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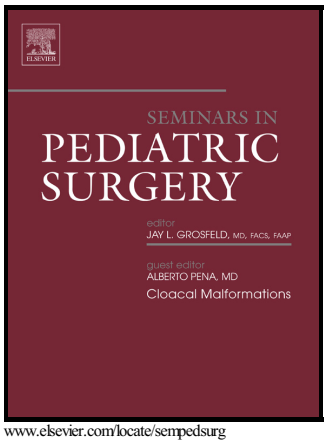

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Assessment and significance of long-term outcomes in pediatric surgery

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Abstract

Treatment modalities for newborns with anatomical congenital anomalies have greatly improved over the past decades, with a concomitant increase in survival. This review will briefly discuss specific long-term outcomes to illustrate which domains deserve to be considered in long-term follow-up of patients with anatomical congenital anomalies. Apart from having disease-specific morbidities these children are at risk for impaired neurodevelopmental problems and school failure which may affect participation in society in later life. There is every reason to offer them long-term multidisciplinary follow-up programs. We further provide an overview of the methodology of long-term follow-up, its significance and discuss ways to improve care for newborns with anatomical congenital anomalies from childhood into adulthood. Future initiatives should focus on transition of care, risk stratification and multicenter collaboration.

Keywords:

Congenital malformation, congenital diaphragmatic hernia, anorectal malformation, esophageal atresia, follow-up, outcome studies, growth, neurodevelopment

Introduction

Treatment modalities for newborns with anatomical congenital anomalies (CA) have greatly improved over the past decades, with a concomitant increase in survival. For many pediatric surgical index diagnoses, mainly children born with multiple congenital anomalies are now at risk of early mortality. Even for congenital diaphragmatic hernia (CDH) mortality rates have decreased from 50% to approximately 25%(1), supported by the success of a new standardized postnatal treatment protocol.(2, 3)

Now more of these critically ill children survive, clinicians are confronted with an increasing number of patients who suffer from long-term morbidities, not only in childhood but also in adulthood. Their interest has therefore shifted from reduction of mortality towards prevention of morbidity.

Historically, outcome studies on morbidity in pediatric surgical patients have focused on direct disease-related morbidity or evaluation of surgical techniques. However, it has become clear that long-term outcome is largely determined by morbidities indirectly related to the anatomical CA, to the treatment or to the natural course of the disease and its impact on family life.

This review will only briefly discuss specific long-term outcomes as many of these will be reviewed by other authors who contribute to this special issue. The outcomes mentioned will serve to illustrate which domains deserve to be considered in long-term follow-up of patients with anatomical CA. We further provide an overview of the methodology of long-term follow-up, significance of follow-up and discuss ways to improve care for newborns with anatomical CA from childhood into adulthood.

Methodology of long-term follow-up:

For a long time, follow-up programs for patients with anatomical CA have been using a monodisciplinary individualized approach based on the patient's condition. In the 1990s the first multidisciplinary clinics for patients with anatomical CA were established.(4, 5) Despite that many centers acknowledge the importance of long-term follow-up, e.g. for patients with CDH or anorectal malformations (ARM), only few offer structured follow-up beyond the first years of life.(6, 7) Study designs such as a cross-sectional study or retrospective chart review in individually treated patients are insufficient to understand the natural course of disease and result in selection bias.

Standardization of follow-up

As descriptive studies with an observational design use structured and validated instruments to collect data, they can easily be performed within the infrastructure of routine patient care. Ideally, data are collected at moments that are medically relevant or dictated by guidelines(8) and at developmental milestones (e.g. speech-language development or voluntary bowel movement control). Additional tailor-made assessments should be offered to individual patients.

Outcome data of children with anatomical CA are ideally compared with those of matched healthy controls. However, longitudinal assessment of healthy controls from the neonatal period into adolescence or adulthood is hardly feasible. Instead, well validated standardized instruments with published data of an appropriate reference population should be used.

Assessments during follow-up

Evaluation of physical growth is simple and important to provide information on the child's nutritional status. Chronic malnutrition – defined as height at least 2 SD below the norm – has been assumed to be related to adverse intellectual outcomes.(9) Early growth impairment should be closely monitored and timely referral to a dietician for nutritional assessment and intervention is then indicated.(10) This is not only important for CDH patients(10) but also for children with other anatomical CA such as esophageal atresia (EA)(11) and ARM(12) who are at risk for growth impairment.

For many different countries national growth charts are available. Alternatives are the Euro Growth references(13) or the World Health Organization (WHO) growth charts.(14, 15) While differences in height-for-age charts from different European countries may reflect true population differences, they also strongly affected by the secular trend in height. Therefore, it is recommended to use national or European height-for-age charts based on recent national data to monitor growth of European children.(16)

For children who suffer from long-term pulmonary morbidity, such as seen in CDH, EA, congenital lung malformations or giant omphalocele, longitudinal spirometry testing before and after bronchodilation may be useful. Appropriate standards for lung function testing and multi-ethnic reference data from 3 to 95 years are available.(17, 18) Assessment of reversibility of airflow obstruction may be important because reversibility has therapeutic consequences. Exercise tests may be useful to evaluate pulmonary condition and fitness as well. For example, the six-minute walk test is suitable for children from the age of 3 years. This test was originally developed to measure the submaximal level of functional capacity in adults with moderate to severe cardiopulmonary diseases. A recent systematic review revealed that studies of children with chronic conditions assessed with the six-minutes walk

test use many different test procedures. Based on current literature it is unclear whether the six-minute walk test can measure significant and important changes in children.(19) Moreover, it reflects an exercise level close to that of daily life activities rather than that of exercise endurance. A maximal exercise test, such as cycle ergometry or a treadmill test (e.g. Bruce protocol) is likely to provide better information on the pulmonary condition in children with anatomical CA. A treadmill test is preferred in younger children with relatively underdeveloped knee extensors.(20) Recent population-appropriate reference data should be used because the maximal exercise capacity of healthy 6-10-year-old children has deteriorated over the past decades. It is thought that spending more time playing computer games and watching television have a role here.(21) Recent studies have shown that children with CDH and EA are at risk for reduced maximal exercise capacity(22, 23) but the reason is not yet clear.

Research has shown that children born with anatomical CA are at risk for neurodevelopmental problems, although some of the findings are contradictory. Research initially focused on developmental outcomes within the first years of life(5, 24-26) but more data have become available on long-term developmental outcomes up till school age.(12, 27-33) The first publications on long-term outcome suggested that short-term outcomes of children born with non-cardiac anatomical CA were predictive of their long-term neurodevelopmental outcome. (28). It was then found, however, that many of 8-year-old ECMO-treated CDH patients needed extra help at school despite that assessments at two, five or eight years showed average intelligence which remained stable over time.(34) The necessity of extra help was attributed to selective attention problems.(34) Selective attention problems have been reported in other groups of children with anatomical CA as

well.(31, 32) All this highlights the importance of multidisciplinary follow-up at school age and beyond.

Age-appropriate developmental tests are available for different stages in life. It is essential to use standardized tests with suitable reference norms, considering that healthy Australian children on average showed significantly higher on the 3rd version of Bayley Scales of Infant and Toddler Development (BSID-III) than did the US reference population.(35) For longitudinal assessments or multicenter studies attention should be paid to using the appropriate test version. Many items of the BSID-III, for example, differ from the corresponding ones in the BSID-II(36), which may have contributed to the difficulties in interpreting outcome data of a European multicenter study in CDH patients.(37)

Points of concern in long-term follow-up

When performing population-based studies on long-term outcome in children with anatomical CA several potential pitfalls need to be addressed. The first is risk of selection bias. Parents of children with only minor morbidities will be less motivated to visit the hospital for routine evaluation.(38) On the other hand, for children with severe long-term morbidities, e.g. oxygen dependency in CDH-patients, travel distances may be too long. For these categories of patients additional data should be retrieved from community-based healthcare services or from other hospitals. Also, among children referred to multidisciplinary teams specialized to treat specific problems – e.g. aerodigestive teams for EA patients – children prone to develop airway infections or feeding difficulties may be overrepresented.(39)

The second pitfall is risk of loss to follow-up. We have noted that parents are motivated to have their child attend follow-up programs if they feel that it is of benefit to the child.

Receiving a report with positive evaluation results may also be important in this respect for parents and children. On the other hand, 5-10% of children with severe disabilities may not be able to undergo standardized tests for motor function evaluation or routine neurodevelopmental tests.(30) The latter group is usually not included in the overall evaluations of treatment modalities, which may result in too optimistic reporting and also contributes to risk of selection bias.

Clinicians looking into long-term outcomes may tend to focus on disease-specific outcomes first. Everyone taking care of children with anatomical CA will realize that those with specific genetic syndromes – such as trisomy 21 or Charge syndrome – may be at risk for neurodevelopmental problems and growth failure. This subgroup of patients is usually well being cared for. However, fewer clinicians may be aware of the more “hidden” morbidity which may affect long-term quality of life of children with anatomical CA and their families. The interactive behavior of mothers of infants with EA was affected during feeding in the sense that they showed more insensitivity, inconsistency, and anxiety.(40) Almost one third of these infants showed infant mental health disorders at one year of age.(41)
Early relational trauma is suggested to be a causative factor of abnormal development of the right hemisphere(42), which is important in all visual-spatial functions. A recent study showed that school-aged children with anorectal malformations have more problems with visual-spatial sustained attention and perceptional organization.(32) Extensive medical treatment to obtain the best possible anorectal function, including frequent anal calibration by the parents, is suggested to be a risk factor for early relational trauma and this risk should be further studied.(32) Moreover, anal calibration performed in ARM patients has been found a risk factor for persistent dissociative symptomatology in adolescence and

adulthood.(43) Dissociative symptoms may contribute to impaired psychosexual well-being, as was reported for adult patients with colorectal anatomical CA. Still, further studies are needed to determine the exact cause of psychosexual problems in these patient groups.(44) All these examples illustrate that the natural course of anatomical CA is complex and that many contributing factors have to be taken into account in the evaluation of long-term outcomes. These factors also include more general medical problems associated with long-term morbidities, such as preterm birth and/or being born small for gestational age, and which are more common in children with birth defects.(45)

Importance of long-term follow-up

From the clinicians' perspective it is important to know about long-term morbidities for several reasons. Firstly, as pointed out in the introduction to this chapter, more children with severe anatomical CA will survive and they may problems that were never encountered in the past. For example, young adult CDH patients who had been ventilated in the neonatal period for a median period of 7 days showed functional and micro-structural changes in mainly the ipsilateral lung. These changes were more profound in an ECMO-treated patient who had been ventilated for 141 days.(46) The question is whether future CDH survivors will show more severe structural pulmonary changes influencing daily life and social participation. Secondly, evaluation of long-term effects of treatment interventions is important. Functional outcomes may be related to treatment, e.g. motor function after application of the component separation technique in children with giant omphalocele(33); neurodevelopmental outcome following exposure to severe hypercapnia and acidosis during minimal invasive surgery in CDH(47); or lung function testing to evaluate the effects of different initial ventilation strategies in CDH patients.(48) In this respect, evaluation of long-

term outcomes after implementation of standardized postnatal treatment protocols(37) is important too.

From the patients' perspective, knowledge on long-term morbidities will help to recognize problems at an early stage so that timely intervention can be offered. For instance, referral to a pediatric physical therapist in the case of persistent gross motor function problems that have implications for everyday activities(31). Explaining long-term outcomes to the child, its parents and other caregivers will have a stimulating effect on care domains such as self-management, family empowerment, and education. Awaiting further research, we hypothesize that long-term follow-up programs are cost-effective as family empowerment is expected to improve outcome(49) and education of other caregivers may result in targeted evaluation without redundant tests. Moreover, outcome research data can form a basis for randomized clinical trials that lead to improved care (Figure).

Future perspectives and challenges

Transition of care

The substantial number of recent studies on outcome of CA in adulthood(44, 46, 50-55) indicates that clinicians pay more attention to long-term outcomes and to transition of care.(56) Nevertheless, facilitating the transition from pediatric to adult services is still not considered as standard of care. A survey on transition of ARM patients among delegates who attended a colorectal meeting showed that one third of respondents routinely suspended follow-up before the age of 10 years and that 72% did not have a protocol for transition.(7) The American Academy of Pediatrics recommends post-discharge follow-up of CDH patients up to the age of 16 years but not beyond that age.(8) In view of the current knowledge on possibly unfavorable long-term outcomes we recommend that follow-up programs include transition of adolescent patients to adult care. Optimal schedules for

multidisciplinary care should be based on standardized outcome research and be supported by international consensus guidelines.(57)

Risk stratification

Risk stratification is helpful to determine which patients should be followed more closely and which less closely. Many different aspects have to be considered. These include disease-specific factors, comorbidities and complications, illness severity, and – especially for neurodevelopmental outcome – general factors such as length of hospital stay, parental socio-economic status, and nature of the parent-child interaction. The potential neurotoxicity of anesthetic drugs in the neonatal period has been addressed in recent literature(58) and may be of interest for future evaluations as all neonates born with anatomical CA are exposed to such drugs. Interaction between all above-mentioned factors contributes to the problem of discriminating specific risks for poor long-term outcome. The published independent determinants of neurodevelopmental outcome(5, 28, 29, 31, 37, 59) should be considered with some caution as these are mainly derived from single-center studies with relatively small study populations. As multicollinearity in regression analyses is more likely to occur in small sample sizes, establishing independent risk factors for poor outcome is more complicated. Multicenter studies may be helpful on the one hand to create larger sample sizes, but may be challenging on the other hand because standardized assessment instruments and appropriate reference data are needed.(37) The use of a standardized clinical assessments and management plans (SCAMP) seems a promising novel approach for future collaboration between centers to assess long-term outcomes and to discriminate risk factors for poor outcome within the different domains.(60) Initially, all patients with a specific CA should be evaluated according to the same assessment plan, the

outcome of which may show whether all or part of the assessments in "low-risk patients" can be done by community-based healthcare providers.

The contribution of international registries

Several international registries have been established with the aim to assess therapies or outcome improvement measures in CDH(61) and ARM.(62) In addition, efforts have been undertaken to standardize reporting systems.(1, 62) Still, apart from the challenges reviewed by Jenetzky and co-workers for the ARM-Net Registry(62), some other issues need to be resolved on the way to uniform data collection in a multicenter international registry of long-term outcome data. First, postnatal treatment protocols need to be standardized. Although registered long-term outcome data may be useful to compare different postnatal treatment strategies, a minimum set of uniform treatment criteria and a substantial number of participating centers for detection of statistically significant differences is required. Second, assessment instruments and outcome scores need to be standardized and validated. Ideally, population specific standard deviation scores are obtained. Third, sufficient resources must be ensured, not only to make long-term follow-up possible, but also to set up registries meeting the institutional criteria of data management for all participants and to maintain registries both at a local and a central level.

In conclusion, the management of the wide range of long-term morbidities seen in children with anatomical CA is a task that cannot be fulfilled by the pediatric surgeon alone. Apart from having disease-specific morbidities that may also deserve a multidisciplinary approach including transition to adult services, these children are at risk for impaired neurodevelopmental problems and school failure which may affect participation in society in later life. There is every reason to offer them long-term multidisciplinary follow-up programs that address a wide range of topics (Table). Achieving optimal risk stratification as well as

tailor-made and standardized follow-up programs requires multicenter efforts with a focus on uniformity of treatment and assessment protocols, standardized instruments and data management. The extra expenses needed for evaluation of outcome data should pay themselves off by improvement of care with concomitant reduction of the burden on the health care system.

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Figure Legend:

Schematic representation of a standardized multidisciplinary approach to optimize care for patients with anatomical congenital anomalies. RCT = randomized controlled trial

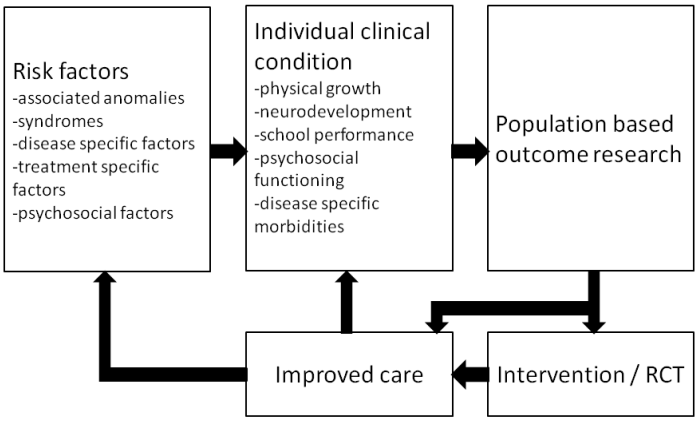

Table: Topics to be addressed in multidisciplinary long-term follow-up of children born with anatomical congenital anomalies

	Specific topics	Relevance/intervention
Infancy	Growth	Hyperalimentation
	Feeding difficulties/oral aversion	Referral preverbal speech-language pathologist
	Psychosocial wellbeing	Psychological support
	Disease-specific morbidity	Specific intervention if indicated
	Neurological impairment	Early recognition, rehabilitation, genetic counseling
	Mental development	Early recognition, rehabilitation, genetic counseling
	Motor development	Referral physical therapist
	Associated anomalies	Organ-specific intervention if indicated
Toddler/preschool age	Growth	Hyperalimentation
	Feeding difficulties/oral aversion	Referral preverbal speech-language pathologist
	Psychosocial wellbeing	Psychological support
	Disease-specific morbidity	Specific intervention if indicated
	Neurological impairment	Rehabilitation, genetic counseling
	Language development	Referral speech-language pathologist
	Mental development	Early recognition, rehabilitation, genetic counseling
	Motor function development	Referral physical therapist
	Associated anomalies	Organ-specific intervention if indicated
School age	Growth	Hyperalimentation, dietary advice
	Feeding difficulties	Management based on cause
	Disease-specific morbidity	Specific intervention if indicated
	Motor function development	Referral physical therapist, sports participation
	Neuropsychological assessment	Early school support
	Self esteem	Early intervention, psychological support
	Associated anomalies	Organ-specific intervention if indicated
Adolescence into adulthood	Growth	Hyperalimentation, dietary advice
	Feeding difficulties	Management based on cause
	Disease-specific morbidity	Specific intervention if indicated
	Neuropsychological assessment	School support, choice of profession/career
	Self esteem	Psychological support
	Associated anomalies	Organ-specific intervention and transition of care if indicated
	Transition to adult care	Involvement of disease-specific health care providers; clinical genetics (counseling)

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