight or more items have not been completed.[3] Consequently, this raises doubt about the usefulness and test results for children below the age of 18 months should be interpreted with caution. Van Zeijl et al.,[441] however, concluded that externalizing behavior at 12 months indeed can be established by means of the CBCL/1½-5. Carter et al. also reported externalizing behavior in children as young as 12 months.[84] Expectedly, both studies found significantly less externalizing behavior at 12 months than at higher ages. Still, based on expert's opinion in the present study, seven of the 24 items in the externalizing scale are not applicable for a 12-month-old child. For example, 'Destroys others' things' and 'Attacks people' are activities not physically very likely in a child of this age in view of its physical development.

The background variables SES, type of congenital anomaly, sex and psychomotor development did not appear to influence problem behavior in the study population. A significant but moderate correlation was found for mental development, in relation to the Internalizing scale ($r = -0.36$). This is not surprising because the sample included nine children with major chromosomal or syndromal abnormality. These children score higher on internalizing behavior because they lack expressive capabilities.[124,125,155]

In the present study surprisingly few infants scored in the subclinical or clinical range. One possible explanation is the fact that children in the present study were born with a severe anatomical congenital anomaly and therefore are not fully comparable to the norm population. We expected however that these children would show more deviant behavior because of their difficult start in life and subsequent medical problems. This expectation was confirmed by the moderate correlation between length of stay and Internalizing behavior ($r = 0.20$, $p = 0.03$), but not as significantly as assumed. On the other hand, we should not forget that it is the parents who report by proxy and who may still be influenced by initial problem denial and protective behavior. As a consequence they may present a too positive picture of their child's behavior.

In the present study agreement between CBCL/1½-5 scores of fathers and mothers was generally high. This finding is more outspoken than the moderate, though significant correlation between scores of fathers and mothers on the externalizing scale for 12-month-old children in a general population sample reported by Van Zeijl et al.[441] One possible explanation for this discrepancy is the fact that children in the present study were born with a severe anatomical congenital anomaly mainly outside the central nervous system. Parents together bear the burden of giving birth to a severely ill child, worrying what the future will bring. They will typically share their emotions, visit

the child together and perform care-giving tasks. This may perhaps explain the higher agreement between scores, as compared with parents of a healthy child.

Limitations of this study

A possible limitation of the study is the fact that we consulted experts from no more than two centers in the Netherlands. They are all qualified developmental psychologists, however, working with younger children in daily practice. There is no reason to believe that a larger panel would have reached a different conclusion. Furthermore, the study did not include a control group from the general population to compare scores with. Also, we refrained from asking parents to indicate which items they considered applicable or not applicable for their child. It would have been interesting to compare parental opinion with the experts' opinions.

Even though use of the CBCL/1½-5 for 12-month-old children is advised against, we feel that early signaling of problem behavior in this vulnerable group of children is important, the more so because behavior at this age is still easily modified. Future research should aim at evaluating the factor structure of the full questionnaire, as Van Zeijl et al. (2006) have done for the Externalizing scale. If results would show the overall factor structure to be incompatible with children below 18 months, efforts could be directed at adapting the questionnaire to target children younger than 18 months.

The impact on parents of having a child with major congenital anomalies: a prospective longitudinal study

Happiness is the consequence of personal effort
You have to fight for it, strive for it, insist upon it and sometimes even travel around the world looking for it
You have to participate relentlessly into the manifestations of your own blessings
And once you have achieved a state of happiness,
you must never become lax about maintaining it,
you must make a mighty effort to keep swimming upward into that happiness forever,
to stay afloat on top of it

Liz Gilbert (1969 -)

ABSTRACT

Objective

To assess long-term psychosocial outcome among parents of children with major anatomical congenital anomalies.

Methods

Mothers and fathers separately completed questionnaires on stress and general health. Parental stress was measured with the Parental Stress Index-Short Form (PSI-SF) at 24 months and 5 years after birth of the child. General health status was measured with the SF-36 at 12 months, 24 months, and 5 years. SF-36 and PSI-SF scores were compared to the norm. Inter-parent agreement and changes over time were estimated.

Results

Over time, mothers and fathers showed parenting stress and general health within the normal range and scores for both parents were comparable. Parenting stress and general health correlated negatively (r ranging from -0.38 to -0.56; $p = 0.000$).

Conclusions

Although parents of children with major congenital anomalies face many challenges, over time many of them adapt their style of functioning and may, in fact, manage quite well with day-to-day problems.

INTRODUCTION

The birth of a child with major anatomical congenital anomalies (CA) might alter family functioning. Parents have to abandon their expectations of a healthy child and have to cope with the painful experience of raising a severely ill child, either temporarily or life-long[320] These circumstances place a heavy burden on parents.[208,340] The frequent hospital visits and the uncertain outcome are only some of the many potential stressors. Once the child is home, they may have to perform special care giving tasks such as nasogastric tube feeding, enterostomy care and giving medication.

An earlier study in our department found that mothers and fathers experienced similar feelings of burden and grief one year after birth of a child with CA.[228] Mothers, however, reported significantly more personal strain than fathers. Foreknowledge from prenatal diagnosis about the anomaly, a low perceived functional health status of the child, and the child having more than one anomaly were associated with a larger burden and more grief.[228] Adaptation to a child's disability has been described for parents of children with spina bifida, Duchenne or other chronic disability.[25,89,94] The process is characterized by stages of grief and chronic sorrow, eventually leading to acceptance. Kovacs et al.[267] found that mothers' initial distress following the diagnosis of insulin-dependent diabetes mellitus in their children diminished over the subsequent 6 years. Dahlquist et al.[112] found that mothers' anxiety following their children's cancer diagnosis had normalized 2 years later.

Most research on parental experience with children with chronic conditions and severe illness has relied on mothers' reports because she is viewed as the parent closest to the child. Only few studies included the perspectives of both parents. In one of these, mothers and fathers had similar views about the functioning of their families;[255] in another, mothers generally reported more stress than fathers.[370]

Evaluation of the impact on parents of having a child with major CA is important to detect psychosocial problems at an early stage, thus enabling adequate intervention if necessary.

The present study is part of a large follow-up study on long-term medical and psychological outcomes in children with congenital anomalies treated in a pediatric surgical service of a university children's hospital, and in their parents. The aim of the present study was to assess long-term parental psychosocial outcome.

METHODS

Setting

Our children's hospital is a university hospital with a pediatric surgical department in which all surgical specialties except open-heart surgery are represented. As the

traditional monospecialistic approach of children with CA was felt to be inadequate, a multidisciplinary support and follow-up team for the management of children with CA and their parents was instituted in 1999. This team consists of pediatricians, a consultant pediatric surgeon, developmental psychologists, a pediatric physical therapist, a social worker, nursing staff, and a clinical geneticist.

Participants

From January 1999 to November 2002 a total of 205 children with CA, admitted to the pediatric surgical department, were eligible for inclusion. Parents of 33 children did not participate in the follow-up program, 26 children died before the age of 6 months and 2 children died after the age of 12 months. Parents of 18 children were unwilling to complete questionnaires. Of those, 50% (9/18) were non-native Dutch.

Parents of 126 children participated in the study, i.e. returned questionnaires for at least one time point (Figure 11.1 and Table 11.1). Largely in line with Ravitch's so-called surgical index diagnoses of CA,[351] the following categories were distinguished:

1. small intestinal anomaly (SIA);
2. abdominal wall defect (AWD);
3. congenital diaphragmatic hernia (CDH);
4. esophageal atresia (EA);
5. Hirschsprung's disease (HD);
6. anorectal malformation (ARM), and
7. a group of miscellaneous diagnoses (see Table 11.1).

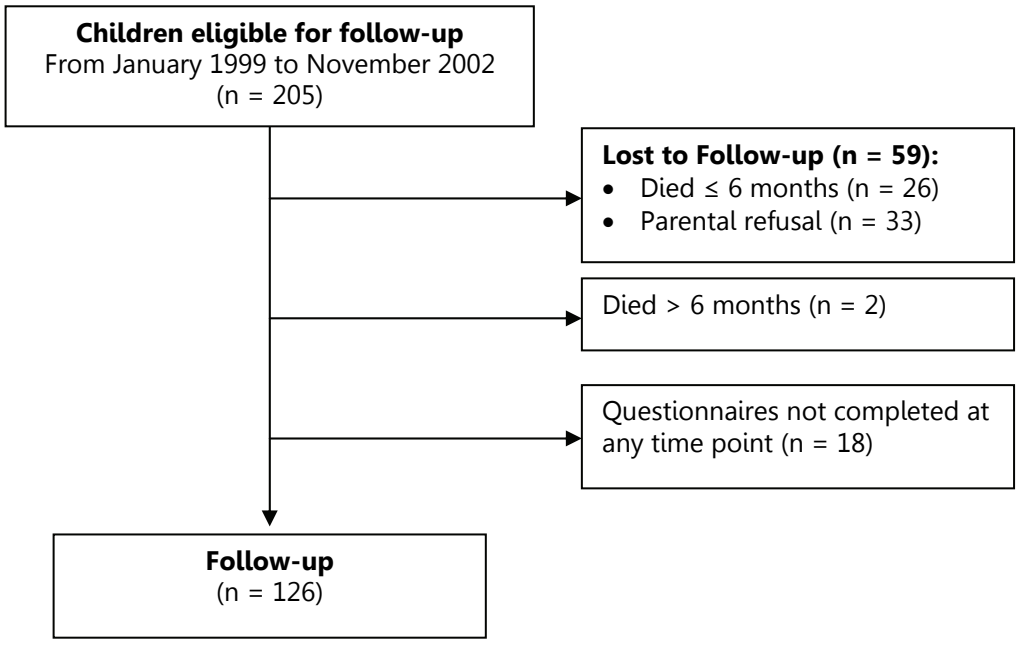


Figure 11.1 *General flowchart.*

Table 11.1 Number of returned questionnaires

		12 months n (%)	24 months n (%)	5 years n (%)	Complete set n (%)
PSI-SF	Mothers	-	103 (81.8)	96 (76.2)	79 (62.7)
	Fathers	-	88 (69.8)	82 (65.1)	65 (51.6)
	Couples	-	87 (69.1)	81 (64.3)	63 (50.0)
SF-36	Mothers	97 (77.0)	101 (80.2)	97 (77.0)	64 (50.8)
	Fathers	87 (69.1)	87 (69.1)	85 (67.5)	55 (43.7)
	Couples	86 (68.3)	84 (66.7)	82 (65.1)	53 (42.1)

Design

This is a prospective, longitudinal cohort study comprising three assessments: at 12 months, 24 months, and 5 years after the birth of the child.

Procedure

The ethical review board agreed with the study, and written parental informed consent was obtained for all subjects. At 12 months, 24 months, and 5 years parents were asked to complete the SF-36;[103,435,462] at 24 months and 5 years parents were asked to complete the Parenting Stress Index – Short Form (PSI-SF).[2,119] Assessments at 12 and 24 months were corrected for gestational age of the child. Parent couples were explicitly instructed to complete the questionnaires independently. The questionnaires were mailed to the parents. Usually the questionnaires were completed at home and returned on the day of the follow-up appointment.

All demographic and medical data as shown in Table 11.2 were collected prospectively from the first day of admission. Ethnicity was categorized as being native or non-native to the country. Socioeconomic status (SES) was assessed according to a national classification as 'low', 'medium', or 'high'.[397] Medical characteristics included type of anomaly, total number of minor and major anomalies, duration of admission in the first 6 months, number of medical appliances at discharge, surgical interventions and additional medical problems in the first 24 months (see Table 11.2). Medical appliances include: medications, oxygen therapy, tracheostomy, nasogastric tube, enterostomy, heart and respiration monitoring, central venous line, airway suction and other medical appliances (e.g. rectal cannula and enema).

Instruments

Parenting Stress Index – Short Form

The parent-child relationship was assessed using a validated Short Form (SF) of the Dutch version[119] of the Parenting Stress Index (PSI).[2] The PSI-SF was designed to assess the degree of stress related to parenting in parents of children ages 2 to 13 years. It consists of 25 items derived from the PSI, which comprise three domains: parental

characteristics (distress), (difficult) child characteristics and situational variables. The items are scored on a six-point Likert scale from strongly disagree (1) to strongly agree (6). A total score is obtained by calculating the scores on the 25 items; total score thus may range from 25 to 150. The higher the score, the more stress reported. Scores were compared with Dutch population norms for mothers (mean 54.4, SD 19,3) and fathers (mean 48.5, SD 16,4) separately.

SF-36

The SF-36 is a generic health status questionnaire.[103,435,462] It consists of 36 questions organized into eight domains:

1. physical functioning;
2. social functioning;
3. role limitations because of physical health problems;
4. role limitations because of emotional problems;
5. general mental health;
6. vitality;
7. bodily pain, and
8. general health.

Two summary measures can be derived: physical health (including domains 1, 3, 7 and 8) and mental health (including domains 2, 4, 5 and 6). Total scores are linearly transformed to range from 0 to 100, with higher scores indicating a better-perceived health status. Dutch population norms adjusted for age (25 - 34 years) were used.[435] A generic measure, the SF-36 has proven useful in surveys of general and specific populations.

Statistical analyses

As measures of central tendency the means (normal distribution) and medians (non-normal distribution) are presented. The standard deviation (normal distribution) and interquartile range (non-normal distribution) served as measures of dispersion. In case of categorical data the numbers and percentages are presented. The Intra-class Correlation coefficient (two-way mixed model) was used to estimate the inter-parent agreement.

Cohen's d (standardized mean difference) was calculated to indicate the magnitude of the differences between mothers and fathers at the three measurement moments only for SF-36.[96] Magnitude was expressed by Cohen's d rule of thumb: small = 0.20, moderate = 0.50 and high = 0.80. Paired-sample t-test was used to determine significant differences for paired samples at each time point only for SF-36, and between assessments of the same parent across time for both PSI-SF and SF-36. SF-36 and PSI-SF scores were compared to the Dutch age norm, using Student t-test.

All statistical testing was performed at the 0.05 level of significance (two-tailed). The software programs SPSS 15.0 for Windows was used.

RESULTS

General characteristics

Characteristics of the 126 children and parents are presented in Table 11.2. The median number of anomalies per child was 2 (IQR: 1-3). Median duration of admission in the first 6 months was 40 days. Children underwent a median of three surgical interventions in the first 24 months. Eighty-seven (69%) children had at least one medical appliance at discharge.

Table 11.2 General characteristics of patients and parents (n = 126)

	n	%	median	IQR
Patients				
Female	60	47.6		
First born	53	42.1		
Primary Congenital Anomaly				
Small intestinal anomaly	43	34.1		
Abdominal wall defect	20	15.9		
Congenital diaphragmatic hernia	18	14.3		
Esophageal atresia	16	12.7		
Miscellaneous	14	11.1		
Hirschsprung's disease	9	7.1		
Anorectal malformation	6	4.8		
Chromosomal or syndromal abnormality	14	11.1		
Congenital anomalies per patient (number)			2	1 - 3
Total admission in first 6 months (days)			40	27 - 72
Medical appliances at discharge [a] (number)			1	0 - 2
Surgical interventions in first 24 months (number)			3	2 - 5
Additional medical problems in first 24 months (number)			2	1 - 4
Parents				
Age mothers at delivery			33	31 - 37
Age fathers at delivery			31	28 - 34
Number of children in the family at 5 years			2	1 - 3
One or both parent(s) non-Dutch	18	14.3		
Parents married or living together at delivery	117	92.9		
Parents married or living together 5 years after birth	94	74.6		
Socioeconomic status				
Low	22	17.4		
Medium	65	51.6		
High	39	31.0		

[a] *Medical appliances includes: medications, oxygen, tracheostomy, nasogastric tube, enterostomy, heartrate and respiration monitoring, central venous line, airway suction and other medical appliances (e.g. rectal canula and clysmata).*

Fourteen children with a major chromosomal or syndromal abnormality (Down's syndrome n = 6, other n = 8) were at risk of severe psychomotor delay. One or both parent(s) of 18 children were non-native Dutch, but had enough command of the Dutch language to fill in the questionnaires.

The median age of the mothers was 33 years; that of the fathers 31 years. The majority (92.9%) of the parents was married or living together when their child was born and 23 (19.7%) couples were divorced or living apart after 5 years. In 69.8% of the 53 families in which the child with CA was first born, additional sibs had been born within 5 years. One or both parents of 44 children (34.9%) had consulted a social worker or were referred to a psychologist for psychosocial and mental health problems within the first 5 years after birth of their child.

Parenting stress

Comparison with population norms

At 24 months, the mean scores of mothers and fathers were 51.2 (SD = 20.23) and 45.7 (SD = 15.5), respectively. At 5 years, the mean scores of mothers and fathers were 49.6 (SD = 20.6) and 50.1 (SD = 20.0), respectively. These scores did not differ significantly from the Dutch population norms.

Parental agreement

The intra-class correlations of PSI-SF scores between mothers and fathers were high and decreased over time from 0.64 at 24 months to 0.52 at 5 years.

Changes over time

Paired measurements showed no significant differences between PSI-SF scores of mothers at 24 months and 5 years ($t = 0.29$, $p = 0.78$, $n = 79$). Paired measurements for fathers showed a significant change over time, with a higher level of stress reported at 5 years ($t = -3.04$, $p = 0.003$, $n = 65$).

Generic health status

Comparison with population norms

Figures 11.2A and 11.2B show the scores of mothers and fathers on the mental and physical component scales, respectively, of the SF-36. At 12 months mothers perceived lower quality of life than the norm group, with significantly lower scores on the domains social functioning, general mental health, vitality (data not shown) and thus on the mental component scale ($t = - 0.2.67$, $p < 0.01$). The mean scores on the mental and physical component scales were 75.0 (SD = 18.9) and 81.4 (SD = 19.8), respectively. Fathers at 12 months reported mental and physical health within the population norm (mean = 81.8, SD = 16.0; mean = 85.6, SD = 18.4, respectively; $p > 0.05$).

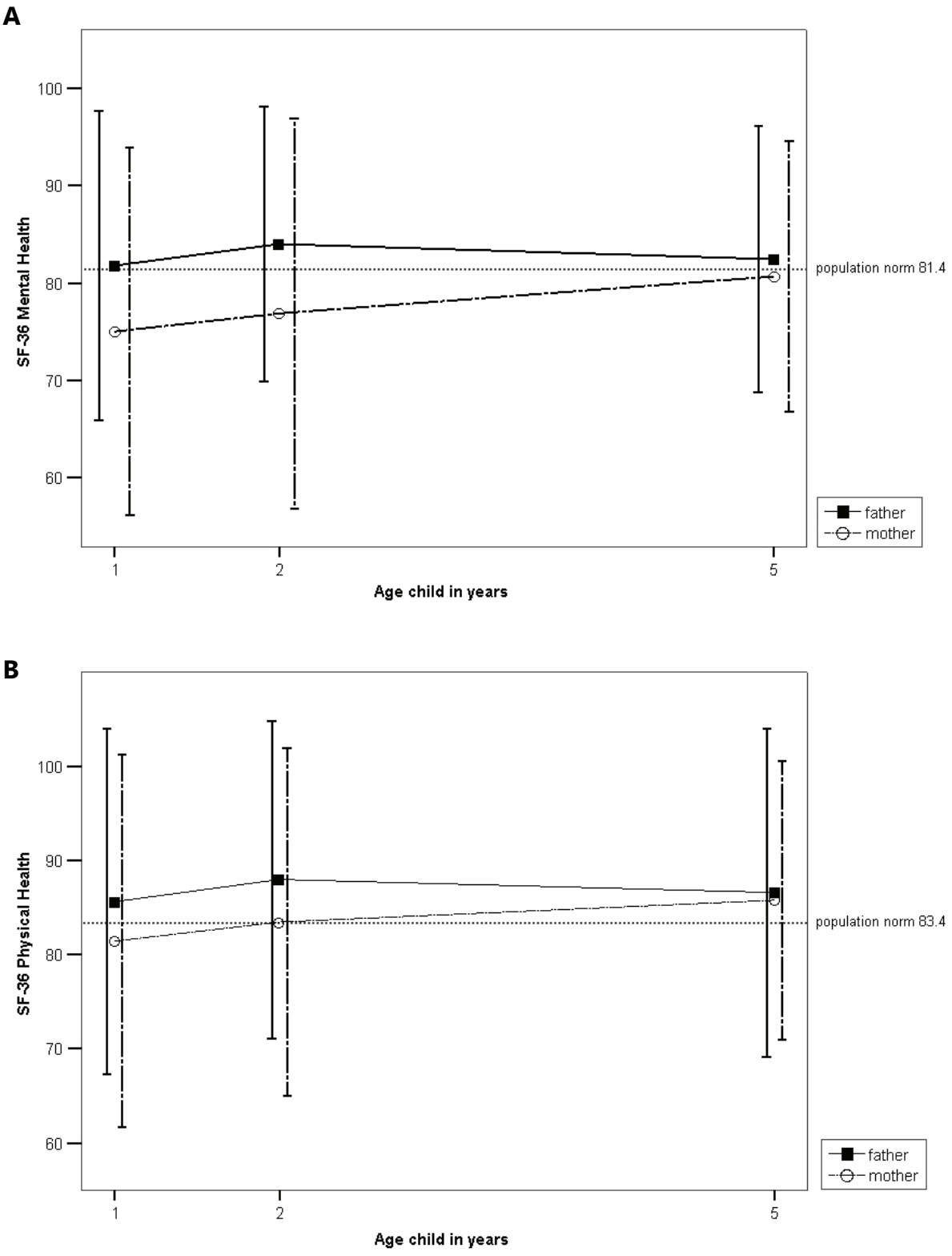


Figure 11.2

At 24 months fathers showed significantly higher scores than the norm group on the domains physical functioning, general mental health and bodily pain (data not shown), but scored within the population norm on the mental and physical component scales (mean = 84.0, SD = 14.1; mean = 88.0, SD = 16.9, respectively; $p > 0.05$). Mothers also

scored within the population norm on the mental and psychical component scales at 24 months (mean = 76.9, SD = 20.1; mean = 83.5, SD = 18.4, respectively; p > 0.05).

Five years after birth, both mothers and fathers scored significantly higher than the norm group on the domain physical functioning (data not shown), but within the population norm on the mental and physical component scales (mothers: mean = 80.7, SD = 13.9; 85.8, SD = 14.8, respectively; p > 0.05 and fathers: mean = 82.4, SD = 13.7; mean = 86.6, SD = 17.4, respectively; p > 0.05).

Parental agreement
At 12 and 24 months, scores on the mental and physical component scales for mothers and fathers showed differences, indicated by Cohen's d (ranging from -0.02 to -0.04). Five years after birth, scores for mothers and fathers were comparable, with all Cohen's d < 0.20.

At 12 months, paired measurements showed that mothers scored significantly worse than fathers on the mental component scale (t = 2.41, p = 0.02, n = 86). At 24 months, this difference had remained and had extended to the physical component scale as well (t = 3.81, p = 0.00, n = 84; t = 2.50, p = 0.01, n = 83, respectively). At 5 years, paired measurements showed no significant differences between mothers and fathers.

At 12 months, the intra-class correlations of scores on the mental and physical component scales for mothers and fathers were 0.30 and 0.43, respectively. At 24 months, the intra-class correlations of scores on the mental and physical component scales were 0.38 and 0.53, respectively. At 5 years, the intra-class correlations decreased to 0.07 and 0.31 for the mental and physical component scale respectively.

Changes over time
In the first two years after birth of their child, only fathers showed significant positive changes: the scores on the mental and physical component scales increased (t = -2.54, p = 0.013, n = 69; t = -2.96, p = 0.004, n = 68, respectively). From 2 to 5 years, only for mothers the scores on the mental and physical component scales increased (t = -2.65, p = 0.010, n = 77; t = -2.12, p = 0.038, n = 78).

Association between parenting stress and general health status
For either parent, there was a significant and negative correlation between PSI-SF and SF-36 at 24 months and 5 years, ranging from -0.38 (p = 0.000) to -0.56 (p = 0.000). In other words, less parenting stress was associated with better-perceived mental and physical health. Correlations were highest between parenting stress and mental health (ranging from -0.51 (p = 0.000) to -0.56 (p = 0.000)).

DISCUSSION

This prospective longitudinal study shows the effects of having a child with a major anatomical CA on parenting stress and parental general health, aspects which both may influence quality of life. One year after the birth of their child mothers showed lower mental health than the normative data. One year later, mental health had normalized. Five years after birth of their child, both mothers and fathers showed normal physical health, however supranormal physical functioning. We speculate that parents over the years apparently assure themselves of such health, because a better overall physical health is needed to answer to the needs of a chronically ill child.

Two and five years after the child's birth, mothers and fathers showed normal parenting stress. After two years the process of parental acceptance apparently has resolved and parental stress has balanced out. Moreover, many children, especially those with isolated small intestinal atresia or uncomplicated abdominal wall defects, are no longer dependent on the medical system five years after birth. No longer being dependent is in stark contrast with the fate of children with chronic illness such as cystic fibrosis and meningomyelocele.

One and two years after birth fathers' and mothers' mental and physical health differ, but there is comparable stress. At five years, mental and physical health as well as parenting stress in general were comparable for both parents. For some individual parent couples, however, there was a discrepancy for mental health. Knowledge of parental differences might be practical in helping parents to understand each other and also in targeting adequate support.

For both parents, parenting stress was negatively related with general health; implicating that lower stress is favorable for mental and physical health. It seems that a mentally and physically healthy parent is able to cope with the situation of having a child with CA and thus shows less stress. Good adaptation strategies make parents less vulnerable to stress. Otherwise, parents with young children find themselves in earlier stages of adjustment in which their family interaction patterns are undergoing changes. In contrast, at five years of age adjustment to the child's condition is more likely to have stabilized because the child and family over time adapt to managing adverse conditions. Although it is encouraging to find that parents in our study in general exhibited normal parenting stress and general health over time, it is important to mention that this finding cannot be generalized to all parents in this study group.

Preliminary evaluation showed that medical conditions have an adverse effect on parenting stress and general health. Parents are struggling to care for their child as they deal with the array of systems involved in meeting their child's needs. However, over time parents adapt their style of functioning and may, in fact, manage quite well. The presence of a stressor, such as having to care for a child with a chronic condition,

challenges families to use internal resources and to develop internal strengths for managing their situation. Studies showed that even in the face of adverse life conditions, some families not only do all right, but actually become stronger with family communications improving and parental sharing of responsibilities.[301,328,363] Several experts on childhood chronic conditions (e.g. cystic fibrosis, meningomyelocele) suggested that variability in family impact may be more related to characteristics of the condition, such as age of onset, prognosis, course, or type of incapacitation rather than diagnosis per se.[331,399]

This study has several strengths. Long-term impact on parents of children with congenital anomalies has seldom been performed. Moreover, most studies on impact do not differentiate between fathers and mothers separately. The available medical characteristics did not allow a prediction of outcome in terms of parenting stress and general health. On the other hand, outcome over time appeared to be within the normal range. Future research should elucidate the predicting capacity of extended medical characteristics.

Another limitation might be the fact that the majority of children had two-parent families. Study-design did not allow to separately analyze the single parents. Two-parent families may be able to share responsibilities in caring for their child, and for addressing other normative tasks and responsibilities of family life, in contrast to single-parent families where the responsibility is more likely shouldered by one parent. Furthermore, parenting stress could not be measured earlier than 2 years after birth of the child because PSI is only validated from two years of age. In future research it would be interesting to evaluate parenting stress before the age of two years. Moreover, we cannot preclude that parents consulted with each other on responses to the questionnaires, which may have influenced parental agreement. Finally, this study presents data of parents who had all enough command of the language to understand and fill in the questionnaires. Future research about quality of life of parents of other and more diverse cultures is needed to become aware of their needs and to tailor support according to those needs. As another recommendation, future studies would do well to evaluate coping style in relation to parenting stress. Parents who use more avoidant or less problem-focused coping could be at risk for more parenting stress on the long term.

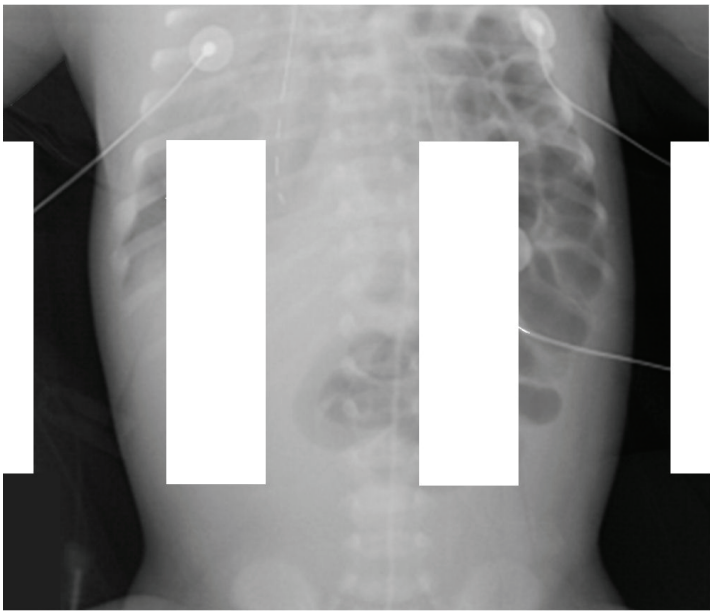
Conclusion

Although parents of children with major CA face many challenges, over time many of them adapt their style of functioning and may, in fact, manage quite well with day-to-day problems. A mentally and physically healthy parent is able to cope with the situation of having a child with CA. Good adaptation strategies make parents less vulnerable to stress.

ACKNOWLEDGEMENTS

We gratefully acknowledge the kind co-operation of all patients and their parents who participated in the study; without them this study would not have been possible. Also, we thank Ko Hagoort for editing and Anne Vroegindeweij for her help in data retrieval.

PART



MULTIDISCIPLINARY SUPPORT

Telephone helpline for parents of children with congenital anomalies

People use what they called a telephone because they hated being in the hospital but they were scared of being alone

vrij naar Chuck Palahniuk (1962 -)

ABSTRACT

Aim

To evaluate how often and for what reason parents of children born with severe anatomical congenital anomalies use a 24-hour telephone helpline. Secondary aim was to identify differences between callers and non-callers.

Background

Children born with severe congenital anomalies often remain dependent on medical care and technology after discharge home. Adequate medical consultation in the home situation may lower parental burden.

Methods

Observational study of telephone contacts from 2000 to 2006 with parents of congenital anomaly patients discharged home after neonatal intensive care admission. Frequency of telephone calls was categorized per type of anomaly. Resulting interventions in terms of consultation and hospital admission were registered. Finally, costs of personnel needed to provide 24-hour telephone helpline availability were calculated.

Results

670 calls came in outside office hours, from 34.4% of all parents. 23.7% of these calls concerned feeding problems. Parents of patients with esophageal atresia, urogenital malformation and congenital diaphragmatic hernia called most frequently (44.3% to 50.6%). Nurses handled 24.5% of calls by themselves. 20.2% of calls led to emergency room consultations resulting in 4.9% admissions. First contact took place at median age 3 months, last contact at median age 8 months. Total personnel costs amounted to € 27,191 per year.

Conclusions

A 24-hour telephone helpline provides easy access to adequate medical and supportive care for parents of children with congenital anomalies at relatively low cost. Nurses can effectively run this telephone helpline with pediatrician back up.

INTRODUCTION

More and more children with anatomical congenital anomalies are now successfully treated and survive their often life-threatening conditions. In many cases, however, they remain dependent on the medical system and medical technology after discharge home. Most western societies promote home rather than hospital based care, which implies that parents may be made responsible for (part of) specialized care. Since most anatomical congenital anomalies are rare (incidences from 1:2,500 to 1:40,000), falling back on general practitioners and general pediatricians may prove difficult, as most will have limited knowledge of the day-to-day problems related to the care of these children. Lack of back up increases parental burden and responsibility and asks for parental resilience in an already difficult situation.

Studies confirm that parents highly appreciate receiving detailed practical information about the anomaly and the consequences for daily care, and are glad with support given to ease the multiple stresses they are facing.[83,126,347,386,471] Depending on the specific diagnosis specialized nursing care, for example for diabetes or asthma, may be provided, both face-to-face and by telephone consultation.

Telephone counseling is a recognized way of supplying parents with extra support. Studies in pediatric and adult patients show that telephone triage and advice by nurses and paramedics can be safe and effective, both in general practice and in an accident and emergency department setting. This leads to fewer out of hours consultations and visits.[23,72,113]

BACKGROUND

Wellness, wholism, and systems thinking are foundational to a nurse run telephone line. Thus, this approach can be placed within the nursing conceptual model of the Neuman systems model.[318] Neuman has viewed health as optimal system stability at any designated time. In this model the practice of nursing focuses on promoting system stability through attaining, retaining, and maintaining optimal wellness and wholeness. The telephone helpline promotes system stability by strengthening the parent and promoting wellness after treatment, while creating a linkage among the parent, the environment, health, and nursing.

The children with congenital anomalies admitted to our pediatric surgical department differ from most other pediatric patient groups, such as oncology patients and premature neonates. They show many and very diverse physical problems often requiring involvement of a range of different (organ) specialists.

Parents inevitably need information, and will have to plan arrangements and supportive care before and after hospital discharge of their child. This combination of tasks can best be provided by an expert team with thorough knowledge of the specific medical, social and psychological problems.[386] These children often remain dependent on medical technology in the home situation, which places an enormous burden and responsibility on parents, resulting in a stressful impact on family relationships.[83] Preventing such impact requires a balance between positive aspects of being in the home environment and the challenges of administering complex therapies at home. Additional support for caregivers is needed to reduce their physical, emotional, social and often also financial burdens.[471]

Supportive care for parents and caregivers in the home situation by expert teams contributes to the general wellbeing of the whole family system. Such care has been shown to increase competence and confidence of parents of children with various rare diseases (frequency < 5 per 10,000 inhabitants) by empowering parents and reducing social and emotional isolation.[126]

There is insufficient evidence on the potential and limitations of a 24-hour telephone counseling service for parents of children with severe congenital anomalies. Similarly, little has been reported on the costs of organizing such a service.

STUDY

Aim

To evaluate how often and for what reason parents of children born with severe anatomical congenital anomalies use a 24-hour telephone helpline. Secondary aim was to identify differences between callers and non-callers.

Design

The study is designed as an observational study in which all telephone calls of parents of patients with congenital anomalies participating in the department's support team received over a 5-year period were analyzed.

Setting

The level III ICU in our hospital is the only pediatric surgical facility in the southwestern region of the Netherlands, with a referral area of 4 million and 44,000 newborns annually. All children with congenital anatomical anomalies are referred to this hospital.
In order to provide these children and their parents with the best possible care during admission and after discharge, a follow-up program was started in 2000, run by a multidisciplinary team consisting of a pediatric intensivist, a pediatrician, two psychologists, ten nurses, a physiotherapist, a social worker and a surgical consultant. Children are seen at 6, 12, 18 and 24 months and 5, 8, 12 and 16 years to evaluate

physical, developmental and psychosocial functioning. Monitoring aims at reducing overall morbidity associated with severe congenital anomalies and alleviating parental burden.

Sample

Eligible for this study were parents of patients with one or more severe anatomical congenital anomalies admitted to our department from 2000 to 2006. Parents on discharge of their child from the hospital received a phone number with 24-hour availability, to be called in case of medical questions or anxiety about their child. General information had already been given both verbally and in writing during admission.

Data collection

Ten fully trained pediatric ICU nurses were assigned to run the telephone helpline to answer questions from parents.

In several meetings a pediatric intensivist provided guidelines and training on how to answer parental questions, e.g. on fever, diarrhea and problems with central venous catheters. The nurses themselves provided answers to questions not covered by the available guidelines or contacted the intensivist on call.
Regularly, cases were discussed and guidelines further developed. Being on call for the telephone helpline could coincide with being on call on the ward, but sometimes nurses were on call outside regular shifts.

Duties were: 1) calling parents within 2 weeks after discharge home, in order to identify any specific problems and to further explain functioning of the helpline, 2) assessing incoming calls from parents, aiming for triage and advice. On weekdays from 07.30 to 17.00 hrs (office hours) calls were directed to the ward, preferably to be handled by one of these ten nurses, otherwise by one of the intensivists. On weekdays from 17.00 to 07.30 hrs and in the weekends (hereafter referred to as out of office hours) calls were directed to the nurse on call. The nurse on call carries a laptop with all case record forms providing immediate access to medical and relevant psychosocial data on all participating patients. Contacts with parents are recorded immediately so that up to date information on patients is always available. Entries include the nature of the question(s), time of the call, patient's symptoms and advice given. Nurses had to register hours worked for the support team outside office hours in order to receive financial compensation.

To explore the cost consequences of the 24-hour telephone counseling service, we calculated the direct costs of personnel. These included costs of nurses (both for running the telephone helpline and for training and meetings), a coordinating pediatric intensivist, and a secretary. Due to insufficient data, only costs of calls during out of office hours could be calculated. We followed established methods of cost calculations,

by using the Manual for Costing Research.[327] Calculations of personnel costs were based on the Collective Employment Agreement for University Medical Centers. Taking into account public holidays, vacation, illness, and study leave, the number of working hours per person per year was set at 1,540 (non-medical staff) and 2,100 (medical staff), respectively. This calculation method resulted in hourly personnel costs of € 32 (nurses), € 71 (coordinating pediatric intensivist), and € 23 (secretary), including increments for holiday allowances and social security expenses. To these costs, we added costs of allowances for working irregular hours and for working on-call shifts. All costs were calculated for the year 2007 and reported in euro.

Ethical considerations

The ethical review board approved the study, and written parental informed consent was obtained for all participants.

Data analysis

All data were coded and analyzed using SPSS 14.0. Disease-related and family factors were compared between callers and non-callers by Chi-square test (with Yates' correction for 2 by 2 tables). Mann-Whitney U-test as appropriate to compare callers and non-callers. A logistic regression analysis was performed to evaluate influences of congenital anomalies, sociodemographic and other medical variables on parental use of the helpline simultaneously. Multicollinearity was tested with the Variance Inflation Factor (VIF). To this aim a multiple regression analysis including all explanatory variables was performed. VIF should not exceed 10 for any of the variables. Statistically significant variables were described in terms of Odds Ratios (OR) and p-values. P-values lower than 0.05 were considered significant for all of these tests.

RESULTS

From mid 2000 until mid 2006, 500 parents were invited to use the 24-hour telephone helpline service. Parents of 32 children who died within 28 days after birth (68.8% had CDH) were excluded from analysis. Of the remaining 468 parents, 161 (34.4%) called 670 times (1 to 24 calls per family) outside office hours. Table 12.1 gives details of primary reasons for calling.

Parents of children in diagnosis groups esophageal atresia (50.6% of 77 patients) and CDH (44.3% of 70 patients) and miscellaneous (33.8% of 68 patients) represented the highest proportions of callers. Less frequent contacts were with parents of children in diagnosis groups abdominal wall defects (28.8% of 73 patients) and anorectal malformations or Hirschsprung's disease (27.1% of 70 patients) and small intestinal anomalies (25.5% of 110 patients). First telephone contact took place at median age 3 months (IQR 1 to 6 months) and last telephone contact at median age 8 months (IQR 3 to 16 months).

Table 12.1 Primary reasons for calling (n = 670 telephone calls)

	n (%)
Feeding problems	160 (23.7)
Intestinal problems*	110 (16.4)
Respiratory problems	107 (16.0)
Fever	55 (8.2)
Medication	46 (6.9)
Information#	47 (7.0)
Skin problems	37 (5.5)
General malaise	26 (3.9)
Urinary tract problems	25 (3.7)
Drains or tubes	23 (3.4)
Vaccinations	12 (1.8)
Central line sepsis	7 (1.0)
Social	7 (1.0)
Pain/crying	5 (0.7)
ALTE	3 (0.4)

Abbreviations: ALTE, acute life threatening event; n, number,
** Including diarrhea (n = 42), constipation (n = 31),*
 # Including e.g. visitors' risk of infection, medical supplies, scheduled surgery, insurances.

Telephone calls resulted in different interventions. In half of the calls (50.7%) the attending pediatric intensivist was needed to answer the questions by telephone. Nurses' advice was sufficient in 24.5% of all calls, in some cases, however, after consultation with the intensivists. In 20.2% of calls parents were asked to bring the child to the emergency department. Readmission resulted 28 times (4.2%) for the following reasons: feeding difficulties/dehydration (n = 9), respiratory tract infections (n = 8), other infections or fever of unknown origin (n = 3), Apparent life threatening event (ALTE) (n = 3) and miscellaneous (n = 5). In 0.4% of calls parents were referred to a general practitioner.

Table 12.2 shows illness-related and family-related factors broken down for 'callers' and 'non callers'. Illness-related factors are significantly associated with a higher proportion of callers.

In logistic regression analysis all variables from the bivariate analyses (table 12.2) were entered. VIF as calculated in a multiple regression analysis remained below 2.5. Parents of children on medication after discharge were more than twice as likely to call (OR 2.12, $p = 0.006$) ; immigrant parents were three times less likely to call than native Dutch parents (OR 0.31, $p < 0.0001$). The three parents for whom we had arranged interpreter support because of language barriers never called the support team.

Table 12.2 Illness-related and family-related factors (excluding 'early deceased')

	Callers (n = 161)	**Non Callers** (n = 307)	**p-value**
Illness-related factors	**n (%)**	**n (%)**	
Requiring medical aids at discharge	86 of 161 (53.4%)	127 of 307 (41.4%)	0.008[1]
On medication at discharge	128 of 161 (79.5%)	175 of 307 (57.0%)	< 0.001[1]
Total hospital stay first 6 months of life (in days)[#]	38 (23 to 81)	31 (18 to 57)	0.002[2]
Diagnosis Congenital diaphragmatic hernia	31 of 161 (19.3%)	39 of 307 (12.7%)	0.06[1]
Diagnosis Esophageal atresia	39 of 161 (24.2%)	38 of 307 (12.4%)	0.001[1]
Family-related factors			
First born child	94 of 161 (58.4%)	201 of 307 (65.5%)	0.16[1]
Parents divorced/separated*	6 of 154 (3.9%)	13 of 270 (4.8%)	0.84[1]
Ethnicity: both parents non-Dutch	17 of 161 (10.6%)	75 of 307 (24.4%)	< 0.001[1]

[#] Median (IQR),
** Missing data,*
[1] Chi-square test,
[2] Mann-Whitney U-test.

The results of the cost calculations can be summarized as follows. The total number of hours per year worked by nurses outside office hours was 280. Including costs of allowances for working irregular hours and for working on-call shifts and including costs for training, this translated to yearly personnel costs for nurses of € 22,527. Compared to this, the costs for the coordinating pediatric intensivist (60 working hours per year) and the secretary (18 working hours per year) were relatively minor: € 4,249 and € 415 respectively. Thus total yearly costs amounted to € 27,191. The health insurance companies pay these costs.

Discussion

The children with congenital anomalies represented in this study comprise a very diverse group with regard to diagnoses, physical problems and parental responsibilities for medical care. At discharge home many required continued use of some kind of medical aid, varying from medication to tracheostomy care. Our results show that parents of children requiring medical aid or medication called more frequently than other parents. The first few months after discharge from the hospital parents most frequently sought telephone counseling. Thereafter the child's condition usually would have improved, with parents becoming more confident with their child and finding their way in the primary care circuit. Most calls concerned feeding problems, either related to parental insecurity or to the underlying anomaly, for example (functional) short bowel, gastro-esophageal reflux or failure to thrive. Respiratory tract related questions often reflected fear of severe lower respiratory tract infection in children who had been dependent on artificial ventilation for a long time. The relevance of the parents'

questions is brought out by the fact that half of the questions were referred to an intensivist; in addition, in 3 cases parents called about ALTE.

Most calls concerned conditions known to bring many problems and sequelae, such as CDH and esophageal atresia. The fact that 22 of the 32 early deceased infants had CDH probably reduced the number of calls in this group. The fact that 20% of calls resulted in a visit to the emergency department underlines their medical urgency.

A literature analysis of specialist home-based nursing services shows limited effectiveness of specialist pediatric nurse home visiting.[104] Burke and colleagues, however, reported greater parental ability to cope and greater satisfaction in family functioning in families with a child with chronic illness as a result of nursing support before and after scheduled hospital admissions.[73] These studies nevertheless did not specifically involve telephone help lines. Lattimer and colleagues showed that nurse telephone consultation in a general practice is both safe and effective, but also cost effective for both adults and children.[276,277]

Telephone consultation can provide a less disruptive model of care, supplying parents of chronic patients with reassurance and streamlined access to hospital services for their child. Moreover, follow-up calls initiated by the hospital can prevent stress and anxiety at least in adults. Follow-up calls by a hospital pharmacist were found to reduce medication-related problems and return visits and to increase patient satisfaction.[134,135]

To the best of our knowledge, this study is the first to document the costs of a hospital-based telephone helpline for parents of children with severe congenital anomalies. Still, several limitations should be borne in mind when interpreting the results. The calculations were limited to the personnel costs of running the helpline, including costs for training the nurses, coordination by a pediatric intensivist, and secretarial support. Calls by parents during office hours and costs of pediatric intensivists assisting nurses in answering questions could not be accounted for. The costs of equipment were minimal and thus could be ignored. Given all this, we feel that the 24-hour telephone helpline service can be provided efficiently at a reasonable cost. It would be of interest to investigate whether a telephone helpline would affect health care utilization (e.g., admission to the emergency department or the hospital), as compared with the situation without a telephone helpline. Bensink et al., who are planning a study of the cost-effectiveness of video telephone support for pediatric oncology patients, acknowledged that providing this kind of support may be associated with savings on the costs of health service use.[36]

Service utilization shows that a considerable number of parents used the telephone service, especially those with children with CDH and esophageal atresia, and after long hospitalization. Looking at our data we feel that we might have referred more often to a

primary care supplier, especially with guaranteed back up from the tertiary care center, thus further reducing the use of tertiary hospital resources.

The helpline is an example of how nursing expertise can be used to bridge the gap between hospital and home situations. It provides a client-centered approach in line with an increasing demand for personalized services in health care.

Conclusions

Children with congenital anomalies often have associated morbidity extending far beyond the time of initial admission. Parents may feel less burdened when easy access to adequate medical and supportive care for their children is guaranteed. A 24-hour telephone helpline provides this service at a relatively low cost, and can effectively be run by nurses with back up by a pediatrician or pediatric intensivist. Care would be further improved, however, by transferring a larger part of day-to-day care to the primary care setting, while still ensuring easy access to specialized care.

Acknowledgements

We would like to thank all the nurses participating in the telephone helpline for the energy they put into this work.

Parents' satisfaction with follow-up care for children with severe birth defects

Failure is success if we learn from it

Malcolm Forbes (1919 - 1990)

INTRODUCTION

Advancements in pediatric and neonatal intensive care facilities have led to much better survival rates in newborns with a congenital anomaly.[192,211] Healthcare teams concomitantly have started to wonder whether improved survival does not come at the expense of poor health-related quality of life (HRQoL). Poley and colleagues studied HRQoL in young and adult individuals born with anorectal malformations or congenital diaphragmatic hernia (CDH).[340] They found considerable morbidity and mortality in the youngest children. HRQoL appeared to improve with age, but many adults still suffered from disease-related symptoms. Thus, there clearly is a need to closely follow these children into adulthood. Encouragingly, follow-up of neonates with congenital anomalies or other health problems is receiving increasing attention in the Netherlands. Follow-up studies in prematurely born patients,[218,401] ECMO-treated neonates,[196] and meningococcal septic shock survivors[75] have been published meanwhile.

The parents play a critical role in the care for these children. Some care-giving tasks even require specific skills (e.g., giving enemas or changing stoma bags), are unpleasant, or have to be performed at night. Hassink et al. found that especially the parents of older boys who suffered from fecal incontinence as a result of anorectal malformations experienced stress when caring for their child.[207] Finally, Chen and co-workers showed that the impact of having a child with CDH on the parents' family life and HRQoL is profound, especially when the child's clinical problems persist.[88] These studies underline the need for family-centered long-term follow-up and support of families with a child with major congenital anomalies. Therefore, dedicated teams have been set up to provide support. One way to evaluate effectiveness of these teams is to assess the parental perspective. Knowledge of their needs and experiences might guide health care teams toward a patient driven care. Various strategies have been identified to evaluate the needs and experiences of parents.[323] These strategies are both qualitative with in depth interviews as well as quantitative with assessment instruments. However, needs assessment is not synonymous with establishing parent satisfaction but it partly explains the level of parental satisfaction. Satisfaction data may facilitate the evaluation of services and implementation of quality initiatives.[185,275] Within this context it would seem essential to pay equal attention to patient and family care elements, both in the clinical environment and follow-up care.[273]

While the literature on patient satisfaction in health care is extensive, only a few studies concentrate on parental satisfaction.[274] To evaluate our follow-up team, including both clinical and outpatient services, we had to develop a questionnaire because existing ones were not applicable.

The aim of the present study was to evaluate the services of our follow-up team for children with congenital anomalies from a parental perspective, with the further aim of optimizing these services.

METHODS

Setting

The level III Intensive Care Unit (ICU) in the Erasmus MC-Sophia Children's Hospital is the only pediatric surgical facility in the Southwestern part of the Netherlands, with a referral area of 4 million general population and 44,000 newborns annually. All children with congenital anatomical anomalies are referred to this hospital. Admission, depending on the level of care needed, is to our ICU, High Care or Medium Care facility supervised by specialized physicians and nurses.

In order to provide these children and their parents with the best possible care during admission and after discharge, a follow-up program was started in 1999. The program is run by a multidisciplinary team consisting of pediatricians, psychologists, nurses, a physiotherapist, a social worker, a clinical geneticist and a pediatric surgical consultant.

During hospital admission, the program provides for weekly updates on the child's condition; support from a medical social worker if necessary, referring families to patient organizations; providing supportive counseling. The team facilitates smooth transitions from the intensive care unit to the medium care unit, to other hospitals or to home.

After discharge, children and parents are seen at set time points (6, 12, 18 and 24 months and 5, 8, 12 and 16 years) to evaluate the child's physical, developmental and psychosocial functioning as well as psychosocial functioning of the parents. Monitoring aims at reducing overall morbidity associated with severe congenital anomalies and to reduce parental burden and improve quality of life. The team intervenes as necessary. A 24-hour telephone helpline run by ICU nurses is available at all times.

Participants

Participants were parents of children with severe anatomical congenital anomalies admitted to the department of pediatric surgery of the Sophia Children's Hospital in the period 1999 to 2007.

Procedure

As validated satisfaction instruments suited to our aim were not available, a psychologist who is not a member of the follow-up team (MVD) developed a tailor-made questionnaire to measure parental satisfaction with the services provided (see appendix). It was reviewed and approved by a psychologist and pediatric intensivist, both members of the follow-up team.

In October 2007 parents of 469 patients received the questionnaire by mail including an informative letter and a prepaid return envelope. The questionnaire was not sent to parents whose child was known to have died at the time or who joined the program

later than mid 2006. Inclusion criterion was participation in the follow-up program for at least 6 months.

Parents who were known to have problems with the Dutch language (n = 19 parents) and did not respond to the first mailing received a Turkish or Arabic version if applicable. After 6 weeks a reminder was sent out to all parents who had not responded.

The study protocol was reviewed and approved by the Erasmus MC medical ethical review board.

Questionnaire

The questionnaire asked parents to express degree of satisfaction with the support from the various disciplines on a 5-point Likert scale (0 = very dissatisfied to 5 = very satisfied). "Not applicable" was to be scored when parents had not been in contact with a certain discipline.

Next, parents were asked to indicate agreement with seven negative and positive statements on the follow-up team as a whole. Parents could add a self-formulated statement if they wanted.

Then, parents were asked to rate intensity of use of the telephone helpline. Three response categories were available: never, not often, and often. In an open question we asked them what the nature of the questions had been.

Furthermore, parents were asked to express satisfaction with IC and MC hospital stay on a 5-point Likert scale (0 = very dissatisfied to 5 = very satisfied). Not-applicable responses were added because not all children are admitted to both units. We left room for parents to provide additional remarks. Lastly, using an open-ended question, we asked parents how the functioning of the follow-up team could be improved.

The questionnaire was not anonymous because we aimed to associate the parents' responses to intensity of contact with the follow-up team and to the child's type of anomaly. We put some effort into a nice and comprehensive lay-out (see appendix). The questionnaire had to be concise and different response categories were chosen to improve attention and to prevent automatic responses.

Data analysis

Results are given as mean and standard deviation (SD) for normally distributed data and as median (range) for data that deviate from normality. Chi-square tests are used for comparisons between groups on nominal variables. T-test was used to compare differences between two groups on normally distributed variables and Mann-Whitney test for non-normally distributed variables.

In the analysis, we distinguished parents as to ethnicity into "Dutch" (both parents born in the Netherlands and speak fluent Dutch) and "non-Dutch" (at least one parent born outside the Netherlands). We also distinguished between socioeconomic status, based on the profession of the parent who worked the most hours.

RESULTS

The overall response rate was 70.8% out of 469 surveys sent (Figure 13.1). Four of the 19 translated questionnaires (21%) were returned. Characteristics of the respondents and non-respondents are listed in Table 13.1. These groups differed significantly on two aspects: the proportion of parents of non-Dutch origin was lower among respondents ($p = 0.038$) and so was that of those who never showed up for follow-up evaluations ($p < 0.001$).

Two hundred and six questionnaires were completed by mothers (62.0%), 22 by fathers (6.7%) and 99 (30.3%) by parent couples in unison. For five questionnaires this information was missing.

Degree of satisfaction with the different disciplines is given in Figure 13.2. Eighty percent of the respondents were very satisfied or satisfied about the services of the social workers, to 92.3% of the parents about the nurses. Not applicable was to be scored when parents had no contact with the specific professional or did not remember it. For almost half of the respondents (48.0%) this applied to the psychologist, for 37.5% to the social worker, for 10.9% to nurses, and for 3.1% to physicians.

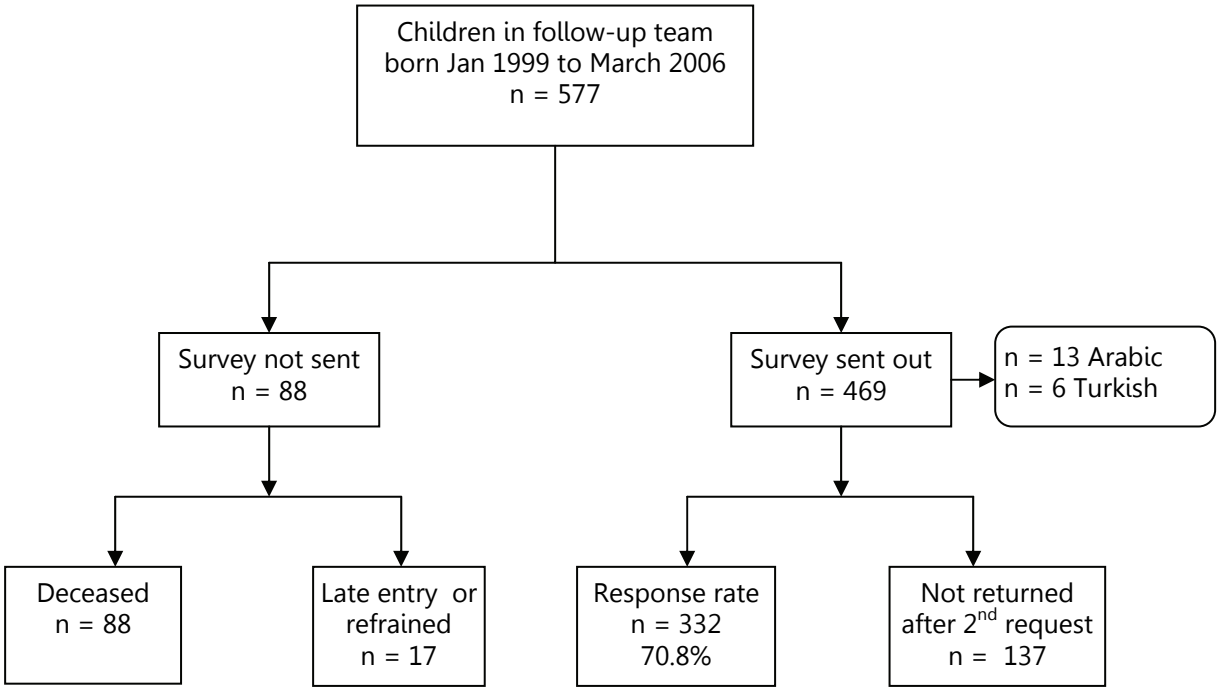


Figure 13.1 *Flowchart of sample.*

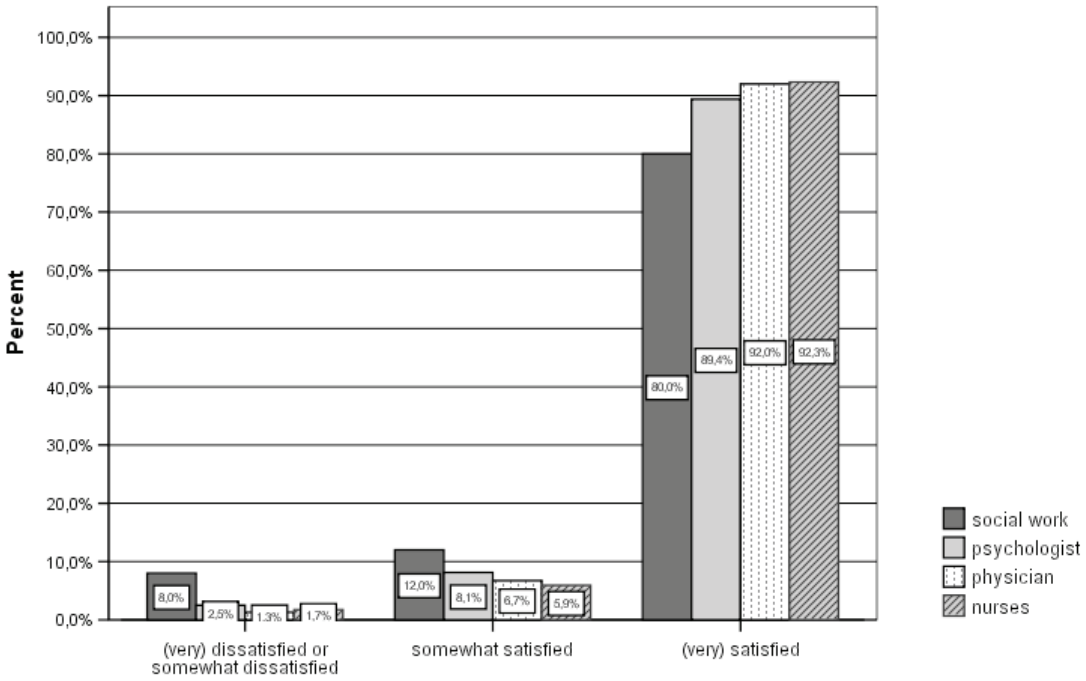


Figure 13.2 *Overall satisfaction with the various disciplines.*

Proportions of parents agreeing with the given statements are presented in Table 13.2. Seven parents (2.1%) did not address any of the statements nor added a self-formulated statement. More than half of the respondents agreed with the statement '*gives peace of mind because of regular check-up*'. Eighty-one respondents (24.4%) considered the follow-up team redundant (statement 3 in Table 13.2) or/and not needed anymore (self-formulated statement). The distribution of diagnoses did not significantly differ between 'redundant' and 'not redundant' groups (Chi-square test, p = 0.73). The children of the 'not redundant group' had significantly longer ICU stay in the first year of life (Mann-Whitney U-test, p = 0.02). The 'redundant' group included slightly, but significantly older children at the time of the questionnaire (56.3 SD 27.1 months versus 49.3 SD 26.8 months, t-test, p = 0.04), more parents with high SES (48.6% vs. 29.8%, Chi-square test, p = 0.01) and fewer parents of non-Dutch origin (8.7% vs. 19.4 %, p = 0.008).

Seventy-nine parents added self-formulated statements. Forty-four were positive (e.g. gives tailored support) and comparable to the positively formulated statements in Table 13.2. Seven statements were more or less negative; too little or too much supportive care, communication problems and taking up too much time.

Suggestions for improvement

One hundred and sixty-one parents (48.4%) provided suggestions for improvement. It appeared however that only 69 suggestions bore a direct relation to the team's functioning. Recommendations were made on improving visibility (number of the 24-hour telephone line, a face book showing a picture of all team members, a website and leaflets), communication (e.g. more focus on coping with the situation, more coordination of total care) and planning of outpatient clinic activities.

Table 13.1 Background characteristics of children and parents

	Respondents n = 332	**Non-Respondents n = 137**	**p-value**
Boy/Girl	190/142	76/61	0.41
Child's age at survey in months			
Median (IQR)	50 (28 to 73)	46 (24 to 69)	0.23
Range	6 to 103	6 to 104	
Diagnoses			
Intestinal anomaly (%)	84 (25.3)	26 (19.0)	
Hirschsprung's disease/anorectal malformation	53 (16.0)	26 (19.0)	0.10
Esophageal atresia	54 (16.3)	23 (16.8)	
Abdominal wall defect	45 (13.6)	28 (20.4)	
Congenital diaphragmatic hernia	58 (17.5)	14 (10.2)	
Miscellaneous	38 (11.4)	20 (14.6)	
Number of anomalies			
One	172 (51.8)	73 (53.3)	0.79
Two	80 (24.1)	35 (25.5)	
Three or more	80 (24.1)	29 (21.2)	
ICU stay during first year of life in days			
median (IQR)	12 (6 to 33)	15 (7 to 36)	0.13
SES			
Low	70 (21.1)	35 (25.5)	
Middle	129 (38.9)	42 (30.7)	0.12*
High	106 (31.9)	30 (21.9)	
Unknown	27 (8.1)	30 (21.9)	
One or both parent(s) non-Dutch origin*	57 (17.2)	35 (25.5)	0.038
Compliance with follow-up program after discharge home	24 (7.2)	18 (13.1)	< 0.001

** Parents born in Suriname or Dutch Antilles are considered Dutch. Twenty nationalities represent the non-Dutch parent(s) group,*
*** p < 0.001 when missing included in Chi-square test,*
Abbreviations: SES = socioeconomic status, ICU = intensive care unit, IQR = interquartile range.

Telephone contacts with 24 hour helpline

Twelve percent of respondents had called often, 49.2% not often and more than one third of the respondents (38.8%) had never called.

Intensity of seeking contact was significantly associated with diagnosis (Chi-square test, p=0.002). Percentages of callers (not often and often combined) varied from 80.8% of parents of children with esophageal atresia to 50.0% of parents of children with intestinal anomalies. Reasons for calling could be classified in three types. First, care-related or anomaly-related, such as questions about medication, defecation and nutrition (92 times). Second, general topics, such as practical issues, sleeping pattern,

cognitive development and behavior, crying and pain (57 times). Finally, somatic reasons, including colds, vomiting, fever and respiratory distress were indicated 43 times.

Satisfaction with hospital stay

Parental satisfaction rates with the MC and ICU are shown in Figure 13.3. Sixty-seven children never stayed at the MC. More than eighty percent of the other parents were satisfied or very satisfied with care provided in the MC. Even more parents (94%) were (very) satisfied with PICU care. Ninety-one respondents added comments about the ICU and/or MC stay. Of these, 35 were in line with the satisfaction scores given. Eleven remarks were neutral, e.g. referring to the fact that hospital stay was such a long time ago. Forty-five remarks were negative, of which 27 concerned the MC. Parents found the transition to the MC difficult and mentioned errors or communication problems. Most other negative remarks described the communication problems with physicians (n = 8). Other remarks varied from 'lack of a family-room' to 'lack of attention for the new mother'.

Table 13.2 Agreement (% of 332 parents) on statements about follow-up team*

		%
1	Gives peace of mind because of regular check-up	52.7
2	Offers indispensable support	37.0
3	Is superfluous in our situation	17.6
8**	Not needed (anymore)	8.1
4	Takes up a lot of time	7.6
5	Should be better organized	3.9
6	Gives insufficient support	3.3
7	Replaceable by general practitioner	3.0

** Parents could agree with any number of statements, ** self-formulated statement.*

DISCUSSION

The majority of parents who responded to this questionnaire were positive about the services of the follow-up team. Still, almost one-fourth of the 332 respondents – with an overrepresentation of parents of higher SES and with older children – indicated these services were not or no longer needed. There is every reason to assume that a considerable proportion of non-responding parents considered the follow-up team no longer needed as the morbidity of most of the children last not more than one year after birth. Only few of the parents of non-Dutch origin found the follow-up team redundant or no longer necessary.

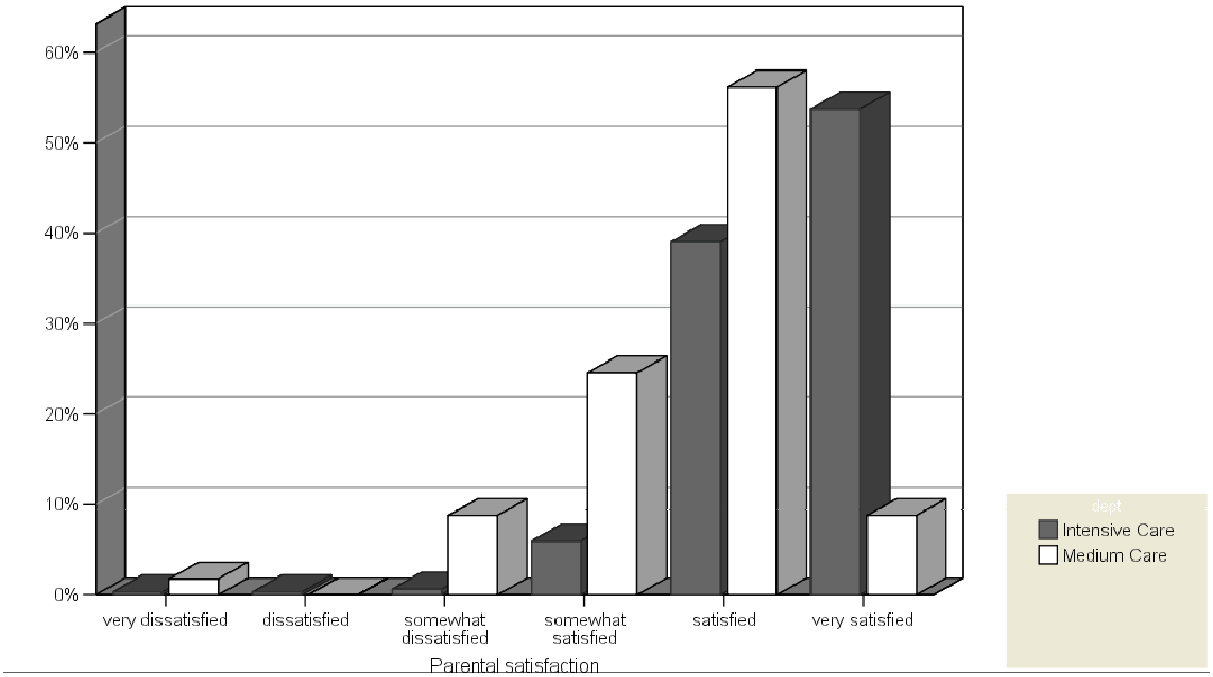


Figure 13.3 *Overall satisfaction with Medium and Intensive Care in percentages.*

There was a relatively high proportion of parents of non-Dutch origin (25.5%) among the non-responders. The response rate among parents who had received an Arabic or Turkish translation was only 21%, much lower than for the Dutch questionnaire. With more than 20 nationalities included in the sample, we may have missed a number of these parents due to language barriers and even illiteracy. Therefore, given the relatively low response rate among non-Dutch parents, our results may overestimate parental satisfaction, as we suspect that parents of non-Dutch origin experience more communication problems and cultural barriers than Dutch parents. A large telephone survey in the US among 36,238 parents of children with special health care needs, revealed that black and Hispanic parents were less likely to be satisfied with health care than white parents.[319] Language barrier was considered one of the key determinants of dissatisfaction and ease of using health care services.

In the present study satisfaction with social work was high, but nevertheless somewhat lower than that for the other disciplines. Interestingly, the 'not applicable' ratings for social work indicate that more than one third of the parents had no contact with the social worker. In future studies it would be valuable to document whether parents have declined support from a social worker, and if so, for what reason. Forty-eight percent of parents indicated 'not applicable' for the psychologist. This may be due to the fact that our psychologists do not offer services during hospital stay. Also focus is on developmental screening and child raising advice when parents encounter them at the outpatient clinic. Parents may therefore associate psychologists primarily with psychotherapy and therefore do not realize they represented the follow-up team.

Parents provided helpful suggestions for improvement. We learned, among other things, that the workings of the follow-up team should be explained more than once, notably before the child is discharged home. We also developed a refrigerator magnet with the relevant telephone numbers because parents indicated that they had problems contacting the team.

The 24-hour telephone helpline was useful for more than 60% of the respondents and most questions were related to the anomaly or co-morbidities. Elsewhere we have reported that this service was especially useful after initial discharge.[171] Satisfaction with transition from ICU to MC warrants attention. A transition program is now being developed in order to guarantee better continuity of care.

Measuring satisfaction is a complex phenomenon. Yet there are two validated parental satisfaction instruments for the PICU environment.[274] One of these instruments consisted of closed-ended questions using a Likert scale and parents were invited to provide comments. The combination of quantitative and qualitative data enabled the healthcare team to identify their best practices and 10 areas for improvement.[193] In line with this methodology of combining closed and open questions we developed our own instrument. The results of the present study, especially the explicit suggestions given by the parents, indicate that the services of the follow-up team can be improved by enhancing its visibility.

This study is relevant for several reasons. In today's health care arena, there is an increasing interest in cost-effective and patient-centered care. Along with cost-effectiveness, patient perceptions of the quality of services provided is a key factor in determining a health care organization's competitive advantage and survival, as observed by Ford et al.[159] This can be further clarified as follows. First, with the advent of consumerism and patient-centered care, it is increasingly important that health care organizations measure up to the expectations and needs of their patients. From this perspective, the findings of this study are positive, as the parents were highly satisfied on the follow-up team. Second, in the years ahead, there will be growing pressure on health care professionals and institutions to show that their treatments are worth the cost. Therefore, a complete evaluation of the follow-up team would have involved an assessment of all relevant costs and effects, such as the costs of organizing the team, possible savings on resource consumption, reduced productivity losses in the parents, and effects on the children's and parents' quality of life. This was however beyond the scope of the current study.

Limitations of this study

We refrained from using one of the existing validated surveys, such as the MAPS[236] because we felt these are not tailored to our specific parent group. Instead, we developed a new, short questionnaire that targeted the specific topics we wanted to address. By using a written self-report format we will have missed the parents who are

not able to write or who had insufficient command of the Dutch, Arabic or Turkish language. As the survey was sent from our institute and was not anonymous, parents might have felt reluctant to be completely open, bearing in mind that there is a dependent patient-doctor relationship. Furthermore, this survey was cross-sectional and therefore children's ages vary from 6 months to 8 years and with this the amount of contact the parents may have had with the follow-up team. Also, parents might have suffered from recall bias, especially those of the older children. Logistically challenging and scientifically more sound would be to ask parents to evaluate the follow-up team repeatedly and at set times.

CONCLUSIONS AND FUTURE DIRECTIVES

To conclude, it is increasingly acknowledged that children with severe congenital anomalies require continued care. The results of this study demonstrate that this multidisciplinary follow-up team responds in general to the needs of parents with a child born with a severe anomaly. In the future, we should strive to maintain and further improve the services of the follow-up team, for example by enhancing the visibility of the follow-up team and by optimizing the planning and coordination of care. Furthermore, it would be worth to use mail questionnaires in conjunction with other methods to generate patient satisfaction data, such as onsite personal interviews, focus groups, and employee feedback programs.

Parents are important partners in care, particular in this vulnerable patient group. Health care professionals should continue to carefully listen to parents and use their feedback to improve health care.

Hieronder staan een aantal vragen om de tevredenheid met het supportteam te meten.
Na het invullen van de vragenlijst deze graag in bijgevoegde antwoordenvelop opsturen.
Wij waarderen u mening zeer!

tevreden?

1. Wie heeft deze vragenlijst ingevuld?
   Juiste antwoord aankruisen aub.

☐ MOEDER
☐ VADER
☐ SAMEN

2. Graag met een cijfer van 0 tot 5 aangeven hoe tevreden of ontevreden u bent over de opnames in het Sophia. Omcirkel het meest toepasselijke cijfer of nvt als dit voor u niet van toepassing is.

0=zeer ontevreden en 5 =zeer tevreden

A.	Over de IC - Kinderchirurgie	0	1	2	3	4	5	
B.	Over de Medium Care	0	1	2	3	4	5	nvt

Eventuele toelichting:

_____

_____

_____

3. Graag met een cijfer van 0 tot 5 aangeven hoe tevreden of ontevreden u bent over de hulpverleners van het supportteam? Omcirkel het meest toepasselijke cijfer of nvt als dit voor u niet van toepassing is.

0=zeer ontevreden en 5 =zeer tevreden.

Artsen	0	1	2	3	4	5	nvt
Psychologen	0	1	2	3	4	5	nvt
Verpleegkundigen	0	1	2	3	4	5	nvt
Maatschappelijk werk	0	1	2	3	4	5	nvt

Eventuele toelichting:

_____

_____

_____

_____

4. Wat is voor u van toepassing op het supportteam? Aankruisen waar u het mee eens bent en meer dan één antwoord mogelijk.

Het supportteam.....

- ☐ Biedt onmisbare begeleiding
- ☐ Geeft rust omdat mijn kind regelmatig wordt onderzocht
- ☐ Kost wel erg veel tijd
- ☐ Is overbodig in onze situatie
- ☐ Zou beter georganiseerd kunnen worden ✎ zo ja, graag aangeven bij vraag 7
- ☐ Kan door de huisarts vervangen worden
- ☐ biedt te weinig begeleiding
- ☐ .....(door uzelf in te vullen)

5. Kunt U inschatten hoe vaak u het supportteam heeft gebeld om advies rond de zorg voor uw kind?

- ☐ Nooit
- ☐ Weinig
- ☐ Vaak

6. Waar gingen uw vragen over, voor zover u zich weet te herinneren?

_____

_____

_____

7. Heeft U nog suggesties voor het supportteam? Te denken valt aan de manier van introduceren, uitbreiding taken en verbeteren van communicatie.

_____

_____

_____

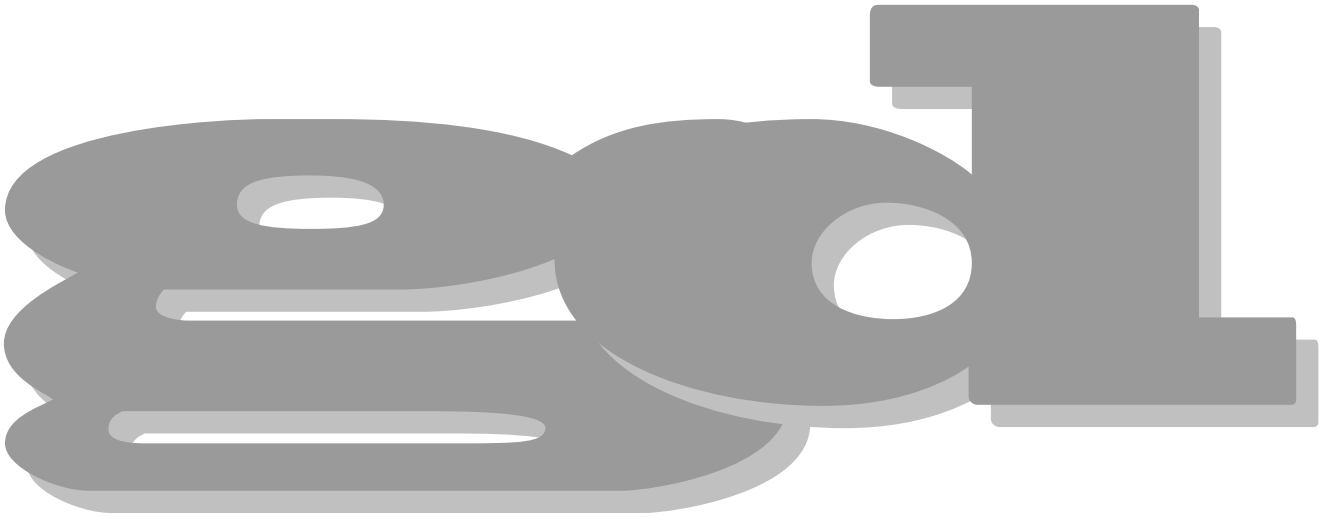
_____

_____

_____

_____

Hartelijk dank voor het invullen en opsturen van deze enquête!



General discussion

HOW TO IMPROVE CARE FOR THE CHILD WITH CONGENITAL ANOMALIES

Medicine is not only a science; it is also an art
It does not consist of compounding pills and plasters; it deals with the very processes of life, which must be understood before they may be guided

Philipus A. Paracelsus (1493 - 1541)

ANATOMICAL CONGENITAL ANOMALIES, AN OVERVIEW

Anatomical congenital anomalies are relatively rare. They occur in 2 - 3% of all neonates in the Netherlands.[140] Prevalence rates worldwide range from 2.6 to 6.9%, depending on inclusion criteria and surveillance systems.[140,76,345,472] Cardiac anomalies are by far the most common with an incidence of one in 120 to 160 neonates.[359] Incidences of the so-called index diagnoses[351] are lower. Of these, congenital diaphragmatic hernia (CDH) occurs most frequently, in about one in 2,300 neonates, followed by intestinal atresia (1 in 2,500), and esophageal atresia and gastroschisis (both 1 in 3,500). Omphalocele, Hirschsprung's disease and anorectal malformations are even more rare, with incidences of one in 5,000 neonates. While first relatively stable, the incidence of gastroschisis appears to have been increasing over the past two decades.[77,290,349,408,469]

Research into the etiology of the different congenital anomalies is ongoing in our institution: Klaassens et al. investigated the genetic origins of CDH,[177,253,254,375] and Felix et al. published on environmental origins of esophageal atresia.[151,152,153] Still, for almost 80% of congenital anomalies the etiology is still partially or completely unknown. Prognosis for a large part depends on associated anomalies, found in 30 - 70% of children with one of the index diagnoses.[210] Not surprisingly, parents step into a period of fear and insecurity when their (unborn) child is diagnosed with a congenital anomaly. Antenatal ultrasound and amniocentesis for chromosomal or genetic analysis often do not fully answer diagnostic questions, further adding to parental insecurity.[45] Eventually, parents of a child with a congenital anomaly always have three universal questions:

1. Will our child survive and can it be cured?
2. What is the exact diagnosis and what is the underlying cause of the anomaly? Moreover, what are the implications for future pregnancies, older siblings and other members of the family?
3. What about quality of life if our child survives, and how will it impact ourselves now and later?

In spite of ever improving surgical reconstructive techniques and supportive intensive care treatment modalities – such as high frequency oscillation, inhaled NO, and ECMO – many children will continue to suffer from health related problems. We have encountered, among other things, persistent respiratory and gastrointestinal problems in CDH and EA, motor function developmental delay, impaired exercise tolerance, and severe psychomotor developmental delay in children with syndromal or chromosomal diseases. All these could have a major impact on the children's and parents' lives. Other sequelae, however, such as impaired physical growth, will have much less influence.

In view of these problems, follow-up by a pediatric surgeon only is thought insufficient. Friedman et al. advocate a multidisciplinary and holistic approach that allows not only for signaling, but also for follow-up of persisting neurodevelopmental or physical

problems not directly related to the surgeon's field.[165] Such an approach would also cover family-related physical and psychosocial aspects.

Nevertheless, multidisciplinary long-term follow-up of congenital anomalies is still relatively rare. Apart from the group of Friedman, Lally and colleagues made a plea for this approach in patients with CDH, in view of the complex morbidity.[165,271] Feldkamp and Botto recently sent out a call for multidisciplinary follow-up and research of children with gastroschisis.[148] Furthermore, there have been multidisciplinary registries aimed at improvement of patient care for pediatric surgical patients.[82,132] However, the 2004 AAP guideline for follow-up of prematurely born neonates published in 2004 still explicitly excludes children with congenital anomalies, as incidences are low and phenotypic expression shows overt variability.[158]

January 1999 – that early – saw the birth of a dedicated multidisciplinary follow-up team for children with congenital anomalies in the Erasmus MC-Sophia Children's Hospital. In 2001 children treated with ECMO became a target group as well, and a multidisciplinary intestinal failure team started activities in 2003. The ultimate goal of these initiatives: alleviating the burden of disease for both child and parents by offering even better care and lines of communication. For example, many children treated with ECMO show physical, but also developmental and behavioral problems.[35,34,62,71,172,308,348] Comparable neurocognitive problems are also found in pediatric and adult patients after having been on cardiac bypass.[300,364,379] Many of the problems encountered in ECMO-treated patients are also found in children with major congenital anomalies, and the patient populations partly overlap. The same holds true for patients with a short bowel syndrome, which condition mostly originates from a congenital anomaly.

PHYSICAL ASPECTS

After having followed 101 surgical neonates with different anomalies until the age of 2 years we could conclude that mainly children with CDH or esophageal atresia show impaired growth. Children with complicated abdominal wall defects show growth disturbances too. Children with small-intestinal atresia who did not develop a short bowel syndrome were found to grow normally.

Neurological deficit as defined in Chapter 1 was most prominent in children with CDH (24% suspect, 16% abnormal) and children with syndromal or chromosomal anomalies. Delayed psychomotor development was found in children with multiple anomalies or single anomalies that hampered mobility, such as large omphaloceles. Factors indicative for severity of disease have a negative influence on mental and psychomotor developmental outcome (Chapter 1). Chen et al. reported that up to 90% of a group of CDH patients showed psychomotor developmental delay.[86] We also showed that CDH patients had the worst neurodevelopmental outcome. Overall psychomotor scores were

significantly lower than mental scores, with lowest scores for CDH (-1SD at 6 and 12 months) (Chapters 1 and 2). In 2008 Friedman et al. showed that most of initially 112 CDH patients showed pulmonary morbidity, GER and neurodevelopmental delay at both 1 and 3 years of age.[165] Crankson confirmed these observations in a group of 45 CDH patients.[108] Persistent respiratory and gastrointestinal morbidity have been reported for children with esophageal atresia.[24,90,91,93,106,107] We found that these conditions persisted at least until the age of 5 years, and also noted persisting growth failure in CDH patients of this age. Persistent respiratory pathology and a persistent increased work of breathing may play an important role in growth failure (Chapter 2).

Esophageal atresia patients, too, showed growth failure and persistent respiratory morbidity as well as neurodevelopmental delay, again related to severity of illness and associated CA as negative predictors of outcome (Chapter 2). Likewise, several long-term follow-up studies in large groups of EA patients showed both respiratory morbidity and gastro-intestinal problems, varying from gastro-esophageal reflux to severe dysmotility and growth failure.[136,260,268,298]

South et al. showed normal neurodevelopmental outcome at two years of age in a group of 27 gastroschisis patients.[390] In our study population most patients with abdominal wall defects (n = 30) had an uneventful and mild clinical course. Neurodevelopmental delay in the first two years of life was noted in only two patients with a giant omphalocele: in one child with a chromosomal anomaly and one with hypoxic brain damage.

Patients with uncomplicated intestinal atresia without major chromosomal anomalies seem to have the best outcome of all patients followed by our team. Growth and neurodevelopmental outcome of these children at two years of age were within the Dutch norms (Chapter 1). Piper at al. (2008) recently reported good neurodevelopmental outcome in a group of 132 patients with intestinal atresia, dependent on associated anomalies and birth weight, but independent of the level of the intestinal obstruction. The maximum duration of follow-up was two years.[335]

There were relatively few neonates with anorectal malformations or Hirschsprung's disease in the present study (n = 6 and 7 respectively). These were the ones who had received intensive care; those admitted to the medium care units did not participate in the follow-up program at the time. In view of these low numbers and the fact that they cannot be considered representative for the whole group of neonates with these diagnoses we did not present outcome data on them. Others have reported normal growth for these children and acceptable fecal continence on the whole: good function in 58%, fair in 38% and poor in 4%.[18,357,358] Outcome in children with anorectal malformation varies with severity of the anomaly and with absence or presence of sacral agenesis.[282,357] Forty percent suffer from constipation up to age 5 years. In a large study by Peña soiling occurred in 57% of patients between 6 months and 13 years. From 0-

33% of adolescents with a low anomaly and up to 10% of patients with a high anomaly suffered from urinary incontinence. Adult patients with high anomalies tend to have fewer offspring, which points at infertility problems.[330] Both children and adults may show neurological deficit on the basis of spinal anomalies and a tethered spinal chord.

Most studies on neurodevelopmental outcome of children with congenital anomalies concentrate on the first three years of life.[165,173,299,316] Recently, de Kleine et al. advocated assessment of motor development in 5-year-old preterms with the Movement ABC, after having demonstrated that the pediatrician's evaluation generally is not sensitive enough to detect functional motor problems.[122] We therefore asked a pediatric physical therapist to administer the Movement ABC to 5-year-olds. Specifically gross motor function tasks were problematic in children with esophageal atresia and CDH. Severity of initial illness, number of associated anomalies and respiratory morbidity negatively influence the percentile score of total impairment on the Movement ABC (Chapter 2). Others have shown impaired motor function in children with congenital heart disease.[47,224] We also showed impaired maximal exercise capacity in patients with CDH and esophageal atresia (Chapter 3), like Zaccara and colleagues in patients with CDH and tracheo-esophageal fistulas.[474,475] We suggest that longitudinal follow-up and interventions aimed at stimulating motor function performance are important to prevent deterioration of motor function development and exercise capacity as a result of physical inactivity.

Genetics

In this thesis we have introduced the term multiple congenital anomalies (MCA), which refers to any combination of two or more major congenital anomalies (e.g. CDH, AWD, EA, cardiac defect, missing limb, etc). These anomalies develop before birth as a result of faulty development, infection, heredity, or injury. MCA may co-occur with minor structural abnormalities, either overt or subtle, e.g. syndactyly, clubfoot, abnormally formed ears. A clinical geneticist evaluated all children immediately after birth and several times thereafter, since many subtle dysmorphologic features tend to develop into overt ones. Esophageal atresia is commonly associated with anomalies of one or more organs.[120] Children with anorectal malformations often have associated anomalies or genetic defects, and in Hirschsprung's disease genetic defects are found as well.[66,74] Cohen et al. described that gastroschisis is associated not only with intestinal atresia but also with other anomalies in up to 17%.[98] Up to 69% of children born with omphalocele show associated anomalies.[157,408] Careful evaluation of our patients revealed a number of unexpected and rare diagnoses influencing short- and long-term outcomes (Chapters 5a and 5b). This knowledge gives families a better grip on their situation and enables them to make well-funded decisions about future pregnancies. The geneticist turned out to be indispensable in the follow-up team. Not only for physical examination of the patients and their families searching for dysmorphic features, but also for detecting chromosomal or genetic anomalies with new and advanced diagnostic techniques such as array comparative genomic hybridization and MLPA (Chapters 4 and 5). What's more,

genetic counseling rates improved after structural assignment of the clinical geneticist to the team (Chapter 4).

PSYCHOLOGICAL ASPECTS

Cognitive and psychomotor development

The present study yielded several new and interesting findings on development of children with anatomical congenital anomalies. Notably those with abdominal wall defects and CDH are prone to delayed psychomotor development within the first two years of life. Children with small intestinal anomalies had the best development, i.e. those without genetic defects (Chapter 1). Risk factors for mental and psychomotor developmental delay include length of hospital stay, number of surgical interventions, time on the ventilator, use of supplemental oxygen and septic complications. These factors are all indicative of severity of disease. Number of congenital anomalies, socio-economic status, and being (non-native) Dutch were also predictive of outcome and were risk factors for developmental delay in the long run.

We found developmental recovery to some extent at 2 years of age. Developmental assessment over the first 2 years, however, is still highly predictive of cognitive and motor outcomes at five years of age. Low mental and psychomotor scores are equally predictive for unfavorable cognitive and motor outcomes at 5 years of age (Chapter 7).

Contrary to many other studies aimed at assessing developmental outcome, we used a non-diagnosis-specific approach to inclusion in the study, based on the notion that merely having a major congenital anomaly is a common denominator. In our analyses type of anomaly did not predict development over the first 5 years (Chapter 7). Thus, we assumed that children with congenital anomalies have other common denominators, e.g. extended hospitalization, surgical interventions in the neonatal period, chromosomal anomalies and the like, which are more predictive for developmental outcome than a specific congenital anomaly. This could also explain that the developmental outcomes in our study are comparable with neurodevelopmental outcomes at 5 years in neonates treated with veno-arterial ECMO, seeing that these children have comparable severity of illness in the neonatal period.[34,35,173,174,196]

Our study included a substantial proportion of children (13.2% of 144) with additional syndromal or chromosomal disorders, conditions which as such may already give rise to severe psychomotor delay. These children are usually excluded from outcome studies, so that there are hardly any follow-up data for this group. This, as well as the fact that these disorders are frequent in children with congenital anomalies, formed the rationale to include these children. For the record, an analysis excluding these children revealed that mental development at an early age is still predictive for development at 5 years (Chapter 7).

So, all in all it is possible to make at early age a reasonably precise prediction of later cognitive development. Thus, parents of children with congenital anomalies may receive an early warning of foreseen problems and prepare themselves.

Earlier studies in our institution showed that up to 45% of children with congenital anomalies attend special education.[59,57] The present study revealed that 47% of the 144 children receive some form of support in education at age 5 years. Still, 86.3% is attending regular school at this age, albeit with some form of support in 38.6% (e.g. remedial teaching or medical support for physical disabilities).

Psychosocial development

Children with major congenital anomalies are generally considered to be at risk for problems in psychosocial functioning, as they have to undergo major neonatal surgical interventions and will experience temporary or persisting subsequent medical sequelae. From the perspective of developmental psychopathology, unsuccessful adaptation processes lead to problematic behavioral patterns.[92] Apparently, psychosocial problems are mainly caused by internal, rather than external influences, such as the fact of the anomaly. Wallander and Varni assumed that internal strengths moderate the influence of risk factors like congenital anomalies.[461] Adjustment to chronic illness in childhood could thus be moderated by internal strengths. Average or high mental development (as internal strength) might therefore protect from developing adjustment problems and behavioral problems. This is in line with our findings of a significant correlation for mental development, in relation to internalizing problem behavior, in the first 2 years as evaluated by CBCL (Chapter 10). At age 5 years relatively few children showed major problems. It should be noted, however, that children in general will not yet show many psychosocial problems at this age. In addition, many patients with isolated congenital anomalies have regained (almost) normal health status at 5 years, as was described for simple abdominal wall defects and isolated small bowel atresia without concomitant short bowel syndrome.[114,217,295,390] Children with persistent health problems interfering with normal social life, like children with anorectal malformations, show persistent or even emerging psychosocial problems at a later age when social acceptance of fecal incontinence becomes an issue and sexual functions start to develop.[207] Thus, clinicians should be aware that psychosocial problems might be present, even though patients do not explicitly report them, or could emerge at a later age.

Parents in our study population rarely report early psychopathology (before or at 2 years) as measured by the CBCL⁄1½-5 (Chapter 10). It could be that the relief parents feel after their child survives the neonatal period results in an initial tendency to problem denial. In general it may be difficult for parents to objectively judge their child's behavior, especially when it is the first-born. Moreover, it may be difficult for parents to admit to or recognize problem behavior in their child. Nevertheless, most of the parents in the present study seem to have adequate abilities to deal with their

child's psychosocial problems. As early as 1994 Cappelli et al. established this ability for parents of children with spina bifida.[81]

Parental burden, stress and quality of life

Parents of children with congenital anomalies are subject to many potential stressors which may place a heavy burden on them, especially in the initial period after birth.[83,208,340] Many studies on parental stress employed structured interviews and generic questionnaires not specifically geared to the parents of these children.[63,76,117,228,365] For this reason, we developed the Impact of a Child with Congenital Anomalies on Parents (ICCAP) questionnaire with specific domains of impact on parental burden. It can be used as an alert system to identify parents at risk of threatened quality of life and those in need of support from a psychologist or a social worker (Chapter 9). We suggest that discrepancies between parents may be due to lack of communication, unequal burden and other possible disturbances in parental relationship. Thus, in these cases parents might benefit from professional psychosocial support.

Severity-of-illness variables correlated with parental state of mind and feelings of fear and anxiety. The level of fear and anxiety felt for the child's future appeared to decrease over time. Parenting stress as well as parental mental and physical health were found to be comparable to the normal population after 5 years (Chapter 11). The acute severity of disease and the child's discomfort will mostly have abated over time. The literature also provides evidence that family functioning as a whole and quality of the parental relationship in the long run is mostly normal.[59] Families appear to have coping mechanisms which help them adapt to the difficulties they encounter when a child in the family has a serious medical problem.[309] Persisting severity of disease of the child, however, is a risk factor for parenting stress and parental general health.[22,81,207,269,429,] A Dutch nationwide multicenter evaluation of a group of children with anorectal malformations showed that parents of older incontinent children experienced relatively more stress, especially when the child was male.[204,205]

Rosenthal et al. described that parental burden and coping are influenced by the child's anticipated future and potential medical complications, life expectancy, recurrence risks, finding sources of social support, and ensuring that the child is receiving appropriate treatment. Burden could thus be alleviated by adequate and timely information to parents. In this respect, a significant contribution can be made by a social worker. A social worker can help patients and their families to cope with the practical and emotional concerns raised by the diagnosis and treatment of congenital anomalies. The social worker can also assist parents and siblings of the affected child in adjusting to illness and hospitalization, counsel families confronted with social and financial difficulties, intervene in crisis situations and provide information and referral on community resources for treatment and support. For this reason a social worker is a full

member of our multidisciplinary follow-up team. Moreover, it is the very reason why the social worker first introduces the team to parents.

PARENTAL INFORMATION AND EDUCATION

Parents should receive information on future perspectives as early as possible after the diagnosis, so as to reduce feelings of insecurity. Not only information on the physical aspects of the disease and the possible complications, but also on prognosis on the short and long term, and on genetic counseling.

Once children are discharged home, parental discipline strategies or skills become increasingly important for raising the child and managing child behavior, often more so than in healthy children.[21] From a developmental perspective, parenting issues shift from primarily providing nurturing and protection to providing firm support and setting limits.[393] In our experience, parents will tend to be overprotective, especially if the child has been severely ill and suffers from physical sequelae. It is important to educate parents on normalization strategies. This means treating the child as "normal" as possible, while still meeting special health care needs. Nurses can anticipate parental grief, reassure parents in their feelings, reinforce normalization strategies, and help separate their parental issues and feelings from those of the child.[240,241] In our multidisciplinary follow-up team, this role can also be fulfilled by the social worker. Adequate parenting may prevent behavioral problems. Moreover, different studies showed higher parental burden when children show behavioral problems.[296,307] Discussing parenting skills and attitudes as well as the child's future perspectives should therefore remain a focus of attention during the initial hospitalization and during the follow-up outpatient visits.

COSTS OF CARE

The fact that many different (para)medical specialists are involved may greatly complicate coordination of the patients' care: neither the organ specialist, nor the local physician usually assumes the duties of coordinator of care. It is unrealistic to expect effective and holistic care by individual specialists without the involvement of some coordinator of care who keeps a helicopter view of the patients and their families. Coordinating care is one way to reduce costs.

When initiating new teams into existing healthcare systems, assessment of the impact of such a team on the quality and cost of patient care is recommended. A review of the literature on multidisciplinary teams for meningomyelocele, Down syndrome or cystic fibrosis, mainly shows quality of care related outcome measures.[179,220,247,305,333] Cost effectiveness has rarely been evaluated for pediatric multidisciplinary teams. Still, cost

effectiveness for surgery of anorectal malformations and CDH has been established in our hospital.[340,338,339,341] Costs per quality adjusted life year (QALY) of treatment for both conditions were such that treatment for anorectal malformations has a favorable cost-effectiveness ratio compared with other evaluated healthcare programs.

Treatment of congenital anomalies often requires more than one hospital admission in the first years of life and many visits to the outpatient clinics.[86,87,209,315,466] For patients with esophageal atresia we found a mean of 30 outpatient visits in the first 2 years. Streamlining of outpatient logistics is recommended. Involvement of many different organ specialists often causes redundancy in diagnostics and results in many separate and uncoordinated visits to the hospital. This was previously shown for children with meningomyelocele, Down syndrome and craniofacial anomalies, and was the major reason for setting up multidisciplinary teams. Not only do these teams improve communication with the patient, but also communication lines between the different (para)medical specialists, eventually leading to coordinated care and a reduction in the overall cost of medical care[65,85,100,166,200,212,220,247,306,342,362,376,392] Improved communication between different subspecialists ensures better care.

Since not only primary but also secondary costs will eventually be reduced, the follow-up team ideally should prove to be cost effective. In this study, initial admission proved to consume most costs of care for children with short bowel syndrome. Furthermore, early introduction of home parenteral nutrition proved feasible for these children with the support of multidisciplinary intestinal failure team. Since this could significantly shorten the initial admission, health care costs may dramatically decrease.

The development of so-called clinical pathways is an important step in visualizing the different steps and responsibilities within the concept of resource utilization. These pathways will reveal redundancy of care, deficient infrastructure and the persistence of non-evidence-based procedures. It would seem, therefore, that clinical pathways extending from the initial admission into the period of outpatient care are useful instruments to evaluate the complex care for children with (multiple) congenital anomalies.

In this train of thought, our evaluation of patients with short bowel syndrome served as a model for evaluating resource consumption and achieving a climate in which there is room for considerations on resource utilization and eventually cost effectiveness (Chapter 6).

We also showed the feasibility of running a 24-hour telephone helpline at relatively low cost with a possible reduction in hospital visits and admissions and thus in costs. (Chapter 12)

ETHICAL CONSIDERATIONS

As advanced technology has increased the possibilities of survival, surgeons and pediatricians face the serious challenge of addressing the issue of futile treatment. Furthermore, now that many children born with congenital anomalies reach reproductive age, consequences for future generations should also be considered, including genetic and hereditary aspects, as well as health care costs.

With regard to end-of-life decisions before and after birth, we could distinguish between six outlooks:

1. potential for total recovery;
2. prospect of nearly normal life;
3. permanent medical care needed;
4. somatic and developmental sequelae;
5. serious somatic and mental damage, and
6. anomalies incompatible with life.

Decision making on what, when and how to treat should be tailored to the outlook foreseen for the individual child, and also take into account life years gained and quality of the rescued life.[334]

Some of these children are left with major physical, developmental or psychosocial sequelae. Psychosocial sequelae may not come to full expression until age 5 years, as there is still relatively limited social interaction with peers before this age. From our own experience and from other studies[59,167,201,233,310,454] we know, however, that children with chronic disease may develop more and more problems over time, especially when they have visible deformities or impaired continence and sexual function. We are thus obliged to consider the ethical aspects of improved survival, increased morbidity and chronic disease.

Consequences in terms of benefit of treatment and the potential for enhancing quality of life are not always clear. As Caniano stated, treatment options in cases in which there is significant prognostic uncertainty of outcome, should uphold the ethical values of respect for patient's best interests and parental authority to make medical decisions.[80] Full treatment does not necessarily justify ongoing treatment if the burdens of therapy become excessive, or significantly diminish the infant's quality of life. Deciding not to start or to withdraw life-prolonging treatment when there is no chance of survival is considered good practice both for pediatric surgeons and neonatologists in Europe.[111,211] The doctor's duty is not only to restore health but also to relieve suffering. This does not imply prolongation of life at any cost. The option of withdrawal of treatment may give parents time to consider their choices.[210] Parents' participation in the decision-making process is possible and valuable only when they have good understanding of the consequences of their choices and decisions.

Ethical dilemmas and resource utilization are inseparable. Improved survival rates in neonatal surgery are associated with a relevant rise in health care costs. A recent study in our institution showed that 4.4% of children admitted to the ICU were so-called long-stay patients. They formed 3.4% of total admissions and yet consumed 63% of the admission days, with concomitant costs (Naghib 2008, submitted). Meaningful ethical decisions and better insights into the effects of early-life surgical interventions on quality of life might help us to redirect financial sources to better treatment of treatable neonates.[211]

The overall outcome in this study would lead us to conclude that treatment is the most logical option. In individual cases, however, we should do well to decide whether treatment is in the child's best interest. Parents must be fully informed on possible risks and morbidity, so that they can prepare themselves for anticipated problems. Disease-related problems will typically manifest themselves in the first years of life, although some morbidity may not show until a much later age. Individualized follow-up is certainly indicated for children with specific diagnoses with a documented high risk of deviant outcome.

AT RISK POPULATION

One of the aims of this study was to identify children at risk for persistent morbidity: physically, developmentally, and psychosocially. We also sought to define parents at risk for increased parental burden, parenting stress and suboptimal adaptation to a child with congenital anomalies.

Child at risk

From a number of our studies (Chapters 1, 2, 3, 7, and 9) we concluded that having multiple major congenital anomalies increases the risk of persistent morbidity. Factors that unfavorably influence growth, mental and psychomotor development and motor function are: number of anomalies, length of initial hospital stay, number of surgical interventions, need for prolonged artificial ventilation and supplemental oxygen, extended use of sedatives, the need for medical appliances at home after discharge, as well as chronic physical morbidity and constant dependency on the medical system.

Below-average motor and mental development at a young age (from 6 months) are factors that predict poor outcome at age 5 years (Chapter 7).

Children with major neurological damage and those with chromosomal or syndromal anomalies are particularly at risk for developmental delay and numerous medical problems, like feeding difficulties, respiratory tract infections, and growth impairment. Clinicians need to be aware of these risk factors and initiate early evaluation and adequate support for the child.

Furthermore, parent-related factors could negatively influence the child's developmental outcome. Low socioeconomic status is a known risk factor. Comparable studies have reported that the neurological score together with the nature of the home environment and the child's family background are important determinants of cognitive development for very low birth weight children.[128,465] The study of Weisglas-Kuperus and colleagues compares well to the present study, because it was conducted in a similar setting. A parent not being native Dutch is another negative predictor. This is also dependent on the language spoken at home. If the first language of the child is not Dutch, it is more likely that the child will encounter learning difficulties in school. This has a negative influence on long-term motor and mental development and puts the child at a disadvantage. Remedial teaching should be considered for these children at an early age.

Specific risk factors

As shown in the Table gd.1 each individual index diagnosis carries specific additional risks.

Table gd1 Focus of attention for physical follow-up

	CDH	EA	AWD	SIA	ARM/HD	ECMO
Growth failure	++	+	+	+/-	?	+
Gastro-esophageal reflux	+	+	+/-	+/-		
Respiratory morbidity	++	++	+/-			+
Cardiac evaluation (RVH)	+					+
Motor function development	+	+	+	+/-	?	+
Abdominal muscle strength	+		++	+	?	?
Impaired exercise tolerance	+	+	+		?	+
Neurological complications	+				+	+
Audiometry	+					+
Scoliosis and/or chest wall deformity	+	+			+/-	
Sufficiency of scars	+	+	+	+	+/-	+
Vascular problems due to venous/arterial line/cannula	+		+/-	+/-		+
Fecal and urinary continence					+	
Chromosomal disorder	+	+	+	++	+	
Associated anomalies	+	+	+	+	+	+

Abbreviations: ECMO, Extracorporeal membrane oxygenation.
+ and ++ = evaluation (strongly) advised, +/- = evaluate on indication, depending on severity of anomaly, ? = Unknown and/or not evaluated in this study.

Congenital diaphragmatic hernia

Physical risk factors. Initial respiratory morbidity in CDH is determined by persistent pulmonary hypertension and the amount of lung hypoplasia.[131] These factors influence not only the need for artificial ventilation and supplemental oxygen, but also the need for ECMO therapy. This treatment modality is in itself a risk factor for unfavorable physical and neurodevelopmental outcome, as shown in Chapter 8.[196] Children with CDH had a 50% chance to develop moderate to severe bronchopulmonary dysplasia and 55% had recurrent respiratory infections in the first 5 years (Chapter 2). Muratore et al. and IJsselstijn et al. also showed increased pulmonary morbidity with mild persistent airway obstruction up to adolescence.[234,315] Therefore, long-term follow-up of lung function evaluating diffusion capacity, lung volumes, and reversibility of airway obstruction should be standard procedure. Severe respiratory morbidity may be associated with right ventricular hypertrophy. Liberal treatment with therapeutic antibiotics or even prophylactic use of antibiotics may be helpful to overcome a prolonged period of recurrent infections.

We showed significant growth failure without a tendency for catch-up growth as far as BMI was concerned, until the age of 5 years (Chapter 2); an observation in line with Cortes[105] but not with Marven.[299] We would advise early consultation by a dietician, since growth failure might be based on increased work of breathing and be alleviated through better caloric intake.

In our study 80% of CDH patients had a history of gastro-esophageal reflux, and 35% of all patients underwent a Nissen fundoplication. Reflux and persistent feeding problems are also described in the literature.[227,244,261,316,444] Therefore, evaluation of reflux is important, especially when children show impaired growth.

Septic complications, prolonged use of diuretics, and ECMO treatment are risk factors for sensorineural hearing loss.[105,272] Hearing should not only be screened in the neonatal period but also at age 5 years, because hearing loss may not manifest itself until a later age.

Anomalies of the diaphragm and lung hypoplasia are both associated with chest wall deformities and scoliosis.[271,294,422,443] During physical examination special attention should be paid to these deformities.

We also showed impaired motor function development, mainly of gross motor function skills, and decreased exercise tolerance. Several factors may contribute to these problems:

1. highly severe illness, hindering the child in motor development;
2. increased respiratory and gastrointestinal morbidity;
3. overprotective behavior of the parents as described in Chapter 3.

The latter factor has been suggested to be of importance in children with congenital cardiac anomalies.[47,224] Early intervention by a pediatric physical therapist in combination with education of the parents may be useful to prevent problems.

Developmental risk factors. Determinants of neurodevelopmental outcome are: duration of artificial ventilation and supplemental oxygen, and ECMO treatment.[9,105,165,350] We confirmed these findings in Chapters 2 and 8. Even though total IQ scores are within the norm, children after ECMO treatment have disharmonic cognitive profiles and are at risk for attention deficit.[35,235,271,321] Thus, as we suggested in Chapter 7, concentration and memory should be targets of neuropsychological assessment at 8 and 12 years.

Esophageal atresia

Physical risk factors. Patients with esophageal atresia are at risk for persisting respiratory morbidity, on the basis of tracheomalacia and recurrent infections.[8,90,106,280] We found recurrent infections and increased small airway obstruction in 74% and 26% respectively (Chapter 2). Long-term pulmonary follow-up is indicated. Children with recurrent respiratory tract infections should be given antibiotics liberally.

Gastro-esophageal reflux and feeding problems were found in 80% of patients. As in CDH patients, 35% underwent a Nissen fundoplication (Chapter 2). The number of respiratory infections did not differ between children with and without a Nissen fundoplication, implying intrinsic pulmonary morbidity and not reflux as a cause.[280] Persistent abnormal esophageal motility was also described in the literature but not investigated by us.[93,136,280]

We found growth failure mainly in the first few years, with catch-up growth by age 5 years. This might be due to the initial morbidity we found in 70% of patients, including respiratory infections, reflux, and strictures of the anastomosis. Thoracic deformity, either as a result of thoracic surgery or on the basis of vertebral anomalies, should be evaluated. In general, associated anomalies are found in up to 50% of esophageal atresia patients. We showed that 78% of patients had associated major and minor anomalies (Chapter 2).

Developmental risk factors. Esophageal atresia patients are also at risk for abnormal motor development and decreased exercise tolerance, to the same extent as CDH patients (Chapter 3). Similar contributing factors need to be evaluated and addressed:

1. severity of illness, hindering the child in motor development;
2. increased respiratory and gastrointestinal morbidity;
3. overprotective behavior of the parents.

Early intervention by a pediatric physical therapist in combination with education of the parents may be useful in these patients as well.

Abdominal wall defects

Physical risk factors. The outcome for children with omphalocele depends on size of the defect and on the presence or absence of associated anomalies, including syndromal and chromosomal anomalies.[425] There is a risk for persisting gastro-intestinal morbidity and growth failure. Especially giant omphalocele may be associated with persistent respiratory morbidity. Long-term morbidity in children with gastroschisis is related to the presence of intestinal hypoperistalsis and the occurrence of necrotizing enterocolitis. Moreover, the co-occurrence of intestinal atresia and possibly short bowel syndrome determines morbidity or even mortality at a later stage. Some of the patients may end up with end-stage liver failure due to a combination of parenteral nutrition-associated cholestatic jaundice and recurrent central venous line infection.[325]

Developmental risk factors. The abdominal musculature, as in all patients after abdominal surgery, may have weakened even at older age, with an increased risk for low back pain as described in Chapter 3. Early intervention by a pediatric physical therapist is advisable for these children as well.

Small intestinal anomalies

Physical risk factors. Children with small intestinal anomalies are at risk for persistent gastro-intestinal morbidity including short bowel syndrome as described above. This risk is low for isolated and uncomplicated cases. Especially associated chromosomal anomalies, such as Down syndrome in duodenal atresia, tend to lead to persistent morbidity as also described in Chapter 5a. Active screening for associated anomalies in the neonatal phase is considered state of the art in this patient population.

Developmental risk factors. As in all patients undergoing abdominal surgery, there is a risk of abdominal muscle weakness. Screening as described in Chapter 3 is advisable and intervention by the pediatric physical therapist should be initiated if indicated. Children with home parenteral nutrition will have restricted movement due to the central venous line; this may be an important cause of developmental delay.

Anorectal Malformation and Hirschsprung's disease

Physical risk factors. Children with anorectal malformations or Hirschsprung's disease are at risk of severe constipation, fecal incontinence, urinary incontinence, and impaired sexual function. These morbidities are more prominent in children with more severe forms of the anomalies. Children with severe forms of anorectal malformation, especially those with sacral agenesis, are at risk for a tethered cord with concomitant morbidity. Careful neurological evaluation is indicated. Children suffering from neurological dysfunction or those with severe vertebral anomalies should also be screened for orthopedic problems such as scoliosis. For each individual group the associated anomalies may further increase morbidity.

Developmental risk factors. Children with fecal and urinary incontinence, and at a later age sexual dysfunction, are at risk for deterioration in disease-specific functioning or psychosocial competencies and might, therefore, require extra care, both physically and psychosocially.[204] Social isolation and low self-esteem have been documented for these children. The above also holds true for children and adolescents with a severe form of the disease (e.g. the presence of an enterostomy) or with additional congenital anomalies. Moreover, Hartman et al. reported that adolescent and adult patients feel they need more non-medical and psychosocial support.[206] Early information may reduce problems.

Parents at risk

Children making more physical demands on the parents negatively predicts parenting stress and the parents' general health (Chapter 10). Persisting dependency on the medical system predicts negative parental outcome (Chapter 11). Early support by a social worker during admission and referrals for psychological support after discharge are to be considered. We feel it is very important to give parents adequate information on the child's medical condition and have found that the same information has to be given repeatedly. Our experience is that in the initial phase emotions seem to interfere with processing of the information given.

Furthermore, low socio-economic status and parents not being native Dutch are demographic risk factors. We experienced that a language problem further hampers the information exchange with parents in an already difficult situation. Moreover, parents who are not native Dutch often have a harder time finding their way in the medical system and in our opinion need more support. Also, cross-cultural differences and culture-determined views on parental duties, the meaning of disease and family centered care may warrant extra attention of the medical and psychosocial support services.[307] Earlier studies show that pre-existing coping strategies are predictive for parental outcome.[37,94,252,281,473]

STRENGHTS AND LIMITATIONS OF THE STUDY

Strengths

This study is the first Dutch study that provides longitudinal prospective data on a large group of patients with different major congenital anomalies. It became apparent that they share many common characteristics. Usually these children are excluded from follow-up studies of neonatal or pediatric intensive care. We showed that it is not always necessary to exclude them from follow-up studies, since many psychosocial and developmental aspects are comparable to those in prematurely born children or children with chronic disease.

Follow-up is planned to extend until the age of 18 years. Thus continuity of care over the years can be guaranteed, enabling smooth transition of care to specialists for adults. The multidisciplinary follow-up program focuses on medical, developmental and psychosocial issues. This results in all-round care for the patient, rather than just focusing on physical function and disability. Moreover, early signaling of developmental problems facilitates targeting for early intervention.

Another strong point is that the impact on parents was evaluated for mothers and fathers separately. They were found to react differently. Moreover, mothers and fathers also separately evaluated child behavior, which provided a more than monistic view on the child. Furthermore, we assessed parental satisfaction with the multidisciplinary care as described in Chapter 13.

Limitations

The separate diagnosis groups included only limited numbers of patients, which hampered comparison to existing literature. This was the case especially for Hirschsprung's disease and anorectal malformations. Moreover, the patients with these two index diagnoses were not representative for the anomalies, because they suffered from major syndromal or associated anomalies. Still, these patients generally are known to be at risk for long-term physical and psychosocial problems.[19,20,183,194] On the other hand, an approach as described here has seldom been reported for these children.

Initially children were only included in the follow-up program after initial admission to the intensive care unit. This design reduced the total number of patients included and influenced the severity of disease of children initially included. Thus, the overall picture might not be fully representative of the entire spectrum of disease in this population.

Follow-up data so far do not extend beyond age 5 years. The picture presented is still limited, therefore, and sometimes difficult to interpret, e.g. in the case of pulmonary function, but also abdominal muscle strength. Pulmonary function testing was hampered because technical skills of most 5-year-olds were insufficient. Thus we have to continue pulmonary function testing in older children to be able to make adequate predictions.

A relatively large number of patients were lost to follow-up. This may have influenced our results in several ways. A number of parents of children with good outcome considered follow-up unnecessary (Chapter 13). This might have negatively influenced our findings. A number of children with syndromal or chromosomal abnormalities were referred to specific programs for the mentally severely handicapped. Follow-up was often also handed over to these care systems in order to avoid redundancy.

Although they are known to have a higher risk for additional problems, the children and their parents that were not native Dutch were often (partially) lost to follow-up. One

possible reason is the language problem. Alternatively, it might even be more reflective of cross-cultural differences. From the survey described in Chapter 14 we know that children with over 20 different nationalities were enrolled in the program. So far we have gathered insufficient information to be able to pinpoint the specific problems in this group of patients and their parents.

Our study describes a single center experience, except for the follow-up of ECMO patients. Earlier multicenter studies have been performed in the Netherlands under the guidance of the Dutch Society for Pediatric Surgery, such as the NAHO study on long-term outcome for patients with anorectal malformations or Hirschsprung's disease as described by the group of Aronson.[204]

Finally, with regard to costs involved, our study did not extend to evaluating secondary costs like parental medical consumption and loss of productivity in work. Still, the infrastructure we built forms the basis for future evaluation of resource utilization for the specific diagnoses.

CLINICAL IMPLICATIONS

- Severity and complexity of the defects in patients with congenital anomalies require a structured long-term program of care, aiming primarily at the best functional outcome, with a minimum of procedures and optimal cost-effectiveness. A multidisciplinary team optimally provides this comprehensive and coordinated care. There is international consensus about the fundamental elements of treatment of congenital anomalies: multidisciplinary teamwork, centralization, team continuity, long-term treatment planning from birth to adulthood, standardized protocols, documentation, evaluation, follow-up studies, research, training and quality assurance. The multidisciplinary team should consist of pediatric intensivists/pediatricians, pediatric surgeons, psychologists, clinical geneticists, pediatric physiotherapists, pediatric nurses, and social workers.
- The follow-up program should include pulmonary function testing for children with congenital diaphragmatic hernia, esophageal atresia, giant omphaloceles, as well as children treated with ECMO, and others with structural pulmonary pathology.
- Long-term follow-up into adulthood of these children and their families is needed to provide them with optimal care; physically, neurodevelopmentally, and psychosocially. The appendix provides the scheduled approach.
- Optimal cooperation between the hospital-based care facilities and primary caregivers should be aimed for. One of the ways to reach this is to develop a personalized health 'passport' for each patient in which medical characteristics and possible complications are outlined. Moreover, general practitioners have to be better informed by the secondary and tertiary caregivers on the entire spectrum

of pathology and morbidity in these children. A standardized discharge protocol including information to primary caregivers may help in reaching this aim.

- Counseling by a clinical geneticist should be an integral part of multidisciplinary care. It should, moreover, be extended from the early childhood phase, in which mainly the parents are counseled, to counseling of the patients themselves, covering health risks for future offspring and pregnancy-related morbidity.
- Early intervention programs that stimulate the cognitive development of children with congenital anomalies are best applied as early as possible.
- Early discharge, if necessary with use of medical appliances at home, should be aimed for. In spite of increased parental burden, this approach is of major benefit to both for child and parents.[368] This implies early parental involvement in care-giving, as shown for home parenteral nutrition in patients with short bowel syndrome.
- Twenty-four hour access to expert care is highly appreciated by the parents and contributes to their wellbeing.
- Contact with a social worker should be stimulated for all parents from the beginning of the initial admission and preferably already before birth of the child, if an antenatal diagnosis has been made. This could alleviate initial parental burden and may promote information processing by the parents.
- The findings from this study can be directly used to inform parents of children with congenital anomalies. The message to parents should be that certain characteristics lead to higher risk for developmental, psychosocial and behavioral problems, which might abate when properly anticipated.
- Initially parents react differently. After five years, however, fathers and mothers show comparable reactions and parental burden. This knowledge provides directions for better targeting psychosocial support services, for example to place a focus on coping strategies.
- The multidisciplinary partnership of this follow-up team forms a blueprint for a successful collaboration, which may be duplicated by dedicated follow-up teams for other pediatric diseases. Apart from direct patient-centered and disease-targeted care, an effective program needs to address administrative issues, patient recruitment, ongoing team education, and community outreach.
- We aim at early risk identification of child and parents during the initial admission and development of a tailor-made follow-up program based on identifiable risk factors. This is superimposed on a generic follow-up program of all children with a major congenital anomaly and their families, both in time and structure.
- In order to ensure optimal quality of care and optimal use of data both for patient care and research, a data manager and a database storing all relevant data are indispensable. Data to be collected should be standardized in all Dutch intensive care units interested in follow-up care of children after intensive care treatment.

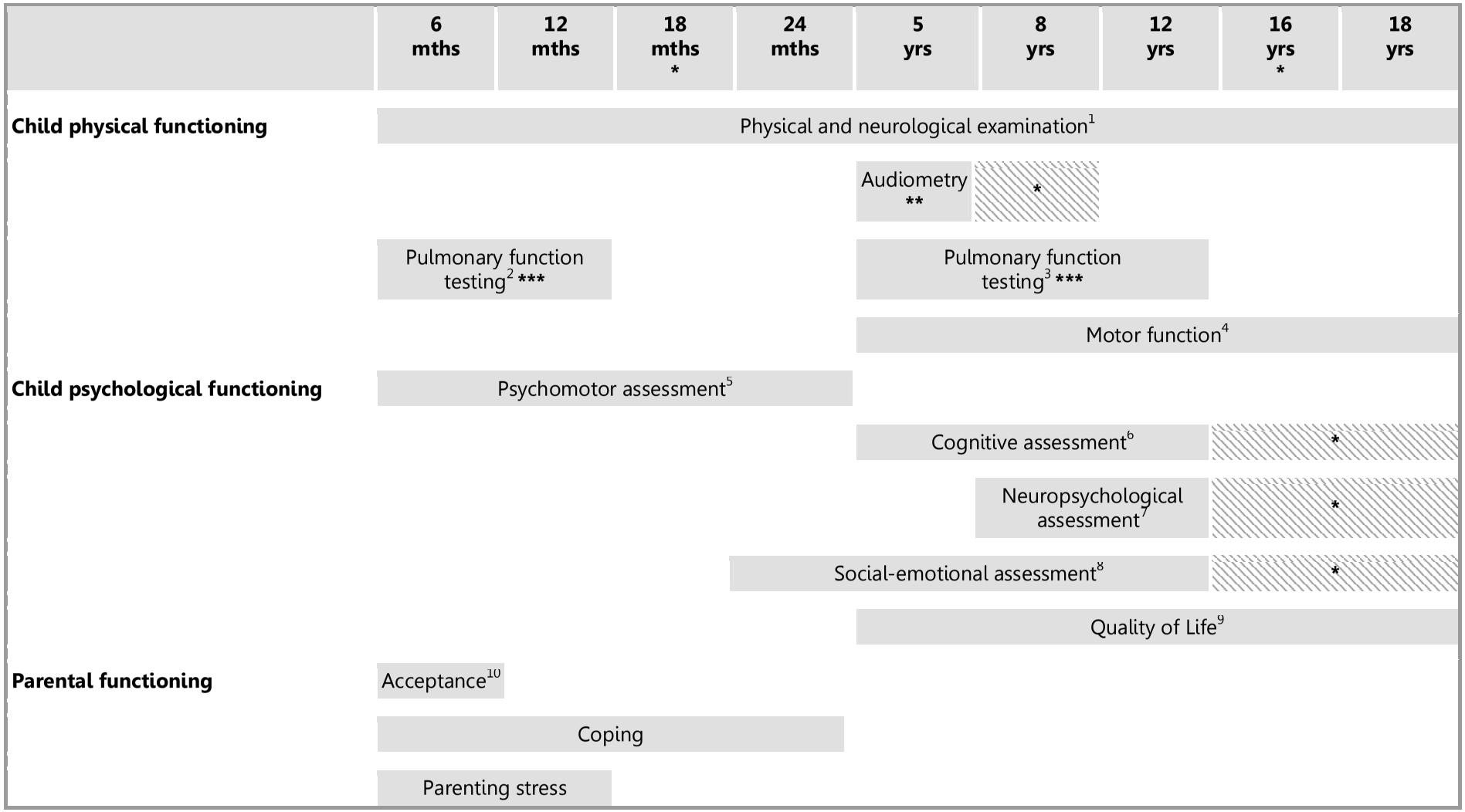
Areas of future research

- We need to get an early impression of respiratory morbidity. Thus we might be able to prevent secondary morbidity by early therapeutic interventions. This implies infant lung function testing in designated patient populations as shown in Appendix.
- More patients should be included in follow-up studies, notably those with anorectal malformations, Hirschsprung's disease or abdominal wall defects. One of the means to reach this goal would be to include children admitted to the medium care wards as well. A second option is setting up multicenter studies, an approach which additionally provides better representativity of the patient group.
- Extended, structured and standardized follow-up studies until adolescence addressing issues like growth, puberty, respiratory morbidity, abdominal muscle strength and its physical consequences, such as backache at a later age, will help us to adequately target care and interventions and to prevent unnecessary morbidity.
- Evaluation of the results of extended follow-up until the age of 18 will lead to information needed to develop a transition program to adult medicine, as also described by Van Staa et al.[440]
- Now that many children born with congenital anomalies reach reproductive age, consequences for future generations should also be analyzed. An important consideration is the risk of anomalies being transmitted, an aspect that might be vital in opting to have offspring or not.
- One of the future challenges will be to link phenotypes derived from mice gene knockout studies to phenotypes of human patients. This will yield information about the roles of genes involved in abnormal embryology leading to human anomalies. Moreover, routine karyotyping together with molecular genetic evaluation of DNA and tissue of patients with congenital anomalies will gain more insight into the etiology of these anomalies.
- Several aspects studied have not been analyzed sufficiently:
- Language development, especially early discrepancy between active and passive language development, is important as an early indicator of mental development;
- Behavioral development is important both for evaluating the child's psychosocial development and for targeting parental education;
- Quality of life across time from 5 years of age onwards assessed by both the child and the parents is essential in all-round care.
- Further analysis of the above aspect will broaden our knowledge on the development of these children.

Other areas of future research are the following:

- Further research into the level of education and additional support children receive within the educational framework.
- Research into the impact of the antenatal diagnosis of a child with a congenital anomaly on parental state of mind, and the influence of antenatal psychosocial support on postnatal parental burden.
- The impact of the birth of healthy children on parents who already have a child with a congenital anomaly and analysis of considerations playing a role in deciding on future pregnancy.
- Further research into the implications of having a child with congenital anomalies in the non-native Dutch population. In Rotterdam over 35% of the population is non-native Dutch and the birth rate in this population is more than twice that in the native Dutch population at this time. Thus it is important to know how, when and where to target support in this population.
- Quantification of economic consequences and secondary medical consumption by parents (e.g. evaluating use of '*PersoonsGebondenBudget*', medical consumption, change in paid jobs) in collaboration with the Erasmus MC institute of Health Policy and Management, iBMG. Previously Brouwer et al.[262,430,431,437,438] published on economic considerations on informal care. Moreover, resource consumption and cost-effectiveness as previously analyzed by Poleij et al. should be further documented.[339,340] Cost efficiency and effectiveness are gaining importance in medicine and should be integrated into our thought processes on medical care. Coordinated care in an early phase is likely to reduce secondary medical costs and medical consumption of both the patient and the primary caregivers in the long run.
- Both follow-up and research should be extended to other patient categories, eventually including all patients who underwent intensive care treatment. This research should be in the form of a multicenter study in order to obtain larger numbers of patients and should include patients with complex cardiac anomalies, heart transplant patients, patients with traumatic brain injury and sepsis patients.

APPENDIX A suggested approach for follow-up of children with congenital anomalies and their parents



** Optional test moments, indicated by clinical problems,*
*** Only for patients at risk for sensorineural hearing loss,*
**** Only for patients treated with ECMO, CDH and esophageal atresia patients.*

[1] Standardized physical and neurological examination including weight, height and head circumference. Standardized neurological examination.

[2] Pulmonary function tests: at age 6 and 12 months: FRC_p by whole-body plethysmography, $Vmax_{FRC}$ and LCI.

[3] Pulmonary function tests: at age 5 years: flow-volume curves before and after bronchodilation with 400 µg salbutamol and measurement of the fraction of exhaled NO (FeNO) and LCI. At 8, 12 16 and 18 years, flow-volume curves before and after bronchodilation with 400 µg salbutamol and measurement of the fraction of exhaled NO (FeNO). bodyplethysmography, He-dilution spirometry, diffusion capacity, LCI.

[4] Instrument: Movement Assessment Battery for Children (M-ABC) used from the age of 5 years and/or Movement Assessment Battery for Children, second edition (M-ABC-2) used for children from 3 years to 16 years and 11 months,[215,216,387] motor coordination,[467] Bruce protocol for maximal endurance testing,[68] Beigthon score for hypermobility.[432]

[5] Instrument: Assessing the mental and psychomotor development using the Bayley Scales of Infant Development–Second Edition–Dutch version. (BSID-II-NL).[30,433]

[6] Instrument at 5 and 8 years of age: the short version of the Revised Amsterdam Children's Intelligence Test (RAKIT) for children aged 4 to 11 years.[49,50] From the age of 12 years: Wechsler Intelligence Scale for Children Derde Editie NL (WISC-III-NL).[266] At the age of 18 years: the Dutch version of the Kaufman Adolescent and Adult Intelligence test (KAIT).[314]

[7] Instruments: The Developmental Test of Visual-Motor Integration for children aged from 3 to 18 years (VMI-Beery).[32] Bourdon-Vos Test, for assessing selective-attention for children aged from 6 to 18 years.[458]

[8] Instruments: Child Behavior Checklist/1½-5 (CBCL/1½-5),[3,354] Child Behavior Checklist for Ages 6 - 18 (CBCL/6-18),[4,451] Teacher's Report Form for Ages 6 - 18 (TRF),[5,452] Youth Self-Report for Ages 11 - 18 (YSR),[6,45] Self-Perception Profile for Children (SPPC),[203,449] Self Perception Profile for Adolescents (SPPA)[202,424]

[9] Instruments: The Pediatric Quality of Life Inventory (PedsQol).[29,44,447]

[10] Instruments: The Impact of a Child with Congenital Anomalies on Parents (ICCAP) questionnaire; a psychometric analysis ICCAP (also used at 6 weeks after birth).[304]

Summary

Samenvatting

No burden is too heavy when shared with a friend

Anon

SUMMARY

Survival of children with major anatomical congenital anomalies is improving. This coincides with proportionately more morbidity. To gain more insight on these children's development over time, we started a multidisciplinary follow-up program designed to monitor these children and their parents from birth until adolescence. It was hoped we could thus alleviate their burden of disease. In this thesis we describe the results of the first five years of the program.

Part 1 goes into different physical aspects.
Chapter 1 describes a study performed from 1999 to 2003 of 101 children with major congenital anomalies, admitted to the intensive care unit. In this study we looked at outcomes over the first 24 months and tried to establish determinants of outcome. Children with congenital diaphragmatic hernia or esophageal atresia showed impaired growth. Overall neurological outcome was normal, but 40% of patients with congenital diaphragmatic hernia showed suspect or abnormal outcome. Three characteristics proved to be significant determinants of mental and psychomotor outcome as determined with the Bayley Scales of Infant Development: number of major anomalies, length of initial hospital stay, and number of surgical interventions. Overall mental development was normal, but psychomotor scores were significantly lower than the norm (95% CI 82.6 to 90.7 at 6 months and 89.2 to 99.2 at 24 months respectively). Sex, socioeconomic status, type and number of congenital anomalies, severity-of-disease, and need of medical appliances at home could significantly predict negative outcome ($p < 0.05$). Overall, survivors of congenital anomalies are at risk for impaired growth and psychomotor developmental delay up to age 2 years.

Chapter 2 describes a prospective comparative study on growth, persistent gastro-intestinal and respiratory morbidity, physical condition and motor development in children with esophageal atresia (EA) or congenital diaphragmatic hernia (CDH). Children were seen at 6, 12 and 24 months and at 5 years of age. Both groups showed significantly impaired growth. In esophageal atresia patients, though, catch-up growth was seen at the end of the study period. ECMO treatment in CDH patients was a negative predictor for growth. Both groups showed gastro-esophageal reflux and feeding problems; a Nissen fundoplication to surgically treat the gastro-esophageal reflux was needed for 35% of children in either group. Respiratory morbidity in the form of bronchopulmonary dysplasia was found in 50% of CDH patients (81% of ECMO-treated CDH patients), and recurrent respiratory tract infections were found mainly in EA patients. In both groups, pulmonary function testing revealed abnormally low % predicted of FEV_1 in 25% of patients. Although tracheomalacia is well known in patients with EA, the incidence of other persistent respiratory morbidity was found to be underestimated. These conditions require structured evaluation by a pediatric pulmonologist.

Both in EA and CDH patients the maximal exercise tolerance was significantly below the norm ($p = 0.02$ and $p = 0.012$, respectively). Motor function assessment by M-ABC at 5 years of age showed normal motor function performance in 63.6% of EA patients and 61.1% of CDH patients. All other patients showed borderline motor performance, i.e. were at risk for impaired motor function. These proportions are significantly different from the expected proportions ($p = 0.02$ and $p = 0.01$ for EA and CDH, respectively). We concluded that both EA and CDH patients are at risk for diverse persistent morbidity.

Chapter 3 describes the detailed motor development as tested by M-ABC, and maximal exercise capacity of 79 children with different congenital anomalies at the age of 5 years. Again, severity of initial illness, number of associated anomalies and respiratory morbidity negatively influenced outcome. 73.4% had a total impairment score within the normal range, 16.5% were classified as borderline and another 10% as having a motor problem. This distribution is significantly different from the distribution in the norm population (Chi square $p = 0.01$). Ball skills were impaired in CDH and EA patients; both EA and small-intestinal atresia patients had more problems with balance. The total percentile score of M-ABC correlated negatively with the total number of major anomalies ($r_s = -0.35$, $p < 0.01$), and positively with the number of dynamic sit-ups ($r_s = 0.44$; $p < 0.01$, $n = 71$) and the maximal endurance time from the Bruce test ($r_s = 0.31$; $p = 0.01$, $n = 62$). We observed more motor problems, especially on gross motor function tasks, in children with EA and CDH. These were associated with long-term respiratory morbidity and other problems such as gastro-esophageal reflux, feeding difficulties and impaired growth. Morbidity leads to physical inactivity whilst lack of motor practice may lead to motor developmental delay. This in turn results in further motor problems and reduced exercise tolerance. Early focus on stimulation of motor development is advisable. Risk groups are: children with associated anomalies, those with a high degree of long-term morbidity, and those with weakened abdominal muscles following abdominal surgery.

Chapter 4 describes a longitudinal study evaluating effects of structural, proactive genetic counseling of parents with children with major congenital anomalies. This study also determined factors influencing parental decision to seek genetic counseling. Two cohorts were seen: parents of patients born from January 1999 through the first half of 2001 and those of patients born from the second half of 2004 to the end of 2006. In the latter period, genetic counseling was offered proactively, both during first admission and in the outpatient follow-up clinic. Proactive counseling almost doubled the frequency of genetic counseling but at a later moment in time, when child and parents seem to have adapted to their situation. The second cohort comprised significantly fewer children with 3 or more anomalies. Moreover, in the second cohort more anomalies were adequately diagnosed antenatally. Analysis revealed a higher chance of seeking counseling when a proactive approach was used, and also for parents of Dutch origin, children with 3 or more anomalies, antenatally incomplete diagnosis and positive history of familial malformations. Structural, proactive genetic counseling with the geneticist as

identifiable member of an interdisciplinary team increased the frequency of counseling in parents of malformed children. Parents with different cultural backgrounds and/or prenatally incompletely or undiagnosed children warrant more attention.

Chapters 5a and 5b Two examples of patients with multiple anomalies fitting into a known pattern are described. Final diagnosis on these patients was not complete until after careful re-evaluation of physical characteristics and genetic analysis. This illustrates that the contribution of a clinical geneticist specialized in dysmorphology is indispensable in a multidisciplinary team caring for children with congenital anomalies.

In **Chapter 6** we describe a study on the first 10 patients treated by the multidisciplinary short bowel syndrome team. Seven patients were discharged with home parenteral nutrition. Duration of total follow-up varied between 9 months and 5.5 years (median 1.5 years). Six patients could be weaned off parenteral nutrition and 5 patients off enteral tube feeding, resulting in full oral intake. Seven patients had normal growth. Median duration of initial hospital admission was 174 days, and average costs of initial admission amounted to 166,045 euros. Total admission days varied from 84 to 478 days with a median of 409 days. Average total costs were 269,700 euro reaching to maximum of 455,400 euros. Treatment of short bowel syndrome requires considerable resource consumption, especially when patients depend on parenteral nutrition. As 82% of the costs comprise those of hospital admissions, early home parenteral nutrition could contribute to costs reduction. Multidisciplinary teams have the potential to facilitate home parenteral nutrition and thus reduce health care costs, while at the same time benefiting patients' health.

Part 2 describes different psychological aspects.
In **Chapter 7** we describe a group of 5-year-old patients whose developmental assessment over the first 2 years is highly predictive of cognitive and motor outcomes at 5 years of age. Low mental and psychomotor scores are equally predictive for unfavorable cognitive and motor outcomes at 5 years of age. Even the separate scores obtained as early as at 6 months are predictive for cognitive development at 5 years. In addition to early developmental outcome, also socioeconomic status, being (non-native) Dutch and number of congenital anomalies were predictive of outcome. Low socioeconomic status, being non-native Dutch and a higher number of congenital anomalies were risk factors for developmental delay in the long run.

In **Chapter 8** we report long-term morbidity and neurodevelopmental outcomes at 5 years in a nationwide Dutch study in neonates treated with veno-arterial extracorporeal membrane oxygenation (ECMO). Ninety-eight 5-year-olds from the two designated ECMO centers in the Netherlands, (Erasmus MC-Sophia in Rotterdam and Radboud University Medical Center in Nijmegen) were assessed. The protocol included medical assessment, neuromotor assessment and psychological assessment by means of parent and teacher questionnaires. We found neurological deficits in 17% of the 98 children included. Six of

those 17 (6% of total) showed major disability. Two of those six had a chromosomal abnormality. Three were mentally retarded and profoundly impaired. The sixth had a right sided hemiplegia. These six did not undergo neuromotor assessment. Motor difficulties were found in 26% of the remaining 92 children. Fifteen percent actually had a motor problem and 11% were at risk for motor problems. Cognitive delay was identified in 14%. The mean IQ score (100.5) was within the normal range. The study revealed that neonatal ECMO in the Netherlands is associated with considerable morbidity at 5 years of age. Due to cooperation between the two centers and relatively small traveling distances in the Netherlands, follow-up appeared possible in 87% of survivors. Objective evaluation of this highly invasive technology applied in the neonatal period is feasible through nationwide consensus on the interdisciplinary follow-up protocol.

In **Chapter 9** we describe the development and psychometric analysis of a questionnaire designed to assess early impact of a child with congenital anomalies on parents (ICCAP). We showed that severity-of-illness variables correlated with parental state of mind and feelings of fear and anxiety. The level of fear and anxiety felt for the child and its future appeared to drop over time, coinciding with the fact that severity of disease abated over time in most children. The ICCAP should be considered a reliable and valid instrument for clinical practice. It enables early signaling of parental quality of life as a result of early stress. Thus early intervention can be targeted.

In **Chapter 10** we describe an explorative study into the usefulness of the Dutch version of the Child Behavior Checklist/1½-5 (CBCL/1½-5) as an instrument for early identification of problem behavior for twelve-month-old children with anatomical congenital anomalies. Parents reported little problem behavior, and inter-parent agreement was high. Mental development was correlated with problem behavior. Children with lower mental development showed more internalizing problem behavior. Experts judged a number of items of the CBCL/1½-5 as not applicable to children aged 12 months. This study shows that the CBCL/1½-5 is not suitable to assess problem behavior in these children at age 12 months, so the instrument should be used with caution.

In **Chapter 11** we describe long-term psychosocial outcome among parents of children with major anatomical congenital anomalies. Parents completed two questionnaires at 12 months, 24 months, and 5 years after birth of the child, the Parental Stress Index-Short Form and the SF-36. The latter measures general health status. Over time, mothers as well as fathers showed normal parenting stress and general health; scores for both parents were comparable. Parental stress and general health status were negatively related; implicating that lower stress is favorable for mental and physical health. Although parents of these children face many challenges, many of them adapt their style of functioning over time and may, in fact, manage quite well with day-to-day problems. A mentally and physically healthy parent is able to cope with the challenges presented. Good adaptation strategies make parents less vulnerable to parental stress.

Part 3 describes multidisciplinary support of parents.
Chapter 12 reports on the feasibility of running a 24-hour telephone helpline. Calls were received from 34.4% of parents. 23.7% of these calls concerned feeding problems. Parents of children with esophageal atresia, urogenital malformation and congenital diaphragmatic hernia called most frequently (44.3% to 50.6%). Nurses handled 24.5% of calls themselves, and 20.2% of calls led to emergency room consultations resulting in 4.9% admissions. Total personnel costs amounted to € 27,191 per year. Children with congenital anomalies often have associated morbidity extending beyond the time of initial admission. Parents may feel less burdened when easy access to adequate medical and supportive care for their children is guaranteed. A 24-hour telephone helpline provides this care for parents of children with congenital anomalies at relatively low cost.

Chapter 13 describes parents' opinions on the follow-up team. From a questionnaire it appeared that the majority of parents were positive about the services of the follow-up team. Almost one-fourth indicated that they considered the follow-up team redundant or no longer needed. This is not surprising as some anomalies require surgery early on in life but give no major medical or psychosocial problems after the first hospital admission. A relatively low percentage of foreign parents found the follow-up team redundant or no longer needed. Satisfaction with social work was high but somewhat lower compared to satisfaction with other caregivers. More than one third of the parents recorded 'not applicable' for opinion on social work. A high percentage of parents indicated 'not applicable' for the psychologist. This may be due, on the one hand, to the fact that psychologists are not part of the health care team during hospital stay. On the other hand, in the outpatient clinic their focus is on developmental screening and not on the psychotherapy with which parents primarily tend to associate psychologists. The suggestions for the follow-up team were helpful. We noted that information on the team should be given more than once. Parents who receive information during their child's hospitalization may forget this after the child has returned home.

In the last chapter, the **General Discussion**, we conclude that children with anatomical congenital anomalies are at a certain risk of physical sequelae and developmental delay. However, early signaling and intervention with the help of a multidisciplinary follow-up team may prevent or reduce this risk and adequately prepare parents for the care of their child. Both medically and ethically we owe these children long-term follow-up to evaluate the effects of our intensive care treatment in the neonatal phase. Other patient categories treated on neonatal and pediatric intensive care units with either congenital or other severe disease should also be targeted with follow-up programs aimed at identifying specific areas of physical, developmental and cognitive functioning. Only then will we be able to judge whether the often aggressive and invasive therapies with which we treat children in our top clinical centers not only prolongs life but also leads to an acceptable quality of life.

SAMENVATTING

Een toenemend aantal kinderen met ernstige aangeboren afwijkingen blijft in leven. Het aantal kinderen met een restafwijking neemt hierdoor evenredig toe. Het lijkt ons belangrijk te weten hoe het op de lange duur met deze kinderen gaat en hoe we hun ziektelast kunnen verlichten. Daarom volgen wij nu deze kinderen, en hun ouders, in multidisciplinair verband tot ze – volgens plan – de volwassen leeftijd hebben bereikt. In dit proefschrift beschrijven we hoe het de kinderen en ouders vergaat gedurende de eerste vijf jaar na de geboorte en na behandeling in ons ziekenhuis. De focus in dit proefschrift ligt met name op kinderen met een zogenaamde indexdiagnose. Dit zijn de volgende diagnoses: slokdarmatresie, congenitale hernia diafragmatica (een gat in het middenrif), dunne darmatresieën, buikwanddefecten, de ziekte van Hirschsprung en anorectale malformaties.

Deel 1 besteedt aandacht aan lichamelijke aspecten.
Hoofdstuk 1 beschrijft de uitkomsten van onderzoek bij 101 kinderen die tussen 1999 en 2003 op onze intensive care afdeling hebben gelegen vanwege een ernstige anatomische aangeboren afwijking. We hebben getracht te bepalen welke medische en sociodemografische kenmerken uiteindelijk bepalend zijn voor de ontwikkeling van deze kinderen gedurende de eerste 24 maanden. Groeiachterstand werd gevonden in kinderen met een congenitale hernia diafragmatica of met een slokdarmatresie. Gekeken over de gehele groep was de neurologische ontwikkeling normaal, maar voor 40% van de kinderen met een congenitale hernia diafragmatica was deze abnormaal of in het grensgebied. Het aantal grote aangeboren afwijkingen, de initiële opnameduur en het totaal aantal chirurgische ingrepen onder narcose waren significante determinanten voor zowel de mentale als de psychomotore ontwikkeling. De ontwikkeling werd bepaald met behulp van de Bayley ontwikkelingsschalen. De mentale ontwikkeling viel binnen de norm, maar de psychomotore ontwikkeling was significant slechter dan de norm (95% CI 82.6 - 90.7 op de leeftijd van 6 maanden en 89.2 - 99.2 bij 24 maanden). Geslacht, sociaaleconomische status, soort en aantal aangeboren afwijkingen, mate van ziek zijn, en het gebruik van medische hulpmiddelen na ontslag uit het ziekenhuis bepaalden significant een slechte uitkomst ($p < 0.05$). Over het geheel genomen hebben kinderen die een anatomische aangeboren afwijking overleven een groter risico op groeiachterstand en psychomotore ontwikkelings-achterstand.

Hoofdstuk 2 vergelijkt kinderen met een slokdarmatresie en kinderen met een congenitale hernia diafragmatica wat betreft aanhoudende gastro-intestinale en luchtwegklachten, lichamelijke conditie en motorische ontwikkeling. We zagen de kinderen terug op de leeftijd van 6, 12 en 24 maanden en 5 jaar. Beide groepen vertoonden een significante groeiachterstand in vergelijk met de Nederlandse norm. Alleen in de groep kinderen met een slokdarmatresie werd aan het eind van de studieperiode inhaalgroei gezien. ECMO-behandeling was een negatieve voorspeller

van groei in kinderen met een hernia. Beide groepen vertoonden gastro-oesophageale reflux en voedingsproblemen; 35% van de kinderen in beide groepen werd hiervoor operatief behandeld met een Nissen fundoplicatie. De helft van de kinderen met een hernia had luchtwegklachten in de vorm van bronchopulmonale dysplasie (en zelfs 81% van hen die met ECMO waren behandeld). De kinderen met een slokdarmatresie hadden met name last van recidiverende luchtweginfecties. Bij een kwart bleek uit longfunctieonderzoek een abnormaal laag voorspeld percentage FEV_1. Tracheomalacie (een te slappe luchtweg) is een bekend fenomeen bij kinderen met een slokdarmatresie, maar de incidentie van andere persisterende luchtwegklachten wordt over het algemeen onderschat. Deze kinderen dienen dan ook regelmatig gezien te worden door een kinderlongarts.

Voor beide groepen was de maximale inspanningstolerantie significant beneden de norm: $p = 0.02$ bij slokdarmatresie; $p = 0.012$ bij hernia diafragmatica. Uit evaluatie met de M-ABC op de leeftijd van 5 jaar bleek dat 63.6% van de patiënten met een slokdarmatresie normale motoriek had, tegen 61.1% van de kinderen met hernia. De meetwaarden voor de overige patiënten in beide groepen vallen in het risicogebied. Genoemde percentages verschillen significant van die in de gezonde populatie (respectievelijk $p = 0.02$ en $p = 0.01$ voor slokdarmatresie en hernia). Wij concludeerden dat beide patiëntengroepen een verhoogd risico hebben op persisterende luchtwegklachten en motorische problemen en daarom extra aandacht behoeven.

Hoofdstuk 3 gaat in op de motorische ontwikkeling bij 79 vijfjarigen met verschillende aangeboren afwijkingen. Deze werd beoordeeld met behulp van de M-ABC en aan de hand van de maximale inspanningscapaciteit. Ook hier bleken de ernst van de aandoening, het aantal bijkomende afwijkingen en persisterende luchtwegklachten een negatieve invloed te hebben op de ontwikkeling. Voor bijna driekwart van de kinderen (73.4%) bleven de scores binnen de norm, 16.5% had verhoogd risico, en 10% had inderdaad problemen met de motoriek. Deze verdeling is significant verschillend van de normpopulatie. (Chi kwadraat $p = 0.01$). Minder balvaardigheid werd geconstateerd bij kinderen met een slokdarmatresie en kinderen met een hernia diafragmatica; de eersten vertoonden ook evenwichtsproblemen, net als kinderen met afwijkingen aan de dunne darm. The totale percentielscore van de M-ABC vertoonde een negatieve correlatie met het totale aantal ernstige aangeboren afwijkingen ($r_s = -0.35$, $p < 0.01$), en een positieve correlatie met het aantal dynamische sit-ups ($r_s = 0.44$; $p < 0.01$, $n = 71$) en de maximale inspanningsduur getest met het Bruce-protocol ($r_s = 0.31$; $p = 0.01$, $n = 62$). De problemen met de motoriek bij kinderen met een slokdarmatresie of een hernia diafragmatica bleken samen te hangen met luchtwegklachten op de lange termijn en met andere problemen zoals gastro-oesophageale reflux, voedingsproblemen en groeiachterstand. Deze kinderen zijn vaak betrekkelijk inactief en lopen daarom een motorische ontwikkelingsachterstand op. Dit verergert de motorische problemen en leidt uiteindelijk ook tot een verminderde inspanningstolerantie. Wij adviseren vroegtijdige aandacht voor de motorische ontwikkeling, met name als er sprake is van

geassocieerde afwijkingen, hogere morbiditeit op de lange termijn, of verminderde buikspierkracht ten gevolge van abdominale chirurgie.

Hoofdstuk 4 beschrijft longitudinaal onderzoek naar de uitwerking van een proactieve strategie voor genetische counseling van ouders van kinderen met ernstige anatomische aangeboren afwijkingen. Eén van de vragen was wat ouders ertoe beweegt zich te laten counselen. Genetische counseling werd proactief aangeboden vanaf medio 2004, zowel tijdens de eerste opname als bij onze latere follow-up. De klinisch geneticus was in deze periode een duidelijk herkenbaar lid van het behandelteam. We vergeleken ervaringen met ouders van kinderen geboren na die tijd met die van ouders van kinderen geboren enige jaren eerder. Tijdens de periode van proactief counselen lieten bijna twee keer zo veel ouders zich counselen, maar op een later tijdstip na de geboorte, als kind en ouders zich inmiddels aan de nieuwe situatie hadden aangepast. Dit waren vooral ouders van Nederlandse origine, ouders van kinderen met 3 of meer afwijkingen, ouders waarbij aangeboren afwijkingen in de familie voorkwamen, en ouders van kinderen waarbij een antenatale diagnose gesteld was, die bij geboorte onvolledig bleek. De frequentie waarin ouders van kinderen met aangeboren afwijkingen genetisch gecounseld werden nam toe bij een proactief beleid. Wij concluderen dat een groter percentage ouders gecounseld wordt bij een proactief counselingbeleid met de klinisch geneticus als een duidelijk herkenbaar lid van het behandelteam. Ouders van kinderen met een niet-Nederlandse culturele achtergrond en ouders van kinderen waarbij de diagnose antenataal niet of onvolledig gesteld is verdienen extra aandacht.

Hoofdstuk 5a en 5b In elk van deze hoofdstukken wordt een patiënt met meervoudige aangeboren afwijkingen en typerende uiterlijke kenmerken beschreven die uiteindelijk binnen een eerder beschreven patroon blijken te vallen. De uiteindelijke diagnose bij deze beide patiënten kon uiteindelijk pas gesteld worden na nauwkeurige her-evaluatie van de uiterlijke kenmerken en na zorgvuldige DNA diagnostiek. Beide gevallen illustreren dat een klinisch geneticus die is gespecialiseerd in de dysmorfologie – patroonherkenning – onmisbaar is in het multidisciplinaire behandelteam van een kind met aangeboren afwijkingen.

In **Hoofdstuk 6** beschrijven we de eerste tien patiënten die door het ‘darmfalen–team’ van het Sophia Kinderziekenhuis behandeld werden. Zeven patiënten werden naar huis ontslagen met parenterale voeding. De kinderen werden gevolgd gedurende een periode variërend tussen de 0 maanden en 5,5 jaar (mediaan 1,5 jaar). Zes konden uiteindelijk zonder parenterale voeding en vijf hadden niet langer sondevoeding nodig, resulterend in volledige orale voeding. Zeven patiënten groeiden normaal. De mediane duur van de eerste ziekenhuisopname bedroeg 174 dagen, en de gemiddelde kosten daarvoor bedroegen 166.045 euro. De totale opnameduur varieerde van 84 tot 478 dagen met een mediaan van 409 dagen. De gemiddelde totale kosten van behandeling bedroegen 269.700 euro, met als hoogste bedrag 455.400 euro. De behandeling van

kinderen met het korte darmsyndroom is dus kostbaar, zeker bij afhankelijkheid van parenterale voeding. Aangezien 82% van de kosten is toe te schrijven aan de ziekenhuisopname zelf, kan er veel bespaard worden als kinderen eerder ontslagen worden met parenterale voeding. Dit is zeer goed mogelijk met steun van een multidisciplinair team, en is uiteindelijk ook beter voor de ontwikkeling van het kind en het vormen van een band tussen kind en ouders.

Deel 2 besteedt aandacht aan psychologische aspecten.
In **Hoofdstuk 7** tonen we aan dat de ontwikkeling van kinderen met ernstig aangeboren afwijkingen over de eerste twee jaar in hoge mate voorspellend is voor de cognitieve en motorische ontwikkeling op de leeftijd van 5 jaar. Lage scores op de mentale en psychomotore tests kunnen evenzeer een ongunstige cognitieve en motorische uitkomst op de leeftijd van 5 jaar voorspellen. Zelfs de scores voor de eerste tests op de leeftijd van 6 maanden zijn al voorspellend voor de cognitieve ontwikkeling op de leeftijd van 5 jaar. Daarnaast zijn sociaaleconomische status, etniciteit en het aantal aangeboren afwijkingen voorspellende factoren. Een lage sociaaleconomische status, ouders van niet- Nederlandse origine en een hoog aantal aangeboren afwijkingen vormen een risico voor ontwikkelingsachterstand op de lange termijn.

In **Hoofdstuk 8** wordt beschreven hoe het op 5-jarige leeftijd staat met kinderen die als pasgeborenen met ECMO zijn behandeld. Op deze leeftijd staan kinderen aan het begin van de basisschool en worden belangrijke beslissingen genomen voor de verdere schoolcarrière. Het ging om 98 kinderen die waren behandeld of in het Erasmus MC-Sophia of in het Radboud Ziekenhuis in Nijmegen. Ze kregen een medisch onderzoek, een neuromotorische beoordeling en een psychologische evaluatie, onder meer met behulp van vragenlijsten voor ouders en leerkracht. Bij 17 kinderen werden neurologische afwijkingen gevonden. Bij zes was dit een ernstige neurologische afwijking; twee daarvan hadden een chromosomale afwijking, drie waren mentaal geretardeerd en motorisch gehandicapt, en de zesde had een rechtszijdige hemiplegie (éénzijdige verlamming). Deze zes kinderen werden niet neuromotorisch getest. Van de overige 92 kinderen had 15% daadwerkelijk een motorisch probleem en 11% bevond zich in het risicogebied. Bij 14% van de kinderen werd een cognitieve achterstand gevonden. De gemiddelde IQ score was normaal (100,5). De resultaten tonen aan dat ECMO – een zeer invasieve techniek – geassocieerd is met aanzienlijke morbiditeit op de leeftijd van 5 jaar. Dankzij samenwerking tussen de twee Nederlandse ECMO-centra was het mogelijk het hoge percentage van 87% van de overlevende kinderen terug te zien en kan aan de bevindingen een hoge mate van betrouwbaarheid worden toegeschreven.

In **Hoofdstuk 9** beschrijven we de ontwikkeling en psychometrische analyse van een vragenlijst waarmee de eerste impact van de geboorte van een kind met aangeboren afwijkingen op de ouders kan worden gemeten (Impact of a Child with Congenital Anomalies on Parents (ICCAP)). De ernst van de aandoening correleerde met de

gemoedstoestand, angst en zorgen van ouders. De mate waarin ouders zich zorgen maakten om het kind met aangeboren afwijkingen en zijn toekomst, leek over de tijd te verminderen. Dit hing samen met de vermindering van de ziektelast bij de meeste kinderen. De ICCAP-vragenlijst kan beschouwd worden als een betrouwbaar en valide instrument voor de klinische praktijk. Hiermee kunnen we de kwaliteit van leven van ouders in reactie op de aanvankelijke gevoelens van stress evalueren. Indien wenselijk en gewenst kan dan gerichte interventie worden toegepast.

Hoofdstuk 10 betreft een exploratieve studie naar het gebruik van de Nederlandse versie van de Child Behavior Checklist/1½-5 (CBCL/1½-5) voor identificatie van probleemgedrag bij 12 maanden oude kinderen met anatomische aangeboren afwijkingen. Ouders rapporteerden weinig probleemgedrag en de correlatie tussen de scores van vaders en moeders was hoog. De mentale ontwikkeling van het kind was gecorreleerd aan probleemgedrag. Kinderen met een slechtere mentale ontwikkeling vertoonden meer internaliserend probleemgedrag. Een aantal items van de CBCL/1½-5 werd door professionals beschouwd als niet toepasbaar op deze leeftijd. Deze studie laat zien dat de CBCL/1½-5 eigenlijk niet geschikt is om probleemgedrag op de leeftijd van 12 maanden te beoordelen. Het instrument moet dan ook zeer terughoudend worden toegepast.

In **Hoofdstuk 11** beschreven we het psychosociaal welzijn van ouders van kinderen met ernstige anatomische aangeboren afwijkingen. De ouders vulden twee vragenlijsten in bij 12 en 24 maanden en 5 jaar na de geboorte van hun kind. Stress ten gevolge van het ouderschap werd gemeten met behulp van de Parental Stress Index-Short Form (PSI). Hun algemene gezondheidstoestand werd gemeten met behulp van de SF-36. Over deze vijf jaar rapporteerden vaders en moeders vergelijkbare stress en algemene gezondheid, binnen de norm. Stress en algemene gezondheid correleerden negatief met elkaar. Dit houdt in dat minder stress gepaard gaat met betere mentale en fysieke gezondheid.

Hoewel ouders van kinderen met aangeboren afwijkingen tegen veel problemen aanlopen, passen zij zich aan in de loop van de tijd. Uiteindelijk kunnen de meesten goed omgaan met dagelijkse problemen. Een ouder die mentaal en fysiek gezond is, kan uiteindelijk omgaan met het hebben van een kind met aangeboren afwijkingen. Ouders die goede adaptatiestrategieën hanteren zijn minder vatbaar voor hogere draaglast. Desondanks is met name in de eerste jaren goede begeleiding noodzakelijk.

Deel 3 beschrijft de multidisciplinaire zorg voor kinderen met aangeboren afwijkingen.
Hoofdstuk 12 beschrijft de haalbaarheid van een 24-uurs telefonische hulplijn voor de ouders. Het bleek dat 34.4% van de ouders de hulplijn hadden gebeld. Bijna een kwart van deze telefoontjes betroffen eetproblemen. Voor ouders van kinderen met een slokdarmatresie, urogenitale afwijkingen of congenitale hernia diafragmatica lagen de percentages bellers het hoogst (44.3% tot 50.6%). De verpleegkundigen konden 24.5%

van de telefonische oproepen zelf afhandelen. Naar aanleiding van 20.2% van de telefoontjes werden kinderen op de spoedeisende hulp gezien. Dit leidde tot een opname in 4.9 % van het totaal aantal telefoontjes. De totale personele kosten bedroegen € 27,191 per jaar. Kinderen met aangeboren afwijkingen vertonen vaak nog restverschijnselen tot ver na de eerste opnamen. Als de ouders gemakkelijk toegang hebben tot goed advies en bijstand, dan vermindert dit hun draaglast. Met deze 24-uurs telefonische hulplijn kunnen we deze service tegen relatief lage kosten aanbieden.

Hoofdstuk 13 beschrijft de resultaten van een enquête gericht op het functioneren van het follow-up team. De meerderheid van de ouders was positief over de service die het follow-up team bood. Bijna een kwart van de ouders gaf aan dat zij het follow-up team niet (meer) nodig hadden. Dit is begrijpelijk als men zich realiseert dat een aantal aangeboren afwijkingen na chirurgische behandeling weinig tot geen medische of psychosociale problemen oplevert. Een relatief laag percentage allochtone ouders had het gevoel het follow-up team langer nodig te hebben. Ouders waren tevreden over de hulp van de maatschappelijk werker, maar in verhouding tot de andere zorgverleners in iets mindere mate. Meer dan een derde van de ouders gaf indirect aan dat ze geen contact hadden gehad met de maatschappelijk werker. Voor een relatief hoog percentage ouders geldt dit ook ten aanzien van de psycholoog. Als verklaring mag gelden dat psychologen geen deel uitmaken van het behandelend team gedurende de tijd dat het kind in het ziekenhuis ligt. Op de polikliniek richten zij zich vooral op de ontwikkeling van het kind en niet op de psychotherapie waar ouders psychologen over het algemeen mee associëren. Ouders gaven nuttige suggesties ten aanzien van het functioneren van het follow-up team. Zo hebben we geleerd dat informatie over het follow-up team meer dan eens moet worden gegeven. In de thuissituatie blijken ouders vaak de informatie die in het ziekenhuis wordt gegeven weer te zijn vergeten. Bovendien werd in de eerste fase waarin deze begeleiding voor ouders werd opgezet maatschappelijk werk wel standaard aangeboden, maar gebeurde er niet standaard een intake bij iedereen. Inmiddels hebben alle ouders in elk geval een oriënterend gesprek met de maatschappelijk werker.

In het laatste hoofdstuk, **de Discussie**, concluderen we dat kinderen met aangeboren anatomische afwijkingen wel degelijk een risico hebben op een verstoorde ontwikkeling, maar dat vroegtijdige en goede begeleiding van kind en ouders een aantal problemen kan voorkomen of verminderen. Bovendien vinden we dat wij het zowel medisch als ethisch aan deze kinderen verplicht zijn hen langdurig te vervolgen en ook op de lange termijn te beoordelen wat de gevolgen zijn van de intensieve behandeling in de neonatale fase. Ook voor andere groepen kinderen die met ernstige ziektebeelden op de intensive care verpleegd worden moet een langdurige en op kind en ziektebeeld toegespitste follow-up komen. Alleen op die manier zullen wij kunnen beoordelen of wij niet alleen verlenging van leven maar ook kwaliteit van leven bieden met de vaak agressieve therapieën waarmee wij kinderen in onze topklinische centra behandelen.

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A painter paints pictures on canvas. But musicians paint their pictures on silence

Leopold Stokowski (1882-1977)

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Abbreviations

Wat moeilijk is, is niet altijd belangrijk; het is ook moeilijk om een mosterdzaadje door het oog van een naald te werpen

Desiderius Erasmus (1469-1536)

AAP	American Association of Pediatrics
ADHD	Attention Deficit Hyperactivity Disorder
ARM	Anorectal Malformation
ASD	Atrial Septal Defect
ATS	American Thoracic Society
AWD	Abdominal Wall Defect
BMI	Body Mass Index
BOS 2-30	Bayley Scales of Infant Development
BPD	Bronchopulmonary Dysplasia
BSID-II	Bayley Scales of Infant Development–Second Edition–Dutch version
CA	Congenital Anomaly
CBCL	Child Behavior Checklist
CBS	Centraal Bureau voor de Statistiek
CDH	Congenital Diaphragmatic Hernia
CFNS	Craniofrontonasal Syndrome
CI	Confidence Interval
CPCCRN	Collaborative Pediatric Critical Care Research Network
DSLD	Developmental Speech Language Disorder
EA	Esophageal Atresia
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
ELSO	Extracorporeal Life Support Organisation
ERS	European Respiratory Society
FEV1	Forced Expiratory Volume in 1 second
GER	Gastro-esophageal Reflux
HD	Hirschsprung's Disease
HFO	High Frequency Oscillation
HR	Heart Rate
HRQoL	Health Related Quality of Life
iBMG	Instituut voor Beleid en Management in de Gezondheidszorg
ICCAP	Impact of a Child with Congenital Anomalies on Parents
ICU	Intensive Care Unit
IQ	Intelligent Quotient
LOS	Length of Stay
M-ABC	Movement Assessment Battery for Children
MCA	Multiple Congenital anomalies
MDI	Mental Developmental Index
MLPA	Multiplex Ligation-dependant Probe Amplification)
NO	Nitric Oxide
NICU	Neonatal Intensive Care Unit
OR	Odds-Ratio
PDI	Psychomotor Developmental Index
PDMS	Patient Data Management System

PELOD	Pediatric Logistic Organ Dysfunction
PFT	Pulmonary Function Test
PICU	Pediatric Intensive Care Unit
PSI-sf	Parenting Stress Index-short form
PTSD	Post Traumatic Stress Disorder
QOL	Quality of Life
RAKIT	Revised Amsterdam Children's Intelligent Test
RTI	Respiratory Tract Infections
SBS	Short Bowel Syndrome
SD	Standard Deviation
SDS	Standard Deviation Score
SES	Socioeconomic Status
SF-36	Short Form-36
SGA	Small for Gestational Age
SIA	Small Intestinal Atresia
TIS	Total Impairment Score
TISS	Therapeutic Intervention Scoring System
TRF	Teacher Report Form
VIF	Variance Inflation Factor
VSD	Ventricular Septal Defect

Curriculum Vitae

We kunnen het niet allemaal,
En sommigen van ons doen het niet.
En dat is alles wat ik ervan zeggen kan

Eeyore

Er is niks aan iets spannends te beleven in je eentje,
het is veel gezelliger samen

Winnie the Pooh

Onderschat nooit de waarde van nietsdoen,
Zomaar een beetje lopen
en luisteren naar al die dingen die je niet horen kunt,
En je nergens wat van aantrekken

Winnie the Pooh

Curriculum Vitae Saskia Gischler

Saskia Gischler was born in The Hague, the Netherlands in 1960. After having completed gymnasium education at the Maerlant Lyceum, The Hague, she spent a year at the State University New York, premedical school in Fredonia, New York, USA. She then started her medical study at the University of Utrecht, and graduated in 1987. In 1987-1988 she worked at the Lady Willingdon Hospital in Manali, Himachal Pradesh, India (L. Varghese). The following year she completed residencies in internal medicine, surgery and obstetrics/gynecology at the Lange Land Hospital in Zoetermeer. From 1990 to 1995 she trained as a pediatrician in the Sophia Children's Hospital in Rotterdam (H.K.A. Visser), the Zuiderziekenhuis in Rotterdam (R.N. Sukhai) and the Great Ormond Street Hospital for Children in London (P.G. Rees).

In 1995 she joined the pediatric surgical intensive care unit of the Sophia Children's Hospital in Rotterdam (head Dick Tibboel), where she continued working after she became a pediatric intensivist in 1997.

A long-term follow-up program for children with congenital anomalies was started in 1999. She is now working as a pediatric intensivist at the Intensive Care Unit of the Sophia Children's Hospital and as coordinator of the long-term follow-up program. She is head of the medical ethical case committee of the Sophia Children's Hospital.

In 1998 she started training as an acupuncturist at the NAAV, Breukelen, the Netherlands, and qualified in 2001. She then completed her studies with a bachelor's degree in pediatric Traditional Chinese Medicine with Alex Tiberi at Qing Bai, Amersfoort, the Netherlands, from 2001 to 2003. Since 2001 she runs an acupuncture practice in Schiedam.

Curriculum Vitae Petra Mazer

Petra Mazer was born in The Hague, the Netherlands in 1973. In 1992 she obtained her atheneum certificate at the Christelijk Scholengemeenschap Zandvliet, The Hague, and went on to study psychology at Leiden University. In 1997 she graduated in developmental and educational psychology. During her study she gained experience at the 'Ambulatorium', Leiden, and completed an in-service training period as a psychologist at Scholengemeenschap Speciaal Onderwijs de Wissel, Leiden. Furthermore, she performed a research project entitled "Young children's organizational strategies on a same-different task: A microgenetic study and a training study", supervised by Mrs A. W. Blöte, PhD, and Mrs W.C.M. Resing, PhD. As from 1997 she acted as a (freelance) consultant in psychodiagnostic assessment within the framework of various research projects in the Erasmus MC-Sophia Children's Hospital, Rotterdam, and the Leiden University Medical Center.
In 1999 she joined the follow-up team for children with congenital anomalies, instituted by the Department of Pediatric Surgery and the Intensive Care Unit in the Sophia Children's Hospital. She is coordinating developmental psychologist, and together with Saskia Gischler (pediatric–intensivist) performs the research reported in this thesis.

Publications

Verborgen talent bezorgt geen roem

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Dankwoord

Teachers open the door,
You enter by yourself

Chinese Proverb

Voor de totstandkoming van dit proefschrift zijn veel mensen voor ons belangrijk geweest. Een aantal van hen willen wij in het bijzonder bedanken.

Allereerst gaat onze dank uit naar de kinderen en hun ouders die deel uitmaakten van onze onderzoeksgroep. Zonder jullie medewerking was dit proefschrift nooit verschenen. Jullie zijn bijzonder in de ruimste zin van het woord en blijven een grote inspiratiebron voor ons!

Prof. dr. D. Tibboel, mijn promotor. Beste Dick, alweer 9 jaar geleden kwam ik op jouw Intensive Care Chirurgie te werken. Toen wist ik nog niet dat een promotie in het verschiet lag. Jouw gedrevenheid heeft van de follow-up een groots project gemaakt, waarin onderzoek en patiëntenzorg op een unieke manier met elkaar verweven zijn. Ik bewonder je brede visie op de kinderchirurgie, waarin ruimte is voor de psychosociale aspecten van zorg. Op de juiste momenten wist jij het schip van de promotie op koers te houden, overtuigd van een goede afloop. Dank je wel voor je vertrouwen.

Petra.

Prof. dr. D. Tibboel, mijn promotor. Beste Dick, in 1995 kwam ik op de ICC met het idee maximaal 2 jaar te blijven voor het 'gouden randje' aan mijn algemene pediatrie opleiding. Wie schetst ons beider verbazing dat ik nu het staflid ben, dat het langst ooit op jouw afdeling heeft gewerkt. Je hebt me niet alleen het vak geleerd en me opgeleid tot intensivist, maar me uiteindelijk ook weten te bewegen tot het schrijven van dit proefschrift. Patiëntgericht onderzoek was het toch meer dan de ratjes. Hoewel het niet altijd makkelijke jaren waren heb ik je enorm leren waarderen als dokter, als wetenschapper en als mens. Jouw brede visie op de toekomst van de kinderchirurgie, de intensive care en de lange-termijn follow-up maken deze afdeling tot wat hij is. Het is een eer jouw 50e promovendus te zijn.

Saskia.

Dr. M. van Dijk en Dr. H. Meijers-IJsselstijn, onze copromotoren.
Beste Monique, in de laatste fase van ons onderzoek bracht jij orde in de chaos, licht in de duisternis en enthousiasme in onze wetenschappelijke carrière. Jij had oog voor de persoon achter de promovendus. Bedankt!
Beste Hanneke, ook jij kwam in een laatste fase van ons onderzoek. Jij bracht een ongekend inzicht mee, dat verder ging dan 'alleen' de kindergeneeskunde. Zonder jou waren er aanmerkelijk meer punten op de i verloren gegaan. Bedankt voor je scherpe en kritische blik en je onvoorwaardelijke steun en vriendschap!

De leden van de gezamenlijke kleine en grote promotiecommissies, prof. dr. N.M.A. Bax, prof. dr. F.W.J. Hazebroek, prof. dr. A.J. van der Heijden, prof. dr. J. Passchier, Prof. dr. F.C. Verhulst en Prof. dr. I.D. de Beaufort willen wij hartelijk danken voor de bereidheid om in de promotiecommissies plaats te nemen. Dr. A.P. Bos, Bert, ook aan jou dank voor deelname aan de 'grote commissie'.
Frans, zonder jouw steun was deze chirurgische follow-up niet mogelijk geweest. Gelukkig hadden Dick en jij 10 jaar geleden al de visie om follow-up belangrijk te vinden, zodat we nu de best georganiseerde follow-up van Nederland hebben.

Dr. H.J. Duivenvoorden, beste Hugo, jouw enthousiasme voor het verrichten van wetenschappelijk onderzoek was zeer aanstekelijk. De begeleiding van de statistische analyses was leerzaam en plezierig. Je hebt een groot aandeel in de totstandkoming van dit proefschrift.

Marjan de Jong, beste Marjan, bedankt voor je inzet en betrokkenheid bij het opsporen van data. Het is veel meer werk dan het lijkt. We hadden niet zonder je gekund.

Ko Hagoort, beste Ko, bedankt voor je (snelle) hulp bij het corrigeren van de teksten. Zonder jou waren er aanmerkelijk minder volzinnen geweest.

Margo en Vera Terlouw, beste Margo, bedankt voor de leuke laatste fase van ons proefschrift. Mede door jouw creativiteit en nauwkeurigheid is het prachtig geworden! Beste Vera, wat een verrassing toen jij met een ontwerp voor de omslag kwam; je wist direct wat we bedoelden. Wat een talent!

Marcel Albers, beste Marcel, collega-intensivist, maar in dit geval vooral degene die ons hielp met de eerste opzet van een database. We konden er vrijwel alles in kwijt.
Gerard Verbruggen, beste Gerard, pas na jaren kwamen we erachter dat het ook heel handig is als de ingevoerde data ook weer uit de database komen. We zijn nu bijna zover dat het allemaal werkt! Bijna jammer dat we al een proefschrift hebben!

Manon Hanekamp, beste Manon, samen met jou hebben we de ECMO follow-up vorm gegeven en het 1e follow-up artikel geschreven. Bedankt voor de prettige samenwerking!
Monique van der Cammen-van Zijp, beste Monique, van kinderfysiotherapeut uit de follow-up, werd jij mede auteur van diverse artikelen in ons proefschrift. Jouw collegialiteit en je enthousiasme zijn van een bijzondere waarde. Op naar jouw boekje.

Ook willen we de leden van het follow-up team, voor zover nog niet eerder genoemd bedanken voor hun steun, interesse en medeleven: Yolande van Bever (klinisch geneticus), Joke de Graaf (orthopedagoog), Manon ter Horst-de Ronde (fysiotherapeut), Conny Meeussen (kinderchirurg), Adriana Pieter en Petra Schenk (secretariaat), Marjolein

Spoel (arts), Daniel Stuit (maatschappelijk werker), Anne Vroegindeweij (ontwikkelingspsycholoog), alle medewerkers van de longfunctie afdeling, stagiaires en studenten.
Het supportteam, inmiddels de chirurgische lange termijn follow-up, zou het supportteam niet zijn zonder de IC verpleegkundigen die de telefonische hulplijn bemannen of bemand hebben. Dank voor jullie inzet en voor de goede zorg voor 'onze' kinderen en ouders.
In 1999 begonnen wij met zijn tweetjes, maar nu staat er een heus multidisciplinair team. Geweldig!

(Petra)
Alle artsen, verpleegkundigen en overige medewerkers van de kinderchirurgie en de ICK bedankt voor de prettige samenwerking en voor jullie getoonde interesse!

Paranimfen, Annemieke Beijlevelt en Karin Honig. Lieve Annemieke jij begreep als geen ander wat mijn wereld was. Bedankt voor je altijd luisterende oor en goede raad. Lieve Karin, jouw onvoorwaardelijke hulp en oprechte interesse in mijn werk en gezin ervaar ik als bijzonder. Ik ben er trots op dat jullie nu naast mij staan.

Lieve Saskia, medepromovendus, alweer ruim 9 jaar werken we samen aan 'onze' follow-up. Jij bent een geweldig kinderarts, met oog voor de mens achter de patiënt. Dat kindergeneeskunde en kinderpsychologie onlosmakelijk met elkaar verbonden zijn, draagt onze vriendschap uit. Van een 'unkown woman' werd jij een bijzonder persoon in mijn leven.

Lieve familie en vrienden, de afgelopen periode is er veel tijd gegaan naar mijn werk. Niet zelden moest ik verstek laten gaan. Ik verheug me op weer veel gezellige momenten met jullie.

Lieve Diana, ik heb me gesteund gevoeld door jouw interesse, positieve inslag en enthousiasme.

Lieve ouders, bedankt voor de kans die jullie mij gaven te studeren en te ontplooien en voor jullie onvoorwaardelijke steun en begrip.

Lieve Niels en Eva en ….. Mijn grote geluk! Zonder jullie grenzeloze liefde en vertrouwen had ik dit promotietraject nooit succesvol kunnen afronden.
Ik hou van jullie!

(Saskia)
Wat is een IC zonder collega's?
Robert Jan, op het moment dat we dachten dat er echt nooit meer iemand bij ons wilde werken kwam jij. Voorbereid op onze ietwat bizarre werkelijkheid door Michael Voets. Je bent een bijzondere collega en een bijzonder mens. Zonder jouw vriendschap, collegialiteit en je begrip voor de wanhoop van weer een afgewezen artikel was het een stuk moeilijker geweest. Eindelijk weer tijd voor DE-momenten.

Irwin Reiss, kleiner Mann, het was even wennen die Nederlandse wereld, maar inmiddels heb je met je charme en je enorme collegialiteit de weg naar mijn hart gevonden. We kunnen niet meer zonder je.

Anke Top, collega op afstand inmiddels. Van onzekere fellow naar fantastische collega en bijzondere vrouw. Het was een genoegen de afgelopen jaren met je te werken en af en toe even als vrouwen onder elkaar te kunnen uithuilen. Dank!

'Nieuwe' ICK collega's en fellows, dank ook voor jullie medeleven in de laatste fase. Corinne, de follow-up wordt mooi!

Kinderchirurgen, zonder jullie geen follow-up van chirurgische patiënten. Dank voor het aanmelden van alle gemiste patiënten en voor de samenwerking van de afgelopen jaren.

Verpleegkundigen van de ICC en de ICK, jullie hebben jaren moeten aanhoren dat er een boekje kwam en jullie waren niet de enigen die het niet meer geloofden. Met jullie voor al onze patiënten te zorgen was een genoegen.
Inge, toen je jaren geleden wegging had ik niet durven hopen dat je terug zou komen. Hou vol!

Paranimfen, Alexandra Guldemeester en Frank Garssen. Lieve Alexandra, jaargenoten tijdens de opleiding en collega van het eerste uur op de ICC. Je bent een bijzonder mens en een bijzondere vriendin. Ik vind het fantastisch dat je naast me staat bij deze promotie en op vele andere momenten. Ik hoop dat we nog lang dezelfde weg mogen lopen.
Frank, wat ik met jou heb is heel speciaal. Van Zomerzooi tot Sinterklaaspromotie, we zijn een eind gekomen. Ik ben heel blij dat je de weg gevonden hebt, die je gevonden hebt en nog blijer dat je hier naast me wilt staan.

Collega's van het PMC, jullie hielden me op de been met 'mijn' woensdag in de week. Dat is pas echt complementaire zorg.

Lieve Petra, medepromovendus, zonder elkaar hadden we het niet gered! Het is geweldig om met je te werken en je vriendin te zijn. Jouw aandacht voor de mensen om

je heen, of het nu patiënten zijn, of collega's en vrienden, maakt je tot een bijzonder mens. Ik denk dat voor ons de follow-up belangrijker was dan het boekje, but we did it woman! Lief en leed, bergen en dalen, werk en vriendschap, wat wil je meer. Het is magisch. Winnie de Pooh zei het al: in je eentje is het niet zo leuk. Op naar de volgende fase.

Lieve familie en vrienden, de afgelopen jaren hebben jullie vaak van me moeten horen dat er weer iets niet kon vanwege de diensten of 'het boekje'. Het is fantastisch om te merken dat desondanks jullie er altijd zijn als ik jullie nodig heb. Dank daarvoor.

Lieve Ralph, het beste voor het laatste. Dank voor alle jaren geduld. Het boekje is af en ik hou van je!

A true friend is someone who is there for you
when he would rather be anywhere else

Len Wein (1948-)