From bowel to brain

Outcomes of patients with surgical congenital malformations in multidisciplinary follow-up after surgery

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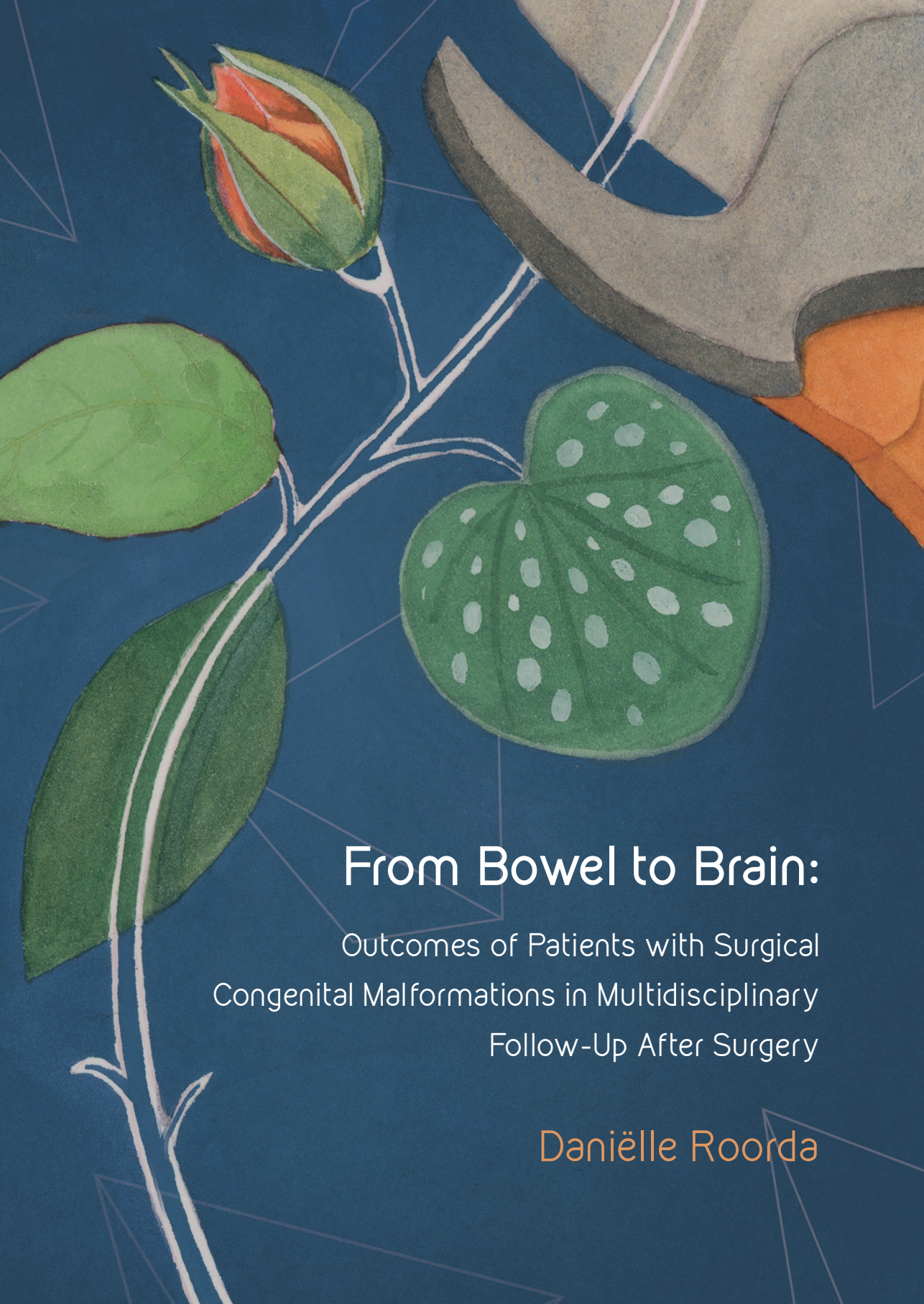

From Bowel to Brain:

Outcomes of Patients with Surgical Congenital Malformations in Multidisciplinary Follow-Up After Surgery

Daniëlle Roorda

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From Bowel to Brain: Outcomes of Patients with Surgical Congenital Malformations in Multidisciplinary Follow-Up After Surgery

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CHAPTER 1

General Introduction

BACKGROUND

Epidemiology of surgical congenital malformations

Surgical congenital malformations are birth defects that may require surgical treatment at infant age. Congenital malformations occur in about 281,7 of every 10.000 live births in the Netherlands and can occur in various functional systems of the body, including the nervous system, limbs, cardiac, digestive, urinary and respiratory system. 1 The cause of surgical congenital malformations is multifactorial, the result of an interaction between genetic abnormalities and multiple environmental factors including maternal nutrient imbalances, maternal smoking and alcohol use, pesticides, tap water disinfection by-products, plastics and plastics components, solvents, metals, and numerous air pollutants.2 In the Netherlands, it depends on the type of birth defect who provides surgical treatment. Birth defects of the digestive system, abdominal wall and respiratory system are treated by pediatric surgeons. This thesis covers the multidisciplinary outcome of patients with surgical congenital malformations treated by the pediatric surgeon.

Epidemiology and pathophysiology of Hirschsprung disease

Hirschsprung disease (HD) is one of the birth defects of the digestive system that occurs in about 1,2 of every 10.000 live births in the Netherlands.[1] HD is characterized by the absence of neuronal innervation in the most distal segment of the large intestine, as a result of disturbed migration, proliferation, differentiation and apoptosis of myenteric neural precursor cells from the neural crest.[3] Although we know some genetic abnormalities and genetic syndromes that are associated with Hirschsprung disease, the cause for disturbance of this process remains unknown in the majority of patients. In normal embryologic development neural crest cells migrate from proximal to distal, following the growth of the gastrointestinal tract, resulting in ganglion formation in two layers of the colonic wall: the myenteric plexus (Auerbach) and the submucosal plexus (Meissner).[4] In patients with HD this process is disrupted and the distal segment of the gastrointestinal tract therefore remains aganglionic. The junction between the aganglionic segment and normal ganglionic bowel is characterized by hypodense and/or non-circumferentially distributed ganglions, ectopic ganglions and hypertrophic nerve fibers, and is called the transition zone.[5] Since the aganglionic segment is not innervated, this segment is hypertonic and unable to pass feeds and stools, resulting in neonatal bowel obstruction. The length of the aganglionic segment varies between patients, which may explain differences in clinical presentation. In about 85% of patients aganglionosis is restricted to the rectosigmoid colon. When aganglionosis extends further proximal, up to the descending, transverse or ascending colon this is called long-segment Hirschsprung disease, which occurs in about 10-12% of patients, and when the whole colon is affected this is called total colonic aganglionosis. Total colonic aganglionosis occurs in about 2-5% of patients. Hirschsprung

disease is diagnosed by histopathological examination.[6] Whereas the majority of patients present with neonatal bowel obstruction, some patients present with Hirschsprung-associated enterocolitis (HAEC).[7] HAEC is a severe bowel inflammation that is associated with substantial morbidity and may even result in mortality. Other patients may not present as neonates, but at older age. Patients who present with HD in childhood are often characterized with recurrent symptoms of constipation, and may have a higher risk of postoperative complications.[8,9]

Surgical treatment of Hirschsprung disease

After diagnosis, patients with HD receive surgical treatment. Surgical treatment consists of resection of the affected bowel segment, followed by restoring bowel continuity. Although performing no surgical intervention would increase the risk of mortality, surgery is not without risk. Surgical procedures are conducted under general anesthesia and may result in postoperative complications, including anastomotic leakage, bowel obstruction or bowel paralysis, and postoperative infections.[10,11] There are several operation techniques for restoration of bowel continuity, some of which include the creation of a straight anastomosis (including the transanal endorectal pull-through (TEPT) according to Swenson, Soave, Rehbein and de La Torre), whereas others include the creation of a pouch (including Duhamel, or a J-pouch), or the creation of a Z-shaped anastomosis.[12-17] Over the course of the past decade the surgical approach has shifted from mainly open mobilization of colon, towards laparoscopic mobilization of colon or a completely transanal approach. There has also been a shift in the surgical techniques that are most used, although to date no technique has been proven to be superior.[18,19] The operation techniques that are currently used most often are the TEPT according to de la Torre and the Duhamel. Also the optimal timing for surgical resection of aganglionosis remains unclear from current evidence.[11,20]

Gastrointestinal functional outcome after surgical treatment in patients with Hirschsprung disease

Although survival in patients with HD has strongly increased over the past decades, morbidity remains high.[21] Even after surgery, patients with HD are at risk for poor bowel function. Although the majority of patients achieves spontaneous defecation after surgery, some patients suffer from obstructive defecation problems.[22] Obstructive defecation problems in patients with Hirschsprung disease can have several underlying causes, including mechanical obstruction (as a result of a stricture, anastomotic twist, or megapouch), residual aganglionosis or transition zone bowel in the anastomosis, internal anal sphincter hypertonia (as a result of an absent rectoanal inhibitory reflex (RAIR) or internal anal sphincter achalasia), dyssynergic defecation or stool holding behavior.[23,24] Patients with obstructive defecation problems may need laxative medication or rectal irrigation to improve defecation.[25] Others may benefit from botulinum toxin injections

in the internal anal sphincter.[26] Other complaints patients with HD may experience after surgery include episodes of HAEC, complaints of soiling or fecal incontinence. [27-29] In addition, they often need longer time to achieve potty-training. In patients with severely impaired bowel function, including recurrent obstructive defecation problems resulting in severely dilated colon or recurrent episodes of HAEC, additional surgical treatment may be necessary.[30,31] Redo surgery may consist of redo pull-through, anorectal myectomy, or stoma formation.

The current body of evidence on postoperative outcome of patients with Hirschsprung disease is often limited by retrospective, cross-sectional design with small sample sizes. This is a challenge in most research on rare conditions.[32] More so, the current evidence on postoperative outcomes almost exclusively focuses on gastrointestinal functional outcome. Although these studies show large heterogeneity in bowel function of patients with HD, ranging from normal bowel function in most patients to poor bowel function in some patients, factors contributing to this heterogeneity remain poorly understood.

Multidisciplinary outcome monitoring in follow-up of patients with surgical congenital malformations

The focus on disease-specific sequelae in terms of bowel function in patients with Hirschsprung disease is illustrative both for most research on outcome in patients with surgical congenital malformations, as well as for current follow-up practice. However, according to the International Classification of Functioning, Disability and Health (ICF) model of the World Health Organization (WHO) the concept of health is multidimensional and must be understood as a state that is not only characterized by the presence or absence of disease, but also by different aspects of physical and emotional functioning, activities and social participation that is influenced by personal and environmental factors.[33] Other bio ecological models also support this holistic view on human functioning and development.[34,35] There is increasing evidence suggesting that patients with surgical congenital malformations may also be at risk for poor outcome in terms of motor development, cognitive functioning, behavioral and emotional functioning, psychosocial wellbeing , quality of life and psychological functioning of parents.[36-39] This emphasizes the need to approach follow-up care from a holistic, family-centered perspective on health, functioning and development of patients and their parents.

In 2017 a follow-up program based on this approach was implemented in the AmsterdamUMC, called Follow Me Congenital Malformations. This program is part of the Follow Me program of the Emma Children's Hospital of the Amsterdam University Medical Centers with aims to offer high quality standardized prospective multidisciplinary follow-up to all level three pediatric patients. The objectives of the program are: 1) improvement of follow-up care, 2) data driven health care evaluation and improvement of care, and 3) contributing to scientific knowledge on outcome and prognosis. A standardized approach to follow-up of patients with surgical congenital malformations as the Follow Me program

provides, may help to consecutively monitor outcomes in patients with surgical congenital malformation in follow-up care. Standardizing follow-up moments and conducting follow-up regularly contributes to early recognition of impairments in functioning for which appropriate interventions can be set in, but also to individual progress monitoring. By standardizing outcome measurement, including objective clinical outcome measures and patient reported outcome measures (PROMs), a comprehensive picture of outcome and prognosis can be developed, than can subsequently be used for shared-decision making and patient education. A better understanding of outcome of patients with surgical congenital malformations in longitudinal multidisciplinary follow-up and insight in factors contributing to heterogeneity in outcome, may lead to development of prediction models using machine learning approaches. This may positively contribute to personalized treatment and follow-up of patients with surgical congenital malformations. Personalized medicine – or precision medicine – is an emerging approach in medicine that aims to customize health care to the needs of an individual patient, aimed at achieving optimal outcomes.[40,41]

MAIN OBJECTIVES

The main objectives of this thesis were: 1) to elucidate factors explaining poor gastrointestinal functional outcome and treatment strategies for poor gastrointestinal functional outcome in patients with Hirschsprung disease, 2) to explore outcome of patients with surgical congenital malformations in other aspects of health and functioning than just gastrointestinal functional outcome, 3) to explore the possibilities of standardized prospective multidisciplinary follow-up to improve patient outcome, improve quality of care and contribute to scientific research on outcome and prognosis after surgery in patients with surgical congenital malformations.

OUTLINE OF THIS THESIS

Part I Gastrointestinal functional outcome in patients with Hirschsprung disease

Patients with Hirschsprung disease (HD) are at risk for obstructive defecation problems, soiling, fecal incontinence and enterocolitis, which in turn may influence broader functioning and development. Obstructive defecation problems occur in about 30% of patients with HD and may have various underlying causes including mechanical obstruction, transition zone pull-through (i.e., histopathological confirmation of transition zone or residual aganglionosis in the proximal side of the anastomosis), internal sphinter

achalasia, dyssynergic defecation, and stool holding behavior.[23,24]. Transition zone pull-through is one of the underlying causes for poor bowel function in patients with HD, but it remains unknown how often a transition zone pull-through occurs. Therefore, in *Chapter 2* a meta-analysis was conducted to study the prevalence of transition zone pull-through and the relationship between transition zone pull-through and clinical symptoms, as currently reported in all relevant literature. Contrary to a previous meta-analysis that reported prevalence of transition zone pull-through among patients who underwent redo-surgery and acknowledged that this may have resulted in an overestimation of actual prevalence, [42] in our meta-analysis all studies reporting histopathological examination of the anastomosis were included. Also subgroup-analysis was used to compare prevalence after operation techniques in which a straight anastomosis was compared to prevalence after operation techniques in which a pouch was created.

Another cause for poor bowel function in patients with Hirshsprung disease may be related to hypertonia of the internal anal sphincter, as a result of internal anal achalasia and absence of the rectoanal inhibitory reflex. Internal anal sphincter hypertonia may increase the risk of enterocolitis due to fecal stasis, although recent evidence suggest that fecal stasis may not completely explain the development of an Hirschsprung-associated enterocolitis (HAEC). Botulinum toxins (BT) relax smooth muscle cell,[43] and thus we hypothesized that BT injections in the internal anal sphincter may improve defecation and lower the risk of HAEC in patients with Hirschsprung. In *Chapter 3* a meta-analysis was conducted to study the clinical improvement of obstructive defecation problems and HAEC after BT injections in patients with Hirschsprung disease. To further study what factors contribute to the fact that some patients respond well to BT injections and others do not, in *Chapter 4* an observational cohort study was conducted in 131 patients that were treated for Hirschsprung disease in the Amsterdam UMC, since BT injections were introduced.

Fecal stasis cannot completely explain why HAEC occurs in some patients and not in others. An observational cohort study in 146 patients treated for HD in the Amsterdam UMC was conducted to further study risk factors for the development of HAEC before and after surgery, as well to study factors that influence the length of the HAEC free interval. The results of this study are reported in *Chapter 5*.

Some studies have suggested that patients who are surgically treated at older age may be at risk for poor bowel function and that early resection may result in good functional outcomes. To study the influence of age at surgery, a national cohort study was conducted in 830 patients with HD and presented in *Chapter 6*.

Part II Multidisciplinary outcomes in patients with surgical congenital malformations

Although disease-related sequelae in patients with Hirschsprung disease may primarily extend to poor gastrointestinal functional outcome, poor bowel function may in turn impair other aspects of health and functioning, including health-related quality of life.

About 5% of the patients with HD have total colonic aganglionosis, a more severe form of Hirschsprung disease. Total colonic aganglionosis requires surgical removal of the complete colon, thus omitting the colon function of resorption of water and salts in these patients. Patients with total colonic aganglionosis are at risk for poor outcomes in terms of bowel function and impaired quality of life.[44,45] Quality of life is defined by the WHO as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". Health-related quality of life is a more focused concept, that describes an individual's perception of physical, psychological and social functioning. Health-related quality of life can be described as generic or as disease-specific health-related quality of life. The latter describes an individual's perception of functioning with a specific disease. In *Chapter* 7 a national cohort study was conducted, reporting gastrointestinal functional outcome and health-related quality of life in 53 patients with total colonic aganglionosis.

Among the broader aspects of health and functioning that may be impaired in patients with surgical congenital malformations is neurodevelopmental outcome. There is evidence for several factors that may negatively contribute to the development of the central nervous system in patients with surgical congenital malformations, including genetic abnormalities,[46-50] perinatal influences, (including maternal smoking,[51] use of medication,[52-54] preterm birth and low birthweight,[55] early, long and/or repeated exposure to anesthetics necessary for surgical correction(s),[56,57] perioperative hemodynamics and respiratory functioning,[58-60] postoperative inflammatory challenges,[61] and poor nutritional status leading to an altered microbiome, influencing the developing brain through the gut-brain axis.[62,63] These harmful influences to the central nervous system may lead to neurodevelopmental impairment. In *Chapter* 8 a meta-analysis was conducted to summarize the currently available evidence on neurodevelopmental outcome of patients with gastrointestinal congenital malformations. Meta-regression was used to explore sources of heterogeneity in effect sizes between studies. Contrary to a previous meta-analysis [36], all outcomes beyond 2 years of age were included, whilst patients with congenital diaphragmatic hernia were excluded, as these patients have a higher risk of impaired neurodevelopmental outcomes because of pulmonary comorbidity and possible treatment with ECMO.[64,65]

According to the International Classification of human Functioning, disability and health (ICF) and the bioecological model of human development[33,66] health and functioning of human beings is under the influence of multiple environmental and personal influences. In particular in pediatric subjects, there is a large influence of family and parental functioning. Parental psychological wellbeing may be negatively influenced by having a baby with a congenital malformations an already vulnerable period of life, and may even be experienced as traumatic.[67] Also surgery, ICU admission and medical proceedings may induce stress responses in parents of patients with congenital gastrointestinal malformations.[68] In turn, impaired psychological wellbeing of parents may disturb parent-child interaction and family functioning, thus negatively influencing

patient functioning.[69] In *Chapter 9* stress of and symptoms of posttraumatic stress disorder were studied in an observational cohort study that included 79 parents of patients with congenital gastrointestinal malformations.

The fact that adverse outcomes may extent to a broad range of domains of functioning and development and may also influence parents, emphasizes the need for longitudinal multidisciplinary monitoring of outcomes in follow-up. In 2017 structured longitudinal multidisciplinary follow-up was implemented in the Amsterdam UMC for children with congenital malformations. The objectives of the program are: 1) improvement of follow-up care, 2) data driven health care evaluation and improvement of care, and 3) contributing to scientific knowledge on outcome and prognosis. In *Chapter 10* a design for routine outcome monitoring in standardized prospective multidisciplinary follow-up is presented. Furthermore it is discussed how routine outcome monitoring in follow-up may contribute to improvement of health care and health outcomes of patients with congenital gastrointestinal malformations, as well as to scientific insights in outcomes of patients with congenital gastrointestinal malformations in a broad range of domains of functioning. Developing a large longitudinal data set allows for the possibility to use advanced methods for studying relationships between clinical factors and outcomes, as well as relationships between outcomes. In *Chapter 11* this is further explored, by using machine learning algorithms to study the predictive value of intraoperative vital parameters for neurodevelopmental outcomes in infants with congenital gastrointestinal malformations in follow-up.

This thesis concludes with a general discussion and a summary, in *Chapter 12 and 13*, respectively. In the general discussion findings from the above outlined studies are summarized and an elaborate discussion of the meaning of our findings for the outcomes of patients with congenital gastrointestinal malformations is provided, accompanied by a discussion of the methodological considerations that needs to be taken into account whilst interpreting these findings. Finally, a view on future directions for research on outcomes in patients with congenital gastrointestinal malformations and improvement of these outcomes and the role of standardized prospective multidisciplinary follow-up is presented.

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PART 1

Gastrointestinal functional outcome in patients with Hirschsprung disease

CHAPTER 2

The prevalence and clinical impact of transition zone anastomosis in patients with Hirschsprung disease: a systematic review and meta-analysis

H. Labib, D. Roorda, J.P. van der Voorn, J. Oosterlaan, L.W.E. van Heurn, J.P.M. Derikx

Submitted

ABSTRACT

Background

Hirschsprung disease (HD) is characterized by absent neuronal innervation of the distal colonic bowel wall and surgically treated by removing the affected bowel segment via pull-through surgery (PT). Incomplete removal of the affected segment is called transition zone anastomosis (TZA). The aim of the current systematic review is to give a comprehensive overview of the prevalence and clinical impact of TZA.

Methods

Pubmed, Embase, Cinahl and Web of Sciences were searched (last search: October 2020), and studies describing histopathological examination for TZA in patients with HD were included. Data was synthesized into aggregated Event Rates (ER) of TZA using random-effects meta-analysis. Clinical impact was defined in terms of obstructive defecation problems, enterocolitis, soiling, incontinence and the need for additional surgical procedures. Quality of studies was assessed using the Newcastle-Ottawa Scale.

Key Results

This systematic review included 34 studies, representing 2207 patients. TZA occured in 25% of all cases. After excluding series composed of only patients undergoing redo PT, prevalence was 9% (ER=0.09, 95%CI=0.05-0.14, p<0.001, I^2=86%). TZA occurred more often after operation techniques in which a straight anastomosis is created, compared to operation techniques in which a pouch is created (X^2= 19.21, p=<0.001). Patients with TZA often had obstructive defecation problems (62%), enterocolitis (38%), soiling (28%) and fecal incontinence (24%) in follow-up periods ranging from six months to 13 years. Patients with TZA more often had persistent obstructive symptoms (X^2=7.26, p=0.007).

Conclusions and Inferences

TZA is associated with obstructive defecation problems and redo PT and is thus necessary to prevent.

INTRODUCTION

Hirschsprung disease (HD) is characterized by absent neuronal innervation of the distal colonic bowel wall for varying distances. The junction between normal ganglionic bowel and aganglionic bowel is characterized by a hypodense and/or non-circumferential distribution of ganglions and hypertrophic nerve fibers, called the transition zone (TZ).[1, 2] Treatment for HD consists of surgical removal of the aganglionic segment and the transition zone, followed by restoration of bowel continuity with a pull-through (PT) procedure. Different operation techniques can be used to restore bowel continuity, either by creating a straight anastomosis, or by creating a pouch.[3-6] Incomplete removal of the transition zone and/or aganglionic segment, called a transition zone anastomosis (TZA).[7] The occurrence of TZA can be the result of errors in obtaining or interpreting frozen section biopsies. There may also be a discrepancy between the radiological localisation of the transition zone, the intra-operative optical transition between dilated and narrowed bowel and the histopathological localisation of the transition zone.[8-10] This discrepancy may lead to a false presumption about the localization of the proximal border of the TZ during surgery, resulting in a TZA.

A previous systematic review analysing patients who underwent redo-surgery for HD describes that abnormal histological findings on repeated biopsies had occurred in an estimated 35% of patients who underwent redo-pull through.[11] However, only patients undergoing redo-surgery were selected for this systematic review. Selecting only patients undergoing redo-surgery therefore may have led to an overestimation of the prevalence of TZA. Furthermore the clinical symptoms that are associated with a TZA in general remain unclear from this systematic review. Previous studies have suggested that a TZA is associated with persistent obstructive defecation problems, soiling, fecal incontinence and development of Hirschsprung-associated enterocolitis (HAEC), but it remains unclear what the clinical impact of TZA is, and whether TZA necessitates redo surgery in all patients.[12-16]

The primary aim of this systematic review and meta-analysis was to provide a comprehensive overview of the prevalence of TZA. Secondary aim was to provide insight in the clinical impact of TZA after initial corrective surgery in terms of the occurrence of obstructive defecation problems, HAEC, soiling, fecal incontinence and the need for redo pull-through.

METHODS AND MATERIALS

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were used for the design and report of this systematic review.[17]

Eligibility criteria

Studies that met the following criteria were included: (1) studies describing individuals with a histopathological confirmed diagnosis of HD, (2) describing assessments of histopathological results (of either biopsy or resection samples) after initial pull-through, or in patients who underwent redo-surgery (3) with an observational or case-control design, (4) that were published in a peer-reviewed journal and (5) of which the full-text was available. We excluded studies from this systematic review that were (1) case-series with fewer than ten patients, (2) reviews or letters to editors, (3) studies measuring other outcome data and (4) studies in a language other than English or Dutch.

Search strategy and study selection

The search strategy was designed together with a clinical librarian. Pubmed, Embase, Cinahl and Web of Sciences were searched, using both simple search terms and hierarchical family forms (e.g., Medical Subject Headings, Thesaurus, Emtree). Three groups of search terms and their equivalents were used: 1) aganglionosis OR Hirschsprung disease, AND 2) pull-through OR anastomosis OR redo-surgery, AND 3) histopathology OR transition zone OR biopsy. The reference lists of eligible articles were also screened for additional articles. The last search was conducted in October 2020. The full search strategy is presented in the Supporting Information.

Titles and abstracts were screened for eligibility by two authors (HL and DR) using Rayyan, a web-based application for selection of abstracts,[18] followed by full-text review of the selected articles by the same authors, using Covidence.[19] Conflicts in the selection process were solved by consensus, or when consensus could not be reached a third party was consulted (JD). Data was extracted by two authors (HL and DR).

Outcomes and definitions

The primary outcome in this study was the prevalence of TZA. We considered a TZA to be present in case of abnormal neuronal innervation of the proximal side of the anastomosis after initial pull-through, including residual aganglionosis and transition zone (characterized by hypoganglionosis and/or abnormal distribution of ganglions). Abnormalities of neuronal innervation had to be confirmed by histopathological examination, either by rectal biopsy or in the resection specimens. An overview of the definitions and methods of determining a TZA is described in sTable 1 (see Supporting Information). In order to compare prevalence of TZA by operation techniques, we differentiated between pull-through techniques in which a pouch or reservoir was created

(which was defined as a pull-through according to Duhamel), or pull-through techniques in which a straight anastomosis was created (including transanal endorectal pull-through (TERPT), laparoscopic-assisted endorectal pull-through (LEPT), posterior sagittal anorectoplasty (PSARP), pull-through according to Soave, pull-through according to Swenson, pull-through according to Rehbein).

The secondary outcome was to study the clinical impact of a TZA after initial pull-through. Clinical impact was defined as the occurrence of obstructive defecation problems, the occurrence of at least one episode of HAEC, the occurrence of soiling and the occurrence of fecal incontinence and the need for additional surgical procedures. We adhered to definitions that were used in the included studies to define these outcomes.

Quality assessment and risk of bias in individual studies

Two authors (HL and DR) independently assessed the quality of evidence using the Newcastle–Ottowa Scale (NOS)[20]. The NOS allows quantification of the quality of observational studies based on the methods of selecting cases (4 points), (2) comparability of case and control groups (2 points) and outcome measurements (3 points), resulting in a total score ranging from 0-9. In accordance with the Agency for Healthcare Research and Quality (AHRQ) standards,[21] quality of studies was considered: good, fair or poor. Rating discrepancies were resolved by consensus.

Statistics

The overall prevalence of TZA was assessed using Comprehensive Meta-Analysis (CMA). As main summary measure for the prevalence we used the aggregated event rate (ER) by aggregating the event rates of TZA in all studies, using the random-effects model. The prevalence of a TZA was separately aggregated for studies who only included patient undergoing redo-surgery, and for studies who included patients after initial pull-through. This difference in prevalence was compared using the test of subgroup differences (Q) in CMA. We compared the occurrence of TZA after procedures in which a pouch was created with the occurrence of TZA after procedures in which a straight anastomosis was created, using Chi-square testing. Meta-regression analysis was used to test the association between the publication year of each study and the event rate of TZA.

When the studies' data allowed for this, the listed clinical symptoms were compared between patients with and without a TZA, using Chi-square testing. Additionally, we assessed the number of patients that had these symptoms before and after redo pull-through for a TZA, using Chi-square testing.

Heterogeneity was interpreted as small (I^2<=0.25), medium (I^2=0.25 – 0.50) or strong (I^2=>0.50), according to Higgins.[22] The possibility of publication bias was assessed by visual inspection of Funnel plots and by calculating Funnel plot asymmetry expressed as the Eggers regression intercept t.[23] In all statistical analyses an alpha-level of 0.05 was considered statistically significant.

RESULTS

Study population

The search yielded 1054 records, corresponding to 535 unique articles, of which 34 were included (Figure 1; Reference list in Supporting Information). Table 1 describes characteristics of the 34 studies, representing 2207 patients, of whom 1516 (69%) were male. In 19 of the 34 studies a cohort of patients after initial surgery was described, whilst 15 studies described a cohort of patients who underwent redo pull-through. The operation techniques used for initial pull-through (n=31 studies) were: Duhamel (n=712 patients), Soave (n=513 patients), TERPT (n=415 patients of whom 52 one stage and 24 LEPT), Swenson (n=138 patients), Rehbein (n=126 patients), Martin (n=13 patients), Scott-Bolley (n=6 patients), missing (n=208).

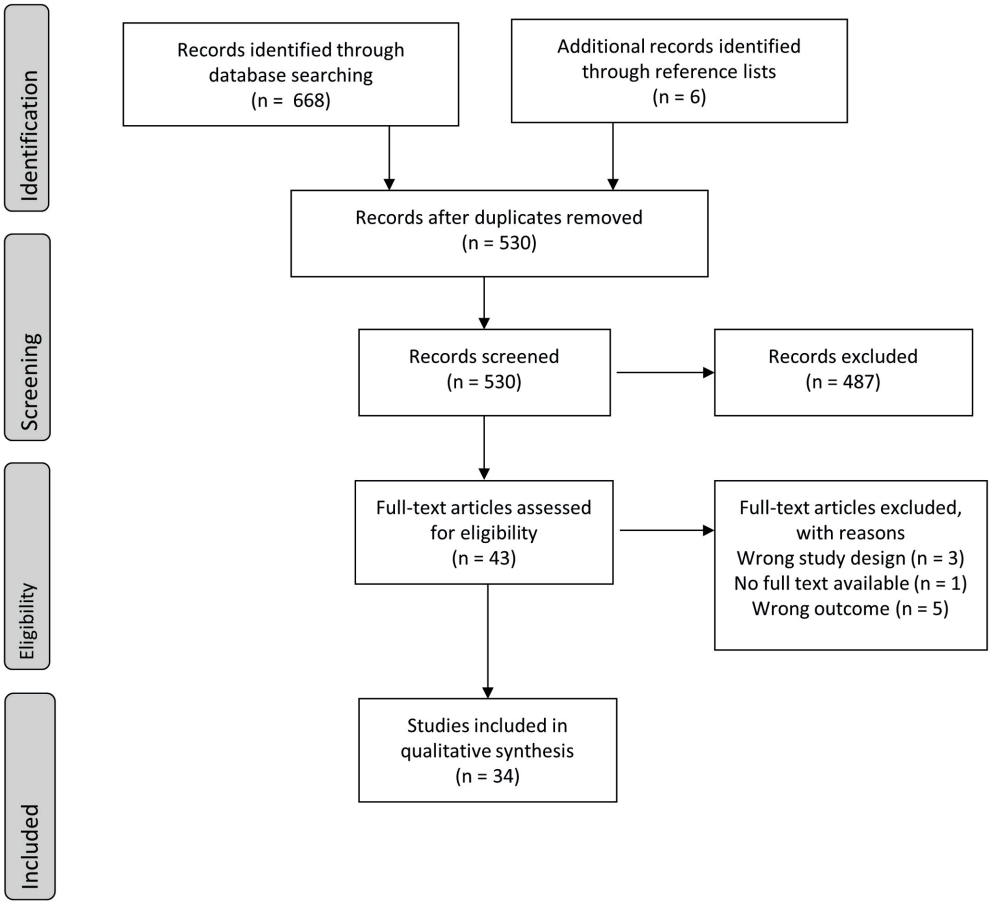

Figure 1 PRISMA Flowchart of selection process

Table 1 Characteristics of included studies

Study	Sample size, n	Male (%)	Mean age (SD) initial corrective surgery in months	Mean age (SD) redo surgery in months	Mean (SD) follow-up in months after redo	Length of aganglionic segment	Operation techniques initial corrective surgery	Number of patients with redo-surgery, n (%)	Operation techniques redo-surgery	Number of TZA, n (%)	Number of patients with TZA of the patients with redo-surgery, n (%)
Chatoor-goon, 2011	17	NR	NR	84	24	NR	17 Duhamel	17/17 (100%)	8 Posterior sagittal approach, 9 transanal Swenson	8/17 (47%)	8/17 (47%)
Coe, 2012	30	73%	10.2 (8.21)	67.0 (42.8)	24.8 (18)	9 short, 3 long, 6 total colonic, 7 NR	17 Soave, 11 Duhamel, 2 Swenson	30/30 (100%)	NR	19/30 (63%)	19/30 (63%
Dinge-mans, 2017	16	63%	NR	NR	NR	NR	8 Soave, 2 Swenson, 3 Rehbein, 3 Duhamel	16/16 (100%)	15 Swenson, 1 Soave	8/16 (50%)	8/16 (50%)
Farrugia, 2003	76	80%	NR	NR	6.0 (4.1)	56 short, 15 long, 5 total colonic	76 Duhamel	5/76 (7%)	NR	18/76 (24%)	3/5 (60%)
Gad El-Hak, 2010	52	63%	3.29 (1.6)	NR	NR	NR	52 Swenson	2/52 (4%)	2 Swenson	2/52 (4%)	2/2 (100%)
Ghose, 2000	13	77%	NR	NR	118	10 short, 3 long	8 Duhamel, 5 Soave	7/13 (54%)	7 Duhamel	13/13 (100%)	7/7 (100%)
Ghosh, 2017	50	78%	NR	NR	NR	36 short, 14 long	50 Soave	0/50 (0%)	NR	8/50 (16%)	NR
Gupta, 2019	32	81%	NR	62.4	43.2	28 short, 24 long, 2 total colonic	24 Duhamel, 6 Scott Boley, 2 Swenson	32/32 (100%)	22 open TEPT Scott Boley/Soave, 5 ileo-anal PT, 5 TEPT	12/32 (38%)	12/32 (38%)
Hadidi, 2007	18	78%	NR	NR	NR	NR	7 Swenson, 9 Soave, 1 Duhamel, 1 Rehbein	18/18 (100%)	18 TEPT	18/18 (100%)	18/18 (100%)
Han, 2019	657	76%	NR	NR	59.6 (53.76)	580 short, 77 long	443 Duhamel, 199 TEPT (Soave like), 12 Martin, 3 Swenson	57/657 (9%)	29 Duhamel, 23 TEPT, 4 Swenson, 1 PSAR	28/657 (4%)	28/57 (49%), 8/28 (29%) underwent 3 times
Imvised, 2016	76	87%	9.9	NR	NR	73 short, 3 long	76 TEPT	0/76 (0%)	NR	2/76 (3%)	0/76 (0%)
Jiang, 2019	31	71%	5	41	NR	NR	18 TEPT, 5 Duhamel, 8 Soave	31/31 (100%)	14 Duhamel, 17 Soave	16/31 (52%	16/31 (52%)

Keshtgar, 2003	19	79%	NR	NR	NR	NR	16 Duhamel, 1 Rehbein, 2 Soave	5/19 (26%)	NR	2/19 (11%)	1/5 (20%)
Kobayashi, 1995	33	85%	NR	NR	29	27 short, 6 long	31 Swenson, 2 Duhamel	1/33 (3%)	NR	2/33 (6%)	1/1 (100%)
Langer, 2000	37	73%	1.0 & 2.0 & 2.5	NR	NR	31 short, 6 long	13 open Soave, 24 transanal Soave	7/37 (19%)	NR	1/37 (3%)	1/7 (14%)
Langer, 2003	141	80%	4.9	NR	20.2 (9.2)	109 short, 32 long	141 1-stage transanal Soave	3/141 (2%)	1 Duhamel, 2 Soave	1/141 (1%)	1/3 (33%)
Langer, 2004	49	84%	NR	NR	NR	27 short, 22 long	9 Swenson, 25 soave, 15 Duhamel	17/49 (35%)	16 Duhamel, 1 Swenson	10/49 (20%)	8/17 (47%)
Lawal, 2011	16	88%	NR	NR	NR	11 short, 2 long, 3 NR	7 transabdominal Soave, 7 transanal Soave, 1 transanal Swenson, 1 Duhamel	16/16 (100%)	15 TEPT, 1 posterior sagittal approach	16/16 (100%)	16/16 (100%)
Peña, 2007	51	67%	68.4	NR	NR	NR	17 Soave, 14 Duhamel, 6 TEPT, 5 Swenson, 1 Swenson J pouch, 1 Soave and right colonic pouch, 7 NR	45/51 (88%)	40 posterior sagittal approach (with or without laparotomy), 5 transanal approach	8/51 (16%)	8/45 (18%)
Peng, 2020	46	83%	18.34 (30.9)	53.6 (37.2)	101.4 (33.2)	NR	38 Soave, 2 Rehbein, 1 Martin, 5 NR	46/46 (100%)	46 Soave	27/46 (59%)	27/46 (59%)
Pini-Prato, 2010	70	60%	22.8 (32.4)	48 (37.2)	94.8 (49.2)	21 short, 4 long, 10 total colonic	37 Soave, 7 Duhamel, 1 Swenson, 2 Rehbein, 23 NR	70/70 (100%)	53 Soave, 9 Duhamel, 7 Swenson, 1 Rehbein/ posterior sagittal approach	51/70 (73%	51/70 (73%)
Pini-Prato, 2020	16	75%	NR	56.7 (37.6)	26	12 short, 2 long, 2 total colonic	NR	16/16 (100%)	NR	10/16 (63%	10/16 (63%)
Polley, 1986	99	70%	NR	NR	NR	73 short, 19 long, 6 total colonic	78 TEPT, 11 Swenson, 5 Duhamel, 1 colectomy, 4 NR	12/99 (12%)	4 Swenson, 1 Duhamel, 2 TEPT, 5 NR	1/99 (1%)	1/12 (8%)
Ralls, 2014	121	74%	26.4 (50.4)	82.8 (110.4)	NR	90 short, 24 long, 7 NR	NR	32/121 (26%)	9 Swenson, 5 Duhamel, 7 transanal, 6 TEPT, 1 Soave, 1 open, 3 NR	12/121 (10%)	12/32 (38%)

Schulten, 2000	101	73%	22.8	NR	54	NR	101 Rehbein	0/101 (0%)	NR	30/101 (30%)	0/101 (0%)
Schweizer, 2007	17	NR	NR	NR	126	NR	13 Rehbein, 3 Soave, 1 Duhamel	17/17 (100%)	17 Duhamel	16/17 (94%)	16/17 (94%)
Sheng, 2012	24	63%	8	NR	30	5 short, 19 NR	9 Duhamel, 12 Soave, 2 Rehbein, 1 Swenson	24/24 (100%)	6 Duhamel, 7 Soave, 3 Rehbein, 1 laparatomy, 7 posterior sagitally	5/24 (21%)	5/24 (21%)
Stensrud, 2010	52	NR	NR	NR	NR	43 short, 9 long	28 TEPT, 24 LEPT	1/52 (2%)	1 LEPT	1/52 (2%)	1/1 (100%)
Van Leeuwen, 2000	19	68%	27.6	64.8	165.6	11 short, 5 long, 3 NR	10 TEPT, 5 Duhamel, 3 Swenson, 1 Rehbein	19/19 (100%)	3 Swenson, 8 TEPT, 8 Duhamel	5/19 (26%)	5/19 (26%)
Vu, 2010	51	65%	0.7 (0.2)	NR	18 (2.4)	47 short, 4 long	51 TOSEPT	2/51 (4%)	NR	2/51 (4%)	2/2 (100%)
Weber, 1999	107	NR	9	NR	102	93 short, 7 long, 7 total colonic	68 Soave, 39 Duhamel	5/107 (5%)	2 Soave, 2 Duhamel, 1 NR	3/107 (3%)	3/5 (60%)
Wilcox, 1998	20	80%	10.8	72	78	NR	10 Duhamel, 3 Soave, 7 Swenson	20/20 (100%)	1 Swenson, 19 Duhamel	10/20 (50%)	10/20 (50%)
Wildhaber, 2004	32	69%	NR	NR	103.2	NR	NR	9/32 (28%)	NR	6/32 (19%)	5/9 (56%)
Xia, 2016	18	89%	5	38	NR	18 short	18 Soave	18/18 (100%)	15 Soave, 3 Swenson	18/18 (100%)	18/18 (100%)

Note. d = days; m = months; NR = not reported; TZA = transition zone anastomosis; TEPT = transanal endorectal pull-through; LEPT = laparoscopic endorectal pull-through; PSARP = posterior sagittal anorectoplasty; TOSEPT = transanal one-stage endorectal pull-through

Table 2 Clinical symptoms described in patients with TZA after initial surgery and after redo surgery

Study	Number of patients with TZA	Mean follow-up after initial PT	Mean follow-up after redo PT	Constipation		Soiling		Enterocolitis		Fecal incontinence		Continence	
				After initial surgery	After redo surgery	After initial surgery	After redo surgery	After initial surgery	After redo surgery	After initial surgery	After redo surgery	After initial surgery	After redo surgery
Chatoorgoon, 2011	8	7y	2m	8/8 (100%)	0/8 (0%)	-	-	-	-	-	-	-	-
Coe, 2012	19	7.8y	25m	19/19 (100%)	0/19 (0%)	-	-	10/19 (53%)	-	-	-	-	-
Dingemans, 2017	8	7.6y	3y	0/8 (0%)	0/8 (0%)	1/8 (13%)	-	-	-	3/8 (38%)	-	-	-
Farrugia, 2003	18	6y		6/18 (33%)	-	2/18 (11%)	-	11/18 (61%)	-	4/18 (22%)	-	-	-
Gad El-Hak, 2010	2	12m		2/2 (100%)	0/2 (100%)	-	-	-	-	-	-	-	-
Ghose, 2000	13	10y		7/13 (54%)	-	5/13 (38%)	2/7 (29%)	1/13 (8%)	-	13/13 (100%)	1/7 (14%)	-	2/7 (29%)
Ghosh, 2017	8	6m		2/8 (25%)	-	-	-	4/8 (50%)	-	-	-	-	-
Hadidi, 2007	18	43m		-	3/18 (17%)	-	1/18 (6%)	8/18 (44%)	2/18 (11%)	-	-	-	-
Keshtgar, 2003	2			2/2 (100%)	-	-	-	-	-	-	-	-	-
Kobayashi, 1995	2	29m		1/2 (50%)	-	-	-	1/2 (50%)	-	-	-	-	-
Langer, 2004	10			5/10 (50%)	-	-	-	5/10 (50%)	-	-	-	-	-
Lawal, 2011	16	6-66m	16m	12/16 (75%)	1/16 (6%)	-	1/16 (6%)	9/16 (56%)	0/16 (0%)	-	-	-	-
Pini-Prato, 2010	51	11.9y	7.9y	25/51 (49%)	-	-	-	8/51 (16%)	-	2/51 (4%)	-	-	-

Pini-Prato, 2020	10		26m	10/10 (100%)	-	-	-	-	-	-	-	-	-
Polley, 1986	1	3m-11y		-	-	-	-	-	-	-	-	-	1/1 (100%)
Schulten, 2000	30	4.5y		6/30 (20%)	-	2/30 (7%)	-	-	-	-	-	-	-
Schweizer, 2007	16		9y	16/16 (100%)	3/16 (19%)	13/16 (81%)	2/16 (13%)	9/16 (56%)	-	-	-	-	-
Sheng, 2012	5	4.5y	2.5y	5/5 (100%)	0/5 (0%)	-	2/5 (40%)	-	0/5 (0%)	-	0/5 (0%)	-	-
Stensrud, 2010	1	5.7m TEPT, 10m LEPT		1/1 (100%)	-	-	-	-	-	-	1/1 (100%)	-	-
Wilcox, 1998	9	12.5y	6.5y	-	0/9 (0%)	-	-	-	-	-	-	-	-
Wildhaber, 2004	6	13.1y	8.6y	6/6 (100%)	-	-	-	1/6 (17%)	-	-	-	-	-
Xia. 2016	18	13-75m		18/18 (100%)	0/18 (0%)	6/18 (33%)	-	-	6/18 (33%)	-	-	-	18/18 (100%)
Total	**261**			**151/243 (62%)**	**7/119 (9%)**	**29/103 (28%)**	**8/62 (13%)**	**67/177 (38%)**	**8/57 (14%)**	**22/90 (24%)**	**2/13 (15%)**	**-**	**21/26 (81%)**

Prevalence of TZA

A total of 34 studies were included in the meta-analysis on the prevalence of TZA after initial pull-through, representing 2207 patients. The aggregated event rate of the occurrence of a TZA was 25% (ER=0.25, 95%CI=0.16 -0.37, p<0.001, I^2=92%). A forest plot is shown in Figure 2. After exclusion of the studies that only included patients who underwent redo pull-through, 19 studies were included in the meta-analysis on the prevalence of TZA, representing 1817 patients. The aggregated event rate of the occurrence of a TZA was 9% (ER=0.09, 95%CI=0.05-0.14, p<0.001, I^2=86%). When including only the 15 studies representing 390 patients who underwent redo-pull-through, the aggregated event rate of the occurrence of a TZA in these studies was 59% (ER=0.59, 95%CI=0.46-0.70, p<0.001, I^2=73%). There was a significant difference in the aggregated event rate of TZA between studies composed of only patients who underwent redo pull-through, compared to studies composed of patients after initial pull-through (Q=49.9, p<0.001). Stratification by operation technique (with or without pouch/reservoir) led to aggregation of 24 studies that allowed for this comparison. This analysis showed that 63 of 641 patients with a pouch had a TZA (10%), whereas 199 of 1137 patients without a pouch (all variations of a straight circular anastomosis) had TZA (18%), (X^2= 19.21, p<0.001). The event rate of TZA was not associated with the year of publication of each study (b=0.84, p=0.176).

Clinical symptoms associated with a TZA

Table 2 shows the clinical outcomes of patients with and without a TZA, as reported in each included study.

Obstructive defecation problems were reported in 62% of patients with a TZA after initial surgery (151 of 243 patients, in 19 studies), after a mean follow-up that ranged between six months and 13 years after initial pull-through. Only three studies compared complaints of obstructive defecation in patients with and without TZA after initial surgery and showed that 15 of 56 patients with TZA had constipation (27%) after initial pull-through and 20 of 170 patients without TZA had constipation after initial pull-through (12%), indicating that prevalence of obstructive defecation problems is significantly higher in patients with TZA (X^2=7.26, p=0.007). Two studies compared complaints of obstructive defecation problems in patients with TZA before and after their redo-surgery and both studies reported in all 27 patients complaints of obstructive defecation vanished after redo-surgery.

Postoperative HAEC after initial pull-through was reported in 38% of patients with a TZA (67 of 177 patients, in 11 studies), after a mean follow-up that ranged between studies from six months to 13 years after initial pull-through. Four studies compared patients with and without TZA with regard to HAEC incidence and reported that at least one episode of postoperative enterocolitis had occurred in 19 of 75 patients with TZA (25%) and in 33 of 182 patients without TZA (18%), indicating that the risk of HAEC was not significantly higher for patients with TZA (X^2=1.71, p=0.191).

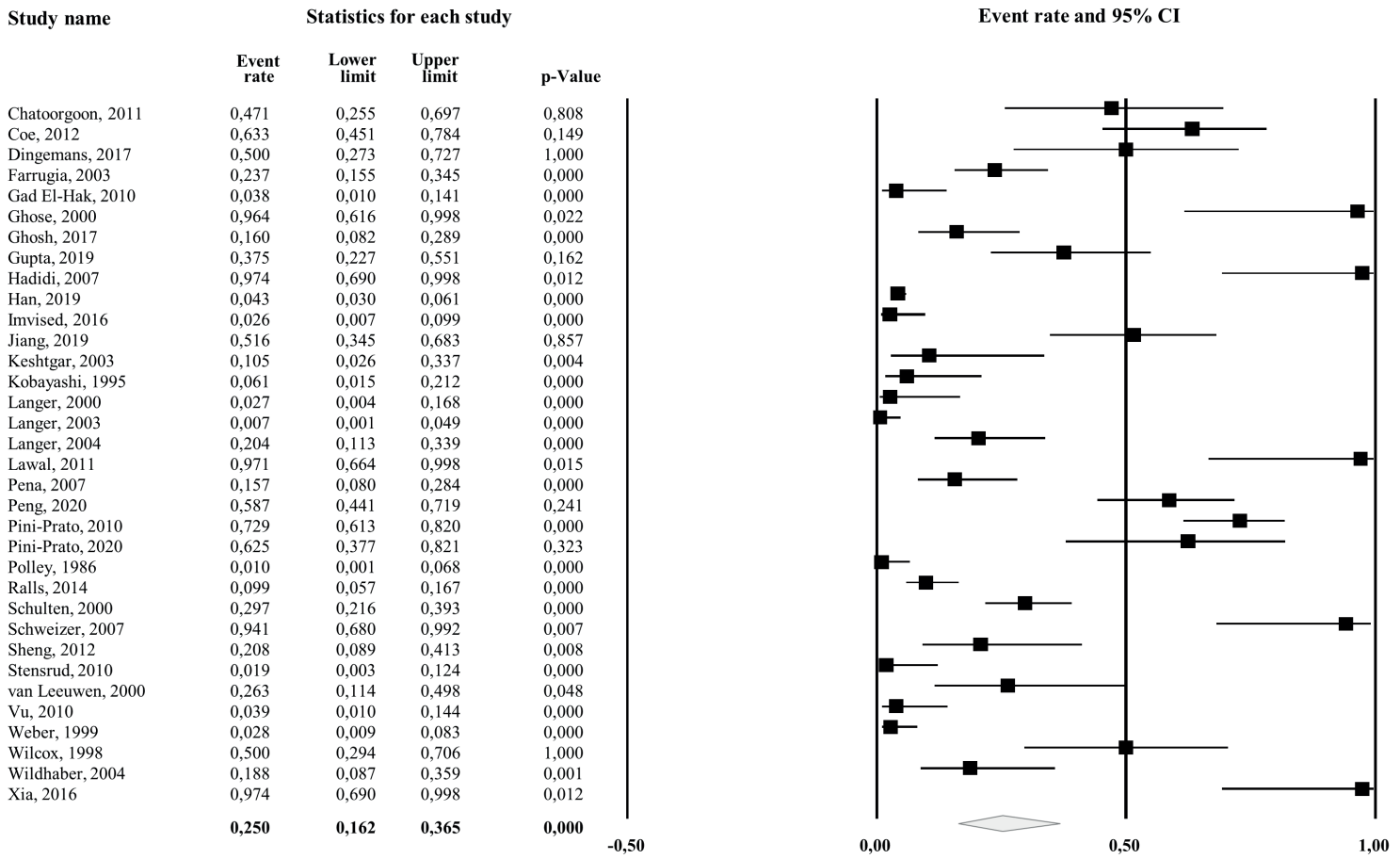

Figure 2 Forest plot of event rates of transition zone anastomosis (TZA)

Table 3 Quality assessment of included studies with the Newcastle-Ottawa Scale (NOS)

Study	Selection	Comparability	Outcome	Total score	Quality
Chatoorgoon, 2011	3	0	3	6	Poor
Coe, 2012	3	0	3	6	Poor
Dingemans, 2017	3	0	3	6	Poor
Farrugia, 2003	4	1	3	8	Fair
Gad El-Hak, 2010	3	0	3	6	Poor
Ghose, 2000	3	0	3	6	Poor
Ghosh, 2017	4	1	3	8	Fair
Gupta, 2019	3	0	3	6	Poor
Hadidi, 2007	3	0	3	6	Poor
Han, 2019	4	1	3	8	Fair
Imvised, 2016	3	0	3	6	Poor
Jiang, 2019	4	0	3	7	Poor
Kesthtgar, 2003	3	0	3	6	Poor
Kobayashi, 1995	4	0	3	7	Poor
Langer, 2000	3	2	3	8	Good
Langer, 2003	3	0	3	6	Poor
Langer, 2004	4	0	3	7	Poor
Lawal, 2011	3	0	3	6	Poor
Pena, 2007	3	0	3	6	Poor
Peng, 2020	3	0	3	6	Poor
Pini-Prato, 2010	4	0	3	7	Poor
Pini-Prato, 2020	3	0	3	6	Poor
Polley, 1986	3	0	3	6	Poor
Ralls, 2014	3	2	2	7	Good
Schulten, 2000	4	0	3	7	Poor
Schweizer, 2007	3	0	3	6	Poor
Sheng, 2012	3	0	3	6	Poor
Stensrud, 2010	3	0	3	6	Poor
Van Leeuwen, 2000	3	0	3	6	Poor
Vu, 2010	3	0	3	6	Poor
Weber, 1999	4	0	3	6	Poor
Wilcox, 1998	3	0	3	6	Poor
Wildhaber, 2004	3	0	3	6	Poor
Xia, 2016	4	1	3	8	Good

Soiling after initial surgery was reported in 28% of patients with a TZA (29 of 103 patients, in 6 studies), after a mean follow-up that ranged between studies from 13 months to 10 years after initial pull-through. No studies compared patients with and without TZA or soiling before and after redo pull-through in patients with TZA.

Fecal incontinence after initial surgery was reported in 24% of patients with a TZA (22 of 90 patients, in 4 studies), after a mean follow-up that ranged between studies from six to 12 years after initial pull-through. One study compared patients with and without TZA with regard to fecal incontinence after initial pull-through and reported more fecal incontinence in patients with TZA (2 of 30 patient) compared to patients without TZA (0 of 71 patients), but did not statistically test this difference.

Of the 389 patients with a TZA in this systematic review, 323 underwent redo pull-through (83%). All indications for redo-pull-through as described in the included studies, are reported in sTable 2 (see Supporting Information). Some patients had multiple indications for one procedure of redo-surgery. Additional surgical interventions after initial pull-through, other than redo pull-through, were indicated in 42% of patients with a TZA (74 of 178 patients, in 11 studies).

Quality of evidence and risk of bias analyses

The quality of studies, as assessed with the NOS, is reported in Table 3. Among the 34 articles, 26 articles were of poor quality, 3 of fair quality and only 3 of good quality. Average quality score was 6,5 (range 6-8). The most common reason for poor quality was the use of an uncontrolled design: these studies carried the risk of selection bias and allocation bias, as these studies that only described series of patients after redo-surgery. Risk of observer bias was also present, as none of the studies were blinded. There was no risk of publication bias, based on visual inspection of the funnel plot (see sFigure 1, in the Supporting Information) and based on Egger's regression (t=0.486, p=0.711).

DISCUSSION

This systematic review and meta-analysis showed that the overall prevalence of a TZA was 25%, but varied between series describing only patients who underwent redo pull-through (59%) and series describing its occurrence after initial pull-through (9%). A large part of studies in the current systematic review consisted of only patients undergoing redo pull-through, which may have led to an overestimation of the prevalence of TZA in the general population, as TZA is often an indication of redo PT. We thus think the actual prevalence may be best reflected by the prevalence of 9%.

Our prevalence findings were lower than in a previous meta-analysis done by Friedmacher et al, who reported TZA in 35% of patients.[11] This difference may be explained by differences in case definition, differences in inclusion criteria, and by the inclusion of

studies (13 studies) that were published after their study period. Our sensitivity analysis in studies with patients who underwent redo PT showed an even higher prevalence, which may suggest that over the past decade there is an increased awareness for the risk of TZA and thus higher detection rate of TZA.[24] However, our data did not show a significant increase in prevalence over the years of our study period. The most accurate way to estimate the actual prevalence of a TZA in all patients who receive pull-through surgery would be based on the histopathological report of the proximal resection plane, but only few of the included studies in the current systematic review describe this for all patients.[25]

There are several factors that account for challenges in the diagnosis of a TZA. An important factor is the current approach to determining the delineation of the transition zone during operation.[8] Most surgeons do this by perioperative single point frozen section, based on radiological and visual assessment of the location of the tapering of the bowel. However, previous studies show the limited validity of single-point biopsy and that radiological and perioperative assessment of a surgeon does not correspond well to the histopathological delineation of the transition zone of the resected bowel.[26, 27] Another important factor is the lack of a clear definition of transition zone bowel. Although insight in histopathological features of the transition zone is increasing,[2, 28, 29] with an increasing number of studies describing histopathological findings in transition zone bowel, a clear definition of the histopathological criteria of the transition zone is still lacking.[24, 30, 31] Moreover, studies that describe histopathological features of the transition zone have shown large variation between patients with regard to the length of the transition zone, the skewness of its proximal delineation and the distribution of ganglions and nerve fibers in the transition zone.[2, 28, 32, 33] These features are more likely diagnosed after calretinin immunohistochemistry, which requires time and therefore cannot be done in frozen perioperative biopsy specimens.[34] In current practice we thus often also determine the presence of ganglion cells in the proximal resection plane specimen. Despite this, in a substantial number of patients in the studies included in this review TZA was detected later in life by repeat biopsy. This emphasizes that not only the presence of ganglion cells may be an important feature to take into account, but also density and distribution of ganglion cells and hypertrophy of nerve fibers.[2, 35]

Our findings suggest that a TZA occurs more often after techniques in which a straight anastomosis is created, compared to techniques in which a pouch is created. It is the purpose of the pouch (which is also aganglionic) to slow down the passage of stools to become more solid before defecation, and thus may not lead to constipation or incontinence. This in turn, may explain the lower rates of diagnosis of TZA in patients with a pouch.

The second aim of this review was to study the clinical impact of a TZA. The evidence presented in this systematic review shows more frequent occurrence of obstructive defecation problems, enterocolitis, soiling, incontinence and redo-surgery in patients with a TZA compared to patients without a TZA. A direct comparison between patients with

and without a TZA showed more obstructive defecation problems in patients with TZA compared to patients without TZA, but could only be based on three studies.[36-38] Thus, conclusions need to be drawn with caution. However, the rates of obstructive defecation problems, HAEC, soiling and fecal incontinence in patients with TZA in the current systematic review seem to be higher compared to what has been described in previous meta-analyses on outcomes after pull-through surgery in patients with HD in general.[13, 14] Note that this comparison has to be made with caution, given the inclusion of 15 (44%) series describing redo procedures, and the limited number of studies in this analysis comparing patients before and after redo PT for TZA.

Lastly, the findings of the current systematic review suggested that patients with a TZA often received redo pull-through (83%), or other types of surgical interventions. We noticed that about half of the redo procedures described in this review were done because of a TZA.

To conclude, our findings suggest that TZA accounts for substantial morbidity in patients with HD and when diagnosed often resulted in redo pull-through. To improve outcomes in patients with HD it is important to early detect TZA, and thus clinical problems in long term and the need for redo pull-through.

Limitations

The interpretations of our findings on prevalence and clinical impact of a TZA need to be considered in the light of the following limitations. First, the aforementioned challenges is diagnosing TZA. Second, we used a liberal definition for a TZA in this study, including both abnormal histological findings of residual aganglionosis, as well as characteristics of a TZ, whilst a clear definition of the histopathological features of the TZ is still lacking. Previous studies have suggested that residual aganglionosis may also be acquired, and may be the result of ischemia, instead of the result of an incomplete resection.[39] Third, heterogeneity in the current meta-analyses was strong for all meta-analytical findings. There was also large heterogeneity in outcome definitions of clinical symptoms between studies, and large heterogeneity in length of follow-up. Although this is inherent to a systematic review, it made it challenging to compare clinical outcomes across studies. In particular with regard to fecal incontinence, of which the definition is depends on age of the patient and whether potty-training had been completed. Last, although an effort was made to not include overlapping cohorts of patients, (partly) overlapping patients between studies could not be fully ruled out on a patient level.

Quality of evidence and risk of publication bias

The quality of evidence retrieved from the majority of studies (65%) was poor, as was reflected by NOS scores. Most studies had a retrospective design and therefore a lot of relevant data on outcome and per-operative details could not be retrieved from the studies.

There was however no significant risk of publication bias.

Clinical implications and future perspectives

These aforementioned limitations highlight the need for higher quality studies reporting the prevalence and clinical impact of a TZA in patients with HD. For future initiatives we would recommend studies that focus on the histopathological features of (the proximal delineation of) the TZ, allowing for a clear definition on the occurrence of a TZA, and a better approach to determining the perioperative level of resection. We further recommend that studies report gastrointestinal functional outcome using more uniform definitions and not focus on single outcomes only, but report outcomes in accordance with a recently developed core outcome set for patients with HD.[40] This would allow for a better comparison of clinical impact in patients with a TZA compared to patients without a TZA, for a better comparison and aggregation of outcomes between studies and ultimately to help us answer the question whether redo pull-through is necessary in all patients with a TZA.

Conclusion

In this study we found that the prevalence of a TZA was 25% in patients with HD after initial pull-through. Prevalence was 9% when excluding series that included only patients undergoing redo PT (of which most were done because of TZA). Patients with TZA have high prevalence of obstructive defecation problems (61%), enterocolitis (38%), soiling (28%) fecal incontinence (24%) and redo pull-through (83%).

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SUPPORTING INFORMATION

Full Search strategy

Pubmed

("Hirschsprung Disease"[Mesh] OR hirschsprung*[tiab] OR congenital megacolon[tiab] OR aganglionic megacolon[tiab] OR rectosigmoid colon aganglionosis[tiab] OR rectosigmoid aganglionosis[tiab] OR congenital intestinal aganglionosis[tiab] OR colonic aganglionosis[tiab] OR total colonic aganglionosis[tiab] OR residual aganglionosis[tiab])
AND
("Anastomosis, Surgical"[Mesh] OR "Reoperation"[Mesh] OR "Hirschsprung Disease/surgery"[MAJR] OR anastomos*[tiab] OR redo surger*[tiab] OR pull through[tiab] OR pullthrough[tiab] OR reoperation*[tiab] OR re-operation*[tiab])
AND
("Pathology"[Mesh] OR "Biopsy"[Mesh] OR patholog*[tiab] OR cytopatholog*[tiab] OR histopatholog*[tiab] OR biops*[tiab] OR transition zone*[tiab])

EMBASE (Ovid):

Database(s): Embase Classic+Embase 1947 to 2019 February 07
Hirschsprung disease/ or (hirschsprung* or congenital megacolon or aganglionic megacolon or rectosigmoid colon aganglionosis or rectosigmoid aganglionosis or congenital intestinal aganglionosis or colonic aganglionosis or total colonic aganglionosis or residual aganglionosis).ti,ab,kw.
AND
exp anastomosis/ or reoperation/ or pull through operation/ or (anastomos* or redo surger* or redo pull-through or transition zone pull through or reoperation* or re-operation*).ti,ab,kw.
AND
exp pathology/ or exp biopsy/ or (patholog* or cytopatholog* or histopatholog* or biops* or transition zone*).ti,ab,kw.

Cinahl (Ebsco):

(MH "Hirschsprung Disease+") OR (TI (hirschsprung* or congenital megacolon or aganglionic megacolon or rectosigmoid colon aganglionosis or rectosigmoid aganglionosis or congenital intestinal aganglionosis or colonic aganglionosis or total colonic aganglionosis or residual aganglionosis) OR AB (hirschsprung* or congenital megacolon or aganglionic megacolon or rectosigmoid colon aganglionosis or rectosigmoid aganglionosis or congenital intestinal aganglionosis or colonic aganglionosis or total colonic aganglionosis or residual aganglionosis))
AND
(MH "Pathology+") OR (MH "Biopsy+") OR (TI (patholog* or cytopatholog* or

histopatholog* or biops* or transition zone*) OR AB (patholog* or cytopatholog* or histopatholog* or biops* or transition zone*))
AND
(MH "Anastomosis, Surgical+") OR (MH "Reoperation+") OR (TI (anastomos* or redo surger* or redo pull-through or transition zone pull through or reoperation* or re-operation*) OR AB (anastomos* or redo surger* or redo pull-through or transition zone pull through or reoperation* or re-operation*))

Web of Science:
TOPIC: (hirschsprung* or congenital megacolon or aganglionic megacolon or rectosigmoid colon aganglionosis or rectosigmoid aganglionosis or congenital intestinal aganglionosis or colonic aganglionosis or total colonic aganglionosis or residual aganglionosis)
AND
TOPIC: (anastomos* or redo surger* or redo or pull through or reoperation* or re-operation*)
AND
TOPIC: (patholog* or cytopatholog* or histopatholog* or biops* or transition zone*)

sTable 1 Definitions and measurements for diagnosing TZA in each study

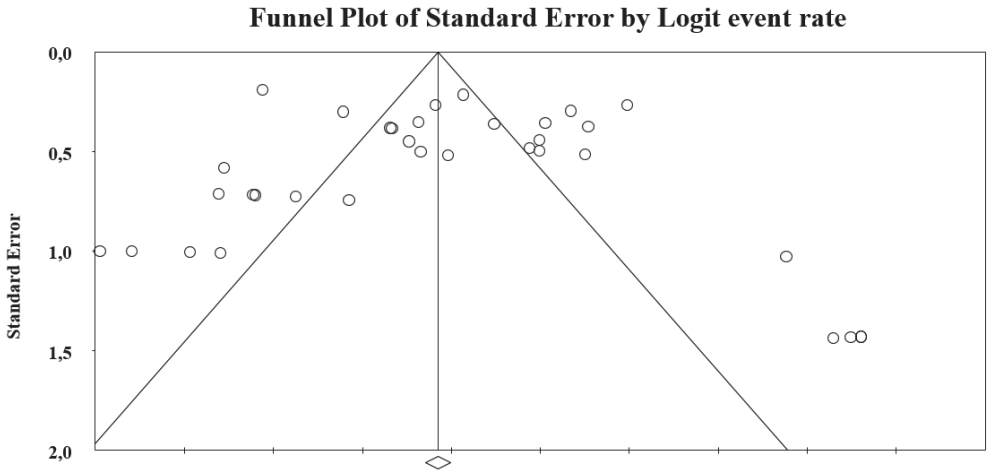
Author	Definition TZ	Determination aganglionic bowel during initial surgery	Determination TZA
Chatoorgoon, 2011	Ganglionic cells with hypertrophic nerves	NR	Full thickness biopsy
Coe, 2012	The presence of ganglion cells in the submucosa or myenteric plexus with hypertrophied and hyperplastic nerves.	NR	Biopsy
Dingemans, 2017	NR	NR	Full thickness biopsy
Farrugia, 2003	Diminished numbers of ganglion cells in the myenteric plexus and submucosa. Whole-mount preparations show increased irregularity and wider spacing of the polygonal network of ganglia and nerve fibers of the myenteric plexus. Occasional acetylcholinesterase staining hypertrophic bundles of extrinsic nerves also are seen	Frozen section biopsy	Biopsy
Gad El-Hak, 2010	NR	NR	Postoperative pathology
Ghose, 2000	More subtle abnormalities of innervation resent between normal bowel and aganglionic bowel.	Frozen section biopsy	Further biopsies were not performed
Ghosh, 2017	Decreased number of ganglionic myenteric nervous plexuses.	Frozen section biops	Frozen section of proximal margin
Gupta, 2019	NR	Frozen section biopsy	Absence of ganglion cells in the proximal-part of the resected bowel
Hadidi, 2007	NR	Frozen section biopsy	Biopsy
Han, 2019	NR	Frozen section biopsy (not all patients)	Contrast study
Imvised, 2016	NR	Frozen section biopsy	Permanent histology report from resected bowel
Jiang, 2019	NR	Frozen section biopsy	Full thickness biopsy
Keshtgar, 2003	NR	NR	NR
Kobayashi, 1995	NR	Frozen section biopsy	NR
Langer, 2000	NR	Frozen section biopsy	NR
Langer, 2003	NR	Frozen section biopsy	NR
Langer, 2004	NR	NR	Rectal biopsy
Lawal, 2011	The presence of hypertrophic nerves in the submucosa, with normal ganglion cells or absent of ganglion cells	Frozen section biopsy	Rectal biopsy

Peña, 2007	NR	NR	Rectal biopsy
Peng, 2020	NR	NR	NR
Pini-Prato, 2010	NR	NR	Rectal/full thickness biopsy
Pini-Prato, 2020	NR	NR	NR
Polley, 1986	NR	Frozen section biopsy	NR
Ralls, 2014	NR	Frozen section biopsy	Biopsy
Schulten, 2000	NR	Frozen section biopsy	NR
Schweizer, 2007	Hypoganglionosis, dysganglionosis, aganglionosis, and a pattern of intestinal neuronal	NR	NR
Sheng, 2012	NR	Frozen section biopsy	Rectal iopsy
Stensrud, 2010	NR	Frozen section biopsy	NR
Van Leeuwen, 2000	NR	NR	Rectal biopsy
Vu, 2010	NR	Frozen section biopsy	NR
Weber, 1999	NR	NR	NR
Wilcox, 1998	NR	NR	Rectal biopsy
Wildhaber, 2004	NR	NR	Rectal/full thickness biopsy and contrast enema
Xia, 2016	The presence of ganglion cells in the submucosa or myenteric plexus with hypertrophied and hyperplastic nerves.	Frozen section biopsy	Rectal biopsy

Note. NR = not reported

sTable 2 Indications for all redo pull-through procedures in this systematic review

Indication redo PT	Number of patients
Transition zone anastomosis	323
Anastomotic stricture	94
Fistulae	31
Mega pouch	25
Chronic constipation	20
Adhesions	10
Intestinal neuronal dysplasia	9
Twisted anastomosis	8
Retraction of bowel	5
Dilated distal bowel segment	5
Narrowed rectal cuff	4
Recurrent Hirschsprung-associated enterocolitis	3
Anastomotic retraction	3
Pouchitis	2
Disruption of the anastomosis	2
Prescacral sinus	2
Bleeding	1
Necrosis	1
Severe fecal incontinence	1
Leak	1
Rectal prolapse	1
Rectal diverticuli	1
Missing	48
Total	**600**



sFigure 1 Funnelplot showing the risk of publication bias

CHAPTER 3

Botulinum toxin injections after surgery for Hirschsprung disease: Systematic review and meta-analysis

D. Roorda, Z.A. Abeln, J. Oosterlaan, L.W.E. van Heurn, J.P.M. Derikx

World J Gastroenterol. 2019 Jul 7;25(25):3268-3280. doi: 10.3748/wjg.v25.i25.3268.

ABSTRACT

Background

A large proportion of patients with Hirschsprung disease experience persistent obstructive symptoms after corrective surgery. Persistent obstructive symptoms may result in faecal stasis that can develop into Hirschsprung-associated enterocolitis, a potential life-threatening condition. Important treatment to improve faecal passage is internal anal sphincter relaxation using botulinum toxin injections.

Aim

To give an overview of all empirical evidence on the effectiveness of botulinum toxin injections in patients with Hirschsprung disease.

Methods

A systematic review and meta-analysis was done by searching Pubmed, EMBASE and the Cochrane Library, using entry terms related to: (1) Hirschsprung disease; and (2) Botulinum toxin injections. 14 studies representing 278 patients met eligibility criteria. Data that were extracted were proportion of patients with improvement of obstructive symptoms or less enterocolitis after injection, proportion of patients with adverse effects and data on type botulinum toxin, mean dose, average age at first injection and patients with associated syndromes. Random-effects meta-analysis was used to aggregate effects and random-effects meta-regression was used to test for possible confounding factors.

Results

Botulinum toxin injections were effective in treating obstructive symptoms in on average 66% of patients [event rate (ER) = 0.66, $P = 0.004$, $I^2 = 49.5$, $n = 278$ patients]. Type of botulinum toxin, average dose, average age at first injections and proportion of patients with associated syndromes were not predictive for this effect. Mean duration of improvement after one botulinum toxin injecction was 6.4 months and patients needed on average 2.6 procedures. There was a significant higher response rate within one month after botulinum toxin injections compared to more than one month after botulinum toxin injections (ER = 0.79, vs. ER = 0.46, Q = 19.37, $P < 0.001$). Botulinum toxin injections were not effective in treating enterocolitis (ER = 0.58, $P = 0.65$, $I^2 = 71.0$, $n = 52$ patients). There were adverse effects in on average 17% of patients (ER = 0.17, $P < 0.001$, $I^2 = 52.1$, $n = 187$ patients), varying from temporary incontinence to mild anal pain.

Conclusion

Findings from this systematic review and meta-analysis indicate that botulinum toxin injections are effective in treating obstructive symptoms and that adverse effects were present, but mild and temporary.

INTRODUCTION

Hirschsprung disease is a congenital absence of ganglions of the distal gut, causing neonatal bowel obstruction. Treatment of Hirschsprung disease consists of surgical resection of the affected aganglionic bowel segment. Despite removal of the affected aganglionic bowel segment, about 8-30% of patients experience persistent obstructive symptoms after corrective surgery, varying from mild constipation to ileus[1]. Causes of obstructive symptoms include: (1) Mechanical obstruction, such as anastomotic stricture or adhesions; (2) Residual aganglionosis; (3) Stool-holding behavior; (4) General motility disorders of the bowel; and (5) Anal outlet obstruction[1,2], caused by the absence of the recto-anal inhibition reflex or anal sphincter defects[1]. When treated inadequately, persistent obstructive symptoms may result in faecal stasis that can develop into Hirschsprung-associated enterocolitis, a potential life-threatening condition that occurs in 25% to 37% of patients after surgery[3]. Therefore, it is important to achieve adequate bowel passage in patients with Hirschsprung disease.

Many patients with Hirschsprung disease use dietary adaptations, laxatives or rectal irrigation to manage bowel passage after surgery. When these conservative measures are not enough, a mechanical obstruction or residual aganglionosis needs to be ruled out, according to current consensus-based practice[1]. Current practice describes administration of intra-sphincteric botulinum toxin (BT) injections as a second step in treatment of obstructive symptoms after surgery, in order to obtain temporary relaxation of the internal anal sphincter, which subsequently improves faecal passage. We know from patients with childhood constipation and chronic anal fissures, that BT can be beneficial in treating constipation, regardless of sphincter dynamics[4], suggesting comparable beneficial effects for patients with Hirschsprung disease. Langer was the first to introduce treatment with BT injections for patients with Hirschsprung disease in 1997, as an alternative to myotomy of the anal sphincter and to use it as a predictive tool to assess necessity of sphincter myotomy[5].

Current consensus-based practice advises administration of 60–100 units BT diluted in 1.0 ml of saline with a maximum concentration of 100 IU/ml, given circumferentially at the level of the dentate line where the internal anal sphincter is located. The guideline also states that, BT injections need to be repeated every 3-6 months as many times as necessary upon clinical improvement, as symptoms often will improve over time and BT injections generally become unnecessary at age older than five years. Alternatively, topical application of nitroglycerin or nifedipine cream or myotomy of the internal anal sphincter may be considered as treatment for post-operative obstructive symptoms. Non-operative management however is recommended, given the risk of faecal soiling after myotomy[1]. All these recommendations however, are consensus-based and are not substantiated by empirical evidence.

A meta-analysis on different treatment strategies for obstructive symptoms showed short-term improvement after BT injections in 77% of patients and decreased to 43% of

patients in the long-term[6]. However, that meta-analysis did neither draw conclusions on effects on the prevalence of enterocolitis, nor on the complication rate and adverse events after BT injections. In addition, that meta-analyses did not assess potential predictors of effectiveness. Better knowledge is clearly needed and would benefit indication for treatment with BT injections and management of expectations of patients and their parents.

The current systematic review and meta-analysis aims to provide a comprehensive overview of all empirical evidence on: (1) Effects of treatment with BT injections on obstructive symptoms after surgery for Hirschsprung disease and factors moderating this effect (type of BT used, dose, age and the presence of associated syndromes); (2) Effects of treatment with BT injections on occurrence of post-operative Hirschsprung-associated enterocolitis; and (3) Complication rate and adverse effects after BT injections in patients after surgery for Hirschsprung disease.

MATERIALS AND METHODS

Search strategy

The search strategy combined two groups of search terms and their equivalents: "Hirschsprung disease" AND "Botulinum toxin injections". The search was performed in the electronic databases PubMed, EMBASE, Web of Science and the Cochrane Database using both simple search terms and hierarchical family forms (*e.g.*, Medical Subject Headings, Thesaurus, Emtree). The reference lists of eligible articles were also screened for additional articles. The last search was conducted in December 2018.

Study selection

A flow diagram of the study search and selection is provided in Figure 1. A total of 193 records were identified corresponding to 92 unique articles. Two authors (DR and ZAMA) independently assessed each article for eligibility. Conflicts in the selection process were solved by either consensus or by consulting a third reviewer (JD). Studies were included in this systematic review and meta-analysis if they: (1) Contained original patient data; (2) Described patients with Hirschsprung disease with post-operative obstructive symptoms or enterocolitis; (3) Described treatment of these patients with BT injections in the internal anal sphincter; (4) Described outcomes in terms of occurrence of obstructive symptoms and/or enterocolitis at follow-up; (5) Were published in a peer-reviewed journal; and (6) Written in the English language. In case multiple articles reported on (partly) overlapping cohorts, we included the article that had the largest sample size to maximize generalizability of the sample and statistical power of our meta-analysis. In case articles reported patients with obstructive defecation problems that consisted of patients with Hirschsprung disease and Internal Sphincter Achalasia and data about patients with Hirschsprung disease could not be extracted separately, the study was still

included and the data were extracted for the total sample. 14 studies were included in both the systematic review as in the meta-analysis[5, 7-17].

Data extraction and synthesis

Primary outcome was effectiveness of BT injections in treating obstructive symptoms in patients after surgery for Hirschsprung disease, expressed as the proportion of patients with clinical improvement as reported in the various studies, the mean duration of improvement in months and the average number of BT injections needed to obtain satisfactory clinical improvement. Secondary outcomes were: (1) The proportion of patients that previously suffered from at least one episode of Hirschsprung-associated enterocolitis and were free of enterocolitis after treatment with BT injection; and (2) The proportion of patients with complications and/or adverse effects after BT injection. Primary and secondary outcome measures with the accompanying samples sizes were extracted from the included articles by two authors (DR and ZAMA) from the articles. In addition, possible confounding factors of effectiveness of BT injections in treating obstructive symptoms or Hirschsprung-associated enterocolitis (e.g., type of BT, average

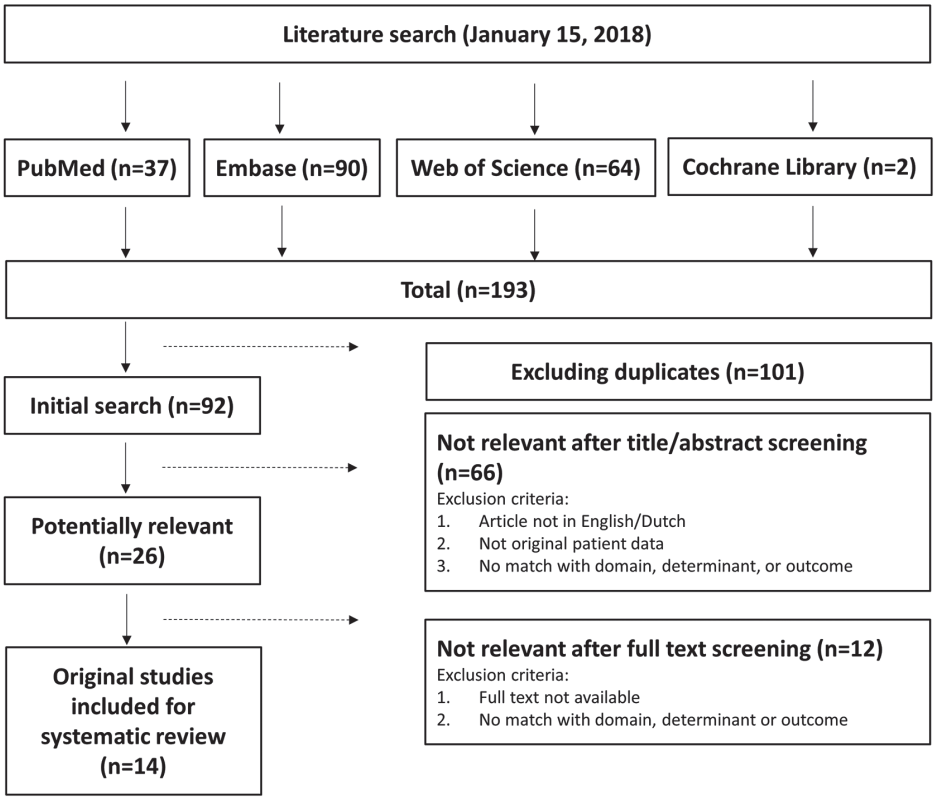


Figure 1 Flow chart illustrating details of the search strategy and the study selection process.

dose, average age at first BT injection, proportion of patients with an associated syndrome and proportion of male patients) were extracted from the articles. In case when studies reported medians, these measures were considered as the best approximation of means.

Quality assessment

The quality of the included studies was evaluated using the Newcastle – Ottowa Quality Assessment Scale (NOS)[18]. This scale assesses study quality based on: (1) Selection procedure (4 points); (2) Comparability of controls (2 points); and (3) Outcome measurement (3 points). Thus, nine points can maximally be assigned to each study. In accordance with the Agency for Healthcare Research and Quality standards, quality of studies was considered "good" (Selection 3-4 AND Comparability 1-2 AND Outcome 2-3 points), "fair" (Selection 2 AND Comparability 1-2 AND Outcome 2-3 points) or "poor" (Selection 0-1 OR Comparability 0 OR Outcome 0 points). Quality assessment was conducted by two independent reviewers (ZAMA and DR) and in case of conflict, resolved with consensus.

Statistical Analysis

Analyses were performed using Comprehensive Meta-Analysis Software (version 3.0, Biostat)[19]. For primary and secondary outcomes, the proportion of patients with clinical improvement on obstructive symptoms and enterocolitis, or with adverse effects was calculated for each study and expressed as the event rate (ER). The individual study's effect sizes were subsequently aggregated across studies into meta-analytic effect sizes using the random model to account for heterogeneity introduced by the included range of outcome definitions, differences in follow-up duration and methods for administering BT injections. Mean duration of improvement and mean number of BT injections needed were calculated by averaging these measurements from the studies. Post-hoc analysis tested differences between the meta-analytic findings pertaining to: Outcomes assessed within one month after administration *vs* outcomes assessed in follow-up longer than one month. If a meta-analytic effect size was built up by a minimum of 10 individual studies' effect sizes, we explored possible moderation effects on the outcomes of: (1) Type of BT; (2) Average dose; (3) Average age at first BT injection; (4) Proportion of patients with associated syndromes; and (5) Proportion of males. Only significant univariate moderators were further analyzed using multivariate meta-regression. Furthermore, post-hoc analysis were performed to test for possible differences between the different types of BT used for the injection, by aggregating effect sizes of observations for each type of BT. Sensitivity analyses were performed by repeating analyses after excluding studies that consisted of both patients with Hirschsprung disease and internal sphincter achalasia. ERs significantly higher than 0.50 are suggestive to be found not by chance and were arbitrarily considered to be clinically relevant. Heterogeneity was interpreted as small ($I^2 \leq 0.25$), medium ($I^2 = 0.25–0.50$) or strong ($I^2 \geq 0.50$), according to Higgins *et al*[20]. The possibility of publication bias was assessed by calculating Funnel plot asymmetry expressed as the Eggers regression intercept t[21], fail-safe n (fail-safe n values > 5 k+10

where considered robust)[22] and by calculating the moderating effect of samples sizes on effect sizes. A *P* value of 0.05 was considered statistically significant.

RESULTS

Characteristics of included studies

In this systematic review and meta-analysis, 14 studies (representing 278 patients) met eligibility criteria and were included. Table 1 describes study characteristics of included studies. Length of follow-up after BT injections ranged from 6 to 126 months. Dysport® (used in 4 of 14 studies) was administered with an average dose of 200 IU per procedure, whereas Botox® (used in 6 of 14 studies) was administered with an average mean dose of 95 IU per procedure, ranging from 60 to 120 IU per procedure. In the other four studies no details on the type of BT was provided. Ultrasonography was used to identify the internal anal sphincter in two studies, whereas in six studies palpation was used. The six other studies did not elaborate on their methods of identifying the internal anal sphincter. Mean age at administration of first BT injection was 4.5 years (SD 1.0 years). Proportion of patients with an associated syndrome was reported in seven studies and was on average 16% (ranging from 0–33%). The proportion of males in the included studies was on average 71% (SD 10%).

Improvement of obstructive symptoms

Primary outcome was reported in all 14 studies including 278 patients. Figure 2a shows a forest plot of the proportion of patients showing overall clinical improvement in each study and the aggregated ER of improvement of obstructive symptoms. Two of the 14 studies showed significant improvement of obstructive symptoms. The other 12 studies found no significant effect of treatment with Botulinum toxin injections. Meta-analytic aggregation of the effect sizes of all 14 studies showed significant effectiveness of Botulinum toxin injections, with improvement of obstructive symptoms in on average 66% of the patients [ER = 0.66, $P = 0.004$; 95% confidence interval (CI): 0.55–0.75, $I^2 = 49.5\%$] (Table 2). There was a significant higher response rate within one month after BT injections (ER = 0.79, $P < 0.001$; 95%CI: 0.71 – 0.85, $I^2 = 24.4\%$, $n = 201$ patients), compared to more than one month after BT injections (ER = 0.46, $P = 0.50$; 95%CI: 0.34-0.58, $I^2 = 61.8\%$, $n = 241$ patients) (Q = 19.37, $P < 0.001$). None of the tested moderators had a significant predictive value for the magnitude of studies' effect sizes in univariate analysis (*i.e.,* mean dose, $n = 228$, $P = 0.28$; mean age at first BT injection, $n = 184$, $P = 0.81$; proportion of patients with an associated syndrome, $n = 160$, $P = 0.10$; sex of patients, $n = 201$, $P = 0.94$). Subgroup comparison showed no significant differences in improvement of obstructive symptoms after administration of Botox® (ER = 0.72, 95 CI: 0.58–0.83, $n = 8$ studies) compared to Dysport® (ER = 0.57, 95 CI: 0.33–0.77, $n = 4$ studies) (Q = 0.46, $P = 0.49$, $n = 242$ patients). Mean duration of improvement after one BT injection was 6.4 months, ranging from 1 to 60 months ($n = 97$).

Table 1 Characteristics of included studies

Study	Study design	Inclusion Period	Sample size n	% Male	% syndromal patients	Total follow-up in months	Number of BT injections needed per patient	Age at first BT* injection (years)	Type BT	Mean dose (IU /injection)	Guidance at BT injection	Definition of outcomes	Improvement in obstructive symptoms <1 month	Prolonged improvement in obstructive symtpoms	Improvement of enterocolitis	Complications/ adverse effects	Decrease in mean resting pressure on anorectal manometry (mmHG)
Basson (2014)	Retrospective	2010-2014	11	67	NR	12-72	1pt: 1BTI 5pt: 2BTI 4pt: 3BTI 1pt: 4BTI	5	Dysport	200	Palpation	Successful - Improvement - Failed Favorable: succesful/improvement	10/11 (91%)	5/11 (45%)	NR**	1 (transient soiling).	NR
Chumpitazi (2008)	Retrospective	1998-2007	30	80	10	41.2 ± 4.9	2.7 ± 0.2	5	Botox	NR	Palpation	Poor - Fair - Good - Excellent Favorable: Excellent/good	27/30 (90%)	11/30 (37%)	NR	8 (7 transients soiling, 1 anal pain)	NR
Chumpitazi (2011)	Retrospective	1998-2016	37	80	23	41.4 ± 4.5	2.8 ± 0.3	NR	Botox	100	NR	Poor - Fair - Good - Excellent Favorable: Excellent/good	33/37 (90%)	NA	NR	NR	NR
Church (2016)	Retrospective	2010-2015	30	NR	NR	20	87% in total: With US: 2 Without US: 1	3.1	NR	40	US-guided	Improvement of symptoms	NA	NR	3/4 (75%)	NR	NR
Han-Geurts (2014)	Retrospective	2002-2013	33	79	0	7.3 years (1-24)	2 (1-5)	3.6	Dysport	200	NR	Poor - Fair - Good - Excellent Favorable: Excellent/good	25/33 (76%)	17/33 (52%)	7/19 (37%)	2	NR

Hemanshoo Thakkar (2017)	Retrospective	2002-2014	6	NR	NR	6 years (1-12)		3	Dysport	200	US-guided	Short-term: postoperative complications <30 days Long-term: Rintala Bowel Function Score (BFS)	1/6 (17%)	NR	NR	NR	NR
Hosseini (2008)	Prospective	2002-2006	16	62	NR		8 pt: 1-3	NR	Dysport	NR	NR	Improvement in Constipation score (good/ recurrence/ non-responders)	14/16 (88%)	8/16 (50%)	NR	NR	NR
Jiang (2009)	Prospective	2000-2008	23	65	NR	12		NR	Botox	120	Palpation	Poor - Moderate - Excellent Favorable: Moderate/ Excellent	NR	21/23 (91%)	NR	9 (anal pain)	8-30
Koisuvalo (2009)	Retrospective	2005-2008	16 *	62	12.5	19 (3 - 43)	2 (1-4)	4	NR	100	NR	No effect - Little effect - Significant effect - Symptoms dissapeared Favorable: Significant effect/ symptoms dissapeared	10/16 (63%)	3/8 (38%)	1/4 (25%)	4 (increased soiling)	28-31 (2w); 8-24 (8m)
Langer (1997)	Prospective	NR	4	50	25		3 pt: 1, 1 pt 2	6	Botox	NR	Palpation	Improvement of obstructive symptoms, presence of incontinence	3/4 (75%)	1/4 (25%)	NR	1 (transient incontinence)	NR
Langer (2004)	Retrospective	NR	14	NR	NR	24	4 pt: 1, 9pt: 1-4	4	NR	150	NR	Improvement of obstructive symptoms, presence of incontinence	9/14 (64%)	4/14 (29%)	NR	NR	NR

Minkes (2000)	Pro-spec-tive	NR	18	78	NR		8: 1; 10: 2-6	NR	Botox	60	Palpation	No response - Significant response	12/18 (67%)	5/18 (28%)	NR	4 (tran-sient incon-ti-nence)	35-37
Patrus (2010)	Retro-spec-tive	1998-2008	22	78	5	5.0 ± 2.9 years (0-10)	2 (1-23)	8.4	NR	120	NR	Improvement of obstructive symptoms, presence of incontinence	18/22 (81%)	6/22 (27%)	NR	0	NR
Wester (2015)	Retro-spec-tive	2007-2014	18	83	33	3,8 years (0,1 - 8,3)	3 (1-13)	2.4	Botox	100	Palpation	Good - Insuf-ficient	NR	13/18 (72%)	NR	NR	NR

Note. NR= not reported; BT = botulinum toxin;

Patients needed on average 2.6 procedures of BT injection (ranging from 1 to a maximum of 23 procedures per patient) before clinical improvement was obtained.

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Basson, 2014	0,743	0,350	0,939	1,238	0,216
Chumpitazi, 2008	0,695	0,458	0,860	1,628	0,103
Chumpitazi, 2011	0,892	0,745	0,959	3,986	0,000
Church, 2016	0,712	0,439	0,887	1,540	0,124
Han-Geurts, 2014	0,646	0,465	0,793	1,586	0,113
Hemanshoo, 2017	0,167	0,023	0,631	-1,469	0,142
Hosseini, 2008	0,726	0,430	0,903	1,518	0,129
Jiang, 2009	0,913	0,711	0,978	3,177	0,001
Koisuvalo, 2009	0,465	0,236	0,710	-0,263	0,793
Langer, 1997	0,500	0,094	0,906	0,000	1,000
Langer, 2004	0,459	0,216	0,724	-0,286	0,775
Minkes, 2000	0,467	0,243	0,706	-0,256	0,798
Patrus, 2010	0,565	0,320	0,782	0,506	0,613
Wester, 2015	0,722	0,481	0,879	1,816	0,069
	0,655	0,550	0,747	2,860	0,004

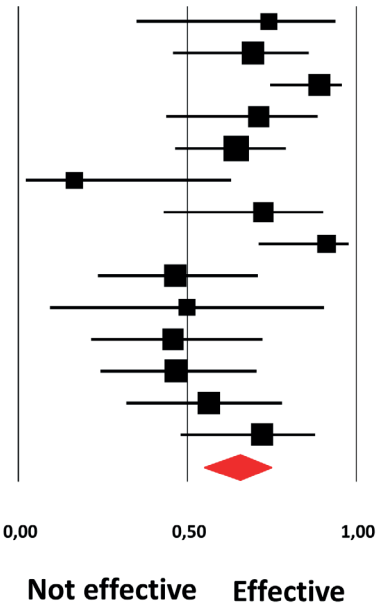


Figure 1 Event rates of effects of Botulinum toxin injections in patients after surgery for Hirschsprung disease. A: effectiveness of treating obstructive symptoms

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Church, 2016	0,824	0,573	0,942	2,421	0,015
Han-Geurts, 2014	0,368	0,187	0,597	-1,133	0,257
Koisuvalo, 2009	0,500	0,168	0,832	0,000	1,000
	0,576	0,265	0,837	0,455	0,649

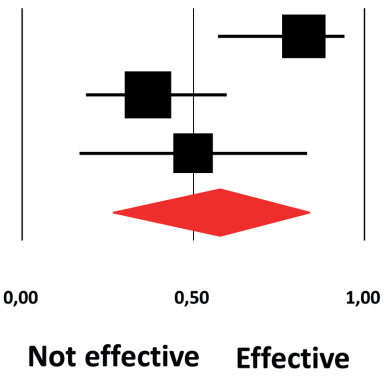


Figure 2 Event rates of effects of Botulinum toxin injections in patients after surgery for Hirschsprung disease. B: effectiveness of treating enterocolitis

Improvement of enterocolitis

In the meta-analysis on effectiveness of BT injections in treating enterocolitis three studies representing 52 patients were included. Figure 2B shows that none of the three studies showed significant effectiveness of BT injections. Meta-analytic aggregation of the effect sizes of all three studies showed non-significant effectiveness of BT injections, with improvement in on average 58% of the patients (ER = 0.58, $P = 0.65$; 95%CI: 0.27–0.84, $I^2 = 71.0\%$) (Table 2). The number of studies describing effects on enterocolitis did not allow for assessment of confounding factors.

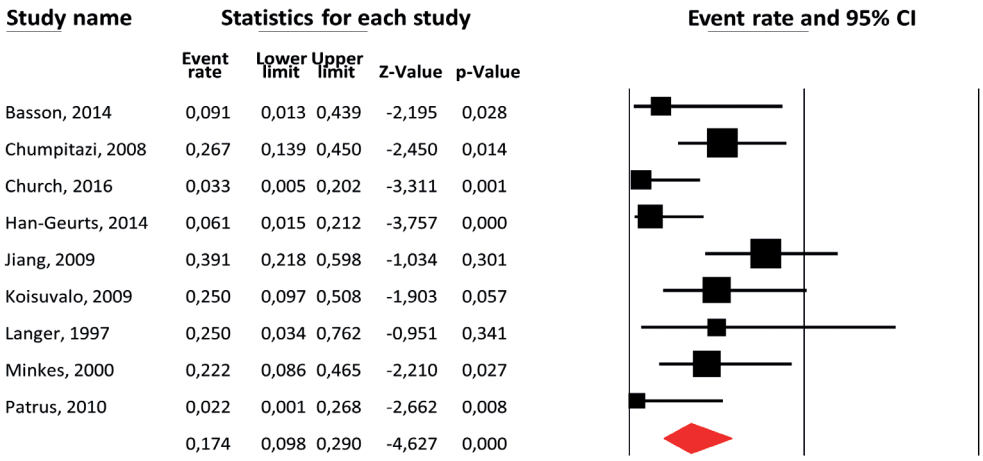


Figure 2 Event rates of effects of Botulinum toxin injections in patients after surgery for Hirschsprung disease. C: adverse effects

Complications and adverse effects

In the meta-analysis on complications and adverse events after administration of BT injections as shown in Figure 2C, nine studies representing 187 patients were included. Meta-analytic aggregation of the effect sizes of all nine studies showed significant occurrence of complications or adverse events in on average 17% of the patients (ER = 0.17, $P < 0.001$; 95%CI: 0.10–0.29, $I^2 = 52.1\%$) (Table 2). The number of studies describing adverse effects of treatment with Botulinum toxin injections did not allow for assessment of confounding factors. Adverse events that were described in the studies were mild and included: (1) Transient soiling or incontinence in a total of 17 patients; (2) Anal pain in nine patients; and (3) Muscle fatigue of the lower extremities in two patients. In two other patients adverse effects were present but not described in detail.

Table 2 Main findings and risk of bias analysis

Effect	# of studies	Event Rate (95% CI)	Heterogeneity (I^2)	Significant predictors	Eggers intercept	Fail safe *n*
Improvement of obstructive symptoms	14	ER*=0.66 95%CI 0.55 – 0.75 a	49.5%	None	-0.42	43
Decreasing enterocolitis incidence	3	ER=0.58, 95%CI 0.27 – 0.84	71.0%	NA**	3.27	0
Adverse effects	9	ER=0.17, 95%CI 0.10 – 0.29 b	52.1%	NA**	-2.78 c	101

Note. a p=0.004, b p<0.001, c p=0.01, * ER = event rate, ** NA = not applicable

Quality of evidence and risk of publication bias

Overall judgement of quality of included studies, as well as scores on each domain of the NOS are presented in Table 3. All 14 studies were of poor quality, because of the observational uncontrolled study design. Funnel plot asymmetry as expressed by Eggers regression intercept was significant for findings on adverse effects (P = 0.01), but non-significant for other findings (P values ranged from 0.69 to 0.78). This indicates that there was a low risk op publication bias for findings on improvement of obstructive symptoms and enterocolitis. The latter observation was further supported by a significant positive correlation between sample size and ERs (t = 0.07, P = 0.01), suggesting there was a low risk of a publication bias. Fail safe *n*'s ranged from 0 to 101, suggesting that only our findings on adverse effects were robust to the influence of publication bias. Results of the risk of bias analysis for every separate finding are presented in Table 2. Main effects were not significantly altered by excluding studies that included both patients with internal sphincter achalasia and Hirschsprung disease.

Table 3 Quality of included studies

Study	Selection	Comparibility	Outcome	Total
Basson (2014)	2	0	3	Poor
Chumpitazi (2008)	3	0	3	Poor
Chumpitazi (2011)	3	0	3	Poor
Church (2016)	2	0	2	Poor
Han-Geurts (2014)	2	0	3	Poor
Hemanshoo Takkar (2017)	3	0	3	Poor
Hosseini (2008)	3	0	2	Poor
Jiang (2009)	3	0	3	Poor
Koisuvalo (2009)	3	0	3	Poor
Langer (1997)	3	0	3	Poor
Langer (2004)	3	0	2	Poor
Minkes (2000)	3	0	2	Poor
Patrus (2010)	3	0	3	Poor
Wester (2015)	3	0	3	Poor

DISCUSSION

Current evidence

This systematic review and meta-analysis aimed to provide a comprehensive overview of all empirical evidence on: (1) Effectiveness of treatment with BT injections for obstructive symptoms; (2) Effectiveness of treatment with BT injections for enterocolitis; and (3) Complications and adverse event after BT injections in patients that underwent surgery for Hirschsprung disease. Our findings indicate that BT injections improve obstructive symptoms in most patients (66%), although the proportion of patients that benefits is significantly higher within one month after administration (79%) compared to the proportion that still benefits after one month of follow-up or longer (46%). This underlines the transient effect of BT injections and explains that most patients will need multiple injections before satisfactory clinical improvement of obstructive symptoms is achieved. Our results further show that current evidence on whether BT injections are effective in reducing Hirschsprung-associated enterocolitis is inconclusive. Our analysis lacked the power to make a very specific point estimate of effectiveness, as shown by the broad CI ranging from effectiveness of 27% to 84%. BT injections were associated with adverse effects in on average 17% of patients, with adverse effects varying from transient incontinence to anal pain and muscle fatigue.

Our results indicated that duration of improvement of obstructive symptoms was on average six months and that most patients need on average two to three injections. This in line with previous meta-analytic findings and with evidence on the effectiveness of BT injections in other patient groups, including chronic constipation, anal fissures and internal sphincter achalasia[4, 6, 23]. In addition, evidence from three studies (all included in our meta-analysis), indicated that short term response was predictive for long-term response, although studies used different cut-off points for defining short- and long term response[7-9].

Our analyses showed that differences between studies in the proportion of patients showing clinical improvement, could not be explained by differences in average dose and type of BT used or by patient characteristics. There was large heterogeneity between studies in the dosage administered, which suggests there is no current consensus on optimal dose. Dysport® was on average administered in higher dosages than Botox®. However, we could not test the unique contribution of dosage and type in multivariate analyses, because only ten studies described both type of BT as well as average dose used. We hypothesize that our findings do not reflect this difference in dosage, as neither type of BT nor average dose used correlated significantly to rates of clinical improvement in univariate analysis. Furthermore, our findings are in line with findings in patients with chronic anal fissures, in whom dose and type of BT were not predictive of clinical improvement[24, 25].

With regard to age at first BT injection, our findings indicated the age at which the BT injection was administered was not correlated to the proportion of patients showing

clinical improvement, suggesting that BT injections can be used at all ages. The proportion of patients with an associated syndrome was not correlated to the effectiveness of BT injection in the treatment of obstructive symptoms, suggesting that our results were not over- or underestimated by patients with an associated syndrome. Moreover, the average amount of patients with an associated syndrome in our study was comparable to what we know from the general Hirschsprung population[26].

Limitations of this study

Because of lack of power caused by the limited number of studies available, the small sample sizes and heterogeneity in outcome definitions, our meta-analysis could not assess the predictive value of a number of possible interesting predictors of treatment effectiveness, including length of aganglionosis (only six studies), type of reconstruction that was done, findings on anorectal manometry (three studies) and specific procedural aspects of BT injections. Individual studies included in this meta-analyses suggest that short-segment disease is associated with better responsiveness to BT injections than long-segment disease[14, 15]. Contrarily one study found no difference between short-segment and long-segment disease[16]. Three studies suggested that mean resting pressure decreases significantly after BT injections[11, 12, 14], but the degree of decrease in pressure was not predictive for clinical improvement[12]. One study by Church further suggests that US-guided BT injections decreases the amount of injections necessary compared to identifying the internal anal sphincter by palpation, although US-guided BT injections were not associated with higher response rates[17]. The study by Church also suggested that BT injection in the external anal sphincter is associated with higher response rates compared to injections in the internal anal sphincter[17]. In the majority of studies included in our systematic review (8/14 studies) residual aganglionosis or a mechanical obstruction was excluded as a cause of obstruction by barium enema and rectal biopsy before BT was administered. The other six studies did not exclude patients with these causes of obstruction from the study, but did not specifically report the cause of obstruction in individual patients prior to BT injections. Therefore we could not compare differences in effectiveness of BT injections between different reasons of obstructive symptoms.

Another limitation of our study is the large heterogeneity between studies in outcome definitions and procedural aspects, including the position of the patients (lithotomy *vs* lateral decubitus position) during BT injection, the amount of injections administered and the number of sites in which Botulinum toxin was injected. This shows the lack of a standardized approach for BT injections.

Quality of evidence and risk of publication bias

Quality of evidence on the effects of BT injections was poor in all studies because of the lack of the use of randomized and controlled designs. Two studies assessed a combined sample of both patients with internal sphincter achalasia and Hirschsprung disease. This could

account for a selection bias, resulting in an overestimation of effects, although sensitivity analyses in which these two studies were excluded showed no significant alteration of main effects. It may be hypothesized that the effects of BT injections are larger in patients with internal sphincter achalasia, as in these patients the absent rectoanal inhibitory reflex is the only explanatory factor for obstruction. The present systematic review and meta-analysis also carries the risk of assessment bias due to large variety of outcome definitions used in the included studies. There is only a risk of publication bias for our findings on complications and adverse effects, but our findings were robust to this influence. For other findings no evidence for risk of publication bias was found.

Conclusions and future implications

In this systematic review and meta-analysis we found evidence for improvement of obstructive symptoms after BT injections in patients that underwent surgery for Hirschsprung disease, although this effect was often transient and most patients needed multiple injections. Future studies using a standardized procedural approach and outcome definitions would be useful to determine dose-response effects and identify optimal dosages. Furthermore, better insight in predictors of clinical response would optimize treatment. Future studies should also assess factors that predict improvement of obstructive symptoms and enterocolitis incidence after BT injection, including length of aganglionosis and functional parameters such as mean resting pressures of the anal canal.

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CHAPTER 4

Intrasphincteric botulinum toxin injections for post-operative obstructive defecation problems in Hirschsprung disease: A retrospective observational study

D. Roorda, J. Oosterlaan, L.W.E. van Heurn, J.P.M. Derikx

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ABSTRACT

Background

Patients with Hirschsprung disease may have obstructive symptoms after resection of the aganglionic segment. Botulinum toxin (BT) injections can help improve faecal passage by relaxing the internal anal sphincter. This study assess effect of BT injections and aims to identify factors associated with receiving BT injections and favourable response to the first BT injection.

Methods

A retrospective study was performed in a cohort of consecutive patients treated for Hirschsprung disease in our centre between 2003 and 2017. The indication for BT injections was obstructive defecation problems that were non-responsive to high-dose laxatives or rectal irrigation, or an episode of Hirschsprung-associated enterocolitis (HAEC). Effectiveness of BT injections was measured in terms of clinical improvement. Relationships between factors associated with receiving BT injections and with response to the first BT injection were tested with group comparison and logistic regression.

Results

Forty-one out of 131 patients received BT injections (31%) with a median of two injections (range 1-11). All patients had obstructive defecation problems non-responsive to high-dose laxatives or rectal irrigation, two patient also had an episode of HAEC. Twenty-five out of 41 patients (61%) had clinical improvement after first injection. In 29 of the 41 patients (71%) spontaneous defecation or treatment with laxatives only was achieved. Adverse effects were seen in 12 out of 41 patients (29%) after 14 injections (16%), and consisted of anal pain, temporary loss of stools and dermatitis. Patients who received BT injections more often had long segment disease, more often required laxatives or rectal irrigation and had longer length of hospital stay, both after corrective surgery and in follow-up. None of the tested factors was associated with clinical improvement after first BT injection.

Conclusion

Our findings show that BT injections effectively treat obstructive defecation problems in the majority of patients with Hirschsprung disease with mild adverse effects.

INTRODUCTION

Most children with Hirschsprung disease can pass stools spontaneously or with the help of laxatives or rectal irrigation after corrective surgery. However, some children still have severe obstructive defecation problems after surgery.[1] Apart from the need to use a large dose of laxatives or rectal irrigation, obstructive defecation problems can increase the risk of Hirschsprung-associated enterocolitis (HAEC), that can be life-threatening.[2] Post-operative obstructive defecation problems in children with Hirschsprung disease can have multiple causes, amongst which anal outlet obstruction is common.[1] As neuronal innervation of the distal bowel is absent in patients with Hirschsprung disease, the rectoanal inhibitory reflex is absent as well, resulting in increased resting pressure of the internal anal sphincter.[3-5] In addition, dyssynergic defecation can cause anal outlet obstruction.

When laxatives or rectal irrigations are not sufficient to treat obstructive symptoms, intraspincteric botulinum toxin (BT) injections might be chosen as additional treatment. BT blocks the release of acetylcholine in the neuromuscular junction, thereby temporarily relaxing the internal anal sphincter.[6] Because of the temporary effects, most patients require repeated injections to sustain therapeutic effects.[7] Previous studies have suggested favourable effects of BT injections on the bowel movements of patients with Hirschsprung disease with persistent post-operative obstructive symptoms.[7-15] Meta-analytic findings showed that 77% of patients with obstructive symptoms after surgery for Hirschsprung disease have short-term improvement of obstructive symptoms within the first month after BT injections. After more than one month, 43% of the patients still had improvement of obstructive symptoms.[16,17] Alternative treatment options for BT injections include topical application of nitric oxide on the anal sphincter, posterior myotomy of the anal sphincter, and redo pull-through or a diverting ostomy.[17] However, these alternative treatment options for BT injections are associated with large risk of complications.[18-20]

Although current evidence suggests that BT injections are effective in the majority of patients, we neither know the factors that make some patients more prone for obstructive symptoms in which BT injections are indicated, nor the factors that predict clinical improvement after BT injections. Determining these factors can help to identify patients who respond favourable to BT injections, and improve patient care by better management of expectations of patients and their parents. Previous studies have suggested that short-term favourable response to BT injections is predictive for favourable response in the long-term,[10,13] although definitions of what was considered as short-term varied largely between the studies. One study has reported that the absence of response to a first BT injection suggests that other obstructive causes than an anal outlet problem may be present, such as a transition zone pull-through or a stenosis, implicating that response to the first BT injection has diagnostic value.[13]

The current study aims to describe the effectiveness of BT injections in treating post-operative obstructive symptoms, to chart possible adverse effects of this treatment and to identify factors that are associated with receiving BT injections and with favourable response to the first BT injection.

MATERIALS AND METHODS

Population

All consecutive patients who underwent resection of aganglionic bowel for Hirschsprung disease between 2003 and 2017 in one of the two academic tertiary hospitals in Amsterdam (Academic Medical Centre and VU medical centre) with a follow-up duration of at least one year after corrective surgery were included in this retrospective cohort study. We started with the use of BT injections in these centres in 2003. Exclusion criteria were: no histopathological confirmation of Hirschsprung disease, primary corrective surgery performed elsewhere or the absence of informed consent. All parents of patients who were included in this study gave informed consent. The local IRB approved of this study (#18.198).

Data extraction

In 2018, medical records of all patients were reviewed by multiple authors (DR, LB, HL, all medical doctors) and stored in a Castor database. Data validation was done by checking 10% of the entered records of each author by another author. In case there were inconsistencies in more than 10% of a record, the complete record was checked by a third author (JD). For most variables taken from the medical records, the percentage of data missing was less than 10%. However, more than 10% of data were missing for gestational age (12% missing) and for the usage of laxatives or rectal irrigation at follow-up visits in the first year of follow-up (24% missing), between 1 and 5 years of follow-up (35% missing) and in more than 5 years of follow-up (69%).

Measurements and definitions

The number of injections, duration of improvement after BT injections, and adverse effects after BT injections were described. Effectiveness of BT injections was measured in terms of clinical improvement, defined as any reduction in the amount of laxatives or rectal irrigation needed to successfully pass stools.

Indications and procedures for the administration of botulinum toxin injections

In our centres, BT injections are administered to patients with obstructive symptoms in whom an anastomotic stenosis has been excluded as cause of obstruction by barium enema or digital rectal examination, and that are non-responsive to high-dose laxatives

or rectal irrigation. BT injections are administered preferably under procedural sedation and/or analgesia (PSA) or general anaesthesia (GA). Patients receive injections in four quadrants in lithotomy position. The internal anal sphincter is identified by palpation, not by ultrasound. Based on the surgeons preference we use two types of BT: Botox® (Allergan Nederland BV) and Dysport® (Ipsen Farmaceutica BV). Botox® by Allergan is used more often (69% of all injections) than Dysport® (31%). A median dose of 100 IU Botox® (range 25 – 500) and 300 IU Dysport® (range 75 – 400) was given per procedure.

Factors associated with receiving BT injections and clinical improvement after first BT injection

Possible factors that were tested for their association with receiving BT injections and clinical improvement after first BT injection were: sex, preterm birth (i.e., gestational age < 37 weeks), low birthweight (i.e., birthweight < 2500 g), age at diagnosis (in months), presence of comorbidity (yes/no), presence of a syndrome (yes/no), occurrence of pre-operative HAEC (yes/no), length of aganglionosis (expressed as the length of aganglionosis in centimeters from the dentate line in the histopathological examination of the resection specimen, as well expressed as short or long segment disease, in which short segment disease was defined as aganglionosis extending up to the sigmoid colon or distal to the sigmoid colon, and long-segment disease was defined as aganglionosis extending proximal to the sigmoid colon), type of corrective surgery (Duhamel or TERPT) and approach (open, laparoscopic or transanal), history of a temporary ostomy (yes/no), post-operative complications < 30 days after surgery (yes/no), length of hospital stay after corrective surgery and due to readmittances in follow-up, occurrence of post-operative HAEC (yes/no) and type of bowel management for obstructive defecation problems at any previous follow-up visit (the use of diet, laxatives or rectal irrigation, yes/no, within the follow-up periods: one year after surgery, one to five years after surgery and more than five years after surgery). The association between the type of BT (Botox/Dysport) and clinical improvement after the first BT injection was also tested.

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA). First the average number of injections received and average duration of improvement after the first injection and after each injection was calculated. Secondly, effectiveness of BT injections was calculated as the proportion of patients showing clinical improvement after first injection. Thirdly, the proportion of the first injections and all injections after which patients experienced adverse effects was also calculated. To study factors associated with treatment of BT injections, patient characteristics were compared between patients who received BT injections and patients who did not receive BT injections using independent sample *t*-test or Mann Whitney U test in case of continuous variables and the X^2 or Fisher's Exact test in case of categorical

variables. Logistic regression analysis was used to derive factors associated with clinical improvement after the first BT injections in patients who received BT injections. A two-step approach was used. First, univariate analysis were used to derive factors significantly associated with clinical improvement. Second, significantly associated covariates were entered in multivariate analysis, with a maximum covariates of one for every ten observations. Missing values were not substituted by estimates. P-values of <0.05 were considered statistically significant.

RESULTS

Population characteristics

We identified 144 patients, of whom 13 were excluded: for five patients primary surgery took place elsewhere, two patients deceased prior to surgery, four patients gave no informed consent to participate in this study, and two patients were treated conservatively (one patient with short segment disease had no symptoms of constipation and had spontaneous bowel movements with laxatives; the other patient was diagnosed late, at the age of five years, and had satisfactory bowel movements with laxatives and rectal irrigation; in both cases an expectative, non-operative approach was chosen in shared decision with the parents). Subsequently, 131 patients were included in this study, of whom ten patients had a follow-up duration of one year, 43 patients had a follow-up duration of more than one but less than five years, and 78 patients had a follow-up duration of more than five years. Median follow-up was 8 years (range: 1 - 17).

Baseline characteristics of the included patients are described in Table 1. Pre-operative HAEC occurred in 12 patients (9%). There were 93 patients (68%) who underwent transanal endorectal pull-through (TERPT), of whom 73 for short segment disease, 18 for long segment disease, and two with an unknown length of aganglionosis. There were 38 patients who underwent a Duhamel procedure (28%), of whom 16 for short segment disease, 21 for long segment, and one with an unknown length of aganglionosis. The choice of corrective technique was based on the surgeons preference. In the first year of follow-up, 37 patients (38%) used medication or rectal irrigation to improve bowel function, of whom 19 had short segment disease and 18 had long segment disease. Between one and five years of follow-up, 48 patients (72%) used medication or rectal irrigation, of whom 30 had short segment disease and 18 had long segment disease. After five years of follow-up, 13 patients (59%) used medication or rectal irrigation, of whom ten had short segment disease and three had long segment disease.

Table 1 Baseline characteristics (n=131 patients)

Baseline characteristics	
Sex, n (%)	
Male	102 (78)
Female	29 (22)
Gestational age in weeks, median (range)	38.9 (29-42)
Gestational age, n (%)	
Preterm (<37 weeks)	20 (15)
Term (≥37 weeks)	106 (81)
Missing	*5 (4)*
Birthweight in grams, mean (SD)	3312 (592)
Birthweight, n (%)	
Very low birthweight (<1500 grams)	1 (1)
Low birthweight (<2500 grams)	11 (8)
Normal birthweight (≥ 2500 grams)	107 (82)
Missing	*12 (9)*
APGAR score, median (range)	
1 min	9 (1-10)
5 min	10 (6-10)
Missing	*57 (44)*
Comorbidity present, n (%)	
Yes	40 (31)
No	91 (69)
Syndrome, n (%) 1	18 (26)
Downs syndrome	12 (17)
Other syndrome	6 (9)
No syndrome	50 (74)
Age at diagnosis in months, median (range)	0 (0-87)
Age at diagnosis, n (%)	
0-1 year of age	122 (93)
>1 year of age	7 (5)
Missing	*2 (2)*
Resected length of aganglionosis in cm, mean (SD)	15.7 (17)
Length of disease, n (%)	
Short segment disease	89 (68)
Long segment disease	23 (18)
Total colonic aganglionosis	16 (12)
Missing	*7 (5)*
Type of operation technique, n (%)	
Transanal endorectal pull-through	93 (71)
Duhamel	38 (29)
Approach to mobilisation of colon, n (%)	
Open	42 (32)
Laparoscopic	68 (52)
Transanal only	20 (15)
Missing	*1 (1)*
History of a temporary ostomy, n (%)	
Prior to pull-through	25 (19)
At pull-through	2 (2)
No	103 (79)
Missing	*1 (1)*
Postoperative complications < 30 days, n (%)	
Yes	26 (20)
No	104 (79)
Missing	*1 (1)*

Length of hospital stay after pull-through in days, median (range)	5 (2-34)
Total length of hospital stay in follow-up in days, median (range)	11 (0-270)
Use of laxatives or rectal irrigation in follow-up, n (%)	
1st year of follow-up (n=131)	
Nothing or diet only	61 (47)
Laxatives or rectal irrigation	37 (28)
Missing	*33 (25)*
1-5 years of follow-up (n=121)	
Nothing or diet only	18 (15)
Laxatives or rectal irrigation	48 (40)
Missing	*55 (45)*
>5 years of follow-up (n=78)	
Nothing or diet only	9 (12)
Laxatives or rectal irrigation	13 (17)
Missing	*56 (72)*

Note. 1 genetic testing was done in 68 patients, in case of clinical suspicion of a syndrome; other syndromes were: MEN2A (n=1), Mowat-wilson (n=1), diGeorge syndrome (n=1), Congenital Central Hypoventilation Syndrome (n=1), Cat Eye syndrome (n=1) and partial trisomy of chromosome 4 (n=1)

Treatment with BT injections

Forty-one out of 131 patients (32%) received a total of 115 Botulinum toxin injections. In all patients there were obstructive defecation problems that were non-responsive to high-dose laxatives or rectal irrigation, two patients also went through an episode of HAEC in between injections. Patients received a median of two BT injections (range: 1 – 11 injections). Of all patients receiving BT injections, 10 (24%) only received one injection, 13 patients two injections (32%), and 18 patients (44%) three or more injections, up to a maximum of eleven injections in one patient. Patients received the first BT injection at a median time of 1.8 years after operation (range 0 - 11 years). Fourteen patients (34%) received the first injection within the first year of follow-up after corrective surgery, 18 patients (44%) in one to five years post-operatively and nine patients (22%) after more than five years of follow-up after surgery.

Differences between patients receiving BT injections and patients receiving no BT injections

Patient and clinical characteristics of patients who received BT injections are shown in Table 2, where they are compared to patient and clinical characteristics of the patients who did not receive BT injections. Compared to patients who received no BT injections, patient who received BT injections had a longer mean aganglionic segment (difference in mean of 9 cm, t = -2.415, p = 0.018), less often had short segment disease, had a longer median length of hospital stay after corrective surgery (difference in median of 2 days, U = 2050.5, p = 0.031), had a longer median length of hospital stay in follow-up due to re-admittances (difference in median of 9 days, U = 1970.5, p = 0.028), and more often used laxatives or rectal irrigation in the first 5 years of follow-up. Longer duration of follow-up was not significantly associated with higher probability of receiving BT injections (OR = 0.95, 95%CI: 0.87–1.033, p = 0.222). Subsequently, we did not correct for differences in follow-up duration in further analyses.

Table 2 Patient and clinical characteristics of patients who did and did not receive BT injections

	Received no BT injections (n=90)	Received BT injections (n=41)	Group differences	*p* Value
Male sex, *n (%)*	69 (77%)	33 (80%)	$X^2 = 0.239$	.625
Gestational age in weeks, *mean (SD)*	38.6 (2.25)	38.9 (2.35)	$t = -0.657$	.513
Preterm birth (<37 weeks), *n (%)*	17 (22%)	3 (8%)	$X^2 = 3.272$	.070
Birthweight in grams, *mean (SD)*	3277 (566)	3386 (644)	$t = -0.929$	.355
LBW (<1500gr), *n (%)*	9 (11%)	3 (8%)	*Fishers exact* = 0.295	.750
Comorbidity present, *n (%)*	25 (28%)	15 (37%)	$X^2 = 1.03$	.310
Syndrome present, *n (%)*	12 (25%)	6 (27%)	$X^2 = 0.011$	.917
Age at diagnosis in months (median, IQR)	1 (2)	0 (1)	$U = 1539.5$	.128
Age diagnosis >1 year, *n (%)*	5 (6%)	2 (5%)	*Fishers exact* = 0.021	1.00
Resected length of aganglionosis in cm, *mean (SD)*	13 (15)	22 (20)	$t = -2.415$	.018 *
Short segment disease, *n (%)*	69 (77%)	20 (49%)	$X^2 = 12.26$	<0.001 **
Pre-operative HAEC, *n (%)*	8 (9%)	4 (11%)	*Fishers exact* = 0.089	.748
Type of operation, *n (%)* Transanal Pull-through Duhamel	 67 (74%) 23 (26%)	 26 (63%) 15 (37%)	$X^2 = 1.664$	.197
Open vs laparoscopic, *n (%)* Open Laparoscopic Transanal only	 25 (28%) 47 (53%) 17 (19%)	 17 (42%) 21 (51%) 3 (7%)	$X^2 = 4.101$	.129
Temporary ostomy, *n (%)*	17 (19%)	10 (24%)	*Fishers exact* = 0.576	1.00
Post-operative complications < 30 days, *n (%)*	15 (17%)	11 (27%)	$X^2 = 2.031$	.154
Length of hospital stay after corrective surgery in days (median, IQR)	4 (3)	6 (5)	$U = 2050.5$	.031 *
Total length of hospital stay in follow-up in days (median, IQR)	9 (21)	18 (25)	$U = 1970.5$	.028 *
Obstructive defecation problems, treated with laxatives and/or rectal irrigation, *n (%)* 1st year of follow-up 1-5 years of follow-up >5 years of follow-up	 17 (26%) 19 (58%) 7 (58%)	 20 (63%) 29 (88%) 6 (60%)	 $X^2 = 12.38$ $X^2 = 7.639$ *Fishers Exact* = 0.873	 <0.001 ** .006 ** 1.00

Note. LBW = Low birthweight; HAEC = Hirschsprung-associated enterocolitis; * $p < .05$, ** $p < 0.01$

Effectiveness of BT injections

Clinical improvement after first BT injections was achieved in 25 out of 41 patients (61%). This was a significant within-group difference pre-post intervention (McNemars test 14.06, $p < 0.001$). There was no improvement after first injection in seven out of 41 patients (17%), whereas in nine patients follow-up data after first injection were not reported. Four

of the 25 patients with clinical improvement, had no repeated injections as they achieved satisfactory defecation. Mean duration of improvement after the first injection in patients who received repeated injections was 3.7 months (SD = 3.0), mean duration of improvement after all injections was 4.3 months (SD = 4.3), but ranged widely from two weeks up to two years. Six out of 41 patients (14%) had a transition zone pull through (TZPT) (one who had no clinical improvement after the first BT injection, five showed clinical improvement after BT injection). Of the five patients with a TZPT and clinical improvement after first BT injection, three underwent redo pull-through at later stage, and successful additional BT injections after the redo pull-through. Four of those seven patients who did not show clinical improvement after first BT injection, received one to three additional BT injections. For one out of four patients this resulted in clinical improvement, the other three patients underwent additional procedures (one patient underwent ten anal dilatations under anaesthesia because of a stenosis, the other underwent a redo pull-through because of a TZPT, the third plication of dilated colon). One of the seven patients without clinical improvement after the first failed injection, who received no additional BT injections, underwent redo pull-through because of a failed construction of the Duhamel pouch. This patient had no TZPT. Overall, spontaneous defecation or defecation with laxatives was achieved in 29 out of 41 patients after BT injections (71%). There was no dose-related effect, as both for Botox and Dysport, no relationship was found between the dosage and the likelihood of clinical improvement after injection (Botox: OR = 1.42, $p = 0.705$; Dysport: OR = 0.71, $p = 0.567$).

Adverse effects

In 12 out of 41 patients (29%) adverse effects after BT injection occurred. This occurred in six out of 41 patients after the first BT injection. After 14 of a total of 90 BT injections (16%) adverse effects occurred (for the remaining 25 injections, data on occurrence of adverse effects was not reported in the medical record). Reported adverse effects were: anal pain ($n = 3$ times), reversible faecal incontinence ($n = 7$ times), reversible soiling ($n = 3$ times) and dermatitis due to softer stools ($n = 1$ time). Faecal incontinence and soiling were temporary, varying from 2 days to 5 weeks. Five of the 7 patients with faecal incontinence were potty-trained at injection (their age at injection varied from 3 to 11 years), two were not (both were 2 years of age at injection). All adverse effects were graded as minor adverse effects, as 13 adverse effects were classified as grade 1 according to Clavien-Dindo, and only the dermatitis that required treatment with crème was classified as grade 2.

Factors predicting adequate effect after first Botulinum toxin injections

In the 33 patients in whom response to first injection was described, logistic regression analysis was used to derive factors associated with clinical improvement after first BT injections. None of the tested covariates was significantly associated with clinical improvement after first BT injection in univariate analysis, therefore no multivariate analysis was conducted (Table 3).

Table 3 Factors moderating the probability of clinical improvement after first botulinum toxin injection

	Odds Ratio (OR) of clinical improvement	*p* Value
Sex		
Male	1.04 [0.17-6.26]	$p = 0.963$
Female	1 [Reference]	
Comorbidity		
Yes	2.75 [0.61-12.48]	$p = 0.190$
No	1 [Reference]	
Syndrome		
Yes	2.17 [0.26-17.89]	$p = 0.473$
No	1 [Reference]	
Length of disease		
Short segment disease	1.67 [0.37-7.57]	$p = 0.508$
Long segment disease	1 [Reference]	
Operation technique		
Duhamel	2.75 [0.61-12.48]	$p = 0.190$
TERPT	1 [Reference]	
Approach to mobilization of colon		
Open	1 [Reference]	
Laparoscopic	0.90 [0.06-12.58)	$p = 0.938$
Transanal	2.5 [0.17-37.26]	$p = 0.506$
Temporary ostomy		
Yes	3.47 [0.71-16.94]	$p = 0.125$
No	1 [Reference]	
Post-operative complications		
Yes	1.80 [0.35-9.28]	$p = 0.482$
No	1 [Reference]	
Length of hospital stay after corrective surgery (days)	0.90 [0.78-1.04]	$p = 0.164$
Type of botulinum toxin		
Botox	3.50 [0.75-16.26]	$p=0.110$
Dysport	1 [Reference]	

Note. There were not enough observations to conduct the analysis of the predictive value of gestational age, birthweight, age at diagnosis and preoperative HAEC. TERPT=transanal endorectal pull-through

DISCUSSION

The first aim of this study was to describe the effect of BT injections in treating obstructive symptoms in patients with Hirschsprung disease. Approximately one third of our patients received BT injections, which resulted in clinical improvement in the majority of patients (61%), which persisted without further injection in a few patients (4 out of 41 patients). However, clinical improvement was temporary in most patients, and the duration of effect was on average 4.3 months after injection, although this varied widely. Most patients therefore needed repeated injections. Our results are in accordance with previous studies [17], and support the idea that BT injections are suitable treatment for patients with obstructive defecation problems, who have a decompensated bowel, and by improving

defecation thus give the decompensated bowel a chance to recover. Adverse effects in our study were mild and limited to some increased soiling for a few weeks (maximum of five weeks), or anal pain for a few days. The proportion of patients in whom adverse effects occurred was comparable to what has been described in previous meta-analytic findings on studies describing the effect of BT injections.[16,21]

The second aim of this study was to determine factors which are associated with a higher probability of receiving BT injections, in order to help identify patients who are more likely to benefit from BT injections. In our cohort, patients that received BT injections, had longer segment disease, had longer length of hospital stay after corrective surgery and in follow-up due to readmittances and more often needed laxatives and rectal irrigation to manage obstructive defecation problems in the first five years of follow-up. This suggest that patients with more severe obstructive defecation problems are more likely to receive BT injections.[7,12,13,22]

Third aim of this study was to identify factors that are associated with clinical improvement after first BT injection in order to identify subgroups with higher chances of beneficial results. None of the tested possible patient and clinical factors in this study were associated with clinical improvement after first BT injections. Patrus et al. and Minkes have suggested that short segment disease is associated with a lower total number of BT injections required[11,22]. Although our findings did suggest patients with short segment disease less often receive BT injections, we found no evidence for a higher likelihood of clinical improvement after first BT injection. Previous evidence supports our findings that age at diagnosis, sex and type of corrective surgery are not associated with response. One study reported that higher age at BT injection[7] was not related to response, but we did not test for this in our study.

Although we did not perform routine anorectal manometry in our centres, and therefore could not test its predictive value, evidence from previous studies is inconclusive whether findings on anorectal manometry can predict clinical improvement after BT injections.[12-15,22] This would be interesting to assess in future studies.

Interestingly, four out of the seven patients that did not respond to their first BT injection underwent reoperation after failed injection (as was the case in three of five patients with a TZPT who responded well to their first BT injection). Although our findings could not fully exclude equal probability, this observation is suggestive for higher odds on a reoperation, when the first BT injection fails. This has also been suggested in a previous study[1], and supports the idea that patients in whom the first BT injection fails, have other reasons for obstruction, such as an anastomotic twist or more severe neurogenic dysfunction (expressed as AchE staining positivity)[15]. It is therefore important to consider alternative explanations for obstructive defecation problems in patients who do not respond to BT injection that may require reoperation.

Limitations

Our findings were limited by the cross-sectional design of our study. Loss-to-follow-up, differences in follow-up duration and the missing data in medical records, may have introduced a bias to our findings. One of the limitations is a bias that results from differences in follow-up duration between patients, given that in general chances of the occurrence of an event increases with longer duration of follow-up. Hence our finding that longer follow-up was associated with a larger proportion of patients using laxatives or rectal irrigation, does not seem to reflect a worsening of bowel function in patients over time.

Differences in procedural aspects (including dosage and type of BT), administration by different surgeons and the lack of a standardized approach to intrasphinteric BT injections, may have also introduced a bias to our findings, although this does reflect the reality in clinical practice. Standardization of dosage would allow for calculating a dose-response relationship, that our data did not allow for.

Our findings on the average duration of improvement and average interval between BT injections was limited by the lack of standardized follow-up in this retrospective study. Measuring functional defecation outcomes at standardized time points after injection, would allow for more accurate findings on average duration of improvement. In addition, the lack of standardized reporting of procedural aspects and follow-up data in the medical record accounted for some missing relevant data and limited the possibility to compare outcome data between patients. However, it can be assumed that in case of clinical outcome of BT injections, no news can be considered good news, suggesting that this influence would rather result in an underestimation of the effectiveness of BT injections than in an overestimation.

Conclusions and implications

Our findings show that BT injections are an effective treatment for obstructive defecation problems after surgical treatment for HD, with mild adverse effects. This study also shows that the likelihood of receiving BT injections was higher in patients with long segment disease. Our findings also implicate that response to the first BT injection is important in determining whether repeated injections would be beneficial, but that there are no specific clinical factors predictive of clinical improvement and therefore no specific subgroups of patients with better chances of benefiting from BT injections. In conclusion, we recommend to use BT injections to treat patients with obstructive symptoms and to repeat injections. We recommend a standardized approach in administration of intrasphincteric BT injections.

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CHAPTER 5

Risk factors for enterocolitis in patients with Hirschsprung disease: A retrospective observational study

D. Roorda, J. Oosterlaan, L.W.E. van Heurn, J.P.M. Derikx

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ABSTRACT

Introduction

Hirschsprung-associated enterocolitis (HAEC) accounts for substantial morbidity and mortality in patients with Hirschsprung disease (HD). The aim of this study was to identify incidence of pre- and postoperative HAEC in our consecutive cohort and to identify patient and clinical characteristics that are associated with developing postoperative HAEC and HAEC-free interval.

Material and methods

A retrospective cohort study was performed with all 146 HD patients treated between 2000 and 2017. Data were retrieved from the medical records. HAEC was defined as presence of clinical signs of bowel inflammation, that required treatment with intravenous antibiotics and admittance to the hospital during at least two days. To identify risk factor for HAEC, patients with and without a history of postoperative HAEC were compared. Kaplan-Meier and Cox-regression were used to assess HAEC free intervals before and after surgery.

Results

Out of 146 patients, 12 patients had preoperative HAEC (8%) and 31 patients had postoperative HAEC (21%). Median preoperative HAEC free interval was 112 days (IQR 182 days). Length of hospital stay due to readmissions was longer for patients with a history of postoperative HAEC compared to patients without a history of postoperative HAEC (9.5 vs 16 days, $U = 1872.5$, $p = 0.047$). Median postoperative HAEC free interval was 226 days. Of the patients who had postoperative HAEC, 66% had their first episode within the first year after surgery. The incidence of HAEC declined over follow-up.

Conclusions

HAEC incidence was relatively low in our population. No patient or clinical characteristics were associated with the risk of postoperative HAEC.

INTRODUCTION

Hirschsprung-associated enterocolitis (HAEC) is a severe complication of Hirschsprung disease (HD) and is one of the significant causes of morbidity and mortality in patients with HD, with an estimated incidence of postoperative HAEC in 10%.[1-3] About 2% -33% of patients with a history of HAEC experience recurrent episodes of HAEC.[1,2,4] Most often HAEC can be treated with antibiotics and rectal irrigation. However, a previous meta-analysis showed that in about 18% of patients surgical treatment is required.[1] Some patients experience an episode of enterocolitis before corrective surgery or even before diagnosis. The estimated incidence of preoperative HAEC is 15-18% [5,6].

HAEC is clinically characterized by abdominal distention, diarrhea, fever, and ultimately sepsis. Diagnosing HAEC remains a challenge because the symptoms are non-specific and may also be present in viral or bacterial gastro-enteritis. As HAEC can have a fast and serious course of disease, it is therefore important to detect HAEC at an early stage. A consensus-based score list based on (1) clinical symptoms, including a history of previous HAEC episodes, bloody, explosive or foul-smelling diarrhea, distended abdomen, decreased peripheral perfusion, lethargy or fever, (2) radiologic findings on abdominal rontgenography including air-fluid-levels, dilated loops, irregular mucosal lining, the absence of air in the distal rectum or pneumatosis, and (3) laboratory findings including leukocytosis and a shift to the left in white blood cells, has been formulated.[7-9] Such a score may help to make the right diagnosis. The consensus-based diagnostic score that Pastor et al. [7] proposed (with a cut-off of 10 points), has been clinically validated by Frykman et al., who proposed a cut-off score of 4 to identify HAEC.[8] Both cut-off values have been clinically validated by Dore et al., who showed that a cut-off of 10 fails to diagnose milder forms of HAEC and the cut-off of 4 diagnosed more patients (98% vs 50%) with suspicion of HAEC.[9] However, the studies of Frykman and Dore describe that a substantial number of patients had no abnormal radiographic findings or laboratory findings at presentation, as a result of which the scores fail to diagnose milder forms of HAEC. In order to identify patients with an increased risk of developing HAEC, it is important to identify patient and clinical characteristics that are available at presentation and that are associated with developing enterocolitis.

The aim of the current study was to determine prevalence and incidences of HAEC in a consecutive cohort of patients treated in our tertiary paediatric surgical centers in Amsterdam and to identify patient and clinical characteristics that are associated with developing postoperative HAEC and with the enterocolitis free interval before and after corrective surgery.

MATERIAL AND METHODS

Inclusion criteria

All patients who underwent corrective surgery for HD between 2000 and 2017 in one of the two academic tertiary hospitals in Amsterdam (Academic Medical Centre and VU medical centre), who had at least one year of follow-up and who gave informed consent, were included in this retrospective cohort study. Excluded from this study were patients who underwent corrective surgery in another centre and patients without histopathological confirmation of HD.

Data extraction

Medical records of all patients were reviewed in 2018 by two of the authors (JD and DR, both medical doctors) and stored in a Castor database. Data validation was done by checking 10% of the entered records of each reviewer by another reviewer. In case there were inconsistencies in more than 10% of a record, the complete record was revalidated by a third author. For the majority of variables data were missing in less than 10% of cases, with the exception of: presence of a syndrome, gestational age (12% missing), APGAR scores after one and five minutes (43% missing), use of laxatives or rectal irrigation in the first year of follow-up (24% missing), between 1 and 5 years of follow-up (35% missing) and more than 5 years of follow-up (69% missing).

Outcomes and definitions

Primary outcome was whether patients developed preoperative and postoperative HAEC. Unfortunately we could not retrospectively find all the data necessary for the construction of the clinical score of Pastor et al, because part of our cohort was treated before these validated scores were developed, and that in patients with a suspicion of mild HAEC no abdominal rontgenography was performed and no blood sample was taken, as this would not have changed treatment strategy. Therefore the following definition of an episode of HAEC was used: (a) presence of clinical signs of bowel inflammation, such as pain, distended abdomen, loose stools, (b) that required treatment with intravenous antibiotics during at least two days and (c) admission to the hospital. Secondary outcome in this study was the risk of developing postoperative enterocolitis and the proportional hazard of patient and clinical factors for developing HAEC.

Factors that were tested for an association with developing HAEC

We tested the influence of age at diagnosis and time between diagnosis and surgery on the risk of preoperative HAEC. We tested the following variables as potential risk factors for developing postoperative HAEC: sex, gestational age, birthweight, APGAR score, presence of (any kind of) comorbidity, presence of a syndrome (which was only tested in patients in whom a syndrome was suspected based on dysmorphic features), age at diagnosis, length

of aganglionic segment (short-segment disease was defined as aganglionosis extending to the rectosigmoid and long-segment disease as aganglionosis extending proximal to the sigmoid), history of preoperative HAEC, age at surgery (in months), type of corrective surgery (Duhamel or transanal endorectal pull-through), presence of a temporary ostomy, occurrence of complications within 30 days after surgery (graded according to the Clavien-Dindo classification of surgical complications[10]), length of postoperative hospital stay after corrective surgery and length of hospital stay in follow-up due to re-admissions.

Factors that were tested for an association with enterocolitis free interval

Age at diagnosis was tested for an association with preoperative enterocolitis free interval, the time between birth and first episode of enterocolitis. The following variables were tested for an association with the postoperative enterocolitis free interval, the time between corrective surgery and the first episode of enterocolitis: history of preoperative HAEC, type of corrective surgery (Duhamel or transanal endorectal pull-through), presence of a temporary ostomy, occurrence of complications within 30 days after surgery, length of postoperative hospital stay, and age at corrective surgery in months..

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA). We calculated the overall prevalence of postoperative enterocolitis as the proportion of patients in our cohort, that had a history of at least one episode of postoperative HAEC. The incidence by length of follow-up was calculated by dividing the number of patients who developed an episode of HAEC in each year of follow-up after corrective surgery, by the total number of patients with that length of follow-up. The incidence over the period of our data collection was calculated by dividing the number of patients who developed an HAEC in that year of data collection, by the total number of patients at risk. Linear regression was used to test for a decrease in incidence of postoperative HAEC by length of follow-up and over the period of data collection. We also compared the incidence of HAEC in the first year of life in patients who were surgically treated between 2000 and 2008 to patients who were surgically treated between 2009 and 2018.

The independent sample *t*-test or Mann Whitney U test was used to compare patients with and without a history of preoperative or postoperative enterocolitis, in case of continuous variables and the X^2 or Fisher's Exact test in case of categorical variables, in order to identify factors that were associated with developing HAEC. Kaplan Meier was used to assess the preoperative enterocolitis free interval and the postoperative enterocolitis free interval. Cox regression was used to test what factors were associated with the length of the preoperative and postoperative enterocolitis free interval. *P*-values of <0.05 were considered statistically significant.

Ethics

The Institutional Board of Review approved of this study (W18_160#18.198) and all included patients gave informed consent.

RESULTS

Population characteristics

A total of 164 patients were treated for HD between 2000 and 2017 in the two participating hospitals. Ten patients were excluded, because primary corrective surgery was performed elsewhere. Two patients deceased before corrective surgery was performed (due to reasons other than HAEC) and two patients were treated conservatively: one patient with short segment disease had no symptoms of constipation and had spontaneous bowel movements with laxatives; the other patient was diagnosed late, at the age of five years, and had satisfactory bowel movements with laxatives and rectal irrigation. In both cases an expectative, conservative approach was chosen in shared decision with the parents. Four patients did not provide informed consent. Subsequently, 146 patients were included in this study.

Of all 146 patients, 10 patients had a follow-up duration of one year, 43 patients had a follow-up duration of more than one but less than five years, and 93 patients had a follow-up duration of more than five years. Baseline characteristics of all 146 patients are provided in Table 1. There was no mortality due to HAEC in our patient group. One patient who went had a history of postoperative HAEC deceased from respiratory insufficiency related to pulmonary comorbidity and therefore unrelated to HD.

Table 1 Patient characteristics

Patient characteristics (n=146 patients)	
Sex, n (%)	
Male	116 (80)
Female	30 (20)
Gestational age in weeks, median (range)	38.7 (27.9-42.3)
Gestational age, n (%)	
Preterm (<37 weeks)	22 (15)
Term (≥37 weeks)	107 (73)
Missing	*17 (12)*
Birthweight in grams, mean (SD)	3301 (634)
Birthweight, n (%)	
Very low birthweight (<1500 grams)	3 (2)
Low birthweight (<2500 grams)	11 (8)
Normal birthweight (≥ 2500 grams)	120 (82)
Missing	*12 (8)*
APGAR score, median (range)	
1 min	9 (1-10)
5 min	10 (5-10)
Missing	*61 (42)*

Comorbidity present, n (%)	
Yes	49 (34)
No	97 (66)
Syndrome, n (%) [a]	
Downs syndrome	15
Other syndrome	5
No syndrome	54
Age at diagnosis in months, median (range)	0 (0-87)
Age at diagnosis, n (%)	
0-1 year of age	137 (94)
>1 year of age	7 (5)
Missing	*2 (1)*
Resected length of aganglionosis in cm, mean (SD)	
Length of disease, n (%)	
Short segment disease	101 (69)
Long segment disease	26 (18)
Total colonic aganglionosis	16 (11)
Missing	*3 (2)*
Age at surgery in months, median (range)	4 (0-92)
Type of operation technique, n (%)	
Transanal endorectal pull-through	93 (64)
Duhamel	53 (36)
Approach to mobilisation of colon, n (%)	51 (35)
Open	73 (50)
Laparoscopic	21 (14)
Transanal only	*1 (1)*
History of a temporary ostomy, n (%)	
Prior to pull-through	31 (21)
At pull-through	2 (1)
No ostomy	113
Postoperative complications < 30 days, n (%)	
Yes	28 (19)
Grade 1-2b	13 (46)
Grade 3-4	15 (54)
No	117 (80)
Missing	1 (1)
Length of hospital stay after pull-through in days, median (range)	5 (2-34)
Total length of hospital stay in follow-up in days, median (range)	13 (0-270)
Use of laxatives or rectal irrigation in follow-up, n (%)	
1st year of follow-up (n=146)	
None	47 (32)
Laxatives	20 (14)
Rectal irrigation	44 (30)
Missing	*35 (24)*
1-5 years of follow-up (n=136)	
None	3 (2)
Laxatives	19 (14)
Rectal irrigation	55 (40)
Missing	*59 (43)*
>5 years of follow-up (n=93)	
None	1 (1)
Laxatives	9 (10)
Rectal irrigation	19 (20)
Missing	*64 (69)*

Note. [a] genetic testing was done 74 patients, in case of clinical suspicion of a syndrome; other syndromes were: MEN2A (n=1), Mowat-wilson (n=1), diGeorge syndrome (n=1), Congenital Central Hypoventilation Syndrome (n=1), Cat Eye syndrome (n=1) and partial trisomy of chromosome 4 (n=1)

Prevalence and incidence of HAEC in our population

There were 12 out of 146 patients who had preoperative HAEC (8%), of whom seven had HAEC before aganglionosis was diagnosed and five had HAEC between diagnosis and corrective surgery. There were 31 out of 146 patients who had postoperative HAEC (21%). Four out of the 12 patients with a preoperative HAEC, also went through at least one episode of postoperative HAEC (33%). Eighteen of the 31 patients with postoperative HAEC (58%) had one episode, whereas 13 out of 31 patients had recurrent episodes of postoperative HAEC: ten out of 31 patients had two episodes (32%) and three out of 31 patients had three episodes (10%).

There was a significant decrease in incidence of postoperative HAEC per year of follow-up *(b* = -0.346, *p* = 0.009*)*, and all postoperative HAEC episodes in our cohort occurred within a maximum of seven years of follow-up after surgery (Fig. 1).

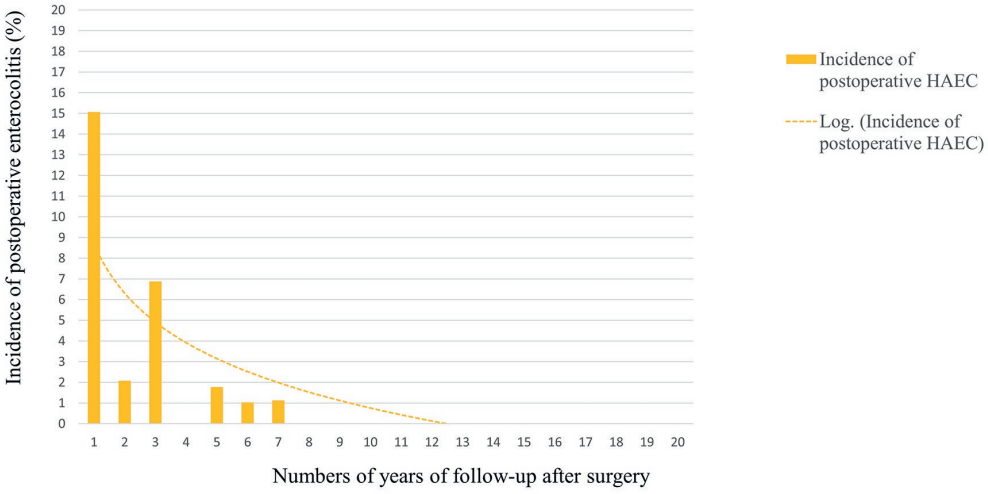

Figure 1 Incidence of postoperative HAEC by year of follow-up

Data of follow-up longer than seven years was present for 79 patients. There was neither a significant decrease in the incidence of postoperative HAEC over the period of data collection (*b* = -0.44, *p* = 0.09), nor a difference in the incidence of postoperative HAEC in patients treated in the first decade of the study period (2000-2008), compared to patients treated in the second decade of the study period (2009-2018) (X^2 = 128, *p* = 0.259).

Factors associated with preoperative enterocolitis

In logistic regression, age at diagnosis (*OR* = 0.99, *p* = 0.93), and the number of days between diagnosis and corrective surgery (*OR* = 1.00, *p* = 0.93) were no risk factors for preoperative enterocolitis.

Table 2 Patient and clinical characteristics of patients with and without postoperative Hirschsprung-associated enterocolitis (HAEC)

	No Postoperative HAEC (*N* = 115)	**One or more episodes of postoperative HAEC (*N* = 31)**	**Group differences**	***p*-value**
Male sex, *n (%)*	88 (77%)	28 (90%)	$X^2 = 2.85$	.091
GA in weeks, *mean (SD)*	38.4 (2.8)	38.9 (1.6)	$t = -1.07$	.286
Birthweight in grams, *mean (SD)*	3270 (642)	3410 (605)	$t = 0.89$	.376
APGAR score, *median (range)*				
1 min	9 (1-10)	9 (5-10)	$U = 567.5$	.350
5 min	10 (5-10)	10 (7-10)	$U = 596.5$	.571
Comorbidity present, *n (%)*	40 (35%)	9 (29%)	$X^2 = 0.36$	.547
Syndrome present, *n (%)*	16 (26%)	5 (42%)	Fischers exact = 0.30	.218
Age at diagnosis in months, *median (range)*	0 (0-87)	0 (0-57)	$U = 1521$	.219
Age diagnosis > 1 year, *n (%)*	5 (4%)	2 (6%)	Fischers exact = 0.216	.643
Age at surgery in months, *median (range)*	4 (1-92)	3 (0-60)	**$U = 1217.5$**	**.012**
Resected length of aganglionosis in cm, *mean (SD)*	16 (18)	13 (14)	$t = 0.651$	.517
Short segment disease, *n (%)*	83 (74%)	18 (58%)	$X^2 = 3.012$	.083
Preoperative HAEC, *n (%)*	10 (9%)	5 (17%)	Fischers exact = 0.31	.172
Type of operation, *n (%)*			$X^2 = 0.54$	.462
TERPT	75 (65%)	18 (58%)		
Duhamel	40 (35%)	13 (42%)		
Open vs scopic, *n (%)*			$X^2 = 1.19$	.551
Open	42 (37%)	10 (32%)		
Scopic	55 (48%)	18 (58%)		
Transanal only	18 (15%)	3 (10%)		
Temporary ostomy, *n (%)*	9 (8%)	0 (0%)	-	
Postoperative complications < 30 days, *n (%)*	24 (21%)	4 (13%)	$X^2 = 1.039$	.308
LOS after corrective surgery in days, *median (range)*	5 (2-34)	6 (2-25)	$U = 1686$	.392
Total LOS in follow-up in days, *median (range)*	9.5 (0-137)	16 (0-270)	**$U = 1872.5$**	**.047**
Total length of follow-up after corrective surgery in years, *median (range)*	7 (1-19)	9 (3-19)	**$U = 2234.5$**	**.030**
Obstructive defecation problems, Krickenbeck grade III/IV, *n (%)*				
1st year of follow-up	49 (43%)	15 (48%)	$X^2 = 2.012$	.156
1-5 years of follow-up	51 (94%)	23 (100%)	$X^2 = 1.33$	.249
>5 years of follow-up	19 (95%)	9 (100%)	$X^2 = 2.012$	.156

Note. GA, gestational age; HAEC, Hirschsprung-associated enterocolitis; TERPT, Transanal endorectal pull-through; LOS, length of hospital stay

Preoperative enterocolitis free interval

In all patients, the median enterocolitis free interval before surgery was 112 days after birth (*IQR*: 152 days). This enterocolitis free interval from birth to corrective surgery was not associated with age at diagnosis (b = -0.001, p = 0.355). In patients with a neonatal diagnosis (within 3 months after birth) only, the median preoperative enterocolitis free interval was 99 days (*IQR:* 86 days).

Factors associated with postoperative HAEC

There were no significant differences between characteristics of patients who had postoperative HAEC and those who did not in terms of sex, gestational age, birthweight, APGAR scores, age at diagnosis, presence of comorbidity or a syndrome, length of aganglionosis, occurrence of preoperative enterocolitis, type of corrective surgical procedure, presence of a temporary ostomy, occurrence of postoperative complications and length of stay after corrective surgery (Table 2). Median age at surgery was lower for patients who had postoperative HAEC (3 vs 4 months, U = 1217.5, p = 0.012). Median length of follow-up was higher in patients who had postoperative HAEC (9 vs 7 years, U = 2234.5, p = 0.030). Also the total length of hospital stay in follow-up was higher for patients who had postoperative HAEC than patients without postoperative HAEC (16 vs 9.5 days, U = 1872.5, p = 0.047), as a result of re-admissions because of obstructive defecation problems, treatment with botulinum toxin injections and intravenous treatment with antibiotics for HAEC.

Postoperative enterocolitis free interval

Fig. 2 shows the interval between corrective surgery and the *first* episode of postoperative HAEC in all patients. Median postoperative enterocolitis free interval was 223 days (0.6 years) and ranged between 6 and 1971 days (5.4 years) after corrective surgery. Of the patients who had postoperative HAEC, 66% had their first episode within the first year after surgery.

Table 3 Proportional Hazards of clinical characteristics on earlier development of postoperative Hirschsprung-associated enterocolitis (HAEC)

	Univariate HR (95% CI)	***p*-values**
Pre-operative HAEC Yes No	 0.87 (0.26-2.96) 1 [Reference]	 p= 0.828
Type of operation technique Duhamel TERPT	 0.85 (0.40 – 1.80) 1 [Reference]	 p = 0.662
Temporary ostomy Yes No	 1.44 (0.58 – 3.60) 1 [Reference]	 p = 0.433
Postoperative complications < 30 days after surgery Yes No	 0.71 (0.24-2.08) 1 [Reference]	 p = 0.533
LOS after corrective surgery in days	1.11 (0.99- 1.24)	p = 0.056
Age at surgery in months	**1.06 (1.01-1.11)**	***p* = 0.027**

Note. TERPT, Transanal endorectal pull-through; LOS, length of hospital stay

In logistic regression, age at surgery was no risk factor for postoperative HAEC (*OR* = 0.97, *p* = 0.297), whilst in cox regression, higher age at surgery was associated with a higher proportional hazard of developing postoperative HAEC (*HR* = 1.06, *95%CI*: 1.01 – 1.11, *p* = 0.027). Having a history of preoperative HAEC, the type of corrective surgery (Duhamel vs. Transanal Endorectal Pull-through), the presence of a temporary ostomy, and the presence of postoperative complications and length of postoperative hospital stay were not associated with a higher or lower hazard of developing postoperative HAEC in univariate analysis. (Table 3) As only one factor was significantly associated with a higher proportional hazard in univariate analysis, no multivariate analysis was conducted.

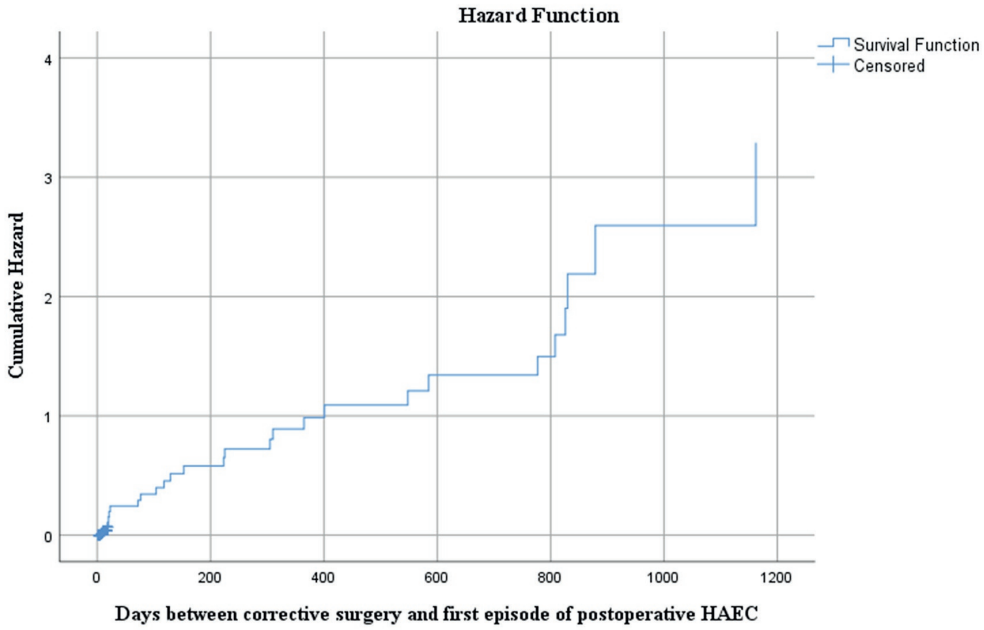

Figure 2 Hazard function of postoperative HAEC

DISCUSSION

This study was the first to show that older age at surgery was associated with a shorter enterocolitis free interval after corrective surgery, and thus a higher hazard of developing postoperative HAEC. The prevalence of preoperative HAEC was 8% in the current study, which is lower than what has been reported in previous studies (between 15% and 18%).[5,6] The prevalence of postoperative HAEC was 21%, which is relatively high compared to what was reported in a previous meta-analysis[1], but lower than in some other reports, which showed prevalences up to 37%[11,12]. Previous studies report that the prevalence of

postoperative HAEC varies highly and incidence has been suggested to decrease over the last decade.[5,6,13,14] This decrease may be explained by the tendency to diagnose and surgically treat HD at younger age,[15] and the introduction of botulinum toxin injections.[16] The incidence of postoperative HAEC in our cohort decreased with each year of follow-up after corrective surgery, but not over the period of data collection. In our sample no episode of HAEC occurred after more than seven years of follow-up after surgery. Differences in incidence findings of postoperative HAEC between studies may be explained by heterogeneity in case definitions and by geographical differences [17], that may relate to differences in clinical characteristics of the cohorts, including type of operation techniques used and differences in the use of laxative medication and rectal irrigation and life style factors such as diet.[18-21]

Our findings suggest that there were no patient characteristics associated with postoperative HAEC. Except age at surgery which was lower in patients who developed postoperative HAEC, although this difference was small. Older age at surgery was associated with increased proportional hazard of developing postoperative HAEC. We would interpret both seemingly contradictory findings as follows: higher age is associated with a higher risk of developing postoperative HAEC earlier in time, rather than developing postoperative enterocolitis more often. Our data did not suggest any particular optimal age for surgery based on the risk of enterocolitis. In our patient group, mean length of stay due to readmission was longer for patients with postoperative HAEC, which may be explained by readmission with possibly more severe obstructive defecation problems, dilated bowel and ileus, requiring treatment strategies such as botulinum toxin injections, or admission with nothing per os and fluid hydration.

Previous evidence on risk factors for developing postoperative HAEC show inconsistent findings. Some studies have suggested that female patients, patients with a syndrome or positive family history and patients with lower birthweight are at higher risk for postoperative HAEC. [4,22] [12] [5,23-25] We could not confirm these associations in our patients. Furthermore, age at diagnosis was not associated with pre- and postoperative HAEC in our sample.[2,22,26,27] Others have also described clinical characteristics, including the presence of long-segment disease, a history of preoperative HAEC, residual aganglionosis or intestinal neuronal dysplasia, and a stricture to increase the risk of postoperative HAEC, but the existing evidence on this is inconsistent.[28] [18,22,23,26,27,29] It is also suggested that patients with a temporary ileostomy, lower weight at surgery, and gastrointestinal comorbidity such as cow milk allergy and IBD have higher risk of postoperative HAEC.[27,30-33] Preoperative HAEC, history of central nervous system infection, and congenital neurologic anomalies have been associated with increased risk of recurrent HAEC.[34]

In our patients there was no relation between long segment disease, postoperative complications, a temporary ileostomy or preoperative HAEC and the likelihood of a postoperative HAEC. In summary, current evidence on risk factors for postoperative

HAEC shows an inconsistent picture and does not allow for clear conclusions. Our findings however implicated that there are no subgroups of patients with higher risk of developing postoperative HAEC.

Lastly, this was the first study to assess risk factors for postoperative HAEC using a hazard function, thus accounting for the factor time. Our findings suggested that a history of preoperative HAEC, length of aganglionosis, type of corrective surgery, presence of a temporary ostomy, and postoperative complications within 30 days after surgery were not associated with higher hazards on developing postoperative enterocolitis.

Limitations

The interpretation of our findings should be considered in the light of the limitations that come with this study. Because of the retrospective design there was a challenge with missing data. Especially with regard to follow-up data on the use of laxatives and rectal irrigation a substantial percentage of cases had missing data. We tried to overcome the influence of this bias as much as possible by only including the cases with complete data in each specific analysis, but that lowered the power of our study. With regard to the outcome data, we assumed that missing data is more likely to represent the absence of pre- or postoperative HAEC. This suggests that our estimation of prevalence is rather overestimated than underestimated.

Another limitation is our use of a liberal case definition, whereas others use clinical scores. We know that the consensus-based score of Pastor et. al.[7] is believed to underestimate prevalence, as it fails to diagnose milder cases of HAEC[8,9]. However, as a viral or bacterial gastro-enteritis may also necessitate admission to the hospital and intravenous treatment with antibiotics, we may have included cases with severe gastro-enteritis in our calculations. Although this made our study more sensitive to identify patients with higher risk of postoperative HAEC based on patient and clinical characteristics, it may account for an overestimation of prevalence and incidence findings, compared to other studies. Our case definition may have also resulted in the exclusion of patients with a very mild form of HAEC, although in our centres we have a low threshold in admission of patients with suspected HAEC and treatment with oral antibiotics or rectal irrigation. Moreover, a diagnosis of HAEC may be uncertain in these patients[12].

A last limitation is a bias as a result of difference in follow-up duration, given that in general chances of the occurrence of an event increase with longer duration of follow-up. We tried to account for this bias, by showing that there was a difference in median follow-up duration between patients with and without a history of HAEC. We found no higher odds ratio on postoperative enterocolitis for longer duration of follow-up, and we used time-dependent models to test for risk factors. We therefore think our findings do not reflect merely the effect of differences in follow-up duration.

Future perspectives

Our findings suggest that there are no subgroups of patients that have a higher risk of postoperative HAEC based on their patient characteristics or disease characteristics. This indicates that the risk of postoperative HAEC may be even more determined by situational factors such as lifestyle, diet, constitution of the microbiome and the effect of strategies that are used for improving defecation, including botulinum toxin injections, rectal washouts and enemas.[16,31,35] Future studies should focus on how to optimize the effect of these factors on the risk of postoperative HAEC and how to optimize preventive treatment strategies to prevent postoperative HAEC. The reuse of clinical care data for research purposes can be improved by implementing standardized registration of outcome data and the use of a core outcome set.[36]

Conclusions

In this study we showed that preoperative HAEC was prevalent in 8% of the patients and postoperative HAEC in 21%. The incidence of postoperative HAEC decreased with every year of follow-up. No patient or clinical characteristics were associated with the risk of postoperative HAEC, whilst older patients developed HAEC earlier in time, not more often.

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CHAPTER 6

Did age at surgery influence outcome in patients with Hirschsprung disease? a nationwide cohort study in the Netherlands

D. Roorda, S.J. Verkuijl, J.P.M. Derikx, M. Trzpis, R.J. Meinds, C.E.J. Sloots, M.J. Witvliet, I. de Blaauw, W.G. van Gemert, L.W.E. van Heurn, P.M.A. Broens

Submitted

ABSTRACT

Objectives

Hirschsprung disease (HD) requires surgical resection of affected bowel, but the current evidence is inconclusive regarding the optimal age for resection. The aim of this study was to assess whether age at resection of the aganglionic segment is a determinant for surgical outcomes

Methods

A cross-sectional cohort study was done including all consecutive patients with HD between 1957 and 2015, aged eight years or older (n=830), who were treated in one of the six pediatric surgical centers in the Netherlands. Primary outcome measures were mortality, postoperative complications, ostomy rate and redo surgery rate, retrieved from the medical records. Secondary outcome was constipation and fecal incontinence rate assessed with the Defecation and Continence Questionnaire (DeFeC and P-Defec).

Results

The medical records of 830 patients were reviewed, and 346 of the 619 eligible patients responded to the follow-up questionnaires (56%). There was a small increase in the risk of a permanent stoma and a temporary stoma with higher age at surgery, regardless of the length of the aganglionic segment and operation technique. Both adjusted and unadjusted for operation technique, length of disease, and temporary stoma, age at surgery was not associated with the probability and the severity of constipation and fecal incontinence in the long term.

Conclusions

In this study we found no evidence that the age at surgery influences surgical outcomes, thus no optimal timing for surgery for HD.

INTRODUCTION

Hirschsprung disease (HD) is characterized by a congenital absence of ganglion cells in a distal segment of the gut.[1] Initial treatment consists of irrigations or creating a stoma, after which a pull-through procedure is planned. There are various techniques for a pull-through procedure, always including resection of the affected bowel segment, but with varying techniques for restoration of bowel continuity, either by creating an end-to-end anastomosis or by creating a pouch. Over the past decades, surgical treatment has evolved from 3-staged procedures (stoma, pull-through and stoma reversal) to one-staged procedures.[2-5]

Based on clinical experience, pediatric surgeons generally prefer to do a pull-through before the age of three months[6], in order to limit the time interval in which irrigations or a stoma are needed, and the risk of preoperative Hirschsprung-associated enterocolitis. Likewise, surgery can be advanced before the age of one month. However, pull-through surgery may also be postponed for several reasons, including total colonic aganglionosis, a delay in diagnosis, more urgent other surgical procedures for cardiac comorbidity, or as a result of the surgeon's preference.[7] Some surgeons advocate 3-staged treatment and postponement of resection of the aganglionic segment, because of the risk of exposure to anesthetics and intraoperative hemodynamics, in a critical time window of brain development.[8-10]

The evidence about the influence early or late resection on surgical outcomes shows contradicting results with regard to postoperative complications,[11-15] length of hospital stay,[11,13] readmission rate[13], colostomy rate[16] and functional outcomes.[11,12,14,16-20] Moreover, various cut-off points to define early or late surgery were used to assess the influence of age. Thus it remains unknown whether age is an important factor in determining the optimal timing for pull-through surgery.

The aim of this study was to assess the influence of age at surgery for Hirschsprung disease on mortality rate, postoperative complication rate, stoma rate, redo pull-through rate, and on long-term functional outcomes including the rate and severity of constipation and fecal incontinence.

METHODS

Design, setting and patients

A nationwide cross-sectional study was performed in 2018–2019, assessing the medical records of all patients with histopathological confirmation of HD, who were eight years or older at the time of the study (n=830 patients), in all of the six pediatric surgical centers in the Netherlands, between 1957 and 2015. Patients who were deceased, patients who had a permanent stoma, patients with intellectual disability and patients living abroad

or without a known postal address were excluded from the assessment of the long-term functional outcomes. With the data collected in this study, a previous study has been published.[21]

Outcome variables

Surgical outcomes that were assessed in this study were: mortality, postoperative complications, the creation of a temporary or permanent stoma, redo pull-through and long term functional outcomes. Data from the medical records of all patients were used to determine overall mortality rate at time of follow-up, postoperative complications within 30 days after surgery, a history of a temporary stoma, a history of a permanent stoma without a scheduled reversal, and a history of redo pull-through.

To assess constipation and fecal incontinence in the long-term follow-up the Groningen Defecation and Fecal Continence (DeFeC) questionnaire was used for adults and the P-DeFeC questionnaire for patients aged 8-17 years.[22] These questionnaires provide a detailed description of the occurrence of specific symptoms of constipation and fecal incontinence and the use of different strategies for bowel management. Reported symptoms were used to determine: the occurrence of constipation according to the Rome IV criteria for functional constipation[23], the severity of constipation according to the Constipation Scoring System from Agachan et al[24], i.e. an 8-item scoring system, resulting in a score varying from 0 for no constipation to 30 for severe constipation, the occurrence of fecal incontinence according to the Rome IV criteria for functional fecal incontinence[25], the severity of incontinence according to the Continence Grading Scale of Jorge-Wexner et al[26], i.e. a 5-item scoring system, resulting in a score varying from 0 for continence to 20 for complete fecal incontinence.

Data analysis and statistics

We used SPSS version 23.0 for Windows (IBM SPSS Statistics, IBM Corporation, Armonk, NY) for statistical analyses. Proportions were reported as percentages; continuous data were presented either as median with the minimum and maximum in the case of skewed data, or as mean (μ) with standard deviation (SD) for normal distributions. Visual inspection of the distribution was done using Q-Q-plots. Comparisons of continuous data were performed using the Mann-Whitney U test. To assess the effect of changes in the common practice over the time of the study period, the mean age at surgery was plotted against the year of operation and the correlation between both variables was determined with a Spearman rank test and expressed as Spearman's rank correlation rho (*r*).

The association between age at surgery and the odds of mortality, postoperative complications, a permanent stoma, redo pull-through and long term constipation and fecal incontinence, was tested using univariate and multivariate logistic regression and was expressed as Odds Ratio (OR). In multivariate analyses the following covariates were included: length of aganglionosis (short vs long segment disease, in which long segment

disease was defined as aganglionosis, extending proximal to the sigmoid including total colonic aganglionosis), operation technique (for each operation technique that was observed at least 10 times in our sample) and the presence of a temporary stoma. A sensitivity analysis on the relation between age at surgery and the risk of a permanent stoma was separately done in patients without intellectual disability, to assess the bias of patients who received a permanent stoma because of intellectual disability, who may have limited possibilities for bowel management with irrigations. To assess the difference between the extremes of age at surgery, the functional outcomes of patients in the first and last percentile of age at surgery were compared to each other. The relationship between age at surgery and severity of constipation or fecal incontinence was assessed using the Spearman rank test and expressed as Spearman's rank correlation rho (*r*). An alpha level of 0.05 was used as the level of statistical significance.

Ethics

This study had the approval code METc 2013/226 and was performed in compliance with the requirements of the local medical ethics review board. Written informed consent was obtained from each participant

RESULTS

Patient characteristics

Patient characteristics of all 830 of the included patients are listed in sTable 1. A total of 619 patients were invited to answer the questionnaires assessing long-term functional outcomes, of whom 346 responded (56%) (sFigure 1). The follow-up cohort was representative.[21]

Age at pull-through surgery

The median age at surgery was 6.7 months (range 0–270 months) in the total cohort, and slightly lower (6.0 months, range 0–169 months) in the follow-up cohort. Distribution across age groups is shown in sFigure 2. For 42 patients (5%) (of whom 7 responded to the follow-up questionnaire) the exact age at operation could not be reconstructed from the data in the medical records.

There was a significant correlation between the year of surgery (resection of aganglionosis) and age at surgery in all patients, showing earlier resection in the recent years (r=−0.266, p<0.001, Figure 1).

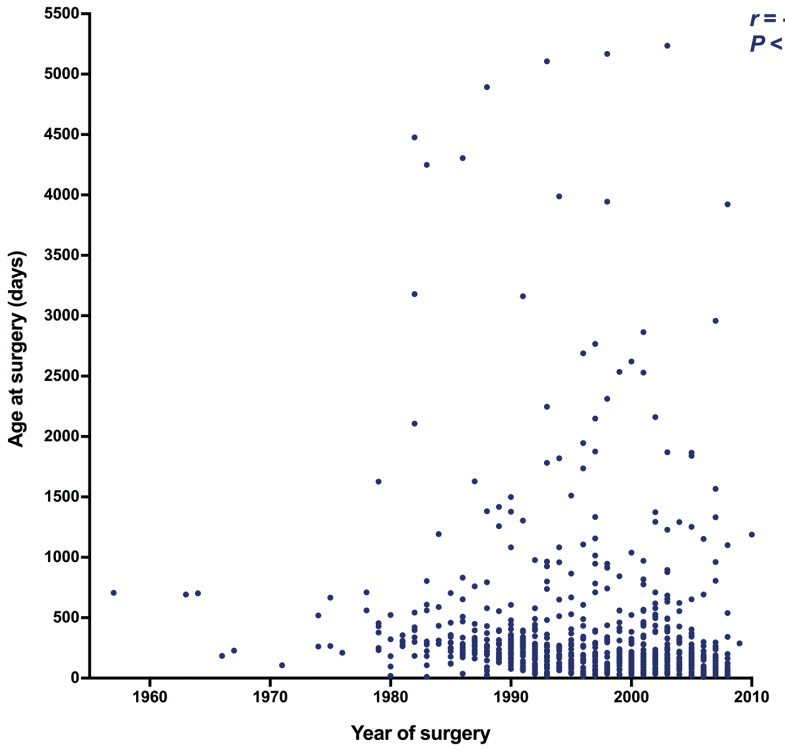

Figure 1 Scatterplot of age at surgery by year of surgery

Mortality, postoperative complications, stomas and redo pull-through

In the total cohort, 43 patients were deceased, accounting for an overall mortality rate of 5%. However, in only 11 (26%) of these patients the mortality was related to HD. The overall postoperative complication rate was 11%. With regard to stomas, 460 of the 830 patients (56%) had a temporary protective stoma and 31 of 830 patients (4%) a permanent stoma. In the total cohort, 51 patients (6%) underwent a redo pull-through (sTable 1). The odds of a permanent stoma increased with 1% for every additional month of the patient's age at surgery, both unadjusted and adjusted for length of disease and operation technique (Table 1). The same applied in the sensitivity analysis with patients without an intellectual disability, both unadjusted and adjusted. The odds of a temporary stoma also increased with 1% for every additional month of the patient's age at surgery, both unadjusted and adjusted for length of disease and operation technique (Table 1). Both the likelihood of a permanent stoma (OR 0.89, 95% CI 0.86–0.93, $p<0.001$) and a temporary stoma (OR 0.86, 95% CI 0.84–0.88, $p<0.001$) were dependent of the year in which resection of aganglionosis took place, with higher odds in earlier years of the study period. Age at surgery was not associated with increased likelihood of mortality, postoperative complications, and redo pull-through (Table 1).

Table 1 Likelihood of survival, complication rate, stomas, or redo-surgery according to age at surgery (in months) within the total cohort (n=830 patients)

	Univariable		Multivariable *(adjusted for type of reconstruction and length of aganglionosis)*	
	Odds ratio (95% CI)	***P-value***	**Odds ratio (95% CI)**	***P-value***
Survival	0.99 (0.97 – 1.02)	0.513	0.99 (0.97 – 1.02)	0.481
Complications within 30 days	1.00 (1.00 – 1.01)	0.272	1.00 (1.00 – 1.01)	0.317
Permanent stoma	**1.01 (1.00 – 1.02)**	**0.019**	**1.01 (1.00 – 1.02)**	**0.014**
Temporary stoma	**1.01 (1.00 – 1.01)**	**0.022**	**1.01 (1.01 – 1.02)**	**0.001**
Reoperation	1.00 (0.99 – 1.01)	0.894	1.00 (0.99 – 1.01)	0.826

Constipation

Multivariable regression analysis showed that age at surgery was not associated with the prevalence of constipation, when adjusted for the length of aganglionosis, the type of reconstruction, and a temporary stoma (Table 2). Age at surgery was also not associated with the severity of constipation (Figure 2A). The median Agachan scores of patients who were in the lowest percentile of age at surgery (e.g. who underwent surgery before 1.7 months of age) were not significantly different from the median scores of patients who were in the highest percentile of age at surgery, i.e. who underwent surgery after at least 31.8 months of age (5.0 vs 5.0, U=495.0, p=0.306).

Fecal incontinence

Multivariable regression analysis showed that age at surgery was not associated with the prevalence of fecal incontinence, when adjusted for the length of aganglionosis, the type of reconstruction, and a temporary stoma (Table 2). Also, the age at surgery was not associated with the severity of incontinence (Figure 2B). The median Wexner scores of patients who were in the lowest percentile of age at surgery (i.e. who underwent surgery before 1.7 months of age) were not significantly different from the median scores of patients who were in the highest percentile of age at surgery, i.e. who underwent surgery after at least 31.8 months of age (3.0 vs 2.0, U=526.0, p=0.514).

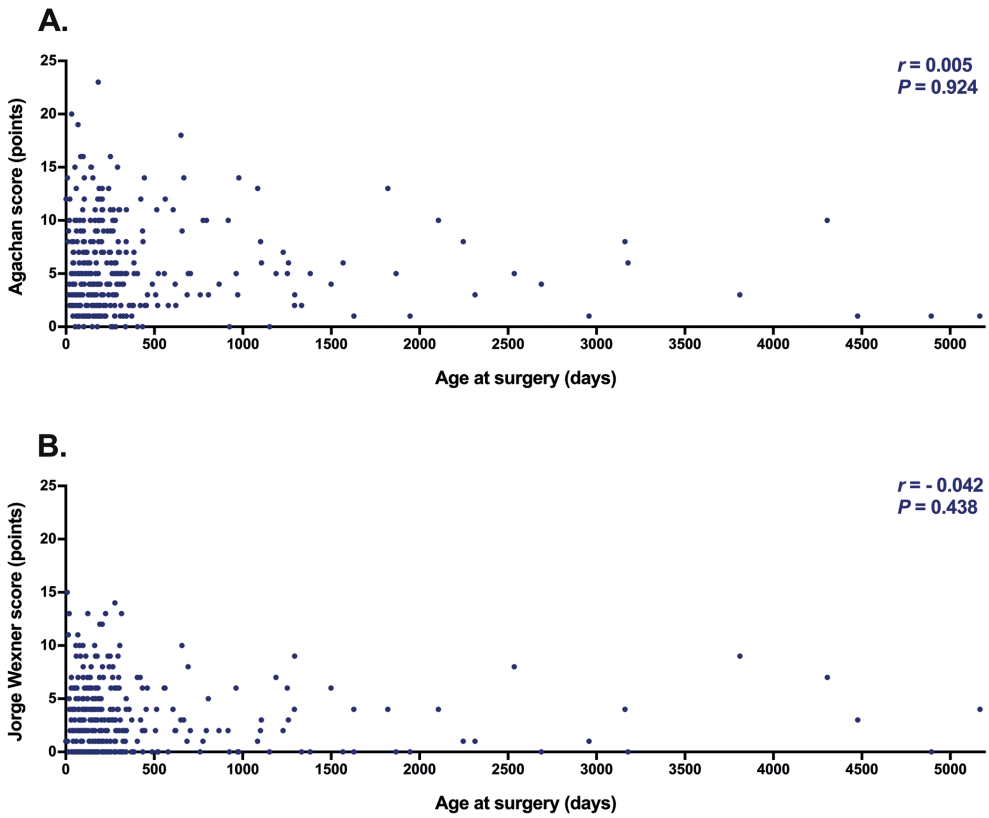

Figure 2 Scatterplot of Achagan and Wexner scores by age at surgery

Table 2 Likelihood of constipation and fecal incontinence by age at surgery (in months) within the follow-up cohort (n=346 patients)

	Univariable		Multivariable *(adjusted for type of reconstruction, length of aganglionosis, and temporary stoma)*	
	Odds ratio (95% CI)	***P-value***	**Odds ratio (95% CI)**	***P-value***
Constipation	1.00 (0.98 – 1.01)	0.613	0.99 (0.98 – 1.01)	0.356
Fecal Incontinence	1.00 (0.98 – 1.01)	0.408	1.00 (0.99 – 1.01)	0.753

Bowel management

Age at surgery was not related to the likelihood of the use of any of these strategies for bowel management in our follow-up sample (data are shown in Supplementary Material, in sTable 2).

DISCUSSION

From this nationwide cohort study in children and adults with Hirschsprung disease we found no evidence that age at surgery is a risk factor for mortality, postoperative complications, redo-pull-through, and long term functional outcomes.

In our sample, higher age at surgery was a risk factor for getting a permanent and temporary stoma. However, we also observed in our sample that the likelihood of a stoma was dependent of the year in which the surgery took place, and we thus think (as also the age at surgery was higher in earlier year of the study period) that the increased risk of a stoma actually reflects this relationship, not an actual increased risk for patients who are older at surgery. Moreover, we noticed that a relatively large number of patients had a temporary protective stoma in our cohort. This may be explained by the fact that three-staged surgery used to be standard practice up to the late nineties, whereas nowadays single-staged surgery is more often practiced.[3] It may also reflect variation in the operation techniques that have been used for restoring bowel continuity, of which some older techniques (including Rehbein) were always done under the protection of a temporary stoma. The small increased risk of a temporary stoma with higher age is as therefore expected. Nowadays patients will only receive a temporary stoma prior to surgery in case surgery is postponed because of total colonic aganglionosis, cardiac comorbidity or a delayed diagnosis.

Our findings were in line with other studies that have reported equal risk of postoperative complications and satisfactory functional outcomes after early and late surgical resection of aganglionic segment.[11,14,17,18,27] However, evidence from previous studies do show some contradictory findings and often group comparisons were used to assess differences in outcomes between groups of different ages, or only patients with a delayed diagnosis were assessed. These group comparisons show large heterogeneity in the cut-off value for age at surgery that is used to compare groups, which reflects the clinical heterogeneity in approach to the age at which pull-through surgery takes place and the randomness of each cut-off value. Patients with a delay in diagnosis form a distinct group of patients with late resection of aganglionosis, in which patients often already have experienced obstructive defecation problems (without bowel management) for a long time prior to surgery, resulting in decompensated bowel, which in turn may be related to poorer functional outcomes after very late surgery.[12,19] In our patients we did not observe poorer functional outcomes after very late surgery, since the patients who underwent very late surgery (i.e., who were in the highest percentile of age at surgery) did not have more severe constipation or fecal incontinence compared to patients who underwent early surgery (i.e., who were in the lowest percentile of age at surgery).

Our findings suggested that age at surgery was no risk factor for any of the outcomes in this study. This indicates that there may be other clinical factors than the factors accounted for in this study that may explain earlier findings that patients with delayed

surgery have worse outcomes in terms of complications and bowel function. One of these factors may be preoperative bowel management. Differences in the rate and frequency of preoperative irrigations or a temporary stoma may account for the differences in outcomes between patients with untreated HD for a longer period of time (e.g. patients with recurrent constipation and an increased the risk of decompensation of the bowel), compared to patients who received adequate rectal irrigation or a stoma prior to pull-through surgery (e.g. those in whom the bowel had time to recover before pull-through surgery was done). A second factor may be the perioperative technical challenges in older patients. Among the specific problems mentioned in patients with decompensated bowel is the mismatch in caliber of the dilated proximal colon and the non-dilated distal rectum, impairing the anastomosis, as well as the increased rigidness and scarring of the pelvis in older patients.[28,29] A third factor explaining differences in outcomes among patients may be the hospital setting, as studies from developing countries (with often greater delays in diagnosis and lesser resources for peri-operative care and follow-up) report even worse outcomes.[16] And a final factor may be, in particular for long-term functional outcome, the influence of psychosocial wellbeing on constipation or incontinence rate and severity.[30,31]

A reason to postpone surgery may be the negative effects of the exposure to anesthetics on the brain, as well as the negative effects of blood loss, hypotension, decreased cerebral flow and hypercapnia during surgical procedures.[10,32-34] When patients are exposed to these negative influences during critical windows of brain development, this may result in impaired neurodevelopmental functioning.[9,33-37] However, the existing evidence from the few well-designed studies with human (especially pediatric) subjects is inconclusive about the potential negative effects of anesthetics on brain development in infants and the existence of critical windows in brain development.

Strengths and limitations

Among the strengths of this study are the large sample size, the long period of follow-up, and the statistical design that was more sensitive to assess the direct influence of age, compared to group comparisons, and the use of validated patient-reported outcomes measures and criteria to measure long term functional outcome. From the field of oncology, we know that patient-reported outcome measurements are more sensitive to measure symptoms than clinician-reported outcome measurements, and that clinician-reported data is often missing or heterogeneously described in medical records.[38-40] The questionnaires we used to assess defecation and continence, although they may be time-consuming, are shown to have good validity and acceptable reproducibility.[22]

Our findings however, have to be interpreted in the light of some limitations. The first limitation concerns the cross-sectional design of this study over a long period of time. The cross-sectional design accounted for a wide range of years, from the 1960s up till the current decade, in which improvements have been made in the process of diagnosis and surgical treatment of patients with HD. Although these improvements are believed to have

resulted in improvements in survival, complication rate and functional outcome, it might also have introduced a bias in our study. The changes in the operation techniques that were used may explain the trend towards earlier resection in our sample. There were patients in our sample who were among the first patients who underwent laparoscopic-assisted pull-through and pull-through with a completely transanal approach, as well as patients who underwent operations with techniques that are currently not used anymore in the Netherlands, including the Rehbein and Soave pull-through. Differences in experience, learning curves for new techniques and worse outcomes after currently omitted techniques may have affected our outcome findings. However, our findings indicated no moderation by operation techniques of the tested effects on age at surgery in multivariate analysis.

A second limitation is the loss to follow-up, a form of selection bias for which follow-up studies are always vulnerable. Patients with good clinical outcomes are more likely to be lost to follow-up and less likely to participate in research projects. Although the response rate to the questionnaires in the current study was satisfactory, a dropout analysis showed more dropout of adult patients compared to children, which might account for bias in the interpretation of problems in adulthood.

A final limitation of this study is that we used the adult Rome IV criteria, while part of the study population consisted of children. The Rome IV criteria have originally been developed to assess constipation in the absence of physiological or anatomical abnormalities. However, as no current validated criteria for constipation in patients with anatomical abnormalities are available, the Rome IV criteria were considered to be the best available alternative. They are well-known, validated and widely used.[25,41]

In conclusion, we found in this study that age at surgery was no risk factor for mortality, postoperative complications, and redo pull-through, and no risk factor for constipation or fecal incontinence rate and severity.

ACKNOWLEDGEMENTS

The authors wish to thank the Hirschsprung patients for completing the questionnaires. The patient support association for Hirschsprung disease in the Netherlands for collaboration with this research project. The authors also wish to thank I.A.M. ten Vaarwerk and E. Visser for their help with the digital questionnaires in RoQua, an online tool for routine outcome monitoring. No preregistration exists for the reported studies reported in this article. No funding was received. There are no conflicts of interest to disclose.

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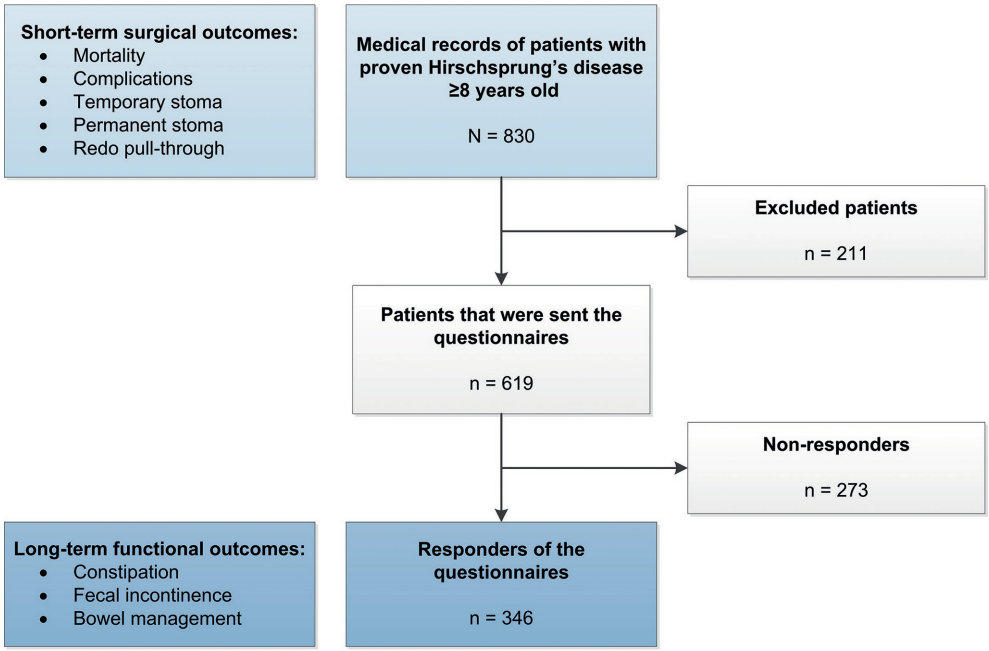
SUPPORTING DIGITAL CONTENT

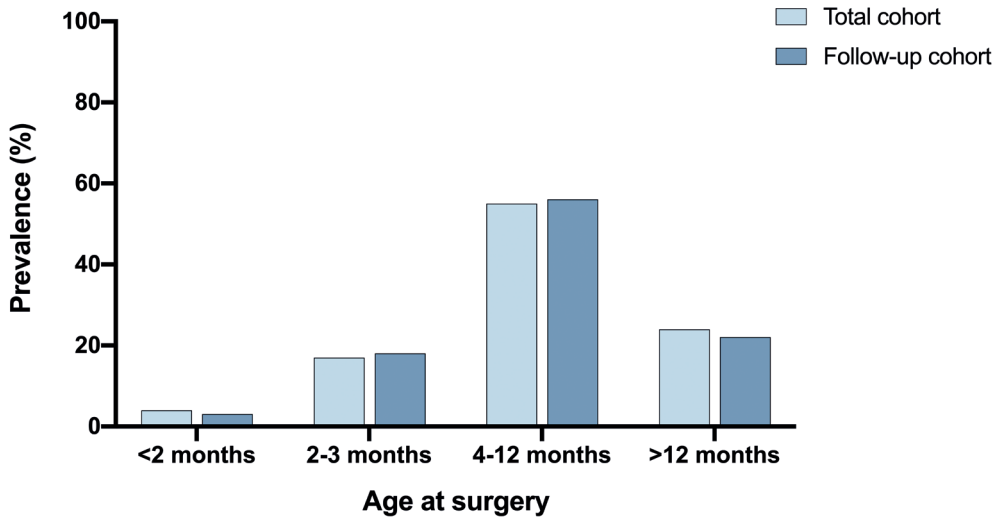


SDC Figure 1 Flowchart of the included patients and outcome measures

SDC Table 1 Patient characteristics of the total cohort and the follow-up cohort

	Total cohort (n = 830)	**Follow-up cohort (n = 346)**
Age at time of follow-up study in years, median (range) [1]	20.0 (8 – 54)	17.5 (8 – 45)
Age at surgery in months, *median (range)* [2]	6.7 (0.3 – 270.7)	6.0 (0.3 – 169.4)
Sex ratio (M:F)	641 : 189	274 : 72
Length of aganglionosis, *n (%)* [3]		
• Ultrashort	17 (2.1)	10 (2.9)
• Rectosigmoid	664 (80.5)	282 (81.5)
• Long segment	71 (8.6)	29 (8.4)
• Total colonic	73 (8.8)	25 (7.2)
Type of reconstruction, *n (%)* [4]		
• Duhamel	446 (59.6)	210 (62.3)
• Soave	2 (0.3)	1 (0.3)
• Rehbein	200 (25.6)	73 (21.7)
• Swenson	4 (0.5)	1 (0.3)
• Laparoscopic assisted pullthrough	80 (10.2)	40 (11.9)
• TERPT	30 (3.8)	12 (3.6)
Temporarily protective stoma, *n (%)* [5]	460 (55.8)	170 (49.1)
Permanent stoma, *n (%)*	31 (3.7)	-
Postoperative complication < 30 days, *n (%)* [6]	90 (11.3)	37 (10.9)
Re-operation, *n (%)* [7]	51 (6.2)	23 (6.6)

Note.
[1] Age at time of study is missing for 119 cases in the follow-up cohort.
[2] Age at time of surgery is missing for 42 cases in the total cohort and 7 cases in the follow-up cohort.
[3] Length of aganglionosis is missing for 5 cases in the total cohort.
[4] Type of reconstruction is missing for 48 cases in the total cohort and 9 cases in the follow-up cohort; TERPT = transanal endorectal pull-through
[5] Temporarily protective stoma is missing for 6 cases in the total cohort.
[6] Postoperative complication is missing for 37 cases in the total cohort and 6 cases in the follow-up cohort.
[7] Re-operation is missing for 5 cases in the total cohort.



SDC Figure 2 Distribution of patients over age-groups in the total cohort (n=830) and the follow-up cohort (n=346) in each age-category

SDC Table 2 The use of postoperative bowel management and the likelihood of use according to age at surgery (in months) within the follow-up cohort (n=346 patients)

	Use of bowel management in follow-up	Likelihood of the use of postoperative bowel management according to age at surgery			
		Univariate		Multivariate *(adjusted for type of reconstruction, length of aganglionosis, and temporary stoma)*	
	N (%)	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Management of constipation					
Use of laxatives [1]	62 (18)	1.00 (0.98 – 1.01)	0.669	1.00 (0.98 – 1.01)	0.689
Use of diet to make stool more loose	27 (8)	1.01 (1.00 – 1.02)	0.116	1.01 (1.00 – 1.02)	0.131
Use of enemas	19 (6)	0.99 (0.96 – 1.02)	0.453	0.99 (0.96 – 1.02)	0.439
Use of rectal irrigation for constipation	58 (17)	1.00 (0.99 – 1.01)	0.965	1.00 (0.99 – 1.01)	0.840
Management of fecal incontinence					
Use of antidiarrheal medication [1]	3 (1)	0.99 (0.92 – 1.07)	0.795	0.99 (0.93 – 1.06)	0.815
Use of diet to make stool more lumpy [2]	10 (3)	1.01 (0.99 – 1.03)	0.487	1.02 (0.99 – 1.04)	0.200
Use of rectal irrigation for fecal incontinence [2]	22 (6)	1.01 (0.99 – 1.02)	0.576	1.01 (0.99 – 1.02)	0.568

Note.
[1] Medication had to be taken at least several times per month
[2] Missing for 179 cases in the follow-up cohort.

PART 2

Multidisciplinary outcomes in patients with surgical congenital malformations

CHAPTER 7

Long-term outcome and quality of life in patients with total colonic aganglionosis in the Netherlands

D. Roorda, M.J. Witvliet, L.M. Wellens, D.V. Schulten, C.E.J. Sloots, I. de Blaauw, P.M.A. Broens, J. Oosterlaan, L.W.E. van Heurn, A.F.W. van der Steeg

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ABSTRACT

Aim

Total colonic aganglionosis (TCA) is a severe form of Hirschsprung's Disease (HD) associated with a high morbidity. This study assessed long-term functional outcome and quality of life (QoL) of patients with TCA in a national consecutive cohort.

Methods

Surgical and demographic data in the medical records of all patients (n = 53) diagnosed with TCA between 1995 and 2015 were reviewed. Functional outcome of all nonsyndromal patients, aged ≥ 4 years (n = 35) was assessed using a questionnaire and in medical records. Generic and disease-specific QoL was assessed using standardized validated questionnaires.

Results

Of 35 patients eligible for follow-up, 18 (51%) responded to the questionnaires. They were aged 4-19 years. A Duhamel procedure was performed in 67% of these patients and a Rehbein procedure was performed in 33%. In the questionnaire, 65% of the patients reported constipation, 47% faecal incontinence and 53% soiling. Moreover, 18% of patients used bowel management (flushing or laxatives) and 29% an adapted diet only. Children and adolescents with TCA had worse perception of their general health and were more limited by bodily pain and discomfort compared with healthy peers. Their quality of life is influenced most by frequent complaints of diarrhoea and other physical symptoms.

Conclusion

Children and adolescents with TCA report lower health-related quality of life compared with healthy peers, especially in the physical domain. We suggest standardized follow-up and prospective longitudinal future research on functionality and QoL of these patients.

INTRODUCTION

Hirschsprung disease (HD) is a congenital cause of neonatal intestinal obstruction (incidence 1:5000).[1,2] In most patients with HD, the aganglionic segment is limited to the rectosigmoid region. Five to 12 % of patients with HD are diagnosed with total colonic aganglionosis (TCA). [1,2] TCA is associated with a higher morbidity and mortality compared to rectosigmoid HD.[3-5] The primary treatment of HD is surgical resection of the aganglionic segment and reconstruction of the continuity of the intestinal tract. [6-10] Over the past decades, treatment has been improved and mortality decreased, but patients with TCA often experience functional complaints such as soiling, faecal incontinence, severe motility problems and enterocolitis.[3,11-19] It is unclear if these functional complaints result in decreased quality of life (QoL).[20] QoL is an important medical endpoint describing one's satisfaction with his or her functioning and is thus subjective.[20] Health-related QoL describes satisfaction with functioning related to health, whereas disease-specific QoL describes the subjective experience of the impact of disease-specific complaints.

Patients with TCA seem to have more emotional/behavioural problems and lower self-esteem than patients with short-segment HD. [11,21] However, health-related QoL in patients with TCA remains largely unclear because it has not been assessed with validated questionnaires.[11,12] Disease-specific QoL has not previously been described. The aim of this study was to describe demographic and surgical characteristics of a national consecutive cohort in the Netherlands and to assess the long-term functional outcome, health-related and disease-specific QoL of nonsyndromal patients with TCA, aged ≥ 4 years.

METHODS

Patient population

Eligible for this study were children with TCA (n = 53) in one of the six paediatric surgical centres in the Netherlands, between January 1995 and July 2015.

Patients suspected of TCA based on clinical symptoms such as a distended abdomen, constipation, vomiting or failure to thrive underwent routine diagnostics, including a contrast enema, but diagnosis was based on histological findings (with acetylcholine-esterase staining to the end of 2011 and calretinin since the start of 2012). When suspicion of TCA was high, patients received a diverting ileostomy before definitive resection of the aganglionic segment and histological colon mapping took place, including histological investigation of the ileostomy. If the level of aganglionosis was not clear during definitive surgical procedure, frozen sections were sent for histological investigation to determine this.

Excluded from follow-up analysis were all patients aged < 4 years (assuming they had not yet finished potty-training) or those with an associated syndrome, as well as patients who had died or had migrated abroad at the time the study took place.

Measures

Sample descriptives

The medical records of all children (n = 53) were analysed to assess patient characteristics (survival, age at time of study, sex, gestational age, birthweight, family history and associated syndromes), as well as to determine symptoms at time of presentation, results of histological investigation for diagnosis and type of operation.

Functional outcome in follow-up

Functional outcome was assessed from the medical records of patients eligible for follow-up (n = 35). Records containing annual updates were considered complete. Involuntary loss of stools was considered to be faecal incontinence, loss of smears of faeces to be soiling. Complaints present at any point in the follow-up were considered as prevalent functional problems. Enterocolitis was considered as present when clinical symptoms of fever and abdominal distension were present necessitating hospital admittance with (intravenous) antibiotics for at least 2 days. Items reporting frequency of complaints in the Hirschsprung Disease/Anorectal Malformation Quality of Life questionnaire (HAQL) were used to assess functional outcomes in the follow-up.

Health-related QoL

The Child Health Questionnaire-Parent Form 50 (CHQ-PF50; in children aged 4-7 years), the self-reported Child Health Questionnaire-Child Form 87 (CHQ-CF87; in children aged 8-17 years) or the World Health Organisation Quality of Life 100 item Questionnaire (WHOQOL-100; in patients aged 18 years or older) were used to measure generic QoL by either parent proxy (CHQ-PF50) or patient report (CHQ-CF87 and WHOQOL-100). [22-24]

The CHQ contains 50 or 87 items, assessing QoL in 15 domains (global health, physical functioning, role/social limitations: emotional, behavioural and physical, bodily pain and discomfort, behaviour, mental health, self-esteem, health perception, changes in health, parental impact emotional and in time, family activities and family cohesion). Items are scored on a 5-point Likert scale. Following the CHQ Manual, scores were transformed to a score of 0 – 100, with higher scores representing better QoL.[25] When parent and self-report yielded the same domain scores, these were pooled and compared with normative data. The reliability of the CHQ was acceptable: Cronbach's alpha was > 0.70 on all scales except physical functioning (0.56).[22,23]

The WHOQOL-100 assessment instrument is a cross-culturally validated questionnaire and contains 100-items, assessing 24 facets (based on four items) in six domains of health (physical, psychological, level of independence, social relationships, environment and spiritual) and one facet on health in general. Items are scored on a 4-point Likert scale, resulting in facet and domain scores ranging from 4 to 20, with higher scores representing better QoL. With Crohnbach's alpha ranging from 0.65 to 0.93, the reliability of this instrument is acceptable.[24]

Disease-specific QoL

The HAQL questionnaire is the only disease-specific QoL questionnaire for HD.[26] It contains 60 items (parent-report) or 63 items (self-report) assessing domains of disease-related impact on QoL (laxative diet, constipating diet, diarrhoea, constipation, faecal continence, urinary continence, social and emotional functioning, body image and physical symptoms. Each item consists of an a-item assessing frequency of complaints scored on a 4-point Likert scale, with a score of 1 representing 'no complaints' and a score of 4 indicating 'very often'. When complaints are present, the b-item assesses impact, also scored on a 4-point Likert Scale, with a score of 1 indicating 'a little impact' and a score of 4 indicating 'a lot of impact'. No normative data are available for the HAQL. Therefore average subscale scores (of 1-4) on frequency and impact were used as dependent measures. The reliability of this instrument is acceptable, with Cronbach's alpha ranging from 0.62 to 0.91 for children (aged 8-11 years), from 0.69 to 0.82 for adolescents (aged 12-16 years) and from 0.57 to 0.91 for adults.[26,27]

Procedure

All six paediatric surgical centres in the Netherlands were approached for participation. Medical records were reviewed and patients eligible for follow-up were sent a demographic questionnaire and two validated QoL questionnaires - one assessing health-related QoL and one assessing disease-specific QoL. Approval of the study design was obtained from the Medical Ethics Committee. Informed consent was obtained from all patients (aged > 12 years) and/or parents who completed the questionnaires.

Statistical analysis

Statistical analysis was performed using SPSS 23 for Windows.[28] For the total cohort, dependent measures were survival, age, gestational age, birthweight, positive family history, associated anomalies and length of resected bowel, which were presented as proportions. These characteristics were compared, using Fisher's exact test, between responder and nonresponders patients eligible for follow-up. Functional outcomes in medical records were considered as missing if records were incomplete or if not explicitly described as absent or present. Scores on QoL subscales were compared with reference scores of healthy peers using the one sample *t*-test. Cohen's d was calculated to quantify the effect sizes (except for the HAQL, as no normative data were available). Missing subscale scores were estimated using regression, with age, sex and other scale scores as predictors. Values of $P < 0.05$ were considered as statistically significant.

RESULTS

Sample characteristics

Demographic characteristics of all patients with TCA in the Netherlands are reported in Table 1. Corrective surgery was performed at a median (range) age of 5.5 months (1-78) months. In 23 patients a complete colectomy was performed and in 30 patients the colectomy was extended with resection of an ileal aganglionic segment. After resection, reconstruction took place with a Duhamel procedure in 31 (58%) patients, a Rehbein procedure in 13 (24%) and a transanal endorectal pull through (TEPT) in six (11%). One patient died before corrective surgery. Two patients received another type of reconstruction.

Before definitive surgery, 44 (83%) patients received a diverting ileostomy. Six patients received primary correction (four Duhamel and two Rehbein). Three patients (one after Duhamel, one after Rehbein and one after subtotal colectomy without primary anastomosis) kept their stoma permanently due to long-term complications.

Two patients had died at time of the study: one of meningitis and the other of sudden infant death syndrome. Seven patients had an associated syndrome, three patients had migrated and six patients were aged 0-3 years, leaving a total of 35 patients eligible for follow-up.

Eighteen (51%) of the 35 questionnaires were returned after a median (range) follow-up period of 11 (4-19) years. Of these 18 patients, 10 (56%) were aged 4-11 years, four (22%) were aged 12-17 and four (22%) were aged 18 years or older. A Duhamel procedure was performed in 12 (67%) patients and a Rehbein procedure in six (33%). There were no statistically significant differences (all values of P were > 0.18) between responders and nonresponders in length of follow-up, baseline characteristics (survival, age at time of study, sex, gestational age, birthweight, family history and associated syndromes) and length of aganglionic segment resected.

Functional outcome (medical records)

Functional outcomes were assessed in medical records after a median (range) of 14 (4-26) years. The records of eight (45%) patients reported involuntary loss of stools (in six patients this occurred only at night). Recorded data did not allow a distinction to be made between soiling and faecal incontinence. Eight (31%) patients reported constipation; in four this required readmission for intensive wash-outs. Ten (40%) patients reported anal obstruction, of whom six were treated with dilatations and four with botox therapy. The records reported readmission of 11 (38%) patients with small bowel obstruction; all were treated conservatively. Three (12%) patients reported the use of rectal irrigation and six (25%) reported the use of laxatives. In 19 (58%) patients, the records reported one or more episodes of enterocolitis.

Table 1 Demographics of all patients with total colonic aganglionosis (TCA) (n = 53) in the Netherlands

Characteristic		Patients with TCA
Gender	male female	41 12
Survival		51
Age in years	0-3 4-11 12-17 18+	 6 19 20 8
Extreme low birth weight (<2400gr)		7
Premature (<37 weeks)		11
Positive family history		10
Associated Syndrome	Down Syndrome Klinefelter syndrome Haddad syndrome Bardet Biedl Syndrome Translocation 20-21	2 1 2 1 1
Aganglionic Bowel *	Total colon Colon and distal ileum Length aganglionosis (median, IQR)	23 30 52 (± 15 cm)
Surgery ** Stoma ***	Duhamel Rehbein TEPT Other Primary correction Defunctioning stoma before definitive correction Definitive stoma	31 12 6 2 5 14 3

Note.
* There were two outliers with aganglionotic bowel > 90cm
** 1 patient died before receiving definitive procedure
*** In 11 patients data was missing

Table 2 Functional problems of non-syndromal patients (n = 17) with total colonic aganglionosis (TCA) aged ≥4 years [based on follow-up data as assessed by parent or self-report (using the Hirschsprung Disease/ Anorectal Malformation Quality of Life (HAQL) Questionnaire)]

Functional problems of patients without a stoma	Proportion of patients
Soiling	9/17
Faecal incontinence	8/17
Constipation	13/17
Loose stools >4x / day (at least one day/week)	15/17 4/15
Use of bowel management Rectal irrigation only Laxatives only Diet only Combination	10/17 3/17 1/17 5/17 1/17

Functional outcome (questionnaires)

Questionnaire-assessed functional outcomes of respondents (n = 18) are reported in Table 2. One patient, aged 16 years, had a definitive ileostomy at the time of this study. This patient reported no problem with stoma leakage, used no laxatives or diet adaptation, but did describe redness of the skin around his stoma. Eight patients did not report on every item in the questionnaire assessing functional outcome, but items that were reported were used in the analysis.

Eleven patients reported complaints of abdominal pain (11/17), of which three reported that these occured 'often'. Eight (8/17) patients reported involuntary loss of stools (four during the day only, three at night only and one both during the day and at night). In one patient, involuntary loss of stools occurred only when provoked by physical activities, emotions, coughing or sneezing. Soiling was reported by nine (9/17) patients, for whom this occurred only at night in six. Four patients reported complaints of both soiling and faecal incontinence, whilst five patients reported soiling only.

Fifteen (15/16) patients reported loose stools on a daily basis; this was reported to occur with a frequency of more than four times a day for four (4/15) patients. Dietary measures to make stools more solid were taken by three (3/17) patients.

Thirteen (13/17) patients reported complaints of constipation. Seven (7/17) patients reported a defecation frequency of less than once a week. Twelve (12/17) patients reported complaints of flatulence; nine without feeling it first.

Thirteen patients reported both loose stools as well as constipation, suggesting the presence of either overflow or overenthusiastic laxative use.

Three (3/17) patients reported the use of rectal irrigation for bowel management; for two patients this was to prevent involuntary loss of stools; for another patient this was to treat constipation. Dietary measures to soften stools were taken by five (5/17) patients. One patient used both rectal irrigation as well as diet adaptations.

Generic QoL

Results for generic QoL are presented in Table 3. Compared with an age-matched reference group of healthy peers, patients with TCA reported significantly worse general health perception (Cohen's d = 1.12, $P < 0.01$). Especially in the physical domain they experienced lower QoL as a result of the limitations in functioning from bodily pain or discomfort (Cohen's d = 0.77, $P = 0.02$).

In the psychological domain, patients with TCA reported self-esteem comparable with the normative population (Cohen's d = 0.17, $P = 0.54$). Also, the reported mental health and behaviour of patients with TCA did not differ from those of healthy peers.

In the social domain, no differences were observed for the impact of physical and emotional problems on the patients' social roles. Parent-reported satisfaction with their time and energy was comparable with that of the normative population.

Table 3 Parent-reported [Child Health Questionnaire-Parent Form 50 (CHQ-PF50)] and self-reported [Child Health Questionnaire-Child Form 87 (CHQ-CF87)] health-related quality of patients with total colonic aganglionosis (TCA)

Scale	Mean scores normative sample (SD)	TCA patients (n=14) Mean (SD)	*P*	*Cohen's d*
Overall				
General Health Perception	73.0 (17.3)	53.5 (23,2)	<0.01	1.12
Physical				
Physical functioning	96.1 (13.9)	88.2 (15.6)	0.08	0.57
Bodily Pain / Discomfort	81.7 (19.0)	67.1 (20,2)	0.02	0.77
Psychological				
Behavior	75.6 (16.7)	78.4 (12,3)	0.42	-0.17
Mental Health	78.5 (13.2)	80.2 (8,9)	0.48	-0.13
Self Esteem	79.8 (17.5)	78,1 (11,2)	0.59	0.10
Social				
Role/Social limitations – Phyiscal	93.6 (18.6)	92.8 (14.2)	0.85	0.04
Role/Social limitations – Emotional behavioral	92.5 (18.6)	95.6 (8.5)	0.19	-0.17
Parental Impact – Emotional	80.3 (19.1)	84.5 (16.3)	0.52	-0.22
Parental Impact – Time	87.8 (19.9)	88.9 (15.7)	0.86	-0.06
Family Activities	89.7 (18.6)	80.4 (23.9)	0.17	0.50
Family Cohesion	72.3 (21.6)	68.6 (22,3)	0.54	0.17

Note. Scales range from 0-100 with higher scores indicating better perceived functioning

The WHOQOL-100 was completed by four adult patients. All scores of individual patients fell between ± 1 SD of the normative mean score.

Disease specific QoL

Results for disease specific QoL are presented in Table 4. Patients with TCA experienced inconvenience as a result of diarrhoea and other physical symptoms, mainly because of the high frequency with which these complaints occur (average frequency scores were 3.0 respectively 2.2, on a 1-4 Likert Scale). Although less frequently described (average frequency score of 1.1) complaints of emotional dysfunctioning were reported to have a higher impact (average impact score of 2.0, on a 1-4 Likert Scale) when present.

Table 4 Parent- and self-reported disease specific quality of life scores [determined using the Hirshsprung Disease / Anorectal Malformation Quality of Life (HAQL) questionnaire] of patients with total colonic aganglionosis (TCA)

Disease specific quality of life Hirschsprung and anorectal malformations quality of life questionnaire (haql)		
Scale	**Average item-scores (sd) on frequency of complaints of tca patients in follow-up * (n=18)**	**Average item-scores (range) on impact of complaints when present ** (n=18)**
Laxative diet	1.3 (0.5)	1.4 (0.9)
Constipating diet	1.3 (0.5)	1.7 (0.8)
Diarrhea	3.0 (1.0)	1.5 (0.8)
Constipation	1.2 (0.5)	1.3 (0.8)
Faecal incontinence	1.7 (0.7)	1.7 (0.8)
Urinary incontinence	1.2 (0.5)	1.8 (0.8)
Emotional functioning	1.1 (0.3)	2.0 (0.9)
Social functioning	1.3 (0.3)	1.6 (0.8)
Body image	1.2 (0.4)	1.9 (0.8)
Physical symptoms	2.2 (0.5)	1.6 (0.5)
Total	1.6 (0.3)	1.6 (0.6)

* scores on frequency with higher scores representing more frequent complaints (ranging from 1 'never' to 4 'very often).
** scores on impact when complaints are present with higher scores representing more impact (ranging from 1 'no impact' to 4 'very much impact').

DISCUSSION

Total colonic aganglionosis (TCA) is a severe form of HD that is accompanied by functional problems varying from severe constipation to faecal incontinence. Patients often need bowel management such as rectal irrigation, laxatives or diet adaptations. In our population, 65% of the patients reported constipation, 47% reported faecal incontinence and 53% reported soiling. This is comparable with, or somewhat higher than, reports in other studies. [2,3,5,11-19,29-31] The use of bowel management was reported by 18% of our patients and an adapted diet by 29%. Functional problems were reported more often in questionnaires than in medical records. Patients with few functional problems are often discharged from follow up or not transitioned to adult care, resulting in missing data and a possible overestimation of functional problems. Data from medical records should thus be interpreted with care. There is also a lack in standardization of interviewing patients and patients might feel more comfortable reporting about embarrassing problems in questionnaires [32]. The use of standardized questionnaires may result in a more accurate assessment of functional problems.

Children and adolescents with TCA report lower health-related QoL compared with normative data, especially in the physical domain. Health-related QoL in patients with HD has been described in a limited number of studies, often assessed without the use of validated questionnaires. [11,33-39] The only study reporting on QoL in patients with TCA, also reported good QoL.[11] Disease-specific QoL in our cohort was most influenced by frequent complaints of diarrhoea and other physical symptoms and has not been described previously in patients with TCA.

Although we only studied four adults, they showed satisfactory QoL in all domains compared with normative data. Other studies also suggest improvement of QoL in adulthood.[11,33-38]. However, longitudinal measuring of QoL can create a response shift bias because adjusting expectations can lead to a change in internal values and conceptualization of QoL. On the other hand, increasing possibilities for lifestyle adaptations in adulthood can result in better QoL.[27,40]

In our population patients with TCA reported self-esteem comparable with that of healthy peers and good family cohesion, which can have a supportive and protective influence on a child's psychosocial development.[41] They reported no elevated levels of emotional/behavioural problems. Other studies suggested lower self-esteem and more behavioural problems.[21] Although in patients with HD there is no evidence for higher rates of psychiatric morbidity [40], we believe that it is important to monitor psychological well-being of patients with TCA and their parents and provide psychosocial support.

Functional problems were present in all age groups, as also suggested by others [12,13,31,33,37,42], whereas some studies suggest a decrease of functional problems over time.[16,18] As a result of male dominance in patients with TCA (4:1), also described by other studies[2], comparison could not be made between male and female patients.

In addition, literature suggests other problems in patients with TCA. For instance, growth can be influenced by TCA, with 25% of the patients having a body weight below the second percentile in childhood.[13,17] In adolescents and adults, weight (and especially height) catches up with those of healthy peers.[17]

Patients with HD can also experience urinary dysfunction (with enuresis in 25%, more nocturnal than in daytime) [43] and sexual dysfunction (11% of male and 53% of female patients).[44] Growth, urinary and sexual dysfunction were not assessed in this study because of our focus on bowel function.

Total colonic aganglionosis is treated with surgical correction, for which different techniques may be used.[8] In the Duhamel procedure, the distal part of the aganglionic bowel is left *in situ*, functioning as a pouch, aiming to preserve to some extent the function of resorption by the colon. In the Rehbein procedure the abdominal portion of the aganglionic bowel is resected, but the rectal segment is left *in situ*. In the TEPT procedure, an ileoanal anastomosis is created, aiming to reduce the risk of faecal stasis and development of enterocolitis. There is currently no consensus on which technique

may be superior in patients with TCA [6-10,12,19,29,30,34,45]. In this cohort we could not test the difference between the different techniques because of the limited number of patients.

Other limitations of the present study are the distribution of age and the cross-sectional design. We thus initiated standardized multidisciplinary follow-up and prospective longitudinal studies with the use of standardized and validated questionnaires to compare treatment strategies and to assess longitudinal trends in functional outcome and QoL of patients with TCA.

Conclusion

Children and adolescents with TCA experienced substantial functional problems in follow-up. They are less satisfied with their general health, are more limited by bodily pain and discomfort. We recommend an international prospective longitudinal follow-up study on functionality and QoL of patients with TCA with standardized validated questionnaires.

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CHAPTER 8

Neurodevelopmental outcome of patients with congenital gastrointestinal malformations: a systematic review and meta-analysis

D. Roorda, M. Königs, L.S. Eeftinck Schattenkerk, A.F.W. van der Steeg, L.W.E. van Heurn, J. Oosterlaan

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ABSTRACT

Aim

Children with congenital gastrointestinal malformations may be at risk of neurodevelopmental impairment due to challenges to the developing brain, including perioperative haemodynamic changes, exposure to anaesthetics and postoperative inflammatory influences. This study aggregates existing evidence on neurodevelopmental outcome in these patients using meta-analysis.

Method

Pubmed, Embase and Web of Science were searched for peer-reviewed articles published until October 2019. Out of the 5316 unique articles that were identified, 47 studies met the inclusion criteria and were included. Standardized mean differences (Cohen's d) between cognitive, motor and language outcome of patients with congenital gastrointestinal malformations and normative data (39 studies) or the studies' control group (8 studies) were aggregated across studies using random-effects meta-analysis. The value of (clinical) moderators was studied using meta-regression and diagnostic subgroups were compared.

Results

The 47 included studies encompassed 62 cohorts, representing 2312 patients. Children with congenital gastrointestinal malformations had small-sized cognitive impairment (d=-0.435, p<0.001; 95%CI -0.567 to -0.302), medium-sized motor impairment (d=-0.610, p<0.001; 95%CI -0.769 to -0.451) and medium-sized language impairment (d=-0.670, p<0.001; 95%CI -0.914 to -0.425). Patients with short bowel syndrome had worse motor outcome. Neurodevelopmental outcome was related to the number of surgeries and length of total hospital stay, while no relations were observed with gestational age, birth weight, age and sex.

Interpretation

This study shows that children with congenital gastrointestinal malformations exhibit impairments in neurodevelopmental outcome, highlighting the need for routine screening of neurodevelopment during follow-up.

INTRODUCTION

Congenital gastrointestinal malformations (i.e., esophageal atresia, gastroschisis, omphalocele, intestinal atresia, Hirschsprung's disease and anorectal malformations), are relatively uncommon conditions with a total prevalence of about 15 per 10 000 European births a year.[1] Although survival in these patients has improved over the past decades, morbidity remains high.[2-8] Recent evidence suggests that there may also be an impact on the central nervous system of these patients[9].

The available literature provides evidence for several pathways implicated in congenital gastrointestinal malformations that may contribute to a negative impact on the developing central nervous system: (1) genetic abnormalities[10,11]; (2) perinatal influences, such as maternal smoking,[12] use of medication,[13,14] preterm birth[15] and low birthweight;[15] (3) early, long and/or repeated exposure to anaesthetics necessary for surgical correction(s)[16-18]; (4) perioperative haemodynamics and respiratory functioning[19-21]; (5) postoperative inflammatory challenges[22,23]; and (6) poor nutritional status that can lead to an altered microbiome, influencing the developing brain through the gut-brain axis. [24-27] All these harmful challenges to the central nervous system may lead to neurodevelopmental impairment, which in turn may interfere with development in important domains of functioning, including academic achievement, behavioural functioning and social and economic well-being.[28-30]

The primary aim of the current systematic review is to quantitatively aggregate all available empirical evidence on the effects of having a congenital gastrointestinal malformation on neurodevelopment using meta-analysis. This review focuses on congenital gastrointestinal malformations other than congenital diaphragmatic hernia (CDH), to not include the confounding effect of the pulmonary comorbidity in patients with CDH,[31-33] which may require treatment with extracorporeal membrane oxygenation (ECMO). [34,35] The secondary aim is to study differences between specific types of congenital gastrointestinal malformations and the contribution of possible moderating factors for neurodevelopmental impairment, using meta-regression.

METHODS

This study was performed according to the PRISMA Guidelines (see Supplementary Material).[36]

Search and Selection

The search strategy combined three groups of search terms and their equivalents: (1) terms related to the congenital malformations of interest, (2) terms defining age groups, (3) terms defining (the validated measures of) the outcomes. The full search strategy can

be found in the online supplemental material. PubMed, Embase and Web of Sciences were searched using both simple search terms and hierarchical family forms (e.g., Medical Subject Headings, Thesaurus, Emtree). The reference lists of eligible articles were also screened for additional articles. The last search was conducted in October 2019.

A flow diagram of the study search and selection is provided in Figure 1. A total of 6675 records were identified corresponding to 5316 unique articles. Two authors (DR and LES) independently assessed each article for eligibility using Covidence, an online tool for systematic reviews.[37] Conflicts in the selection process were solved by consensus, or a third party was consulted.

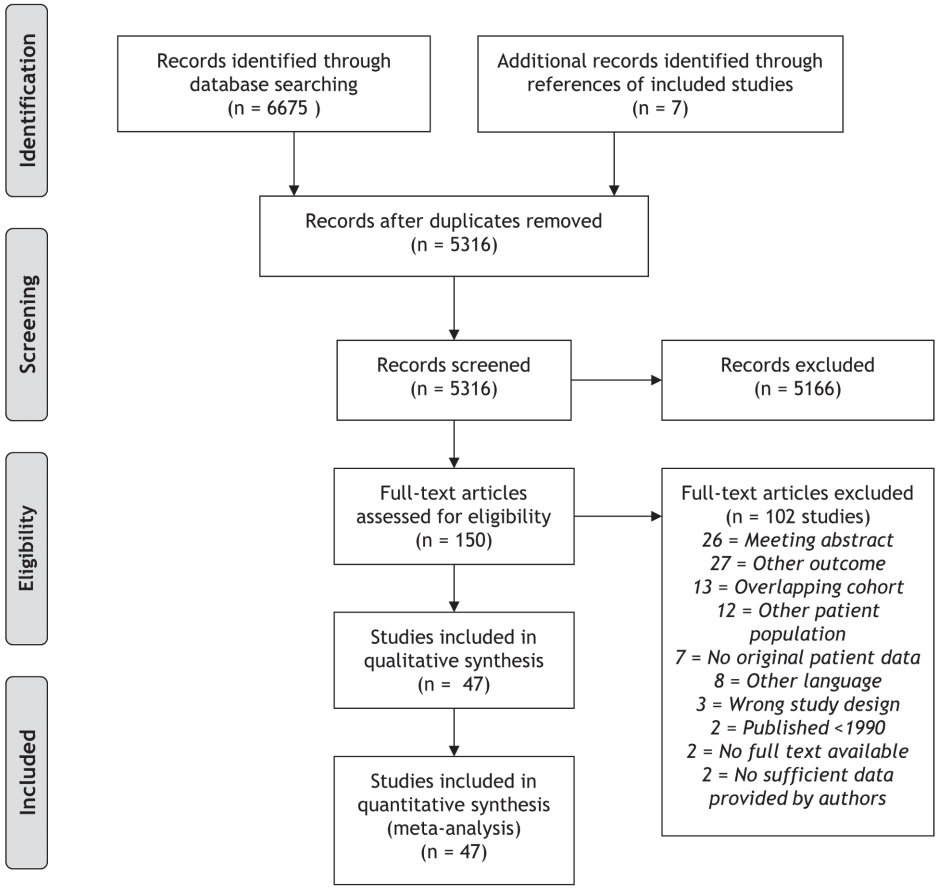

Figure 1 PRISMA flowchart

Inclusion criteria

Studies were included in this systematic review and meta-analysis if they: (1) included patients with a congenital gastrointestinal malformation (i.e., esophageal atresia,

omphalocele, gastroschisis, intestinal atresia, Hirschsprung's disease, anorectal malformations and short bowel syndrome), excluding CDH, (2) included subjects within the age range from infancy to adolescence (0-18 years), (3) reported cognitive, motor or language outcome measured with any standardised and/or validated measure, compared with a selected control group or normative population, (4) used an observational or controlled design, (5) were published in a peer-reviewed journal, (6) were published after 1990, and (7) were written in the English language. Studies reporting on adults only, or studies reporting on both children and adults without detailing the results for only children, were excluded, as well as review papers and case reports. A cohort was defined as a subgroup of the total group of patients included in a study, mostly defined in terms of a particular congenital malformation, and in few studies defined in terms of age at follow-up. How selection was done in case multiple studies reported on (partly) overlapping cohorts, is described in the online supplemental material. Authors of studies were contacted in case a study did not report all data required for the planned analyses. In total, 47 studies were included in the meta-analysis. A reference list is provided in the online supplemental material.

Data extraction

The following data were extracted by two authors (DR and LES): (1) mean raw or standardized scores, accompanying SDs and sample sizes for all outcome measures were extracted for all separate cohorts of cases and, if applicable, control groups. If this information was not available, the proportion of individuals with neurodevelopmental outcome in the standardized normal range was compared between patients and the normative or control sample, in which case sample sizes and relevant p values were extracted. (2) Study characteristics, including: sample sizes, type(s) of malformation(s) assessed, instrument(s) used to assess neurodevelopment, length of follow-up, attrition of the study sample at follow-up; and (3) potential (clinical) moderating factors of neurodevelopmental outcome (listed in online supplemental material tables 1 and 3).

Quality assessment

Quality of the included studies was independently assessed by two authors (DR and LES) using the Newcastle–Ottowa Scale (NOS), based on selection of subjects (4 points), comparability of patient and control groups (2 points) and outcome measurements (3 points).[38,39] Adjustments to the tool according to the manual and scoring methods are described in the online supplemental material. Rating discrepancies were resolved by consensus.

Statistics

Analyses were performed using Comprehensive Meta-Analysis (CMA) software (V.3.0, Biostat). Using the extracted mean (SD) of raw or standardised scores on cognitive, motor

and/or language outcome of cases, and of controls (8 studies) or normative data (39 studies), we calculated effect sizes as the standardised mean difference (Cohen's d) between groups. Outcome measures in the current meta-analyses were: overall neurodevelopmental outcome and three domains of neurodevelopmental outcome: cognitive outcome, motor outcome and language outcome. Overall neurodevelopmental outcome was calculated on a study level by using the built-in function of CMA, which generates the weighted average of study findings across domains (motor, cognitive and/or language outcome). The individual study's effect sizes were subsequently aggregated across studies into meta-analytical effect sizes using the random-effects model to account for heterogeneity introduced by the included range of outcome measures, diagnostic subgroups and age groups. These analyses were rerun, excluding studies that may have included subjects with chromosomal abnormalities, to eliminate the influence of neurodevelopmental impairment related to a syndrome. In case of statistical significant difference in overall neurodevelopmental outcome, differences between the meta-analytical findings for cognitive, motor and language outcome were further explored using subgroup comparisons. If a meta-analytical effect size was built up by a minimum of 10 individual studies' effect sizes, we explored possible moderating effects on the outcomes using univariate meta-regression with a random-effects model. For cohorts that were assessed at multiple assessment points, a weighted average was calculated for the moderator variables at study level and used in meta-regression to calculate the relationship with the weighted average effect sizes of outcome data (Cohen's d) at study level. When studies reported the median with IQRs, means and SD were calculated.[40,41] Furthermore, subgroup comparisons were performed to test for possible differences between diagnostic subgroups (i.e. different types of malformations) and domains of outcome. Effect sizes were interpreted as small (d = 0.2–0.5) medium (d = 0.5–0.8), or large (d ≥ 0.8), according to Cohen.[42] Heterogeneity was interpreted as small ($I^2 \leq 0.25$), medium ($I^2 = 0.25–0.50$) or strong ($I^2 \geq 0.50$), according to Higgins.[43] The possibility of publication bias was assessed by visual inspection of Funnel plots and by calculating Funnel plot asymmetry expressed as the Eggers regression intercept t.[44] To test for bias caused by studies with a fair or poor quality of design, sensitivity analysis were conducted on studies of good quality only.

RESULTS

Sample description

This systematic review and meta-analysis represents a total of 2312 patients described in 47 studies (online supplemental table 1). A detailed sample description in terms of distribution of types of malformation, sex, age groups, birth weight and gestational age can be found in the online supplemental material.

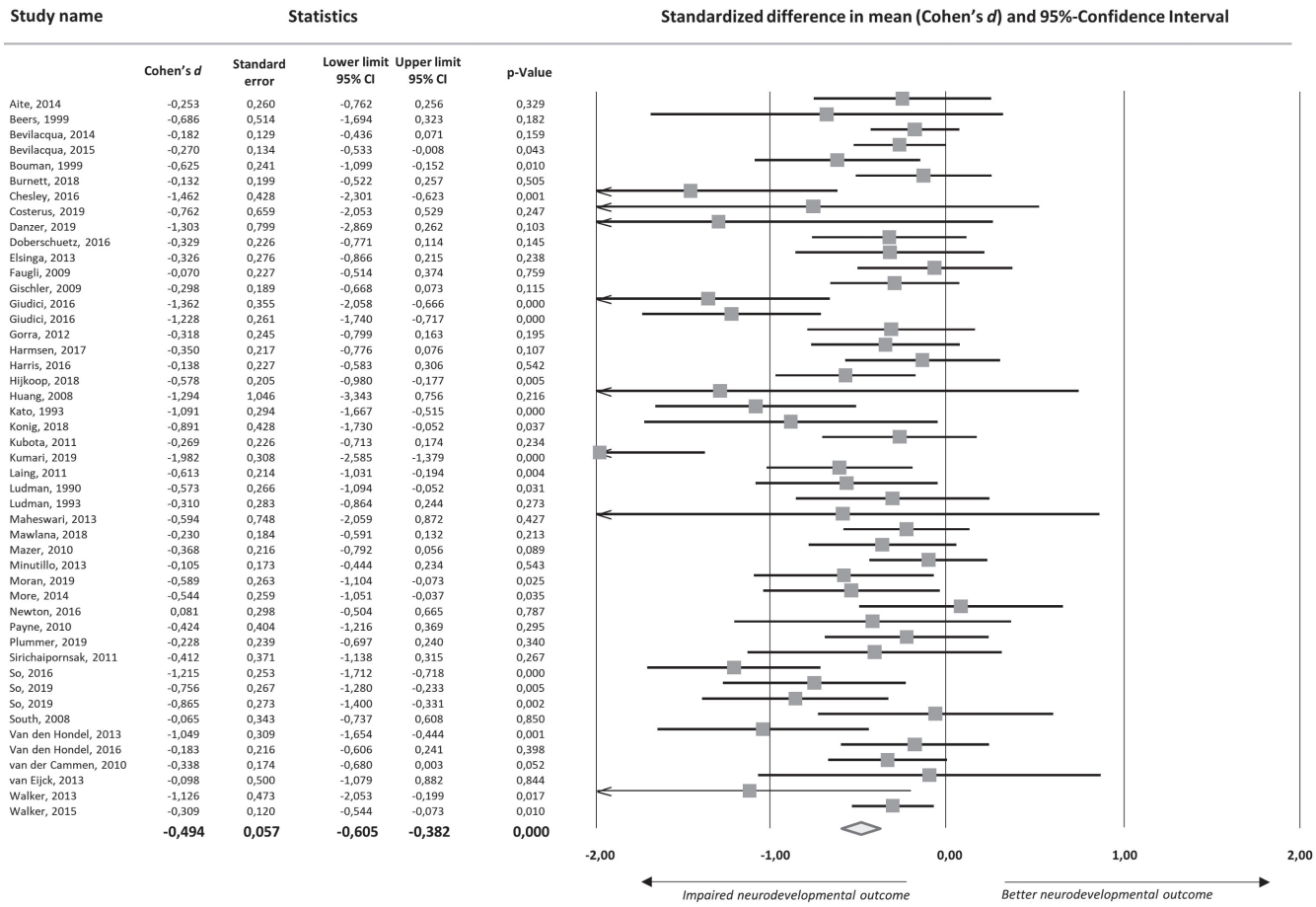

Figure 2 Forest plot of standardized mean differences in overall neurodevelopmental outcome

Overall neurodevelopmental outcome

The meta-analysis on overall neurodevelopmental outcome included all 47 studies (n = 2312 patients; Figure 2). Nineteen of the 47 studies showed significantly poorer overall neurodevelopmental outcome of patients with congenital gastrointestinal malformations compared with normative data or healthy controls. Meta-analytical aggregation of all findings showed a small-sized negative effect on overall neurodevelopmental outcome (d = -0.494, p < 0.001; 95%CI -0.605 to -0.382, I^2 = 56.2%; Table 1).

Cognitive outcome

The meta-analysis on cognitive outcome included 39 studies (n = 2055 patients). In 12 of the 39 studies, cognitive outcome of patients with congenital gastrointestinal malformations was significantly worse compared with normative data or healthy controls. Meta-analytic aggregation showed a small-sized negative effect on cognitive outcome (d = -0.435, p < 0.001; 95%CI -0.567 to -0.302, I^2 = 63.7%; Table 1).

Table 1 Meta-analytical findings for neurodevelopment in children with congenital gastrointestinal malformations

	Number of studies	Number of observations	Cohen's *d* (95% CI, p-value)	Difference between findings on domains of neurodevelopmental outcome	Heterogeneity, I^2	Significant moderators	Eggers intercept
Overall neurodevelopmental outcome	47	2312	-0.494 (-0.605 - -0.382), *p*<.001)		56.2%	Mean length of stay: *b*=-0.005, *p*<.001, Mean number of surgeries *b*=-0.1371, *p*=0.003	-1.874, *p*<.001
Cognitive outcome	39	2055	-0.435 (-0.567- -0.302, *p*<.001)	*Q*=3.194, *p*=0.343	63.7%	Mean number of surgeries *b*=-0.0825, *p*=0.045	-0.711, *p*=.031
Motor outcome	33	1821	-0.610 (-0.769 - -0.451, *p*<.001)		70.3%	Mean length of stay: *b*=-0.005, *p*=.008, Mean number of surgeries *b*=-0.1789, *p*=.001	-2.502, *p*<.001
Language outcome	14	701	-0.670 (-0.914 - -0.425, *p*<.001)		68.4%	-	-2.743, *p*=.013

Motor outcome

The meta-analysis on motor outcome included 33 studies (n = 1821 patients). In 14 of 33 studies, motor outcome of patients with congenital gastrointestinal malformation was significantly worse compared to the normative population or healthy controls. Meta-

analytic aggregation showed a medium-sized negative effect on motor outcome (d = -0.610, p < 0.001; 95%CI -0.769 to -0.451, I^2 = 70.3%; Table 1).

Language outcome

The meta-analysis on language outcome included 14 studies (n = 701 patients). Ten out of 14 studies showed a significant negative difference between language development of patients with a congenital gastrointestinal malformation and the normative population or healthy controls. Meta-analytical aggregation showed a medium-sized negative effect (d = -0.670, p < 0.001; 95%CI -0.914 to -0.425, I^2 = 68.4%; Table 1).

Influence of possible presence of chromosomal abnormalities

Sensitivity analyses excluding three studies that may have included subjects with chromosomal abnormalities showed comparable (if not larger) impairments on overall neurodevelopmental outcome (d = -0.519, p < 0.001), cognitive outcome (d = -0.458, p < 0.001), motor outcome (d = -0.658, p < 0.001), and language outcome (d=-0.780, p<0.001).

Meta-regression of possible moderators of neurodevelopmental outcome

Meta-regression showed that worse overall neurodevelopmental and worse motor outcome were related to longer mean total length of hospital stay, worse overall neurodevelopmental, worse cognitive and worse motor outcome were related to a higher mean number of surgeries, while no relations were observed with mean age, mean gestational age, mean birth weight and percentage of boys in a study, as shown in Table 1 and online supplemental Table 2.

Table 2 Differences between types of malformations in overall neurodevelopmental outcome

Type of malformation	Number of studies	Cohen's *d* (95% CI, *p*-value) on overall neurodevelopmental outcome	Type of malformation vs other types of malformation, Q-values, p-values
Abdominal wall defects (i.e., gastroschisis, omphalocele)	17	-0.375 (-0.567 - -0.182, *p*<.001)	*Q*=1.14, *p*=.286
Colorectal malformations (i.e, hirschsprung disease, anorectal malformations)	10	-0.485 (-0.765 - -0.206, *p*=.001)	*Q*=0.024, *p*=.877
Esophageal atresia	17	-0.521 (-0.713 - -0.328, *p*<.001)	*Q*=0.433, *p*=.506
Intestinal atresia	5	-0.251 (-0.585 - -0.082, *p*=0.140)	*Q*=1.657, *p*=.190
Short bowel syndrome	6	-1.000 (-1.324 - -0.675, *p*<.001)	*Q*=11.639, *p*=0.002

Differences between types of malformations

When comparing meta-analytical effect sizes of subgroups of different types of malformations, we found a significant difference in the magnitude of effect sizes for overall neurodevelopmental outcome (Q = 11.52; p = 0.021) (Table 2), that was traced down in

further analyses to significantly poorer overall neurodevelopmental outcome for patients with short bowel syndrome compared with all remaining patient groups (d = -1.000 and d = -0.412 respectively, Q = 11.639; p = 0.001). Further tests assessing differences between types of malformations are shown in the online supplemental material.

Quality of studies and risk of bias analysis

Results of the quality assessment are presented in Table 3. NOS scores ranged from 4 to 9. Most studies had good quality (77%), with only a minority of studies qualifying as fair (15%) or poor (8%). Results of the sensitivity analysis on studies of good quality, risk of publication bias (see also Table 1) and risk of other bias analyses are described in the online supplemental material.

Table 3 Quality of included studies as assessed with the Newcastle-Ottawa Scale (NOS)

Study	Selection of subjects	Comparability of cases and controls	Outcome measurements	Total score[a]	Quality[b]
Aite, 2014	3	1	2	6	Good
Beers, 2000	4	2	3	9	Good
Bevilacqua, 2014	3	1	3	7	Good
Bevilacqua, 2015	3	1	2	6	Good
Bouman, 1999	3	1	2	6	Good
Burnett, 2018	3	1	2	6	Good
Chesley, 2016	3	1	3	7	Good
Costerus, 2019	3	1	2	6	Good
Danzer, 2019	3	1	2	6	Good
Doberschuetz, 2016	4	2	3	9	Good
Elsinga, 2013	3	1	2	6	Good
Faugli, 2009	2	1	2	5	Fair
Gischler, 2009	3	1	3	7	Good
Giudici, 2016	3	0	3	6	Poor
Giudici, 2016	3	0	2	5	Poor
Gorra, 2012	3	2	2	7	Good
Harmsen, 2017	3	1	3	7	Good
Harris, 2016	3	1	2	6	Good
Hijkoop, 2017	3	1	3	7	Good
Huang, 2008	3	1	3	7	Good
Kato, 1993	2	1	3	6	Fair
Konig, 2018	2	1	3	6	Fair
Kubota, 2011	2	1	2	5	Fair
Kumari, 2019	3	0	1	4	Poor
Laing, 2011	1	1	3	5	Poor

Ludman, 1990	3	2	3	8	Good
Ludman, 1993	3	2	3	8	Good
Maheshwari, 2013	3	1	3	7	Good
Mazer, 2010	3	1	3	7	Good
Mawlana, 2018	3	1	3	7	Good
Minutillo, 2013	3	1	3	7	Good
Moran, 2019	3	2	2	7	Good
More, 2014	3	1	2	6	Good
Newton, 2016	4	2	2	8	Good
Payne, 2010	4	2	3	9	Good
Plummer, 2019	2	1	2	5	Fair
Sirichaipornsak, 2011	3	1	2	6	Good
So, 2016	3	1	3	7	Good
So, 2019	2	1	2	5	Fair
So, 2019	2	1	3	6	Fair
South, 2008	3	1	3	7	Good
Van den Hondel, 2013	3	1	3	7	Good
Van den Hondel,2016	3	1	3	7	Good
Van der Cammen-van Zijp, 2010	3	1	2	6	Good
Van Eijck, 2013	3	1	2	6	Good
Walker, 2013	3	2	3	8	Good
Walker, 2015	3	2	2	7	Good

Note.
a. The Newcastle–Ottowa Scale allows study quality of observational studies to be quantified on the basis of the methods used to select subjects (4 points), comparability of case and control groups (2 points) and outcome measurements (3 points).
b. Scores were converted to the Agency for Healthcare Research and Quality standards, in order to judge quality as 'good', 'fair' or 'poor'.

DISCUSSION

This systematic review and meta-analysis of 47 studies representing 2012 patients revealed evidence for small-sized overall neurodevelopmental impairment in children with congenital gastrointestinal malformations compared with normative data or healthy controls, reflecting small-sized cognitive impairment, medium-sized motor impairment and medium-sized language impairment. These findings translate into an average difference in 6.5 IQ points and implicate a 3.6% increase in the number of children with cognitive delay, a 5.9% increase in the number of children with motor delay and 6.9% increase in the number of children with language delay. Excluding studies that may have included syndromal patients did not lead to altered conclusions. Our findings implicate

that patients with congenital gastrointestinal malformations have increased risk of neurodevelopmental impairment. Our findings are in line with an earlier meta-analysis of cognitive and motor impairment in infants (up to 24 months of age) with non-cardiac congenital malformations,[45] although the slightly larger effects obtained in that meta-analysis may be explained by the inclusion of patients with CDH.[46]

Robust evidence for neurodevelopmental impairment was found in all types of congenital gastrointestinal malformations. Contrary to what has been indicated in previous reports,[46,47] no differences in meta-analytic effect sizes of overall neurodevelopmental outcome were found between patients with specific types of congenital gastrointestinal malformations, except for relatively poorer overall neurodevelopment and motor development in patients with short bowel syndrome.

Considering moderating factors, the results revealed that longer mean length-of-stay and a higher mean number of surgeries were related to greater overall neurodevelopmental impairment and motor development. This may suggest that the more complex the course of disease and/or treatment that is required, the more profound the impact is on neurodevelopmental outcome. The results of our meta-regression analyses showed no differences in the magnitude of effect between the different age groups. This cross-sectional finding suggests that the magnitude of neurodevelopmental impairment remains relatively stable over developmental stages, but remains to be investigated by longitudinal studies.

Although preterm birth and low birth weight are associated with neurodevelopmental impairment,[26,48-50] meta-regression analyses found no evidence for the possibility that our findings reflect the effects of gestational age or birthweight. This suggests that other common aetiological factors for neurodevelopmental impairment may play a (more important) role in the neurodevelopmental impairments of patients with congenital gastrointestinal malformations, such as factors related to intrauterine development,[51,52] surgical treatment,[19,26,53-58] compromised bowel function and feeding support,[50,53,58] and parental social economic status.[59] We consider this an important issue in future research and suggest prospective registration of potential aetiological factors and neurodevelopment outcomes.

The evidence found in this meta-analysis was primarily based on studies with good quality (74%). Excluding studies with fair or poor quality did not result in altered conclusions. Risk of publication bias analyses indicated a potential influence of publication bias on the meta-analytical estimations, indicating that these estimations should be interpreted with caution and emphasising importance for preregistration of study protocols.

Limitations

The findings of the current systematic review and meta-analysis are limited by the use of normative data in the majority of included studies,(38 of 47) which does not control

for differences in variables such as sex and social economic status. Second, there was heterogeneity in the measures used to assess neurodevelopmental outcome, while some evidence suggests that the Bayley Scales of Infant Development (BSID)-III may overestimate neurodevelopment as compared with the BSID-II.[60] Third, the tests of subgroup differences on type of malformations and type of outcome domain, were limited by partially overlapping subjects across subgroups. However, since related observations tend to decrease variance, this would make the comparison more sensitive for group differences, which were not observed. Fourth, the quantity of available literature allowed inclusion of only a limited number of potentially moderating aetiological factors in meta-regression and was subject to distinct heterogeneity in terms of construct definitions. Lastly, due to the limited number of studies, our findings for language outcome and the possible influence of moderating factors on all outcomes awaits replication before a firm conclusion may be drawn.

Conclusions and clinical implications

In conclusion, this systematic review and meta-analysis presents robust evidence that patients with congenital gastrointestinal malformations are at risk of small-sized to medium-sized impairment in neurodevelopmental outcome, emphasising the need for routine neurodevelopmental screening of these patients.

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ONLINE SUPPLEMENTAL MATERIAL

Search strategy pubmed

("Congenital Abnormalities"[Mesh:NoExp] OR congenital abnormalit*[tiab] OR congenital deformit*[tiab] OR congenital defect*[tiab] OR birth defect*[tiab] OR congenital anomal*[tiab] OR "Esophageal Atresia"[Mesh] OR esophageal atresia*[tiab] OR oesophageal atresia*[tiab] OR "Gastroschisis"[Mesh] OR gastroschis*[tiab] OR Congenital Fissure of the Abdominal Cavity[tiab] OR ("Hernia, Umbilical"[Mesh] AND congenital*[tiab]) OR exomphalos[tiab] OR omphalocele*[tiab] OR "Hirschsprung Disease"[Mesh] OR hirschsprung disease[tiab] OR congenital megacolon[tiab] OR hirschsprung's disease[tiab] OR hirschsprungs disease[tiab] OR aganglionic megacolon[tiab] OR Rectosigmoid Colon Aganglionosis[tiab] OR Rectosigmoid Aganglionosis[tiab] OR Congenital Intestinal Aganglionosis[tiab] OR Colonic Aganglionosis[tiab] OR Total Colonic Aganglionosis[tiab] OR "Anorectal Malformations"[Mesh] OR Anorectal Malformation*[tiab] OR Anorectal Anomal*[tiab] OR Anorectal Atresia*[tiab] OR Anorectal Stenos*[tiab] OR "Anus, Imperforate"[Mesh] OR imperforate anus[tiab] OR anal atresi*[tiab] OR "Short Bowel Syndrome"[Mesh] OR Short Bowel Syndrome*[tiab] OR intestinal failure[tiab] OR pediatric intestinal failure[tiab] OR paediatric intestinal failure[tiab] OR "Intestinal Atresia"[Mesh] OR Congenital Intestinal Atresia*[tiab] OR Apple Peel Syndrome*[tiab] OR Apple-Peel Intestinal Atresia*[tiab] OR Jejunal Atresia[tiab] OR Apple Peel Small Bowel Syndrome[tiab] OR Familial Apple Peel Jejunal Atresia[tiab]) AND (Infan*[tiab] OR newborn*[tiab] OR new-born*[tiab OR perinat*[tiab] OR neonat*[tiab] OR baby[tiab] OR baby*[tiab] OR babies[tiab] OR toddler*[tiab] OR minors[tiab] OR minors*[tiab] OR boy[tiab] OR boys[tiab] OR boyfriend[tiab] OR boyhood[tiab] OR girl*[tiab] OR kid[tiab] OR kids[tiab] OR child[tiab] OR child*[tiab] OR children*[tiab] OR schoolchild*[tiab] OR schoolchild[tiab] OR school child[tiab] OR school child*[tiab] OR adolescen*[tiab] OR juvenil*[tiab] OR youth*[tiab] OR teen*[tiab] OR under*age*[tiab] OR pubescen*[tiab] OR pediatrics[mesh] OR pediatric*[tiab] OR paediatric*[tiab] OR peadiatric*[tiab] OR school[tiab] OR school*[tiab] OR prematur* OR preterm*) AND ("Child Development"[Mesh] OR Child Development[tiab] OR Infant Development[tiab] OR neurocogniti*[tiab] OR neuropsych*[tiab] OR cogniti*[tiab] OR neurodevelopment*[tiab] OR developmental[tiab] OR motor*[tiab] OR movement[tiab] OR psychomotor[tiab] OR intell*[tiab] OR intellect*[tiab] OR intellectual[tiab] OR intelligence[tiab] OR psychomotor performanc*[tiab] OR neurocognitive performanc*[tiab] OR psychomotor skil*[tiab] OR neurocognitive skil*[tiab] OR neuropsychological funct*[tiab] OR psychomotor funct*[tiab] OR neuropsychological outcom*[tiab] OR psychomotor outcom*[tiab] OR neurocognitive outcom*[tiab] OR "Wechsler Scales"[Mesh] OR Wechsler Scale*[tiab] OR WPPSI[tiab] OR WISC[tiab] OR Wechsler Intelligence Scale for Children[tiab] OR Wechsler Preschool and Primary Scale of Intelligence[tiab] OR BSID[tiab] OR Bayley[tiab] OR Bayley Scales of Infant Development[tiab] OR MABC[tiab] OR Movement Assessment

Battery for Children[tiab] OR AIMS[tiab] OR Alberta Infant Motor Scale[tiab] OR Infant Motor Scale[tiab] OR BOTMP[tiab] OR Bruininks-Oseretsky[tiab] OR Bruininks*[tiab] OR Griffiths[tiab] OR Griffiths Mental Development Scale[tiab] OR GMSD[tiab] OR Griffith score*[tiab] OR Mullen[tiab] OR Mullen Scales of Early Learning[tiab] OR MSEL[tiab] OR Ages and stages questionnaire[tiab] OR ASQ[tiab] OR CBCL[tiab] OR Child Behavioural Checklist[tiab] OR Child Behavioral Checklist[tiab] OR NEPSY[tiab]) AND ("Case-Control Studies"[Mesh] OR "Cohort Studies"[Mesh] OR "Observational Study" [Publication Type] OR case-control[tiab] OR cohort[tiab] OR retrospective[tiab] OR prospective[tiab] OR observational stud*[tiab] OR descriptive study[tiab] OR "Cross-Sectional Studies"[Mesh] OR cross sectional[tiab])

Selection of studies describing overlapping cohorts

In case multiple articles reported on (partly) overlapping cohorts, we included the article that: (1) reported the longest follow-up period, (2) reported separately on subgroups of patients to allow differentiation for malformation type and/or (3) had the largest sample size to maximize generalizability of the sample and statistical power of meta-analysis (decisions were made in this order).

Adjusted use of the Newcastle Ottawa Scale for quality assessment of included studies

In accordance with the manual, the NOS tool was adjusted to enable quality assessment of observational cohort studies. One aspect of the scale ("demonstration that outcome of interest was not present at start of the study") was not applicable and was therefore omitted from quality assessment. An extra point for selection was given when studies had a design with a control group instead of using normative scores.

In accordance with the Agency for Healthcare Research and Quality (AHRQ) standards, quality of studies was considered:

- 'good', in case of a score of 3-4 points for selection of subjects AND a score of 1-2 points for comparability of cases and controls AND a score of 2-3 points for outcome measurements
- 'fair', in case of a score of 2 points for selection of subjects AND a score of 1-2 points for comparability of cases and controls AND a score of 2-3 points for outcome measurements
- 'poor', in case of a score of 0-1 points for selection of subjects OR 0 for comparability of cases and controls OR 0-1 for outcome measurements

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Sample description

Seventeen studies reported on a cohort of patients with one single malformation, whereas most studies reported on multiple subgroups of different malformations (30 studies), together resulting in a total of 62 cohorts: esophageal atresia (17 cohorts, n=603 patients), congenital abdominal wall defects (18 cohorts, n=585 patients), followed by colorectal malformations (10 cohorts, n=172 patients), intestinal atresia (5 cohorts, n=131 patients) and intestinal failure (4 cohorts, n=102 patients) and a combination of different congenital malformations (8 cohorts, n=486 patients). Neurodevelopmental outcomes in infants or toddlers (up to 36 months of age) were described in 29 studies (n=1,768 patients), whereas in 21 studies (n=794 patients) neurodevelopmental outcomes of children (up to a maximum age of 13 years) were described. Mean birthweight of patients ranged from 1,980 to 3,492 grams, with 13 studies reporting on cohorts with a mean birthweight < 2500 grams. Mean gestational age of patients ranged from 34 to 39 weeks, with 22 studies reporting on cohorts with a mean gestational age below 37 weeks. The mean proportion of males represented was 55% (ranging from 29% to 80%).

Study characteristics of included studies

sTable 1 Study characteristics of included studies

Author	Period of inclusion[a]	Country	Sample size[b]	Assessed type of malformation[b]	Tool[c]	Normative sample	Included in meta-analysis of overall neuro-developmental outcome	Included in meta-analysis of motor outcome	Included in meta-analysis of cognitive outcome	Included in meta-analysis of language outcome	Age at assessment (months) [a,de,f]	Mean (SD) GA (wk)[a,d,f]	Mean (SD) BW (gram)[a,d,f]	Mean (SD) number of surgeries[a,d,e,f]	Mean (SD) length of total hospital stay[a,d,e,f]
Aite, 2014	2008-2012	Italy	30	EA	BSID-III	Italian norm[1]	X	X	X		6 / 12	38 (2)	2635 (470)	1.1 (0.2)/ 1.2 (0.5)	NR
Beers, 2000	NR	USA	8	SB	WISC-III	North-American norm[2]	X	X	X		117	34 (3)	19889 (826)	NR	NR
Bevilacqua, 2014	2008-2010	Italy	150 (37 EA, 43 CDH, 29 MM, 16 CAWD, 25 CR)	Mix	BSID-III	Italian norm[1]	X	X	X		6	38 (1)	2944 (636)	1.7 (1.5)	34.9 (23.2)
			156 (38 EA, 40 CDH, 35 MM, 17 CAWD, 26 CR)	Mix	BSID-III	Italian norm[1]	X	X	X		12	38 (1)	2935 (643)	2 (1.5)	40.4 (30.7)
			84 (15 EA, 30 CDH, 19 MM, 12 CAWD, 8 CR)	Mix	BSID-III	Italian norm[1]	X	X	X		24	38 (2)	2853 (547)	2 (1.5)	40.9 (27.2)
Bevilacqua, 2015	2008-2012	Italy	41	EA	BSID-III	Italian norm[1]	X	X	X		6 / 12	38 (2)	2714 (553)	1.4 (0.8) / 1.4 (0.8)	36. 8 (27.7) / 39.4 (30.7)
			34	IA	BSID-III	Italian norm[1]	X	X	X		6 / 12	37 (2)	2763 (667)	2 (1.5) / 2 (1.5)	56.0 (49.0) / 55.2 (48.8)
			18	GS, OM	BSID-III	Italian norm[1]	X	X	X		6 / 12	37 (2)	2614 (607)	1.4 (0.8) / 1.4 (0.8)	30.4 (9.5) / 30.4 (9.5)

			20	HD, ARM	BSID-III	Italian norm[1]	X	X	X		6 / 12	39 (2)	3326 (618)	2.3 (1.6) / 2.4 (1.8)	33.3 (26.1) / 34.5 (28.9)
Bouman, 1999	NR	Netherlands	36	EA	WISC-RN	Dutch norm[3]	X		X		122	NR	NR	3.4 (1.9)	NR
Burnett, 2018	2006-2014	Australia	39	GS	BSID-III	North-American norm[4]	X	X	X	X	2	36 (2)	2194 (400)	NR	39.6 (25.4)
			20	GS	WPPSI-III	North-American norm[5]			X		72	35 (2)	2304 (614)	NR	47.9 (41.9)
			20	OM	BSID-III	North American norm[4]	X	X	X	X	24	39 (2)	3351 (596)	NR	15.4 (14.3)
			10	OM	WPPSI-III	North American norm[5]			X		72	39 (1)	3492 (532)	NR	11.5 (7.7)
Chesley, 2016	NR	USA	15	SB	BSID-II	North American norm[6]	X	X	X		17	34 (4)	NR	11 (5.7)	145.9 (93.7)
Costerus, 2019	2011-2013	Netherlands	5	EA	BSID-II	Dutch norm[7]	X	X	X		24	38 (2)	2742 (545)	NR	NR
Danzer, 2019	2004-2015	USA	47	OM	BSID-II; BSID-III, WPPSI-III, WPPSI-IV	NR	X	X	X	X	41	35 (3)	2525 (735)	NR	132.8 (86.3)
Doberschuetz, 2016	2008-2011	Germany	40 (9 EA, 9 GS, 5 IA, 4 OM, 3 CDH, 2 ARM, 1 HD, 3 combination)	Mix	BSID-II	Control group – but normative data was included	X	X	X		25	37 (2)	2782 (674)	2.0 (NR)	43.9 (40.3)
Elsinga, 2013	1995-2002	Netherlands	27	IA	M-ABC, WISC-III, NEPSY-II	Dutch norm[8,9,10]	X	X	X		114	36 (3)	2972 (1091)	NR	NR
Faugli, 2009	1999-2002	Norway	39	EA	BSID-II	North American norm[11]	X	X	X		13	NR	2780 (926)	1.4 (0.9)	NR
Gischler, 2009	1999-2003	Netherlands	17	EA	BOS 2-30	Dutch norm[12]	X	X	X		6 / 12 / 18 / 24	39 (3)	2928 (485)	4.4 (4.0)	77.2 (78.8) / 79.8 (80.8) / NR / NR

			34	IA	BOS 2-30	Dutch norm[12]	X	X	X		6 / 12 / 18 / 24	37 (3)	2964 (697)	2 (1.5)	46.1 (44.3) / 49.0 (47.2) / NR / NR
			19	GS, OM	BOS 2-30	Dutch norm[12]	X	X	X		6 / 12 / 18 / 24	39 (3)	2744 (641)	2.3 (1.6)	48.2 (36.8) / 55.4 (52.9) / NR / NR
Giudici, 2016	2003-2013	Argentinia	27/14/13	EA	CAT-CLAMS / PRUNAPE	North American norm (Catclams),[13] Argentinian norm (Prunape)[14]	X	X	X	X	12 / 36 / 72	38 (2)	2917 (440)	NR	NR
Giudici, 2016	2003-2014	Argentinia	52/34/20	GS	CAT-CLAMS / PRUNAPE	North American norm (Catclams)[13] Argentinian norm (Prunape)[14]	X	X	X	X	12 / 36 / 72	37 (2)	2403 (427)	NR	NR
Gorra, 2012	2001-2008	USA	46	GS	BSID-II	Control group – but normative data was included	X				24	36 (NR)	2542 (NR)	NR	54.0 (NR
Harmsen, 2017	1999-2006	Netherlands	54	EA	MABC, MABC-II, WISC-III	Dutch norm[8,15,9]	X	X	X		60 / 96	38 (3)	2798 (816)	NR / NR	84.6 (99.6) / NR
Harris, 2016	1992-2005	Australia	39	GS	WPPSI-III, WISC-IV	Australian norm[5,16]	X		X		120	36 (2)	2496 (174)	NR	NR
Hijkoop, 2017	2000-2012	Netherlands	54	GS	BOS 2-30, BSID-II	Dutch norm[12,7]	X	X	X		12 / 24	36 (2)	2313 (NR)	NR	NR
Huang, 2008	2005-2006	China	8	SB	BSID-I, WPPSI-R, WISC-R, WAIS-R	North American norm[17-20]	X	X	X		80	38 (1)	3291 (377)	NR	NR
Kato, 1993	1978-1983	Japan	8	GS, OM	WISC-R	NR	X		X		107	NR	NR	NR	NR
			6	HD	WISC-R	NR	X		X		101	NR	NR	NR	NR
			13	ARM	WISC-R	NR	X		X		94	NR	NR	NR	NR

Konig, 2018	NR	Germany	12	EA	KTT; DMT	Control group	X	X			84	NR	NR	NR	NR
Kubota, 2011	NR	Japan	20	EA	WISC-III	North American norm[21]	X		X		NR	NR	NR	NR	NR
			25	ARM	WISC-III	North American norm[21]	X		X		NR	NR	NR	NR	NR
Kumari, 2019	2012-2017	India	32	EA	DASII	Indian norm[22]	X		X		17	37 (3)	2360 (639)	NR	NR
Laing, 2011	2002-2004	Australia	46	Mix	BSID-II	North American norm[6]	X	X	X		24	38 (2)	3174 (578)	1.5 (0.9)	28.0 (20.8)
Ludman, 1990	1983-1984	UK	30	Mix	GMDS	Control group	X	X	X	X	12	NR	NR	NR	52.5 (65.6)
Ludman, 1993	1983-1985	UK	29	Mix	GMDS	Control group	X	X	X	X	6 / 36	NR	NR	NR / NR	NR / NR
Maheshwari, 2013	2006-2011	Australia	3	EA	BSID-III	NR	X	X	X	X	5-13	NR	NR	NR	NR
Mawlana, 2018	2000-2015	Canada	182	EA (TEF)	BSID-II	North American norm[4]	X	X	X	X	24	37 (3)	2589 (800)	NR	NR
Mazer, 2010	1999-2002	Netherlands	15	EA	BOS 2-30, MABC	Dutch norm[12,8]	X	X	X		6 / 12/ 24 / 60	NR	NR	NR / NR / NR / NR	NR / NR / NR / NR
			18	IA,	BOS 2-30, MABC	Dutch norm[12,8]	X	X	X		6 / 12/ 24 / 60	NR	NR	NR / NR / NR / NR	NR / NR / NR / NR
			27	GS, OM	BOS 2-30, MABC	Dutch norm[12,8]	X	X	X		6 / 12/ 24 / 60	NR	NR	NR / NR / NR / NR	NR / NR / NR / NR
			6	HD	BOS 2-30, MABC	Dutch norm[12,8]	X	X	X		6 / 12/ 24 / 60	NR	NR	NR / NR / NR / NR	NR / NR / NR / NR
			15	ARM	MABC, BOS 2-30	Dutch norm[12,8]	X	X	X		60	NR	NR	NR	NR
Minutillo, 2013	1997-2010	Australia	67	GS	GMDS	NR	X		X		12	NR	NR	NR	NR
Moran, 2019	2011-2013	Australia	27 (10 EA, 17 CAWD)	Mix	BSID-III	Control group	X	X	X	X	26	38 (32-40)	2940 (NR)	NR	NR
More, 2014	2001-2010	Australia	31	HD	GMDS	British norm[23]	X		X		12	NR	NR	NR	NR
Newton, 2016	2001-2014	USA	34	EA (TEF)	BSID-II, BSID-III	Control group	X				35	35 (NR)	2244 (NR)	NR	57.7 (NR)
Payne, 2010	1999-2007	USA	57	GS	BSID-III	Control group	X				39	36 (NR)	2365 (NR)	NR	54.2 (42.6)

Plummer, 2019	2016-2018	USA	34	CGIA	NIH Toolbox	British norm[24]	X		X	X	56	38 (2)	3220 (690)	NR	NR
Sirichai-pornsak, 2011	2007-2008	Thailand	15	GS	BSID-III	NR	X	X	X	X	22	37 (2)	2289 (477)	NR	42.4 (29.3)
So, 2016	2011-2013	Canada	33	SB	AIMS, MAI	North American norm[25,26]	X	X			11	33 (5)	1877 (1031)	2.4 (0.8)	165.5 (99.6)
So, 2019	2011-2013	Canada	30	SB	MSEL	North American norm[27]	X	X	X	X	12-15 / 26-32	33 (5)	1949 (995)	NR / NR	NR / NR
So, 2019	2015-2016	Canada	30	SB	BOT2	North American norm[28]	X	X			84	35 (5)	2198 (848)	3.6 (2.3)	198.0 (128.4)
South, 2008	2003-2005	USA	17	GS	BSID-II	North American norm[6]	X				20	36 (2)	2360 (731)	NR	NR
Van den Hondel, 2013	1999-2011	Netherlands	37	ARM	RAKIT, MABC	Dutch norm[29,8]	X	X			60	38 (NR)	3010 (NR)	3.9 (3.5)	NR
Van den Hondel, 2016	1999-2006	Netherlands	43	HD, ARM	WISC-III, RAKIT	Dutch norm[9,29]	X	X	X		96	NR	NR	NR	NR
Van der Cammen-van Zijp, 2010	1999-2003	Netherlands	29	EA	MABC	Dutch norm[8]	X	X			71	37 (3)	2839 (913)	NR	76.9 (69.3)
			25	IA	MABC	Dutch norm[8]	X	X			71	37 (3)	2747 (509)	NR	49.4 (51.2)
			24	GS, OM	MABC	Dutch norm[8]	X	X			71	38 (2)	2702 (591)		59.8 (64.5)
Van Eijck, 2013	2004-2007	Netherlands	8	OM	MABC-II	Dutch norm[15]	X	X			72	NR	NR	NR	NR
Walker, 2013	2006-2008	Australia	31	EA (TEF)	BSID-III	Control group	X	X	X	X	12	38 (NR)	2718 (717)	NR	31.1 (30.7)
Walker, 2015	2006-2008	Australia	124	Mix	BSID-III	Control group	X	X	X	X	36	NR	NR	NR	NR

Note.
[a] NR = not reported
[b] ARM = anorectal malformations; BA = biliary atresia; CGIA = Congenital Gastrointestinal Anomalies; EA = esophageal atresia; GS = gastroschisis; HD = Hirschsprungs disease; IA = intestinal atresia / midgut malformations ; NCCA = non-cardiac congenital malformations; OM = omphalocele; SB = short bowel syndrome / intestinal failure
[c] AIMS = Alberta Infant Motor Scales; BSID = Bayley Scales of Infant Development; CATCLAMS = cognitive adaptive test/clinical linguistic and auditory milestone scale; DASII = Developmental Assessment Scale of Indian Infants; DMT = Deutscher Motorik Test; GMDS = Griffiths Mental Development Scale; KTT = Kinderturntest; MABC = Movement Assessment Battery for Children; MELS = Mullen Early Learning Scales; PRUNAPE = prueba nacional de pesquisa, a national screening program in Argentinia; RAKIT = Revisie Amsterdamse Kinder Intelligentie Test (Dutch intelligence test); WAIS = Wechsler Adult Scale of Intelligence; WPPSI = Wechsler Prechool and Primary Scale of Intelligence; WISC = Wechsler Infant Scale of Intelligence
[d] Reported median (range) and median (IQR) were recalculated into Mean (SD) using http://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html
[e] Repeated measures are indicated by a "/" in this table.
[f] For all moderator variables a weighted average was calculated and included in meta-regression.

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Results of meta-regression analyses

The following potential moderating factors were assessed in the current meta-analysis: mean age at neurodevelopmental testing, mean gestational age, mean birthweight, sex, comorbidity, growth impairment, neurological complications, age at primary surgery, number of surgeries, number of anesthetic exposures, length of total hospital stay, mean days of mechanical ventilation, mean days of parental nutrition, educational level of parents and socio-economic status of parents.

sTable 2 Moderating effects of studies' effect sizes of studies' mean age, mean gestational age, mean birthweight and proportion of males on overall neurodevelopmental outcomes, cognitive outcomes and motor outcomes

	Overall neurodevelopmental outcomes		**Cognitive outcomes**		**Motor outcomes**		**Language outcomes[b]**
	Number of patients	***Significance effect in meta-regression***	***Number of patients***	***Statistical effect in meta-regression***	***Number of patients***	***Statistical effect in meta-regression***	
Mean age at testing in months	*n*=1182	*p*=0.43	*n*=847	*p*=0.29	*n*=880	*p*=0.94	NA
Mean gestational age in weeks	*n*=1260	*p*=0.07	*n*=1155	*p*=0.12	*n*=1014	*p*=0.10	NA
Mean birthweight in grams	*n*=1255	*p*=0.08	*n*=1194	*p*=0.07	*n*=1009	*p*=0.45	NA
Sex[a]	*n*=790	*p*=0.24	*n*=608	*p*=0.20	*n*=545	*p*=0.45	NA
Mean total length of hospital stay in days	*n*=1098	*p*<0.001	*n*=931	*p*=0.24	*n*=817	*p*=0.008	NA
Mean number of surgeries	*n*=983	*p*=0.003	*n*=920	*p*=0.04	*n*=834	*p*=0.001	NA

Note.
a. Sex was expressed as the percentage of male subjects in each cohort
b. NA= not assessed

sTable 3 Potential moderating factors not assessed in meta-regression

Author	Comorbidity	Growth	Times exposure to anesthesia	Age at 1st surgery in days	Neurologic complications	Feeding	Ventilation	Parental education	Parental SES
Aite		n (%) weight <5th percentile					Median (range) number of days ventilation	n (%) by categories (below high school, high school, degree) by type of parent	n (%) by categories (salariate, intermediate, working class, unemployed) by type of parent
Beers		n by categories of percentile weight scores (<5th, 5-10th, 10-25th, 25-50th, 75th)							
Bevilacqua	n (%) associated malformations (1, more than 1)							n (%) by categories (primary school, secondary school, high school, degree) by type of parent	
Bevilacqua	n (%) associated malformations (none, 1, more than 1)		Median (IQR) by follow-up duration		n intracranial hemorraghe	n (%) medical appliances for feeding	median (IQR) ventilatory time in hours n (%) medical appliances for respiratory	n by categories (primary school, secondary school, high school, degree) by type of parent	n by categories (class 1-4) by type of parent
Bouman							Proportion assisted ventilation		Categorial (mid, low, high) by type of parent
Burnett	n (%) chromosomal abnormality	n (%) small for gestational age at birth (<10th)		Median (IQR) in days by ype malformation and age		n (%) discharged with tube feeding		n (%) low maternal education	n (%) receiving government assistence
Chesley					n with cerebral palsy	n with TPN; Median (range) number of days exposed to PN			
Costerus	n with comorbidity			Median (range) in days			Median (range) number of days ventilation		
Danzer				Median (range) in days		Mean (SD) age at initial feeding	Median (range) number of days ventilation	n (%) maternal education by categories (none, parttime, fulltime)	n (%) maternal education by categories (high school, partly college/college degree, graduate degree)

Dober-schuetz	n (%) combined malformations		Mean (95%CI) duration in hours	Mean (95%CI) in hours	n with hearing impairment	Mean (SD) / median (range) number of days PN, Mean (SD) / Median (range) number of days tube feeding	Mean (SD) / median ((range) number of hours ventilation, Mean (SD) / Median (range) number of days oxygen		mean score (low, medium, high)
Elsinga	n (%) late onset sepsis or BPD	median weight		Median (range) in days					
Faugli	n with associat-ed malforma-tions					n (%) with feed-ing difficulties	n (%) assisted ventilation	median (range) number of years of maternal education	
Gischler	n (%) addi-tional medical problems, n (%) septic complications, n (%), median (IQR) number of congenital anomalis				n (%) neurologic complications	n (%) NG tube at home, n (%) enterostomy at home	n (%) tracheostomy, n (%) oxygen at home		n (%) by categories (low, middle, high)
Giudici		n (%) weight <10th percentile			n with cerebral palsy; n with hearing loss	Mean (SD) / Median (IQR) number of days PN	Mean (Sd) and median (IQR) number of days assisted ventilation		
Giudici		n (%) weight <10th percentile			n with cerebral palsy; n with hearing loss	Mean (SD) / Median (IQR) number of days PN	Mean (Sd) and median (IQR) number of days assisted ventilation		
Gorra									
Harmsen	n (%) sepsis; n (%) vacterl-as-sociation; n (%) cardiac anomaly		Median (range) in hours, me-dian (range) number of anesthetic exposures			Median (range) number of days PN	Median (range) number of days ventilation		n (%) by categories (low, middle, high)
Harris					n with amblyo-pia; n with cere-bral palsy; n with hearing loss				
Hijkoop	n (%) multiple congenital anomalies, n (%) complica-tions	n (%) SGA at birth	Median (IQR) procedures under GA			n (%) with intestinal failure; Median (IQR) number of days to full enteral feeding	Median (IQR) number of days ventilation by type of malformation		median (IQR) maternal SES score, n (%) low maternal SES score

Huang		weight for age Z-score per subject	age in days per subject		Duration of PN in days per subject			
Kato								
Konig		n (%) weight for age Z-score < 2						
Kubota								
Kumari	n (%) associated congenital anomalies	n (%) -3SD weight for age				n (%) on mechanical ventilation	n (%) graduated mothers	n (%) homemakers and monthly family income
Laing			Median (IQR) in days	n (%) with microcephaly		Median (IQR) hours assisted ventilation	n (%) by categories (<12y schooling, >12y, tertiary or further, bachelor or higher degree) by type of parent	n (%) occupation father (skilled, unskilled, associate professional, professional)
Ludman						n (%) assisted ventilation >4 days		n (%) by categories (manual, non-manual, single mom)
Ludman								
Maheswari								
Mawlana	n (%) VACTERL, n (%) associated anomalies, n (%) chromosomal anomalies	n (%) weight <10th percentile			n (%) with gastrostomy			
Mazer	Median (IQR) number of congenital anomalies, n (%) syndromal / chromosomal abnormality				Median (IQR) medical appliances (O2 or tracheostomy) at discharge	Median (IQR) medical appliances (NG tube or enterostomy) at discharge		
Minutillo								
Moran				MRI abnormalities			n (%) maternal tertiary education	n (%) higher social risk
More			Median (IQR) age in days					
Newton						Mean days on ventilator		
Payne		% weight <10th percentile			n (%) all per oris feeding at discharge	Mean (SD) ventilator days		n (%) single mother

Plummer		weight for age z score			Median (IQR) number of days PN; Percentage PN <>7days; Percentage gastrostomy	Median (IQR) days of assisted ventilation; Percentage >2 days assisted ventilation	n (%) maternal eductation (college or higher)	
Sirichaipornsak								
So				n with cerebral palsy	Median (IQR) number of days PN first year; Percentage patients 100% full enteral feeding first year			
So		weight for age Z-score		n with microcephaly	Median (IQR) number of days PN; % PN dependance at follow-up; % enterostomy			
So				n with CNS comorbidity; n with cerebral palsy; n with hearing loss; n with visual comorbidity	Median (IQR) number of days PN first year/ first two years; n (%) PN at follow-up of two years; n (%) 100% full enteral feeds at follow-up of two years			
South		% weight <10th percentile		n (%) abnormal neurological exam	Mean (SD) number of days to full enteral feedings; mean (sd) number of days PN	Mean (SD) number of days assisted ventilation		
Van den Hondel 2013	n (%) at least 1 major associated anomaly; n with suspected (not diagnosed) syndrome	n (%) Small for gestational age at birth			n (%) gastrostomy			
Van den Hondel	n (%) major comorbidity present		Median (IQR) by type of malformation; Median (IQR) by follow-up duration					n (%) by categories (low, middle, high) by type of malformation

Van der Cammen-van Zijp	n (%) associated malformations	n (%) Small for gestational age at birth					Median (range) days ventilation support, n (%) ECMO		
Van Eijck	n with congenital tethered spinal cord syndrome								
Walker	n (%) of associated malformations								
Walker									
Reason for exclusion from univariate meta regression	Heterogeneity of definitions	Heterogeneity of definitions	Not enough studies	Not enough studies	Heterogeneity of definitions	Too biased by type of malformation	Too biased by type of malformation	Heterogeneity of definitions	Heterogeneity of definitions

Results of subgroup analyses on type of malformation

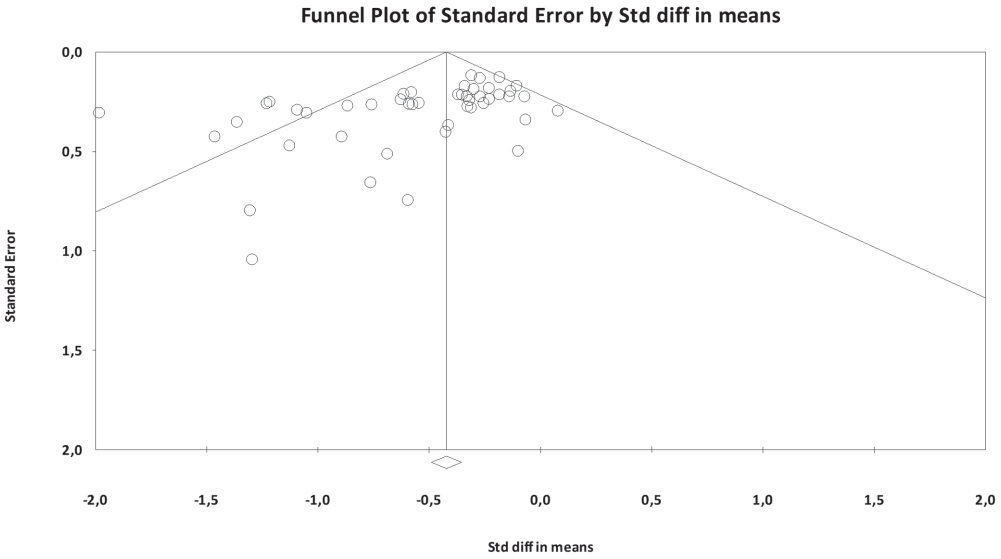
Motor outcomes were significantly different across subgroups of malformations (Q=11.704, p=0.020). Cognitive (Q=3.798, p=0.434) and language outcomes (Q=0.589, p=0.745) did not significantly differ across different types of malformations.

Further analyses showed that patients with short bowel syndrome had significantly worse motor outcomes compared to all remaining patient groups (d=-1.062 and d=-0.474, Q=7.682; p=0.006), but comparable cognitive outcomes (d=-0.241 and d=-0.432,Q=2.875; p=0.09) and language outcomes (d=-0.692 and d=-0.598, Q=0.038; p=0.85).

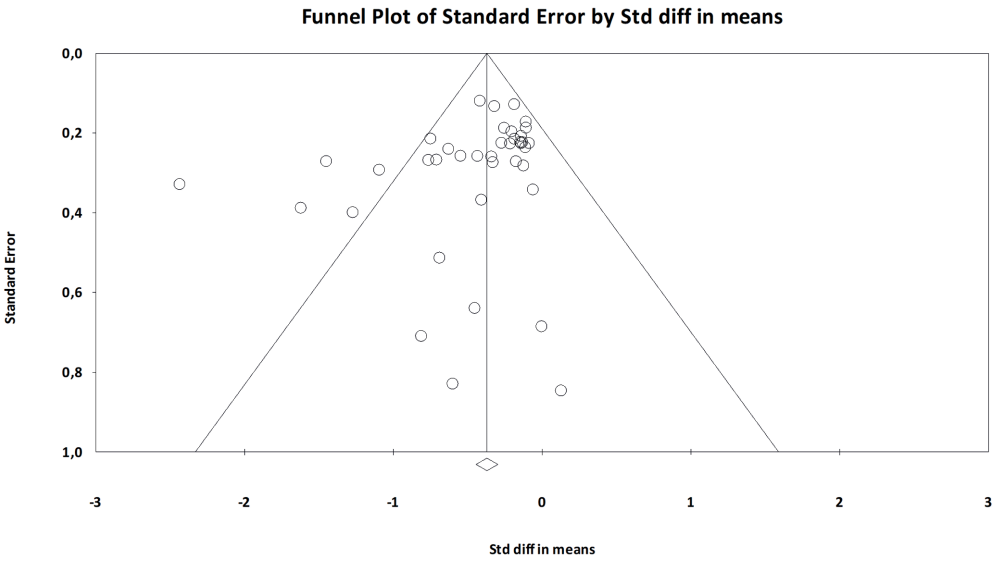
Results of sensitivity analysis of studies of good quality

Effect sizes for overall neurocognitive outcomes and cognitive outcomes differed between studies of different quality ratings (Q=21.46, p<0.001 and Q=45.53, p<0.001, respectively). Sensitivity analysis on studies of good quality (n=36), showed that the reported meta-analytic findings (impairments) were replicated for overall neurodevelopmental outcomes (d=-0.371,95%CI: -0.462 – 0.280, p<0.001), cognitive outcomes (d=-0.281, 95%CI: -0.363 - -0.199, p<0.001), motor outcomes (d=-.0568, 95%CI: -0.738 - -0.398, p<0.001) and language outcomes (d=-0.570, 95%CI: -0.865 - -0.274, p<0.001).

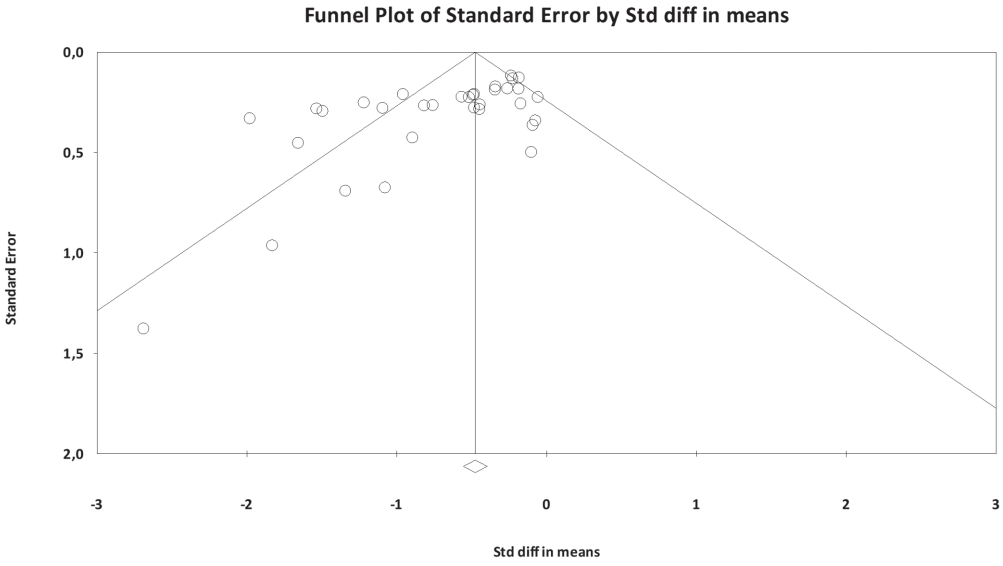
Risk of bias analysis



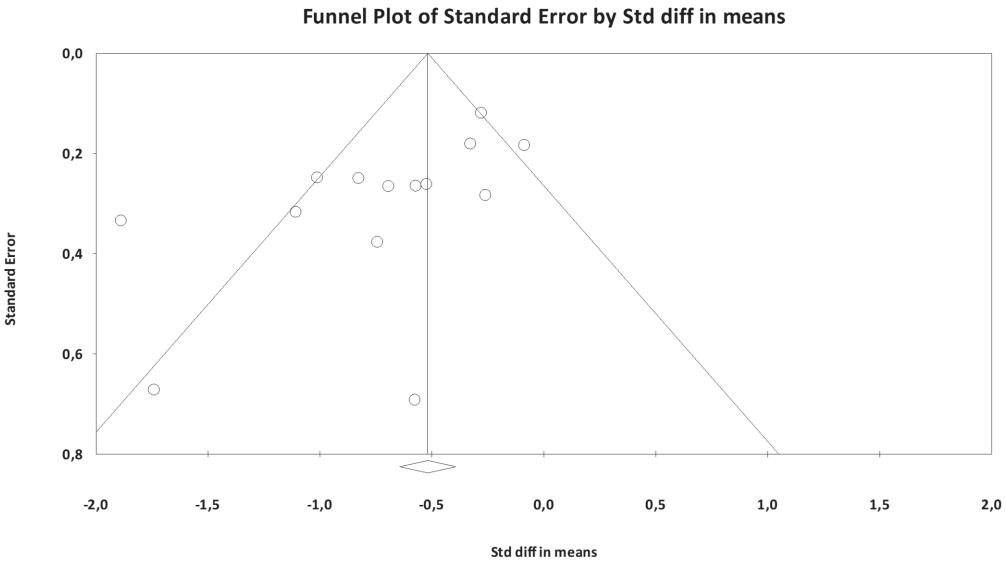
sFigure1 Funnelplot of overall neurodevelopmental outcomes



sFigure2 Funnelplot of cognitive outcomes



sFigure 3 Funnelplot of motor outcomes



sFigure4 Funnelplot of language outcomes

All funnel plots were symmetric on visual inspection and showed no asymmetry. However, Egger's regression showed significant risk of publication bias for all meta-analyses. Risk of potential assessment bias was found for (a) 39 of the 47 studies because these studies compared patient data with normative data standardized for age only, leaving other potentially confounding factors uncontrolled, and (b) 22 of the 47 studies because of loss to follow-up of more than 70% of the participants which may lead to a potential bias either due to loss of high-functioning patients or due to loss of severely impaired patients with co-morbidity and subsequent higher mortality.

CHAPTER 9

Parental distress and symptoms of PTSD in parents of patients with congenital gastrointestinal malformations: a cross-sectional cohort study

D. Roorda, A.F.W. van der Steeg, M. van Dijk, J.P.M. Derikx, R.R. Gorter, J. Rotteveel, J.B. van Goudoever, L.W.E. van Heurn, J. Oosterlaan, L. Haverman, Emma Children's Hospital Amsterdam UMC Follow-Me program consortium

Submitted

ABSTRACT

Background

Congenital gastrointestinal malformation (CGIM) require neonatal surgical treatment and may lead to disease-specific sequelae, which have a potential psychological impact on parents. The aim of this study is to assess distress and symptoms of post-traumatic stress disorder (PTSD) in parents of patients with CGIM.

Methods

In this cross-sectional study, seventy-nine parents (47 mothers and 32 fathers) of 53 patients with CGIM completed the Distress Thermometer for Parents (DT-P) and the Self Rating Scale for Posttraumatic Stress Disorders (SRS-PTSD) as part of the multidisciplinary follow-up of their children (aged 5-35 months). Group differences were tested between parents and representative Dutch reference groups with regard to rates of (clinical) distress and PTSD, and severity of overall distress and PTSD, for mothers and fathers separately. Mixed model regression models were used to study factors associated with the risk of (clinical) distress, PTSD and with severity of symptoms of PTSD (intrusion, avoidance and hyperarousal).

Results

Prevalence of clinical distress was comparable to reference groups for mothers (46%) and fathers (34%). There was no difference in severity of overall distress between both mothers as well as fathers and reference groups. Prevalence of PTSD was significantly higher in mothers (23%) compared to the reference group (5.3%) (OR=5.51, $p<0.001$), not in fathers (6.3% vs 2.2.%). Symptoms of intrusion were commonly reported by all the parents (75%). Longer total length of child's hospital stay was associated with more severe symptoms of intrusion, avoidance and hyperarousal. Child's length of follow-up was negatively associated with severity of intrusion.

Conclusions

Having a child with CGIM has a huge impact on parents, demonstrated by a higher prevalence of PTSD in mothers, but not fathers compared to parents in the general population. Monitoring of symptoms of PTSD of parents in follow-up is necessary.

INTRODUCTION

Congenital gastrointestinal malformations (CGIM) are birth defects of the gastrointestinal tract or abdominal wall (e.g., esophageal atresia, congenital diaphragmatic hernia, gastroschisis, omphalocele, intestinal atresia, Hirschsprung disease and anorectal malformations). CGIM require neonatal surgical treatment and hospital admission early in life and are associated with disease-specific chronic sequelae that require medical treatment at home, which may include: gastro-esophageal reflux and dysphagia or feeding problems requiring parenteral nutrition or gastrostomy in patients with congenital diaphragmatic hernia and esophageal atresia,[1,2] constipation or urinary/fecal incontinence in patients with gastroschisis, Hirschsprung disease and anorectal malformations,[3-6] or the need for dilatations, rectal irrigation, and sometimes catheterization or an enterostomy in patients with Hirschsprung disease and anorectal malformations.[7,8] This may have a psychological impact on their parents.

Parents of patients with CGIM may be vulnerable to psychological distress, because of the potentially traumatic effect of giving birth in general, but on top of that the unexpected and uncertain diagnosis, neonatal surgical treatment and disease-specific chronic sequelae their children may experience. Parents subsequently have complex responsibilities in taking care of the medical care of the child with CGIM, possibly in combination with the care for other siblings. Parents may thus frequently have experiences of loss of control, uncertainty and worries about admissions, treatment and prognosis of their children. All these experiences can be considered as potentially traumatic events, followed by short- or long-term stress responses.[9,10-15 16-19]. These repetitive stress responses can result in post-traumatic stress disorder (PTSD).[9]

Previous studies in parents of patients with CGIM have suggested that they are at risk of anxiety, depression, PTSD, impaired self-efficacy in home care[17,20-22] and financial, practical, social problems.[23-25 26,27] However, previous studies often used small sample sizes and did not compare data on distress and PTSD with data from parents of healthy children. In addition, previous studies made no distinction between mothers and fathers, which may be of interest as studies focusing on other disorders identified significant sex differences in psychosocial experiences of parents.[26,28,29] As psychological distress in parents may influence parenteral quality of life and the parent-child interaction, it may subsequently also impact the wellbeing and functioning of the child.[30] We therefore integrated an online screening of parental psychological wellbeing in the protocols for multidisciplinary follow-up of patients with CGIM in our center.

In the current study, we aimed to assess parental (clinical) distress and PTSD symptoms in mothers and fathers of patients with CGIM in follow-up compared to data from mothers and fathers of Dutch reference populations. In addition, we aimed to study factors associated with (clinical) distress, PTSD and symptoms of PTSD.

METHODS

Participants

In October 2017 a structured multidisciplinary follow-up program was implemented for patients with CGIM. In this program, follow-up visits are scheduled at the ages of 6 months, 12 months, 2, 6, 12, and 16 years of age. Before each follow-up visit, parents complete online questionnaires via the web-based Patient Reported Outcome Measures (PROM) portal KLIK (www.hetklikt.nu). Eligible for this study were parents of patients with esophageal atresia, gastroschisis, omphalocele, Hirschsprung disease, or anorectal malformations. Each parent with a child under the age of 36 months and visiting the follow-up program between implementation and March 2020, was included in this study. Parents were required to have sufficient skills in the Dutch language, and had to provide informed consent. In case parents visited the follow-up program multiple times, only the questionnaires completed at the first follow-up visit were used.

Outcomes and measurements

Socio-demographic background of parents

Parental sex, age, educational level, employment status and parental country of birth were assessed via an online questionnaire administered via the patient portal of our electronic medical record system (EPIC MyChart). Parental educational level was scored on a 1-7 scale, and subdivided in low (0-3.5), middle (4 -5.5) and high (6-7) according to the Gold Standard 2017 (Statistics Netherlands, www.cbs.nl/en-gb). Employment status was defined as the number of parents of a couple that worked full-time (more than 36 hours a week). Parental country of birth was expressed as the number of parents of a couple who were not born in the Netherlands.

Clinical characteristics of the patients

From the medical record type of malformation, length of postoperative hospital stay, and the child's age at follow-up were extracted from the electronic medical record.

Parental distress

Parental distress was measured using the 'Distress Thermometer for Parents' (DT-P).[31] This scale contains 34 or 36 items, depending on the child's age. It yields the following scores: an overall distress score (0=no distress; 10=extreme distress), for which a score of ≥ 4 is considered clinical relevant distress.[32] It further yields six problem domain scores (i.e., practical, social, emotional, physical, cognitive and parenting (an infant or a toddler)), as well as two total problem scores (with and without parenting problem domain score). The parenting domain has two versions (child <2 and child>2 years). The DT-P consist of three additional questions on the prevalence of chronic disease in parents, the

experienced support from social surroundings and the need for psychosocial support. Data of a Dutch reference group of mothers and fathers is available (children aged < 36 months; 188 mothers, 141 fathers) [32] The DT-P has been validated and showed acceptable internal consistency.[31]

Posttraumatic stress

PTSD was measured with the Self Rating Scale for Posttraumatic Stress Disorders (SRS-PTSD) questionnaire.[33] The SRS-PTSD is a self-report questionnaire for adults and contains 22 items that correspond to the 17 symptoms of PTSD as described in the Diagnostic Statistical Manual of Mental Disorders (DSM), the fourth version. The SRS-PTSD consists of the three PTSD symptom domains: intrusion, hyperarousal and avoidance. All symptoms were scored on a four-point Likert scale (0-3), with scores of 2 or 3 reflecting the occurrence of a symptom and higher scores reflecting greater severity of symptoms. Intrusion was considered prevalent in case of at least one occurring intrusion symptom, avoidance was considered prevalent in case of at least three occurring avoidance symptoms and hyperarousal was considered prevalent in case of at least two occurring symptoms.[33] PTSD was considered prevalent when all three symptoms were prevalent. When filling out the SRS-PTSD, parents are asked to keep an event in mind that has had the most impact on them, and report on symptoms that occurred in the past four weeks. The sum of scores on all items was taken as a measure of severity of PTSD, and the sum of scores per symptom domain was taken as measure of symptom severity of intrusion, avoidance or hyperarousal. The rate of PTSD was compared to representative Dutch reference group (1141 females, 1097 males).[34] The SRS-PTSD has shown good reliability, and high sensitivity (86%) and specificity (80%) compared to a structured clinical interview assessing PTSD.[35]

Statistical analysis

Statistical analyses were conducted using SPSS (version 25.0, SPSS Inc, Chicago, IL, USA) and R Studio (version 3.6.1, R Studio Team, PBC, Boston, MA, USA). Descriptive statistics were used to describe the characteristics of the included parents.

First, exploratory group comparisons were done between mothers and fathers of patients with CGIM and sex-matched parents of a Dutch reference group on the following outcome data: rate of clinically relevant distress, overall distress severity score, problem domain scores, total problem scores, answers to the additional questions on the DT-P, and rate of PTSD. In these group comparisons, independent t-tests (t) were used for normally distributed continuous data. For data that were not normally distributed, non-parametric testing was done with the Mann-Whitney U (U) test for the comparison of two groups and Kruskal Wallis test (H) for the comparison of multiple groups. For dichotomous data, X2 test or Fisher's Exact test were used based on the number of patients in each group. Standardized effect sizes were calculated to indicate the magnitude of the observed group differences (Cohen's d for normally distributed continuous data, Rosenthal's r for

non-parametric continuous data and Odds Ratio (OR) for dichotomous data). Further exploratory analyses were done to assess on which specific items on the DT-P parents of patients with CGIM more often reported problems compared to a Dutch reference group.

Second, rate and severity of PTSD and PTSD symptoms were described separately for mothers and fathers within our sample. Furthermore, to assess covariance between answers of fathers and mothers of the same couple, correlations between the overall distress score and severity of PTSD severity score of fathers and mothers from the same couple within our sample were calculated.

Third, univariate and multivariate mixed model logistic and linear regression analyses were used to study risk factors for (clinical) distress, PTSD and PTSD. Mixed model regression analyses were used to account for stronger associations between scores of parents of the same child. Only factors that were significantly associated with outcomes in univariate analysis were entered into multivariate analysis. The following possible risk factors were tested; sex of parent, average educational level of a couple, employment status of a couple, ethnic cultural background of a couple, type of child's malformation, child's age at follow-up, and length of in-hospital stay after surgery. Risk factors were excluded from analysis in case data were missing in more than 30% of the observations (which applied to the average educational level, employment status and ethnic cultural background of parents). In all analyses, an alpha-level of 0.05 was considered statistically significant.

RESULTS

Parent and patient characteristics

The parents of a total of 111 patients were eligible for this study. The parents of 53 of 111 patients (48% response rate) were included. Of the 53 included families, both of the parents were included for 26 families and one of the parents was included for the remaining 27 families. This resulted in the inclusion of 79 parents (47 mothers and 32 fathers), of whom 78 parents responded to both questionnaires, and one parent only to the SRS-PTSD. Of the 79 parents, 64 parents were parenting an infant (<2 year) and 15 were parenting a toddler (2-3 years). Sample characteristics of the mothers and fathers of patients with CGIM included in this study are listed in Table 1.

Table 1 Sample characteristics

	Parents of children with CGIM (n=79)	
	Mothers (n=47)	**Fathers (n=32)**
Parental age in years, mean (SD) *	33.4 (4.6)	37.9 (6.2)
Child's age at follow-up in months, median (range)	8 (5-35)	9.5 (5-26)
Average educational level of parents per couple, median (range)	6 (4.5 – 7)	6 (5-7)
Low (1-3.5), n (%)	0 (0)	0 (0)
Intermediate (4-5.5), n (%)	10 (21.3)	5 (15.6)
High (6-7), n (%)	11 (23.4)	8 (25.0)
Missing, n (%)	*26 (55.3)*	*19 (59.4)*
Number of parents with a country of birth other than the Netherlands per couple, n (%)		
0	16 (34.1)	9 (28.1)
1	5 (10.6)	4 (12.5)
Missing	*26 (55.3)*	*19 (59.4)*
Employment status per couple, n (%)		
0	5 (10.6)	4 (12.5)
1	12 (25.5)	5 (15.6)
2	3 (6.4)	3 (9.4)
Missing	*27 (57.4)*	*20 (62.5)*
Number of responses per follow-up moment, n (%)		
0.5 year	24 (51.1)	16 (50.0)
1 year	12 (25.5)	10 (31.3)
2 years	11 (23.4)	6 (18.7)
Child's type of malformations, n (%)		
Esophageal Atresia	15 (31.9)	11 (34.3)
Abdominal wall defects	9 (19.1)	4 (12.5)
Hirschsprung disease	12 (25.5)	10 (31.3)
Anorectal Malformations	11 (23.4)	7 (21.9)

Note. * Normally distributed data is reported as mean (SD), and not normally distributed as median (range)

Table 2 Parental distress in parents of patients with congenital gastrointestinal malformations

	Mothers CGIM N=46	Normative mothers N=188	Group difference, p-value	Effect size [95%CI]	Fathers CGIM N=32	Normative fathers N=141	Group difference, p-value	Effect size [95%CI]
Clinically relevant distress, *n (%)*	21 (45.6)	90 (47.9)	X^2=0.07, p=.787	OR=0,92 [0.84-1.75]	11 (34.4)	49 (34.8)	X^2=0.002, p=.968	OR= 0.98 [0.44-2.21]
Overall distress scores, *median (range)*	3 (0-10)	3 (0—9)	U=3980.5, p=.401	r=-0.05	2 (0-9)	2 (0-9)	U=2119.0, p=.588	r=-0.04
Problem domain scores								
Practical problem score *median (range)*	1 (0-7)	1 (0-7)	U=4108.0, p=.587	r=-0.04	0 (0-4)	1 (0-7)	U=1973.0, p=.236	r=-0.09
Social problem score, *median (range)*	0 (0-4)	0 (0-3)	U=4580.0, p=.421	r=0.05	0 (0-3)	0 (0-2)	U=1897.5, p=.057	r=-0.14
Emotional problem score, *median (range)*	1 (0-9)	1 (0-9)	U=4686.5, p=.363	r=0.06	0 (0-4)	0 (0-9)	U=1829.5, p=.065	r=-0.14
Physical problem score, *median (range)*	2 (0-7)	2 (0-7)	U=4485.5, p=.690	r=0.03	1 (0-5)	1 (0-6)	U=2121.5, p=.587	r=-0.04
Cognitive problem score, *median (range)*	0 (0-2)	0 (0-2)	U=4731.0, p=.262	r=0.07	0 (0-2)	0 (0-2)	U=2364.0, p=.559	r=0.04
Parenting <2 years of age, *median (range)*	1 (0-7)	0 (0-6)	U=2914.5, p=.006 **	r=0.22	1 (0-7)	0 (0-5)	U=1429.0, p=.072	r=0.16
Parenting ≥ 2 years of age, *median (range)*	0 (0-2)	0 (0-3)	U=178,5, p=.065	r=-0.03	0 (0-1)	0 (0-3)	U=157.5, p=.928	r=-0.02
Total problem scores								
Total problem score, *median (range)*	6 (0-24)	6 (0-24)	U=4517.5, p=.637	r=0.03	2 (0-17)	3 (0-22)	U=1836.0, p=.098	r=-0.13
Total with <2 years parenting, *median (range)*	9 (0-25)	7 (0-27)	U=2699.5, p=.102	r=0.13	3 (0-24)	3 (0-23)	U=1045.5 p=.356	r=-0.08
Total with ≥2 years parenting, *median (range)*	2 (0-16)	6 (0-24)	U=178,5, p=.065	r=-0.22	3 (0-10)	3 (0-19)	U=138.5, p=.562	r=-0.08
Additional questions								
Support from surroundings, *n (%)*	42 (91.3)	171 (91.0)	X^2=0.01, p=.941	OR=1.04 [0.33-3.27]	29 (90.6)	129 (91.5)	X^2=0.03, p=.875	OR=0.89 [0.24-3.39]
People show lack of understanding, *n (%)*	6 (13.0)	30 (16.0)	X^2=0.41, p=.623	OR=0.79 [0.31-2.03]	2 (6.3)	15 (10.6)	X^2=0.57, p=.742	OR=0.56 [0.12-2.58]
Wish to talk to professional, *n (%)*	20 (43.5)	32 (17.0)	X^2=14.97, p<.001 ***	OR=3.75 [1.87-7.52]	6 (18.8)	20 (14.2)	X^2=0.43, p=.584	OR=1.40 [0.51-3.82]
Parent has chronic illness, *n (%)*	7 (15.2)	44 (23.4)	X^2=1.45, p=.228	OR=0.59 [0.25-1.41]	4 (12.5)	16 (11.3)	X^2=0.03, p=.768	OR=1.12 [0.35-3.60]
PTSD								
PTSD, n (%)	11 (23.4)	60 (5.3)	X2=26.45, p<.001*	OR=5.51 [2.67 – 11.35], p<.001 *	2 (6.3)	24 (2.2)	X2=2.00, p=.157	OR=2.98 [0.67 – 13.19], p=.150

Note. * statistically significant, p<.05
"* statistical significance p<.05, ** p<.01, *** p<.001

Parental Distress

In our sample, Cronbach's alphas for the DT-P ranged from 0.70–0.87 for domain scores with the exception of the parenting > 2 years domain score (alpha = 0.31), and from 0.86 – 0.93 for total scores. The prevalence of clinically relevant distress in mothers (45.6%) and fathers (34.4%) of patients with CGIM was not significantly different compared to the sex-matched reference groups (47.9% and 34.8%, respectively). (Table 2). Similarly, overall distress severity scores, problem domain scores and total problem scores of both fathers and mothers on the DT-P did not differ from the sex-matched reference groups (Table 2).

On an item level, the following issues were more often reported by mothers compared to the reference group: problems in social interactions with friends, recurring thoughts about the health issues of their child, feelings of anxiety, problems with sexuality. And on the <2 years parenting domain; problems with taking physical care of the children, problems with following up medical advice, and worries about the development of the children. Fathers of patients with CGIM more often reported issues with mood and (>2year) worries about the development of the children compared to the reference group. No differences were found on the additional questions, except for mothers reporting more often the wish to talk to a professional compared to the reference group. (Table 2). Overall distress scores in fathers and mothers of the same couple (26 couples) within our sample were not significantly correlated (R=0.05, p=0.723).

Univariate mixed model logistic regression showed that none of the four tested factors were significantly associated with the presence of clinical distress. Univariate mixed model linear regression showed that type of malformation was significantly associated with the overall distress severity score, whereas sex of the parent, child's age at follow-up and length of child's hospital stay were not.

Posttraumatic stress

In our sample, Cronbach's alpha for the SRS-PTSD ranged for each domain from 0.74 – 0.81 and was 0.89 for all items together. The prevalence of PTSD in parents of patients with CGIM was 16.5%. Mothers of patients with CGIM had a higher prevalence of PTSD (23.4%) compared to the reference group (5.3%) (X^2=26.45, *OR*=5.51, *95% CI:* 2.67 – 11.35, p<0.001), whereas the prevalence in fathers of patients with CGIM was not significantly different compared to the reference group (Table 2).

Within our sample, 61 of the 79 parents reported symptoms in at least one domain of PTSD (77.2%). Prevalence of intrusion was reported in the great majority of parents of patients with CGIM (74.7%); respectively in 83.0% of the mothers and 62.5% of the fathers. Prevalence of avoidance was reported in 21.5% of parents; respectively in 27.7% of the mothers and 12.5% of the fathers. Prevalence of hyperarousal was reported in 27.8% of the parents; respectively in 38.3% of mothers and 12.5% of the fathers. Mean severity score of PTSD was 24 (22-58); respectively 25 (22-58) in the mothers and 24 (22-39) in fathers. Severity of PTSD in fathers and mothers of the same couple (n=26 couples) in our sample was not significantly correlated (R=-0.29, p=0.841).

Univariate mixed model logistic regression showed that only male sex of the parent was negatively associated with the presence of PTSD. Univariate mixed model linear regression showed that male sex of the parent, child's age at follow-up and that child's length of hospital stay were associated with one of the symptom domains and were included in the multivariate analysis. The results of the multivariate mixed model regression models are shown in Table 3, and show that male parental sex was negatively associated with severity of intrusion, avoidance and hyperarousal, that child's length of hospital stay was associated with severity of intrusion, avoidance and hyperarousal and that child's age at follow-up was negatively associated with severity of intrusion.

Table 3 Risk factors for symptom severity of post-traumatic stress disorder in multivariate mixed model linear regression

	Severity of intrusion **Multivariate Fixed effects, ß (95%-CI), p-value**	**Severity of avoidance** **Multivariate Fixed effects, ß (95%-CI), p-value**	**Severity of hyperarousal** **Multivariate Fixed effects, ß (95%-CI), p-value**
Type of parent Mother Father	0 [Reference] -1.42 (-2.46 - -0.39), p=0.009 **	0 [Reference] -1.12 (-1.80 – -0.43), p=0.003 **	0 [Reference] -1.52 (-2.65 - -0.38), p=0.012 *
Child's age at follow-up	-0.07 (-0.14 – -0.01), p=0.037 *	NA	NA
Child's length of hospital stay	0.03 (0.01 – 0.06), p = 0.009 **	0.03 (0.01 – 0.05), p=0.021 *	0.03 (0.004 – 0.06) , p =0.032 *

Note. * p <0.05, ** p<0.01, *** p<0.001

DISCUSSION

Summary of findings

This study aimed to assess distress and PTSD in parents of patients with CGIM, using data from clinical screening in follow-up, whilst comparing mothers to mothers and fathers to fathers from reference groups.

With regard to parental distress, our findings showed that parents of patients with CGIM experience equal amounts of parental distress compared to reference groups, which is in line with other studies assessing distress in parents of patients with esophageal atresia and anorectal malformations.[10,12] However, some specific problems were reported more often by parents, including problems with parenting, concerns about the development of children, and in mothers emotional problems, problems with social interactions and recurring thoughts about the admission in mothers, in line with higher levels of PTSD in mothers. Mothers also more often expressed the wish to talk to a professional compared to the reference group.

With regard to parental post-traumatic stress, our findings showed that parents of patients with CGIM are at risk for developing PTSD symptoms and that almost a quarter

of the mothers met the criteria for PTSD. Our findings further showed that from the three major PTSD symptoms (intrusion, avoidance and hyperarousal), intrusions were most commonly reported. Intrusions are sudden recalls or nightmares of a certain traumatic experience, that initiate an acute stress response.[36] Also in case no diagnosis of PTSD has been made and intrusions occur secluded from others symptoms of PTSD, intrusions can cause an acute stress response which in turn can contribute to chronically elevated stress levels.[9] Our findings showed that the prevalence and risk of PTSD was higher in mothers with CGIM but not in fathers, compared to Dutch reference groups. This sex difference has been reported more often in previous studies and may be related to stronger perceptions of threat and loss of control in women.[28,37,38] Our findings that mothers of patients with CGIM are at risk for PTSD are in line with a previous study of Le Gouez et al. in parents of patients with esophageal atresia. In that study even higher rates of PTSD were found, and PTSD was found both in fathers and mothers.[11] Le Gouez et al. had included younger patients and only patients with esophageal atresia, which may explain differences. Although we expected that differences in child's type of malformation would explain differences in severity of distress and PTSD symptoms, because of differences in the treatment and disease-specific sequelae between different types of malformations, our findings also did not suggest this.[12,24] The factors that induce a posttraumatic stress response may also be related to premorbid psychological wellbeing of parents, including previous episodes of PTSD, pre-existent personality disorder, depression or anxiety disorder.[36] Other inducing factors may be related to receiving an unexpected diagnosis, general aspects of medical treatment and hospital admission, including communication by health care professionals, that attribute to experiences of uncertainty or experiences of loss of control.[15,18,39] These factors may contribute to developing PTSD regardless of the child's type of malformation, as this is highly dependent on the subjective interpretation of parents rather than the objective information provided. Our findings did suggest that length of child's hospital stay was associated with increased severity of PTSD symptoms. This suggests that being in an environment with stress-inducing stimuli may play a role and create recurrent and stacked stress responses, thus adding to more severe symptoms of intrusions, avoidance and hyperarousal. Previous evidence also shows that giving birth may be a traumatic experience in itself.[40-42] Mothers of patients with a birth defect may have an increased risk, as among the risk factors for traumatic childbirth are psychological difficulties during pregnancy, obstetric or infant complications, and emergency caesarean section. CGIM may be associated with a prenatal diagnosis inducing psychological distress during pregnancy, delivery by caesarean section and infant complications after delivery.[43]

Our findings emphasize the need to pay attention to parents during follow-up of patients with CGIM. Although collecting Patient Reported Outcome Measure (PROM) data in clinical practice has it challenges, our study shows the relevance and usefulness screening of parents for issues in daily life that cause distress and symptoms of PTSD. Early recognition of psychological distress and PTSD symptoms may lead to interventions.

Evidence shows that EMDR has good effects on PTSD symptoms, particularly intrusions.[44] All parents who experience intrusions, not just those with an official diagnoses of PTSD, may benefit from EMDR treatment. Other possible interventions that parents may benefit from are social work, parental support groups, or social media support groups.[45-47] Interventions may prevent further negative consequences of psychological distress and PTSD symptoms from occurring, including disrupted bonding between parents and child, difficulties in the relationship between parents and problems with parenting, which in turn may have negative impact on family functioning and child's functioning.[10,48-50] Moreover, PTSD is associated with higher risk of anxiety and depression disorder,[41,51] and may lead to increased absenteeism from work or social activities.[52]

Limitations

Our findings need to be interpreted in the light of a few limitations that were part of this study. First, there was a risk of inclusions bias resulting in low response rates. We collected PROM data in a multidisciplinary program that was implemented during the study period. Response rates may have been negatively influenced by challenges in the implementation of the multidisciplinary follow-up, including difficulties of parents with the activation of their account on the online portal for questionnaires. Moreover, completing questionnaires can be time-consuming, thus decreasing the response rate. Because we used standardized questionnaires for our outcome measurement, there was no possibility to qualitatively assess aspects of distress and intrusions. Secondly, our sample size, the amount of missing data on socio-demographic characteristics, as well as the exclusion of parents with a limited ability of the Dutch language, limited the possibility to assess factors associated with the risk and symptom severity of parental distress and PTSD. Lastly, because of the number of comparisons done in this study, and the exploratory nature of some of the analyses, the risk of chance findings cannot be ruled out. In particular the findings from the comparison on an item-level of the DT-P between parents of patients with CGIM and references groups thus require caution and await further replication in larger samples.

Future perspectives

We think future studies should focus on identification of factors that contribute to distress and PTSD symptoms in parents of patients with CGIM, including socio-demographic characteristics, premorbid psychopathology, previous traumatic experiences, and aspects of medical treatment or communication by health care professionals. Studies should also focus on how to empower factors that may protect parents of patients with CGIM from developing PTSD, including coping skills, psychoeducational support during hospital stay, and supportive communication by health care providers

For future studies it would further be interesting to use a qualitative approach with interviews or focus groups to assess the nature of the intrusions parents experience and what triggers intrusions. This may provide more insight in the specific experiences that

are traumatic to parents. Insight in factors that contribute to distress and PTSD may lead to interventions to prevent distress and PTSD.

Lastly, we recommend longitudinal monitoring of psychological wellbeing of parents in follow-up of patients with CGIM. This allows for the assessment of longitudinal trends in distress and PTSD symptoms and may provide more insight in the type of PTSD the parents may experience, triggers for intrusion and the effects of interventions, including EMDR, psychoeducational interventions, parent-support groups and online interventions.[44-47,53]

Conclusions

In this study we demonstrated a higher prevalence (23%) of PTSD in mothers of patients with CGIM compared to a reference group (5%), and symptoms of intrusion in a majority of parents (75%). Our findings emphasize the need for monitoring of psychological wellbeing of parents of patients with CGIM in follow-up. In order to provide integrative, family-centered care, we recommend the integration of screening on PTSD symptoms in follow-up of patients with CGIM. Early recognition of PTSD symptoms and distress may improve psychological wellbeing of the parents by providing interventions including EMDR.

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CHAPTER 10

Standardized Prospective Multidisciplinary Follow-Up of Patients with Surgical Congenital Malformations: A Model for Continuous Data Driven Improvement of Health Care

D. Roorda, A.F.W. van der Steeg, J.P.M. Derikx, R.R. Gorter, L.W.E. van Heurn, J. Oosterlaan, Emma Children's Hospital Amsterdam UMC Follow-Me program consortium

Submitted

ABSTRACT

Introduction

Congenital malformations requiring surgery are rare conditions, and despite decreasing mortality, these conditions are associated with substantial morbidity. Although research on outcomes of these patients is mostly focused on short term somatic outcomes, emerging evidence suggests morbidity in other aspects of functioning, such as neurodevelopmental impairment and impaired psychosocial functioning. Therefore prospective multidisciplinary follow-up is important. Moreover, standardizing prospective multidisciplinary follow-up creates the opportunity to use data collected in follow-up for improvement of patient outcomes, routine outcome monitoring aimed at health care evaluation and scientific research.

Methods

In this paper the design of a standardized prospective multidisciplinary follow-up program of surgical congenital malformations in the Amsterdam University Medical Centers is presented. Development of follow-up protocols, the composition of the multidisciplinary team, the process of data collection, all implemented patient-reported and clinician reported outcome measures, the practical design of the follow-up carousel and multidisciplinary team meeting, and the health care evaluation sessions that are implemented in the program are described. Furthermore we describe the data-driven approach to improvement of patient outcome and health care quality, that is integrated in this follow-up program.

Discussion

Standardized prospective multidisciplinary follow-up in patients with surgical congenital malformations offers the possibility to standardize outcome measurements including patient-reported outcomes, thus allowing for 1) early recognition and intervention for poor outcome, thus improving patient outcome, 2) improvement of quality of health care by conducting outcome evaluation, and 3) a contribution to research on outcome and prognosis of patients with surgical congenital malformations.

INTRODUCTION

Congenital malformations occur in about 2.5% of all pregnancies and 2% of all live births in Europe[1], and often require surgical treatment. As a result of improvements in surgical and in-hospital care, survival in patients with surgical congenital malformations has improved over the past decades.[2] Nonetheless, significant physical morbidity is observed in infancy and childhood. This morbidity may pertain to various aspects of physical functioning, including gastrointestinal, [3-6] respiratory,[7-11] or genitourinary problems,[5,12,13] and varies between types of congenital malformations and the required surgical procedures. However, morbidity in patients may also include neurodevelopmental impairment[14,15] and psychosocial problems.[16-19] These morbidity associated with surgical congenital malformations may also negatively impact family functioning and parental psychosocial health in partcular.[20-23] Because various aspects of functioning may be negatively impacted in patients with surgical congenital malformations, high quality multidisciplinary follow-up is required.

The currently available evidence about physical, neurodevelopmental and psychosocial outcome of patients with surgical congenital malformations shows that there is large heterogeneity in functioning between patients. The evidence is almost exclusively limited to small-sized cross-sectional studies that often lack the power to identify factors that contribute to this heterogeneity in outcomes, thus failing to identify risk factors for adverse outcomes. This interferes with the ability of clinicians to provide a reliable prognosis of outcomes and to personalize follow-up care and treatment. Personalized medicine or precision medicine is an emerging approach in medicine that aims to customize health care to the needs of an individual patient, aimed at achieving optimal outcomes.[24,25] To improve the application of precision medicine in surgical congenital malformations, standardized data collection is necessary, as precision medicine is highly dependent of a data driven approach.[26]

Here we present the design of a standardized prospective multidisciplinary follow-up program for surgical congenital malformations that was implemented in our hospital. The program is part of the Follow Me program of the Emma Children's Hospital of the Amsterdam University Medical Centers, the Netherlands, which aims to offer high quality evidence based multidisciplinary follow-up to all level 3 (academic) pediatric patients. The program facilitates standardized data collection, and subsequent data extraction and data evaluation, and allows for multiple potential applications, First, the gathered data allows progress evaluation of individual patient outcome over time, enabling early recognition of impairments in functioning and development, which may facilitate timely and appropriate intervention. Second, the collected data enables periodic evaluation of the long-term outcomes of the surgical interventions and of the follow-up care delivered to patients and their families, enabling the detection of targets for improvement of surgical and follow-up care and paving the road to benchmark with other health care

providers. There are currently only a limited number of quality registrations for surgical congenital malformations that mainly focus on short-term outcomes, including mortality rates and postoperative complications, but do not include long-term outcomes.[27-29] Third, standardized collection of long-term outcomes facilitates scientific research into surgical congenital malformations. Collected data can be used to (a) study (longitudinal trends in) disease-specific outcomes, which can be used for patient education and shared-decision making, (b) build clinical prediction models, that might be used to personalize treatment, and (c) study risk and protective factors that may provide new leads to enhance outcomes of patients with surgical congenital malformations.

The objective of this paper is to describe the design of the standardized prospective multidisciplinary follow-up program for patients with surgical congenital malformations that we have implemented. With this paper we aim to argue that structured collection of long-term outcome data within a standardized prospective multidisciplinary follow-up program, can contribute to a data driven approach to improvement of the quality of care and patient outcomes, and contribute to scientific research.

METHODS

Structure of the follow-up program

The implemented follow-up program is a standardized prospective multidisciplinary program that is offered to all patients aged 0 to 17 years with surgical congenital malformations in the Emma Children's Hospital of the Amsterdam University Medical Centers, Amsterdam, the Netherlands. More specifically, the program targets patients with esophageal atresia, congenital pulmonary malformations, abdominal wall defects, sacrococcygeal teratoma, Hirschsprung disease and patients with anorectal malformations. Besides regular postoperative checkups with the pediatric surgeon had been in charge of the surgical treatment, eligible patients and their parents are invited to the follow-up program at the ages of 6, 12, and 24 months, and 6, 12 and 16 years. These ages represent important transitions in a child's development, including the start of formal schooling and puberty. Parents (at patient age of 0 to 6 years) and patients (at the ages of 12 and 16 years) are invited to complete online questionnaires prior to the consultation. This way the multidisciplinary team can prepare the consultation and focus on specific issues reported in a patient, whilst data on functioning is collected for all patients. During consultation, the patient and parent(s) meet with a multidisciplinary team of health care professionals. The specific composition of the team for each follow-up moment is tailored to the type of malformation and the age at follow-up and may involve a pediatric surgeon, nurse practitioner, pediatric gastroenterologist, pediatric pulmonologist, genetic counselor, physical therapist, psychologist and neuropsychologist. If indicated, patients are referred to other dedicated health care providers, including a dietician, speech therapist, urologist, gynecologist and/or a sexual health counselor.

Development of follow-up protocols

Prior to implementation of the standardized prospective multidisciplinary follow-up program, evidence-based follow-up protocols containing outcomes and corresponding outcome measures were developed based on (in order of preference) international and national guidelines, consensus statements, reviews and meta-analyses, other empirical literature or clinical experience, and to each protocol a protocol holder was assigned. All protocols were developed by the assigned protocol holder and reviewed by the full multidisciplinary team of health care professionals participating in the follow-up program and by members of the Follow Me program team.

For the follow-up by the medical specialists (i.e. pediatric surgeon, pediatric gastroenterologist and pediatric pulmonologist), protocols were developed tailored to the type of malformation. These protocols focus on disease-specific functional gastrointestinal, genitourinary or pulmonary sequelae. The genetic counselor has developed a protocol for genetic examination of those patients with types of malformations that may be syndromal and for which chromosomal or genetic abnormalities are known (i.e. esophageal atresia, omphalocele, Hirschsprung disease, anorectal malformations or sacrococcygeal teratoma). On top of the disease-specific follow-up protocols, generic protocols were developed, used for all types of malformations, and aimed at screening of psychosocial outcomes and neurodevelopmental outcomes. The protocol for the screening of psychosocial outcomes of patients and parents was developed by a psychologist. The protocol for the screening of neurodevelopmental outcomes of patients was developed by a physical therapist, a rehabilitation physician and a neuropsychologist.

Outcome measures

In the standardized prospective multidisciplinary follow-up program, various outcomes are evaluated, including generic somatic functioning, gastrointestinal, genitourinary and respiratory functioning, surgical outcome, perinatal and genetic background, health-related quality of life, psychosocial and neurodevelopmental functioning, and parental psychosocial wellbeing. All outcomes are measured by subjective parent- and patient-reported outcome measures (PROMs) or by objective clinical outcome measures including history taking, physical examination and objective laboratory, radiological or additional diagnostic studies. For PROMs validated instruments with available Dutch normative data are used if available. An overview of all PROMs is provided in Table 1 and an overview of all objective clinical outcome measures is provided in Table 2. A detailed description of all instruments used to assess the various outcomes and (if applicable) their psychometric properties, is provided in the Supplementary Material.

Table 1 Overview of all instruments used for parent- and patients-reported outcome measures (PROMs)

Type of malformation	Outcome domain	Outcome measure	Follow-up moment
All surgical congenital malformations	Surgical outcome	GSFQ	6m, 12m, 24m, 6y, 8y, 12y 16y
	Perinatal background	PBQ	6m
	Health-related Quality of Life	TAPQOL PEdsQL	6m, 12m 24m, 6y, 8y, 12y, 16y
	Psychosocial functioning	CBCL SDQ SWAN CRIES-13	 12y, 16y
	Neurodevelopmental functioning	LQ	24m
	Parental psychosocial wellbeing	DT-P SRS-PTSD	6m, 12m, 24m, 6y, 8y, 12y 16y 6m, 12m, 24m, 6y, 8y, 12y 16y
Esophageal atresia	Gastrointestinal functioning	IGERQ SQ ARQ DHI	6m, 12m 12m 24m, 6y, 8y, 12y, 16y 24m, 6y, 8y, 12y, 16y
Hirschsprung disease	Gastrointestinal functioning	DEFEC-P	8y, 12y, 16y
	Health-related Quality of Life	HAQL	8y, 12y, 16y
Anorectal malformations	Gastrointestinal functioning	DEFEC-P	8y, 12y, 16y
	Genitourinary functioning	Micturition diary	6y
	Health-related Quality of Life	HAQL	8y, 12y, 16y
Sacrococcygeal teratoma	Gastrointestinal functioning	DEFEC-P	8y, 12y, 16y
	Genitourinary functioning	Micturition diary	6y

Note. GSFQ = self-developed generic somatic functioning questionnaire ; PBQ = self-developed perinatal background questionnaire ; TAPQOL = TNO-AZL Preschool Children Quality of Life Questionnaire; PEDsQL = Pediatric Quality of Life Inventory; CBCL = Child Behaviour Checklist; SDQ = Strengths and Difficulties Questionnaire; SWAN = Stenghts and Weaknesses of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behavior Scale; LQ = Lexiquotient; CRIES = Children's Revised Impact of Event Scale; DT-P = Distress Thermometer for Parents ; SRS-PTSD = Self-report Scale for Post Traumatic Stress Disorder; IGERQ = Infant Gastroesophageal Reflux Questionnaire; SQ = self-developed swallowing questionnaire; ARQ = Amsterdam Reflux Questionnaire ; DHI = Dysphagia Handicap Index; P-DEFEC = Groningen Defecation and Continence Questionnaire for Pediatric Subjects ; HAQL = Hirschsprung disease and Anorectal Malformations Quality of Life Questionnaire

Table 2 Overview of all instruments used for objective clinical examination

Type of malformation	Outcome domain	Outcome measure	Follow-up moment
All types of surgical congenital malformations	Growth	· Weight · Height	· 6m; 12m; 2y; 5y; 6y; 8y; 12y; 16y · 6m; 12m; 2y; 5y; 6y; 8y; 12y; 16y
	Genitourinary outcome	· Tanner stadium	· 8y; 12y; 16y
	Neurodevelopmental functioning	· BSID-III-NL · Van Wiechenschema · MABC-2-NL · 6MWT · Fitkids · WISC-V-NL · ETB · Cito scores	· 6m; 12m; 2y · 2y · 5y; 8y; 12y; 16y · 5y; 8y; 12y; 16y · 5y; 8y; 12y; 16y · 6y; 8y; 12y; 16y · 6y; 8y; 12y; 16y · 6y; 8y; 12y; 16y
	Surgical outcome	· History taking · Physical examination	· 6m; 12m; 2y; 5y; 6y; 8y; 12y; 16y · 6m; 12m; 2y; 5y; 6y; 8y; 12y; 16y
Esophageal atresia	Genetic background	· VACTERL screening · Chromosomal Array	· 6m · 6m
	Surgical outcome	· Thoracic X-ray · Spine X-ray	· 5y; 8y; 12y; 16y · 5y; 8y; 12y; 16y
	Gastrointestinal functioning	· HR-Ph-Impedance measurement · Manometry · Esophagoscopy	· 15m; 8y; 16y · 15m; 8y; 16y · 15m; 8y; 16y
	Respiratory functioning	· Spirometry · Bodybox	· 5y; 8y; 12y; 16y · 8y; 12y; 16y
Congenital lung malformations	Surgical outcome	· Thoracic X-ray · Spine X-ray · Thoracic CT-scan	· 5y; 8y · 5y; 8y · 8y; 16y
	Respiratory functioning	· Spirometry · Bodybox	· 5y; 8y; 12y; 16y · 8y; 12y; 16y
Omphalocele	Genetic background	· Chromosomal Array	· 6m
	Respiratory functioning	· Thoracic X-ray · Spirometry · Bodybox	· 5y; 8y; 12y; 16y · 8y; 16y · 8y; 16y
Hirschsprung disease	Genetic background	· Chromosomal Array	· 6m
	Gastrointestinal functioning	· Abdominal X-ray · Abdominal ultrasound	· 6m; 12m; 2y; 5y; 6y; 8y; 12y; 16y · 6m; 12m; 2y; 5y; 6y; 8y; 12y; 16y
Anorectal malformations	Genetic background	· VACTERL screening · Chromosomal Array	· 6m · 6m
	Genitourinary functioning	· Bladder and kidney ultrasound · Uroflowmetry · Abdominal ultrasound of internal genitalia	· 5y · 5y · 12y
Sacrococcygeal teratoma	Genetic background	· Chromosomal Array	· 6m
	Surgical outcome	· Laboratory diagnostics (AFP)	· 6m; 12m; 2y; 5y; 6y; 8y; 12y; 16y
	Genitourinary functioning	· Bladder and kidney ultrasound · Uroflowmetry	· 5y · 5y
Short Bowel Sydnrome	Gastrointestinal functioning	· Abdominal X-ray · Laboratory diagnostics (Blood: Na, K, Hb, CA, P, Mg, Vit A,/D/E/B12, PTH; Urine: Na, K Oxalate) · Bone density scan	· 2y; 5y; 6y; 8y; 12y; 16y · 2y; 5y; 6y; 8y; 12y; 16y · 2y; 5y; 6y; 8y; 12y; 16y

Note. BSID-III-NL = Bayley Scales of Infant Development, 3rd version in Dutch; 6MWT = Six minute walking test; MABC-2-NL = Movement Assessment Battery for Children, 2nd version in Dutch; WISC-V-NL = Wechsler Intelligence Scale for Children, 5th version in Dutch; ETB = Emma Toolbox; CITO = Dutch Institute for Academic Testing in Primary School; AFP = alpha-foetoprotein; Na = sodium; K = potassium; Hb = Hemoglobin; Ca = calcium; P = phosphate; Mg = Magnesium; Vit = Vitamin; PTH = Parathyroid hormone;

Generic somatic functioning outcomes assessed in all patients include growth (height, weight, weight-to-height and body mass index), physical endurance, functioning of feeding, defecation, micturition, sleep and physical activity. Gastrointestinal functional outcomes assessed in patients with esophageal atresia include swallowing, esophageal motility, dysphagia, reflux and esophageal alterations including esophagitis or Barrett's esophagus. Gastrointestinal outcomes evaluated in patients with Hirschsprung disease, anorectal malformation, abdominal wall defects and sacrococcygeal teratoma include defecation and continence, and in patients with Hirschsprung disease enterocolitis and treatment with botulinum toxin injections. Genitourinary functional outcomes considered in patients with anorectal malformations and sacrococcygeal teratoma include micturition, and on indication bladder residuals and the occurrence of urinary tract infections. Respiratory functional outcomes assessed in patients with pulmonary malformations, esophageal atresia with tracheomalacia, and omphalocele include physical exercise endurance, respiratory function, and respiratory tract infections. Surgical outcomes include the occurence of procedure-related sequelae or recurrences rates of specific conditions.

Perinatal background includes data such as perinatal exposure of the mother to alcohol, smoking and drugs and medication, maternal medical problems and treatment during pregnancy, and birth characteristics including type of delivery, birth weight and gestational age.

Genetic background includes the occurrence and prevalence of specific chromosomal or genetic abnormalities.

Psychosocial outcomes assessed in all patients include behavioral and emotional functioning, attention behavior and post-traumatic stress disorder. Neurodevelopmental outcomes assessed in all patients include motor and cognitive functioning, and language development. Health-related quality of life outcomes assessed in all patients are generic health-related quality of life, and disease-specific health-related quality of life is assessed in patient groups for which a disease-specific instrument is available. Outcomes with regard to parental psychosocial functioning include distress and PTSD.

Data collection

The standardized prospective multidisciplinary follow-up program uses e-health applications, which may contribute to increased patient and parent participation. Patients and parents complete PROMs via two web based portals. The web-based survey portal KLIK is used for collecting PROMs on psychosocial outcomes of patients and parents and has shown to be an effective tool to collect PROMs.[30] Data collected in this portal can be viewed in the patient's electronic medical record via an interface. For the collection of PROMs about functional somatic outcomes, the patient portal of our electronic medical record (EPIC MyChart) is used. Data collected with EPIC MyChart is automatically stored in the patient's electronic medical record. Objective outcome data collected from history taking, physical examination, laboratory, radiologic and other diagnostic studies, are

registered in stored in the patient's electronic medical record (EPIC Hyperspace), using discrete registrations.

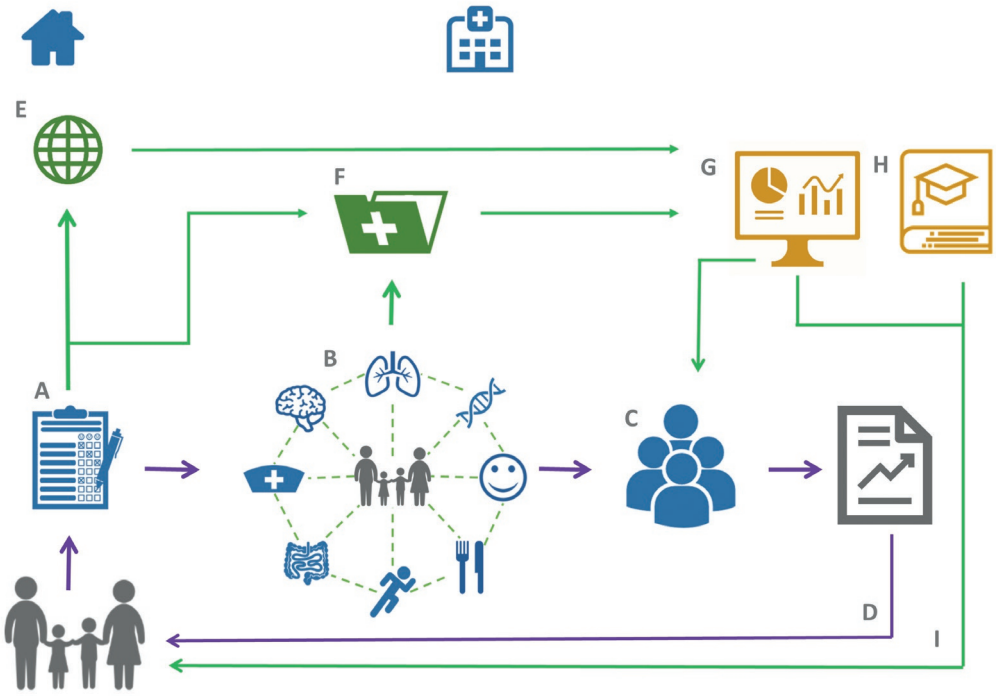

Figure 1 Overview of data collection of patient outcomes in the primary care process (purple arrows) and the cycle of quality evaluation and scientific research (green arrows), describing how patient and parent(s) fill in parent- or patient-reported outcome measures (PROMs) prior to consultation (A), then have successive follow-up consultations with the assigned medical specialist(s), nurse practitioner, physical therapist and neuropsychologist, tailored to the type of malformation and age at follow-up, in which objective clinical measures are registered (B), then the health care professionals meet in a multidisciplinary meeting (C) to integrate findings and formulate a treatment plan if deemed necessary, which is subsequently communicated to the patient and parent(s) (D). All collected data is stored in a local data repository (E) or in the patient's electronic medical record (F) and extracted for the visualization of process and outcome indicators in a PowerBI dashboard (G) used for quality of care evaluation and the use in scientific research (H), which in turn can be used for patient education and shared-decision making (I).

All data from the patient's electronic medical record is stored in a hospital-wide data warehouse and extracted in a standardized format via an SQL-server. All data extracted from the patient's electronic medical record, combined with PROMs on psychosocial outcomes collected via the KLIK portal, are analyzed and visualized in a dashboard built in Microsoft PowerBI. This dashboard is used to support yearly health care evaluation sessions, which are further described in section 2.6. Figure 1 shows the data flow in the primary care process (purple arrows) and cycle of quality evaluation and scientific research (green arrows).

Procedures

Preparation for the follow-up consultations

Eligible patients are invited to the standardized prospective multidisciplinary follow-up program. Invitations are accompanied with patient information about what to expect in the follow-up program, an overview of the health care providers involved in the follow-up, and an invitation to fill in the PROMs via the KLIK and EPIC MyChart portal. Because patients and parents report PROMs prior to the consultation, the consultation can be targeted towards issues that matter most to the patient and parents, without loss of information on domains of functioning in which a patient exhibits normal functioning, thus improving patient centered care and quality of care.[31-33] To prepare for the follow-up consultation, the nurse practitioner (who serves as case manager) and the involved medical specialists assess the quality of life PROMs in the KLIK portal and the functional somatic PROMs in the EPIC MyChart portal; the psychologist assess the psychosocial PROMs of patients and parents in the KLIK portal. The psychologist provides a written evaluation of psychosocial functioning of patients and parents in the patient's electronic medical record and advices the medical specialists on what to discuss with patients and parents with regard to their psychosocial outcomes and on possible interventions. This is organized accordingly to ensure privacy of parents (as the specialists are not their treating physician, but their child's) and because it requires psychological training to adequately interpret the psychosocial PROMs.

Follow-up consultations and multidisciplinary team meeting

Upon arrival at the outpatient clinic, patients and their parents receive a schedule showing the order and duration of the consultations with the various health care providers. Then they successively meet with each of the health care providers. Thereafter, a multidisciplinary team meeting is scheduled, in which all monitored outcomes are shared and evaluated and recommendations for further evaluation and treatment are discussed. In this meeting all interventions are ordered, referrals are made if indicated, and a standardized report of the meeting is written and stored in the patient's electronic medical record. Further follow-up consultations are scheduled, including follow-up consultations with any of the involved health care providers and the next appointment for the standardized prospective multidisciplinary follow-up program.

Feedback reports

The standardized written report of the multidisciplinary team meeting is sent to the general practitioner and any other treating physicians. Patients and parents receive a summary of findings and recommendations for further evaluation and treatment. If required, parents and patients (above 16 years) are also approached by phone to further explain findings and recommendations for interventions that are set in or referrals that were made, as well as

to discuss questions and concerns from patients or parents, or additional questions from the multidisciplinary team.

Yearly health care evaluation sessions

Yearly health care evaluation meetings are organized with representatives of patient organizations, the multidisciplinary team, representatives of the Follow Me program and the Emma Children's Hospital management team. In these meetings, all relevant outcomes obtained in follow-up are evaluated at a population level using dashboards that display real time available process indicators and outcomes. These process indicators and outcomes were identified with a Delphi procedure among members of the multidisciplinary team previous to implementation of the standardized prospective multidisciplinary follow-up program. Additional outcomes that are considered relevant by protocol keepers can also be added to the dashboards upon request. During the evaluation session, the various process indicators and outcomes are evaluated, targets for improvement are selected and accompanying required actions defined. During these sessions the presented data may also give rise to changes in the follow-up protocols.

DISCUSSION

We describe a evidenced-based approach to the standardized prospective multidisciplinary follow-up of patients with surgical congenital malformations and structured data collection of patient outcomes facilitating a data driven approach to continuous improvement of 1) individual patient outcomes, 2) quality evaluation of the long-term outcomes of the surgical interventions and of the follow-up care delivered and 3) scientific research on outcome, prognosis and risk and risk and protective factors in patients with surgical congenital malformations.

Our standardized prospective multidisciplinary follow-up program does not only include a comprehensive assessment of disease-specific physical functioning in the affected tracti of children with surgical congenital malformations, which is common in follow-up, but also of other aspects functioning known to be frequently affected in these children, including neurodevelopment and psychosocial functioning. As child health may also impact parental functioning, our follow-up also focuses on psychosocial wellbeing of parents. Our multidisciplinary holistic approach follows the International Classification of Functioning, Disability and Health model of the World Health Organization, that acknowledges that health is a multidimensional construct that is under the influence of environmental factors. In infants and children this largely constitutes of parental care. Measuring individual outcomes in various outcome domains and changes in these domains over time, allows to identify leads and start interventions that aim to improve integrative individual patient outcomes.

To facilitate health care evaluation and improvement of quality of care, a cycle of continuous data-driven evaluation and improvement has been integrated in our standardized prospective multidisciplinary follow-up porgram.[34] This strengthens a connection between quality of care evaluation and clinical practice. Often the people who provide care are not directly involved in health care evaluation, which is often done by designated quality control departments. As the health care providers who perform quality evaluation in our program are the same professionals who provide care, they are able to directly implement lessons learned from quality evaluation into clinical practice. Moreover, their involvement in clinical practice may yield insight in relevant quality indicators that can directly be taken into account in quality evaluation.[31,35] By integrating the tasks of health care evaluation of and health care provision within one team a cooperative culture of reflection and learning is created, which may contribute to a continuous cycle of improvement of the quality of surgical and follow-up care. The set-up structure of standardized data collection and periodic outcome evaluation also opens-up the possibility of benchmarking between different hospitals.[36]

Standardized prospective multidisciplinary outcome monitoring can contribute to scientific knowledge about the outcomes of patients with surgical congenital malformations and its longitudinal trends. It thereby offers a solution to the challenges that research in the field of rare conditions faces, including challenges associated with small-sized studies, patient selection bias and a limited set of outcomes.[37] Small-sized retrospective cohort studies carry the risk of being underpowered to explore sources of heterogeneity between patients and often fail to identify patients with higher risk of adverse outcomes.[38] Moreover, studies into long-term outcomes, are at risk of a selection bias due to loss to follow-up of patients who function well, and often focus on a limited set of specific outcomes, thus failing to integrate findings in different outcome domains. A structured approach to longitudinal multidisciplinary outcome monitoring allows to create a consecutive cohort, thus creating better insight in outcome and prognosis. It allows to study relations between different dimensions of functioning of a child, including, for example, the relation between impairing disease-specific sequelae and quality of life, or the relation between disease-specific sequelae and neurodevelopmental outcome. Standardized prospective multidisciplinary outcome monitoring may also be a promising strategy to explore causes of heterogeneity between patients and to identify risk and protective factors for adverse and favorable outcomes and build clinical prediction models of outcome.[39] Emerging approaches to improve outcome prediction in small-sized samples, including artificial intelligence strategies are promising tools to contribute to this purpose[40-42]. Furthermore, standardized prospective multidisciplinary outcome monitoring will not only provide answers to scientific questions that may provide new leads to enhance outcomes of patients with surgical congenital malformations, but may also support the generation of new research initiatives and easier implementation of research and intervention studies in follow-up practice. Lastly, increased insight in outcomes and longitudinal trends in

functioning of patients with surgical congenital malformations will aid patient education and shared decision-making.

Standardized prospective multidisciplinary follow-up has challenges and limitations. For example, there may still be a risk of selection bias because patients whose functioning is impaired may be more likely to participate. However, this risk is much lower compared to most cross-sectional studies, as a result of the prospective inclusion of a consecutive cohort in the prospective standardized multidisciplinary follow-up program. The implementation of a new program also comes with technological challenges, including building a structure in the electronic patient file for discrete registration and training end-users how to properly use it, whilst keeping it user-friendly. Implementation of a new program also comes with interpersonal challenges that arise with the creation of a new multidisciplinary team.[34,43] Implementation of new initiatives may come across cautious attitudes among health care professionals and patients and their parents (for example about the relevance and clinical usefulness of standardized outcome measures or the roles of various specialist in the multidisciplinary team), which may have a negative impact on compliance and participation.[44-46] There may also be a lack of agreement on which specific outcomes to assess, and what outcome definitions to use or what instruments to use to measure these outcomes. Also patients and parents may be reluctant to complete the PROMs and to participate in the program,[47-49] as they have no previous experience with it. Lack of completion of PROM's in turn may result in inefficient consultations and an incomplete and biased picture of the patients' functioning.[50] There may further be challenges in the availability of appropriate information technology systems, or lack of time and financial resources.[30,51-53] Given the various types of health care providers who participate in our follow-up program, the logistics of scheduling follow-up appointments can be challenging. One of the consequences of this can be that parents and patients will not see their own surgeon at follow-up, which carries the risk that the continuity of follow-up care is interrupted. In our follow-up program we attempted to tackle these challenges by making the health care providers owners of the follow-up protocol, by addressing logistic and technological challenges in the multidisciplinary meetings and health care evaluation sessions, and by training health care providers in the use of the various digital systems and by stimulating team building activities.

Despite aforementioned limitations, standardized prospective multidisciplinary follow-up has several strengths in terms of supporting multidisciplinary team work and providing efficient integrative family care, monitoring individual patient outcome with patient-reported outcome measures, supporting outcome evaluation as part of quality evaluation and lastly, its flexibility. First, multidisciplinary team work in follow-up provides the benefit of efficiency in terms of one single hospital visit in which all relevant health care providers can be consulted. It also provides the benefit of a providing an integrated advice from various medical specialist instead of assigning the responsibility to integrate medical advices or opposing opinions to parents or patients themselves.

A second strengths is the use of standardized validated parent- and patient reported outcomes prior to consultation. This has a few important benefits: the use of validated instruments (as opposed to unvalidated instruments and history taking only) lowers the risk of heterogeneity in outcome measurements (intra observer heterogeneity), [54] it allows for comparing outcomes of patients in the program with healthy functioning children, and increases efficiency of consultation.[55,56] A third strength is the fact that it creates space for outcome evaluation next to process evaluation in quality evaluation of care. Lots of quality of care evaluation focus on process indicators, as they are sensitive to change and thus improved more easily and directly.[57] However, the endpoint of health care is patient outcome, therefore outcome indicators are of more intrinsic interest to health care and reflect broader aspects of care.[57] Focusing on outcome evaluation is therefore a more patient-centered approach to quality evaluation of care. A last strength is the flexibility of this standardized prospective multidisciplinary follow-up program. Adaptations to the program may arise from health care evaluation sessions, but also from emerging scientific insights on outcome and prognosis of patients with surgical congenital malformations, development of core outcome sets and guidelines for follow-up, and development of new tools or new versions of outcome measurements.[58] Even when such adaptations are made, a solid structure and process is preserved in which outcome monitoring is used for the purpose of patient care, health care evaluation and scientific research.

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SUPPLEMENTARY MATERIAL

In this section an overview and detailed description of all instruments used to measure outcomes in the prospective standardized long term multidisciplinary follow-up program for surgical congenital malformations is provided.

Patient- or parent-reported outcomes

1.1 Generic somatic functional outcome

A custom made Generic somatic functioning questionnaire (GSFQ) was developed to collect information on the patient's demographic background and evaluate medical history and functional outcome including: feeding, defecation, micturition, sleep, physical activity and (satisfaction about) scars. The items included in the questionnaire differed depending on the patient's age resulting in several age-specific versions of the questionnaire.

1.2 Gastrointestinal functional outcome

Gastroesophageal reflux

To evaluate symptoms and severity of gastroesophageal reflux disease in patients with esophageal atresia, The Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R) and the Amsterdam Reflux Questionnaire (ARQ) are used. The I-GERQ-R consists of 13 items, with response categories varying from 2 to 5 categories, with higher scores indicating greater disease burden, and is used in patients of 6 to 12 months. The 13 items yield a total score ranging from 0 to 42, and a total score of 16 or higher indicates clinically meaningful gastroesophageal reflux disease (GERD).[1] The I-GERQ-R has been validated in seven countries.[1] The Amsterdam Reflux Questionnaire is an adaptation of the I-GERQ-R for children of four years and older. It consists of 15 items, assessing the frequency and severity of symptoms of GERD, but does not yield a total score. Six items describe the number of days per week a patient experiences symptoms and the nine remaining items assess the severity of symptoms on a 5 point Likert scale, with higher scores indicating higher burden of disease. Dutch normative values are currently being developed.

Dysphagia

To evaluate dysphagia in patients with esophageal atresia aged 12 months of age, the swallowing questionnaire (SQ) is used. The SQ is a custom made questionnaire consisting of 20 items assessing the presence of symptoms of dysphagia. Item are scored as present or absent.

To evaluate dysphagia in patients with esophageal atresia aged 24 months of age or higher, the Dutch translation of the Dysphagia Handicap Index (DHI) is used.[2] The

DHI has shown good reliability[2] and consists of 25 items describing the handicapping effect of dysphagia on a 3 point Likert scale and one item rating self-perceived severity of dysphagia on a 7 point Likert scale. The DHI yields three subscale scores including the Physical, Emotional, and Functional problems based on the first 25 items and an overall self-perceived severity score based on the last item.

Defecation and Continence

To evaluate defecation and continence in patients 8 to 16 years with Hirschsprung disease, anorectal malformations and short bowel syndrome, the Groningen Defecation and Continence questionnaire for pediatric subjects (DEFEC-P) is used. The Groningen DEFEC is a self-report questionnaire with adequate sensitivity and good specificity to diagnose constipation (75%, 100%, respectively) and fecal incontinence (77% and 94%, respectively).[3]

To evaluate defecation and continence from the age of six months to seven years the above described custom-made generic somatic functioning questionnaire (GSFQ). As far as the authors are aware, there are no parent-proxy reported validated outcome measurement to assess defecation and continence in infants and toddlers.

1.3 Genitourinary functional outcome

Micturition

To evaluate micturition in patients with anorectal malformations and sacrococcygeal teratoma at the age of five years, a parent-reported micturition diary is used, in which parents report diuresis over the period of a week.

1.4 Perinatal background

A custom-made Perinatal background questionnaire (PBQ) was developed to evaluate the perinatal background of the patients. This questionnaire is used for all included patients with surgical congenital malformations at the age of six months. It consists of 31 items, and assesses characteristics of the mothers' pregnancy and the delivery, including the use of alcohol, substances, and smoking during and after pregnancy, as well as medical problems and hospital admissions, use of medication during pregnancy, and perinatal details of the patients are assessed, including length of delivery, type of delivery, and characteristics of the child including gestational age, birthweight, APGAR scores, birth length, head circumference.

1.5 Health-related Quality of Life

Generic health-related quality of life

To evaluate generic health-related quality of life in all included patients with surgical congenital malformations at the age of six to 12 months, the TNO-AZL Preschool Children Quality of Life Questionnaire (TAPQOL) is used.[4] The TAPQOL is a generic instrument consisting of 36 items rated on a 3 point Likert scale (never, sometimes, always), with an additional 4 four point Likert scale that assess the burden of disease for a child for each items that is answered with sometimes or always. The TAPQOL yields four domain scores that cover the domains physical, social, cognitive, and emotional functioning, with scores ranging between 0-100, with higher scores reflecting better quality of life. The TAPQOL has good reliability (α = .60-.88) and validity, and Dutch norms are available.[5,6] The TAPQOL was preferred over the PEDsQL Infant Scales, as no Dutch normative values are available for the PEDsQL Infant scales.

To evaluate generic health-related quality of life of all included patients with surgical congenital malformations at the age of 24 months and older, different age-specific versions of the fourth version of the Pediatric Quality of Life Inventory (PEDsQL 4.0) are used.[7] For the ages of 24 months up to six years, age-specific parent-rating are used, and from the age of 8 years onward, age-specific self-report versions are used. The PEDsQL consists of 23 items, rated on a 5 point Likert scale with higher scores reflecting better quality of life. The PEDsQL yields four domain scores: physical, emotional, social and school functioning. The PEDsQL has adequate psychometric properties and Dutch norms are available for the instrument.[6,8]

Disease-specific health-related quality of life

To evaluate disease-specific health-related quality of life patients with Hirschsprung disease and anorectal malformations the HAQL is used to assess disease-specific quality of life. parent-proxy and self-report at the follow-up from 8 to 16 years.[9] This originally Dutch questionnaire consists of 39 (8-11 years) to 42 items (12-16 years), in which items on sexuality are added, grouped into 10 to 11 scales that cover physical, emotional, and social functions as well as disease-related symptoms. Cronbach's alpha range from 0.62 to 0.91 for parent-rated version (8-11 years), and from 0.69 to 0.82 for the self-report version used in adolescents (12-16 years). As far as the authors are aware, no validated Dutch disease-specific QoL questionnaires currently exist for other congenital malformations targeted in our follow-up program.

1.5 Psychosocial outcome

Behavioural and socioemotional outcome

To evaluate behavioral and emotional problems in all included patients with surgical congenital malformations at the age of 24 months and onwards, the parent-rated Child Behavioral Checklist (CBCL-PRF) is used. In addition, the teacher rated equivalent of the CBCL, the Teacher Report Form (TRF), is filled out by teachers of children at the of six years and onwards.[10] The CBCL-PRF and TRF have shown good reliability and validity.[11,12] A Dutch translation and normative values of the CBCL are available.[12]

In addition, to evaluate behavioral and emotional problems of children aged 6 and older the parent- and teacher-rated Strengths and Difficulties Questionnaire (SDQ) is used. The SDQ consists of 25 items rated on a three-point Likert scale (not true, somewhat true, certainly true), and assesses hyperactivity, conduct problems, peer problems, and emotional problems as well as prosocial behavior. Supplementary questions assess the impact of problems. For the SDQ a Dutch translation with normative values is available.[13,14] The parent and teacher rated SDQ have shown good reliability and acceptable internal consistency, and allows for screening of psychiatric disorders, in particular when multiple informants are used.[13,15-17]

To provide a more in depth assessment of symptoms of inattention and hyperactive-impulsive in all included patients with surgical congenital malformations at the of six years and onwards , the Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behavior Scale (SWAN) are used. The SWAN rating scale consists of 18 items, rated on a 7-point Likert scale (far below average to far above average) and describes attention and hyperactivity behavior, with lower scores representing more severe symptoms of inattention.[18]

Post-traumatic stress

To evaluate symptoms of Post-traumatic stress disorder (PTSD) in all patients with surgical congenital malformations at the ages of 8 to 16 years, the Children's Revised Impact of Event Scale (CRIES-13) is used. The CRIES-13 is an adaptation of the Impact of Event Scale in adults for the use of evaluating symptoms of PTSD in children.[19,20] The CRIES-13 has shown good face and construct validity and reproducibility.[21] It has been previously used to evaluate PTSD symptoms in patients after admission to the pediatric intensive care unit.[22] The CRIES-13 consists of a total of 13 items on 4 point Likert scale in 3 domains (intrusion, avoidance and hyperarousal). The sum of scores also yields a total score, with a cut-off score of ≥30 indicating the presence of PTSD.[21] For the CRIES-13 Dutch normative values are available.[23]

1.7 Neurodevelopmental outcome

Language and speech development

To evaluate language and speech development in all included patients with surgical congenital malformations at the age of 24 months the lexiquotient (LQ) is used.[24] The LQ is an instrument that asks parents to list the words their child produces, in order to assess language production. Age-specific norms exist for the number of words that children on average produce at that age.

1.8 Parental psychosocial wellbeing

Parental distress

To evaluate distress in parents of all included patients with surgical congenital malformations, the Distress Thermometer for Parents (DT-P) is used.[25] The DT-P consists of 41 items, including an overall rating of parental distress, a problem list in which parents can list problems experienced in 6 domains of parental functioning (including practical, social, emotional, physical, cognitive and parenting) and four questions on the presence of chronic disease in parents, experienced support from social environment and the need for psychosocial support. A score of ≥4 on the rating of overall parental distress is considered to be clinically relevant distress.[5] The DT-P has been validated and showed acceptable internal consistency, and Dutch normative values are availabe.[5]

Parental post-traumatic stress

To evaluate symptoms and severity of PTSD in parents of all included patients with surgical congenital malformations, the Self-Rating-Scale for Post-traumatic Stress Disorder (SRS-PTSD) is used.[26] The SRS-PTSD is a Dutch self-report for adults and contains 22 items that correspond to 17 DSM-IV symptoms of PTSD and cluster in three diagnostic symptom domains: intrusion, hyperarousal and avoidance. A diagnosis of PTSD is considered likely if one intrusion symptom is present, three avoidance symptoms and two hyperarousal symptoms.[27] The SRS-PTSD has shown good reliability (Cronbach's alpha: 0.96), and high sensitivity (86%) and specificity (80%) compared to a structured clinical interview.[28] [1990]

2. Clinician reported outcomes

2.1 Generic somatic functional outcome

Growth

At each follow-up visit height and weight are measured, and plotted against the normative values of age-matched Dutch boys and girls. In case of growth impairment, or a flattening of the growth curve, patients are referred to a dietician.

Physical endurance

Physical endurance is evaluated in patients with all included type of surgical congenital malformations at the ages of 5,8,12, and 16 years. All patients undergo two tests to evaluate exercise capacity: the 6-minutes-walk-test and the Fitkids.[29,30] The 6-minutes-walk-test measures the distance in meters that is walked in 6 minutes, and because it is a submaximal physical endurance test, it closely reflects functional exercise capacity at home. It has shown good test-retest reliability.[31] Fitkids is a treadmill based endurance test to examine aerobic exercise capacity in children and adolescents. The Fitkids has shown good validity and reproducibility.[32] Dutch normative values for both instruments are available.[30,31]

2.2 Gastrointestinal functional outcome

To evaluate symptoms of obstructive defecation disorder, X-rays of the abdomen are routinely performed in patients with Hirschsprung disease, anorectal malformations and short bowel syndrome.

To evaluate the presence of esophageal dysmotility and exposure to acidic gastroesophageal reflux episodes at the ages of 15 months, 8 years and 16 years of age, HR-pH-impedance-manometry measurements are used. In addition at these ages, routine esophagoscopy with histological biopsy is used to evaluate histopathological changes in the esophagus, such as eosinophilic esophagitis and Barret's esophagus.

To evaluate metabolic effects of short bowel syndrome at the age of 24 months and onwards, routine blood works (including Na/K/Hb/CA/P/Mg/Vit A,/D/E, PTH, vit B12) and urine tests

(Na/K/oxalaat) are used. Additionally, bone density is evaluated by dexa-scan in patients with short bowel syndrome at the age of 24 months and onwards, in case there is an indication of hypocalciemia or vitamin deficiency.

2.3 Genitourinary functional outcome

To evaluate genitourinary functional outcome in patients with anorectal malformation at the age of ultrasound of the kidneys and bladder (for bladder retention or hydronefrosis) and uroflowmetry are used. To evaluate initiation of puberty, in all included patients with surgical congenital malformations aged eight years and onwards, the Tanner classification is used during physical examination. In addition, female patients with anorectal malformations (in particular patients with cloacal malformation) at the age of 12 years undergo an abdominal ultrasound to evaluate the structure of the internal genitals and adequate ability of the uterus to drain menstrual blood. In case these female patients are not yet in menarche at the age of 12 years, the ultrasound is repeated after menarche has started.

2.4 Respiratory functional outcome

To evaluate pulmonary functional outcome is patients with esophageal atresia and omphalocele at the ages of five years, eight years, 12 years and 16 years of age, routine anteroposterior (AP) and lateral X-rays of the lungs are used, and in patients with congenital cystic adenoid malformations (CCAM) at the age of eight years. Additionally, AP and lateral X-rays of the spine are used to evaluate the effects of thoracotomy, including the presence of rib fusion or scoliosis. To evaluate pulmonary sequelae (including lung fibrosis, emphysema and recurrence of cystic lung lesions) in patients with CCAM at the age of eight and 16 years a CT scan of the lungs is used.

To evaluate lung capacity (in terms of volume and expiration force) in patients with esophageal atresia, omphalocele and CCAM at the ages of 5, 8, 12 and 16 years of age, spirometry examination is used. In addition, pulmonary resistance is evaluated in these patients at these ages, by bodybox examination.

2.5 Surgical outcome

To evaluate recurrence of a sacrococcygeal teratoma in patients with this condition the alpha-fetoprotein is routinely checked at each follow-up visit.[33]

To evaluate the presence of esophageal dysplasia in patients with esophageal atresia histopathological biopsies are routinely done by esophagoscopy at the ages of 15 months, 8 years and 16 years.[34]

2.6 Genetic background

Children with esophageal atresia, omphalocele, Hirschsprung disease, anorectal malformations, and sacrococcygeal teratoma are screened at the age of 6 months by the genetic counselor , or sometimes already during admission before the first follow-up visit. Based on the history and physical examination a chromosome-array or targeted gene-testing is done in patients who are suspected of chromosomal or syndromal abnormalities. In case parents have an ungoing pregnancy wish and an increased risk of having another child with a surgical congenital malformation, parents are referred to an additional consultation for preconceptive counseling by the genetic counselor.

2.7 Neurodevelopmental outcome

Motor development

To evaluate motor development in patients with all included types of surgical congenital malformations at the age of 6 to 24 months of age, the Bayley Scales of Infant Development (BSID), third version (BSID-III-NL) is used.[35] This instrument has shown satisfactory construct validity, satisfactory reliability, good norms are available, moreover it is widely used.[35] Different motor task yield a score on the Motor scale, which is a standardized index score, with a mean of 100 and a standard deviation of 15, for which Dutch norms are available.[36,37]

To evaluate motor development in patients with all included types of surgical congenital malformations at the age of 5 years and onwards, the Movement Assessment Battery for Children, second version in Dutch (MABC-II-NL) is used.[38,39] This instrument has shown satisfactory validity and good reliability, and is widely used.[38,40,41] The MABC-II-NL assesses three domains of motor functioning: manual dexterity, ball skills, and static and dynamic balance and yields standardized scores in each domain, as well as a total score. Standardized scores of the MABC-II-NL have a mean of 10 and a standard deviation of 3. Dutch norms are available.[39,42-44]

Cognitive development

To evaluate cognitive development in all included patients with surgical congenital malformations at the age of 6 months to 24 months of age, the Bayley Scales of Infant Development, third version (BSID-III-NL) is used.[35,36] This instrument has shown satisfactory construct validity, satisfactory reliability, good norms are available, moreover it is widely used.[35] Different cognitive tasks yield a score on the Cognition scale, which is a standardized index score, with a mean of 100 and a standard deviation of 15, for which Dutch norms are available.[36,37]

To evaluate cognitive development in all included patients with surgical congenital malformations at the age of 6 years and onwards, a short version of the Wechsler Intelligence Scale for Children, fifth version in Dutch (WISC-V-NL) is used (composed of the domains Similarities, Vocabulary, Block Design and Matrix Reasoning) to estimate intelligence and the verbal index score.[45,46] The WISC-V-NL has shown adequate reliability, but limited construct validity, but only the psychometric properties of the complete test, not the short version, were assessed.[46] Dutch normative values are available.[47]

Additionally, to evaluate cognitive development in all included patients surgical congenital malformations at the age of six years and onwards, the Emma Toolbox (ETB) is used. The ETB is a computerized test battery to assess cognitive functions in pediatric and adult subjects for which Dutch pediatric norms are currently being developed. Only for a few tasks (Digit-span from the WISC, and the 15-words-test) normative values are available.[48,49]

Language and speech development

To evaluate language development in all included patients with surgical congenital malformations aged 24 months, the Communication domain of the van Wiechen onderzoek is used.[50] The van Wiechen onderzoek as a whole has been validated for screening for developmental delay.[51]

Academic functioning

To assess academic functioning teachers of patients are requested to provide CITO test scores. The Dutch CITO test examines academic functioning midway and at the end of every school year. Dutch normative values are available.

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CHAPTER 11

Predicting early motor development after infant surgery under general anesthesia based on intraoperative vital functions: A machine learning approach

D. Roorda, T. Thijssen, J. Last, M.F. Stevens, L.W.E. van Heurn, J.P.M. Derikx, M. Königs, J. Oosterlaan, Emma Children's Hospital Amsterdam UMC Follow-Me program consortium

Submitted

ABSTRACT

Background

Infants with surgical congenital malformations undergoing surgery are at risk for impaired neurodevelopment, potentially caused by a negative influence of dynamics in intraoperative vital functions. This study aims to 1) asses early motor outcome in patients with surgical congenital malformations, 2) study the correlation between static and dynamic features of intraoperative vital functions and early motor outcome after infant surgery, and 3) explore the value of machine learning algorithms for prediction of patient outcome.

Methods

Included were all patients with surgical congenital malformations (including esophageal atresia, congenital lung malformation, abdominal wall defects, anorectal malformations, Hirschsprung disease or short bowel syndrome) who underwent surgical correction at infant age under general anesthesia and participated in our standardized follow-up program. Early motor developmental outcome was measured at the ages of 6, 12 and 24 months using the Bayley Scale of Infant Development (BSID)-III-NL Motor Scale. Clinical background variables (including perinatal characteristics, type of malformation, length of hospital stay, duration of anesthesia and the surgical procedure) and intraoperative vital function parameter time series of heart rate (*HR)*, systolic- and diastolic blood pressure (*BP)* and oxygen saturation (*SpO2)* from the main corrective surgical procedure were extracted from the patients' electronic medical record. Linear regression (LR) and Support Vector Machine regression (SVR) were used to predict early motor outcome, combining all possible variable subsets (i.e. 1) clinical background variables, 2) static features of vital function parameters and 3) dynamic features of vital function parameters). Performance of the models was evaluated and compared using R^2 and Root Mean Squared Error (RMSE).

Results

Early motor development outcome in the 85 included patients was impaired compared with normative data (t=-2.393, Cohen's d=-0.271, p=0.019). The reference models including only clinical background variables had significantly smaller predictive value (LR: R^2=0.03 [95%CI: 0.02-0.04]; SVR: 0.12 [95%CI: 0.08-0.15], compared with the models including clinical background variables and static features of intraoperative vital functions (LR: R^2=0.05; SVR: R^2=0.19), and the models including all variable subsets (LR: R^2=0.06; SVR: R^2=0.19). Prediction error (LR: RMSE: 0.98 [95%CI: 0.94-1.03]; SVR: 0.83 [95%CI: 0.80-0.86]) was significantly lower in SVR models including clinical background variables and static features (RMSE = 0.78) and all variable subsets (RMSE = 0.78), but not significantly lower in other LR models. There was no significant difference in predictive value and prediction error between models including static compared with models including

dynamic feature variable subsets. All SVR models had significantly higher predictive value (R^2 ranging from 0.12 to 0.19) compared with the LR models (R^2 ranging from 0.03 to 0.06), with significantly lower prediction error (RMSE ranging from 0.78 to 0.83 for SVR models and from 0.98 to 1.71 for LR models).

Conclusions

Our findings suggested impaired early motor outcome in patients with surgical congenital malformations, a potential correlation between features of intraoperative vital function parameters and early motor outcome, but awaits validation in a larger prospective study. SVR models showed better predictive performance compared to traditional linear regression models, emphasizing the promising potential of machine-learning algorithms to capture complex correlations between predictors and outcome compared with traditional statistical models.

INTRODUCTION

Surgical congenital malformations (including esophageal atresia, congenital lung malformation, abdominal wall defects, anorectal malformations or Hirschsprung disease) require surgical treatment at infant age. Because of improvements in perinatal and perioperative care, survival has increased in patients with surgical congenital malformations.[1] Subsequently, the focus of outcome evaluation has shifted from survival to long term sequelae of disease and surgical treatment. Among the concerns are the effects of surgical treatment and anesthesia on neurodevelopmental outcome including early motor outcome.[2,3] [4,5] There is distinct heterogeneity in motor functioning after infant surgery, of which the origin is poorly understood. [5,6]Potential etiological mechanisms may include the neurotoxic impact of anesthesia[3,7-9], the extent of tissue damage with subsequent inflammation[10-12], the use of mechanical ventilation or extra-corporeal membrane oxygenation (ECMO)[13-15], and the intraoperative hemodynamics and oxygenation.[16,17]

To provide and sustain adequate perfusion and oxygenation of the body, a number of vital function parameters (including Heart-rate (*HR*), Blood Pressure (*BP*), respiratory rate (*RR),* Oxygen saturation ($SpO2$), carbon dioxide saturation (*SpCO2*), and cerebral oxygen saturation ($rSO2$) are monitored during surgical procedures. Vital functions are under complex physiological control, and while patterns of variation often reflect normal physiology, they may also represent early signs of impaired perfusion and/or oxygenation. Previous studies have suggested that episodes of bradycardia[18,19], hypotension [20-24], hypoxemia[12,23], and hypercapnia[25] are potential mechanisms of brain injury that may in turn contribute to motor impairment.[4,26] This association between aspects of perfusion and oxygenation and motor outcome, suggests that features from intraoperative vital function parameter time series may reflect pathological processes that negatively affect motor outcome after infant surgery.

The current body of evidence on the correlation between vital function parameters in infants and motor outcome is limited in several aspects. First, none of the available studies used *intraoperative* vital function parameter time series of infants. Other studies used time series from hospital admissions in preterms or patients in the neonatal intensive care unit. Their findings do not directly translate into effects of a surgical procedure, because they reflect a longer time interval, describe effects in other patient groups and other context. Subsequently, the findings also reflect the influence of other factors associated with motor outcome, including medication and mechanical ventilation. Second, studies often include only a single or only few vital function parameters in their analysis to predict outcome, providing a potentially limited view on the relevance of vital function parameters.[20] Third, vital function parameters are often expressed in simple summary statistics (i.e. minimum, maximum, mean), static features that do not capture the dynamics in the measurements over time. Studies using dynamic features (such as variance, time- or area under curve, sample entropy ($SaEn$) and sample asymmetry ($SaAs$)) have shown better predictive

performance.[27,28] Fourth, most studies have used traditional statistical models that build upon the linearity assumption (e.g. linear or logistic regression), that do neither capture the potentially complex relationship between vital function parameters and motor outcomes nor the interactions between vital function parameters.[29] Lastly, prediction models often lack external validation, whilst it is widely recognized that validation in an independent data set is crucial for the assessment of generalizability of study findings.[30,31] Taken together, more advanced representations of vital function parameters should be used with more sophisticated statistical models in order to study the complex relation between intraoperative vital function parameters and early motor outcome after infant surgery. Machine learning models might meet these requirements.[32-35]

The aims of the current study are to: 1) asses early motor outcome in patients with surgical congenital malformations, 2) study the correlation between static and dynamic features of intraoperative vital functions and early motor outcome after infant surgery, 3) to explore the value of machine learning algorithms for prediction of patient outcome.

MATERIALS AND METHODS

Participants

A consecutive cohort of patients with surgical congenital malformations who underwent surgical correction of their malformation at infant age and participated in the standardized prospective multidisciplinary follow-up program of the Amsterdam UMC, an academic hospital in the Netherlands, was taken as the study sample. Patients who received surgical correction after the age of 15 months, patients who underwent surgical correction in another hospital, patients for whom intraoperative vital function parameter time series data were not available, and patients whose first measurement of outcome data was done after the age of 3 years were excluded from this study.

Outcome measurement of early motor development

Motor development was measured in our standardized prospective multidisciplinary follow-up program at the age of 6 months, 12 months, and 24 months. For the assessment of motor development at these ages the Motor Scale of the Bayley Scale of Infant Development (BSID-III-NL) was used.[36,37] This instrument has shown satisfactory construct validity, satisfactory reliability, good norms are available, moreover it is widely used.[37] Raw scores were transformed into z-scores (M=0, SD=1) and compared to Dutch normative population data.[37] In order to minimize time between exposure and outcome measurement, the first outcome measure (e.g., the youngest) for each individual patient was included in the study, in case there were repeated outcome measures.

Predictive variables

Clinical background variables

The following demographic and clinical characteristics of patients were extracted from the electronic patient files: sex (male/female), type of malformation (i.e, esophageal atresia, congenital lung malformation, gastroschisis, omphalocele, anorectal malformation, Hirschsprung disease or short bowel syndrome), birthweight (grams), presence of comorbidity (yes/no), age at surgery (days), American Society of Anesthesiologists Physical Status (ASA) classification, length of surgical time (minutes), length of anesthesia (minutes), type of operation (open/scopic), type of sedative used (six anesthetic agents) postoperative length of in-hospital stay (days), total length of in-hospital stay at follow-up (days), length of stay in the intensive care unit (ICU; days), age at follow-up (months), total number of surgeries at follow-up. Missing values in clinical background variables were imputed using Multiple Imputation by Chained Equations (MICE). Most variables had no missing data, but 3.6% of data was missing for birthweight and 14.6% for American Society of Anesthesiologists Physical Status (ASA) Class.

Vital function parameters

Intraoperative vital function parameter measurements collected during the corrective surgical procedure were obtained from the electronic patient record, including time series of: 1) heart rate (HR), 2) systolic blood pressure (sBP), 3) diastolic blood pressure (dBP) and 4) oxygen saturation (SpO2). HR was measured with a non-invasive a pulse monitor and with the use of an arterial line (HF monitor). The systolic- and diastolic BP was measured using an arterial line (sABP and dABP) and/or with a non-invasive blood pressure (sNIBP and dNIBP) cuff around the upper arm. A pulse oximeter around the finger or toe was used to measure SpO2. All vital function parameters were measured using a Philips MX-800 monitor and measured each minute for HR, sABP, dADP and SpO2 and every three minutes for sNIBP and dNBIP. When there was data available of at least 30 consecutive minutes, the data was considered a complete time series.

Merging invasive and non-invasive measurements

HR and BP data were extracted from invasive and non-invasive measurements), in different resolutions (per minute or per three minutes). In order to increase data availability and to create one single time series per vital function parameter, HR and BP data needed to be merged first before feature extraction could take place. The *HR* data collected with the arterial line was considered the preferential method of measuring HR. Invasive HR measurements were available for all patients. Non-invasive HR measurements from the pulse monitor were used to fill epochs with missing observations from the arterial line in 73% of the patients. The *BP* data collected with the arterial line (ABP) was considered the preferential method of measuring *BP*. ABP data was measured in 89% of the patients. Non-

invasive HR measurements from the pulse monitor were used to fill epochs with missing observations from the arterial line in all patients. After combining the data of invasive and non-invasive measurements of HR and BP, a single time series for each vital function parameter was available. sFigure 1 shows an example of how the different measurement methods for both *HR* and *BP* were successfully combined into a single signal for each parameter.

Deletion of artefacts in vital function parameter time series

Vital function parameter data always contain artefacts due to suboptimal measures in clinical practice (for example a pulsoxymeter that is not attached properly and measures a saturation of 0% or a cuff that does not inflate properly). This requires removal of artefacts and interpretation of missing periods of data. Deletion of artefacts in time-series is more complex than regular outlier detection; an observation being an artefact depends on its surrounding values, rather than the distance from the total sample mean. Lamer et al.[38] proposed a standardized pre-processing algorithm for detecting abnormalities in vital function parameters during anesthesia. Lamer's method offers a solution to the challenges of making optimal use of imperfect data in terms of artefacts and missing time points in time series. In the current study the approach of Lamer et al. for artefact deletion and interpretation of missing data was re-used, but adapted to the resolution of the available vital function parameters time series and adapted to the pediatric context of this study by using the age-appropriate normative values for vital function parameter data. Their approach offers the benefit to define artefacts using predefined thresholds and various measures derived from the vital function parameter time series such as time between measurements and time spent outside predefined thresholds, thus providing adaptability to various clinical situations. The identification of artefacts in the current study was achieved by using the derivative of the moving standard deviation and by visually inspecting the change that an observation causes in the moving standard deviation of a window *i* with window size *W* of observations. The following equation was used to calculate the derivative of the moving standard deviation): $(\sigma_i)\hat{}=\sqrt{(1/((|W|-1)) \sum_{x_m \in W}(x_m-(\mu_i)\hat{})\hat{}2)}$. This way the observations that show extreme values compared to surrounding values could be identified. sFigure 1 shows an example of how artefacts were removed in HR data, whilst other observations remain unchanged.

Feature selection of intraoperative vital function parameter time series

To explore possible relevant features from vital function parameter time series, semi-structured interviews were conducted with pediatric surgeons (n=2) and pediatric anesthetists (n=3). Additionally a literature search was done to identify features of vital function parameter time series that were used in previous studies and their mathematical function. The following five *static* features were selected from each vital function parameter time series (HR, sBP, dBP and SpO2: the mean, minimum, maximum, standard deviation

and the variance, yielding a total of 20 static feature variables. The following *four* dynamic features were selected from each vital function parameter time series: Time Under Threshold (TUT), Area Under Threshold (AUT), Sample Entropy (SaEn), and Sample Asymmetry (SaAs), yielding a total of 16 dynamic feature variables. sTable 1 summarizes the results of the literature search and describes for each vital function parameter feature its mathematical function as applied in previous studies.

Subsets of predictive variables

To compare the predictive value of static and dynamic features from the intraoperative vital function parameter time series on early motor outcome, a total of three subsets of predictive variables were created: 1) a subset containing factors reflecting the clinical background, 2) a subset containing static features from the four intraoperative vital function parameter time series and 3) a subset containing dynamic features from the four intraoperative vital function parameter time series. A detailed description of the factors included in each subset is provided in Table 1.

Table 1 Description of variables included in each variable subset in the current study

Subset	Variables		
Clinical background	Sex, type of malformation, birthweight, presence of comorbidity, age at surgery, ASA classification, length of surgical time, length of anesthesia, type of operation, type of sedative, postoperative length of in-hospital stay, total length of in-hospital stay at follow-up, length of stay in ICU, age at follow-up, total number of surgeries at follow-up.		
Vital function parameters	Heart rate, systolic blood pressure, diastolic blood pressure, oxygen saturation	Static	Minimum, mean, maximum, standard deviation, variance
		Dynamic	Time-under-threshold, area-under-threshold, sample entropy, sample asymmetry

Modelling

Three types of statistical models were used and compared: 1) linear regression (LR) models predicting early motor outcome with all possible combinations of variable subsets, 2) a support vector machine regression (SVR) model estimating the group average of early motor outcome, and 3) SVR models predicting early motor outcome with all possible combinations of variable subsets. SVR models have shown to be very effective in prediction of outcome in high-dimensional datasets with relatively small samples compared to other algorithms.[35] SVR models are often used in medical research for multi-dimensional prediction models.[39-41]

Cross-validation of LR and SVR models

Predictive performance of statistical models is influenced by a certain degree of randomness, causing deviation in prediction errors when models are trained multiple times. Therefore, the data were repeatedly split randomly into a train and test set. On 80%

of the data (i.e. training data), leave-one-out cross-validation (LOOCV) was applied to select the best performing model on all possible train-test splits in the training data.[42] After training the models 100 times, the average predictive performance of each type of model on the test set was taken as the outcome and expressed as a mean with a 95%-confidence interval [95%-CI]. External model validation was performed in the remaining 20% of the data (i.e. test data).

In SVR models it is required to set two hyperparameters that determine the generalizability of the model: *epsilon* and *C*. Optimal settings of these hyperparameters will enable the resulting model to prevent over- and underfitting on the training data. Since SVR models were trained with different combinations of variable subsets, each model had its own 'optimal' set of hyperparameters. A grid search (which can be described as a repetitive process of training with different hyperparameter settings) was used to determine optimal hyperparameters in each model during cross-validation.

Statistical Analysis

Winsorizing was performed on motor outcome data for values below the 5%- or above the 95% percentiles in order to reduce the influence of outliers whilst retaining the position of these observations at the extreme ends of the distribution. Motor outcomes (expressed as z-scores) of patients were compared to the normative population mean z-score (0) using the one-sided one sample t-test.

To evaluate predictive performance of the models, the predictive value and prediction error of the models were evaluated. The predictive value was expressed as the variance in outcome data that was explained by the included subset of predictor variables (R^2). The prediction error was expressed as the Root Mean Squared Error (RMSE). RMSE is used for comparing model performance during hyperparameter tuning because it better captures the magnitude of misprediction, which we want to overcome. The various types of models were compared in terms of predictive value (R^2) and prediction error (RMSE) by comparing the accompanying 95% CIs of the obtained values of each model with that of the reference models.

In order to explore the value of static and dynamic features of a vital function parameter time-series for prediction of early motor outcome, the model performance was compared between the models that included different combinations of variable subsets: 1) clinical background variables only, 2) clinical background variables and static features, 3) clinical background variables and dynamic features, 4) static and dynamic features and 5) all variable subsets. The model that included clinical background variables only was taken as the reference model, because in this model no features of intraoperative hemodynamic and oxygenation were included.

In order to explore the value of machine learning models compared with traditional statistical models, the SVR models were compared to the LR models. LR models were taken as reference models, because LR models are currently often used in literature on

prediction of early motor outcome in pediatric patients. In order to explore the value of machine learning algorithm for individual outcome prediction compared with estimating group average. SVR models predicting group average were taken as a reference model and compared to SVR models predicting individual outcome. Estimating a group average requires less statistical power and sample size (given the lower variance), therefore this comparison provides an indication whether inadequate statistical power influenced the predictive performance of the SVR models predicting individual outcome. When the mean R^2 and/or the mean RMSE of a model was not included in the 95% confidence intervals of R^2 and RMSE of the reference model, this was considered as a significant differences in predictive value and prediction error.

RESULTS

Participants

A total of 85 patients were included in the study. Of the included patients, 57 were male and 28 female. Of the 85 patients, 11 had esophageal atresia, 10 had congenital lung malformations,11 had abdominal wall defects, 22 had anorectal malformations, 25 had Hirschsprung disease, 5 had a combination of esophageal atresia and anorectal malformation and 1 had short bowel syndrome. The mean age at corrective surgery was 112 days (range 0 to 419 days of age). Outcome measurements were done at a mean age of 13 months (range: 5 to 35 months of age).

Early motor outcome

Average early motor functioning in our cohort (mean z-score = -0.2852 , SD = 1.10) was significantly lower (t=-2.393, df=84, Cohen's d=-0.271, p=0.019) compared with the mean z-score of the normative population.

Predictive performance of the models

Predictive performance of static and dynamic features of vital function parameters

Performance metrics of all models are displayed in Table 2. The LR model including only clinical background variables had an R^2 of 0.03 [95%CI: 0.02-0.04]. Compared to this model, the model that additionally included static features, the model that included static and dynamic features only and the model that included all variable subsets had significantly higher R^2 (0.05; 0.05 an d0,06, respectively). The prediction error of all LR models including features of intraoperative vital function parameters had significantly higher prediction errors compared with the model that included clinical background variables only. Taken together, this suggests that in LR models static features of intraoperative vital function parameters contribute to the predictive value of LR models, at the cost of the prediction

Table 2 Predictive performance in terms of predictive value (R2) and prediction error (RMSE) of the various types of models used in the current study in terms of algorithms and types of included predictor subsets

	Support Vector Machine Regression			Linear Regression	
Included predictor subsets	*Hyperparameter settings C and e after optimalisation*	*R^2, M [95%-CI]*	*RMSE, M [95%-CI]*	*R^2, M [95%-CI]*	*RMSE, M [95%-CI]*
Clinical	C=1; e=0,7	0,12 [0.08 – 0.15]	0,83 [0.80 – 0.86]	0,03 [0.02 – 0.04]	0,98 [0.94 – 1.03]
Clinical+Static	C=1; e=0,6	0,19 [0.15 – 0.22]	0,78 [0.76 – 0.81]	0,05 [0.03 – 0.06]	1,23 [1.12 – 1.35]
Clinical+Dynamic	C=1; e=0,5	0,14 [0.10 – 0.17]	0,81 [0.79 – 0.84]	0,03 [0.02 – 0.04]	1,16 [1.09 – 1.23]
Static+Dynamic	C=1; e=0,6	0,14 [0.11 – 0.17]	0,81 [0.78 – 0.84]	0,05 [0.03 – 0.07]	1,19 [1.10 – 1.29]
All	C=1; e=0,6	0,19 [0.15 – 0.22]	0,78 [0.76 – 0.81]	0,06 [0.03 – 0.08]	1,71 [1.49 – 1.93]

Note. SVR = support vector machine regression; C is, a measure of the margin used in the separating hyperplane; e= epsilon, a measure of tolerance given to errors; R-squared = a measure of explained variance and prediction accuracy; RMSE = root mean squared error, a measure of prediction error

error. This indicates that that intraoperative hemodynamics and oxygenation processes influence motor development of patients undergoing surgery under general anesthesia at infant age.

With regard to differences across the SVR models with various combinations of subsets of predictor variables, we observed that the models that included only clinical background variables had the lowest predictive value (R^2=0.12 [95%CI: 0.08-0.15]). The model that included a combination of clinical background variables and static features of intraoperative vital function parameters had higher predictive value compared with the model with clinical background variables only, with an R^2 of 0.19. The model with this combination of variable subset also exhibited lower prediction error, although not significantly lower.

The SVR model that included clinical background variables and dynamic features of intraoperative vital function parameters and the SVR model that included static and dynamic features of intraoperative vital function parameters, did not have significantly higher predictive value (R^2=0.014 and R^2=0.014, respectively) and did not have significantly lower prediction error (RMSE=0.81 and RMSE=0.81, respectively) compared with the SVR model that included clinical background variables only. This suggests that static features of intraoperative vital function parameter contributed to the predictive performance of the SVR models, whilst no attributive predictive performance of dynamic features of intraoperative vital function parameters was demonstrated. Taken together, these findings suggest that intraoperative hemodynamics and oxygenation processes influence motor development of patients undergoing surgery under general anesthesia at infant age.

Predictive performance of traditional statistical models compared with machine learning models

Compared with the reference linear regression models, All SVR models had significantly higher R^2 values (R^2 ranging from 0.12 to 0.19) compared with the LR models (R^2 ranging from 0.03 to 0.06), whilst they had significantly lower RMSE values (RMSE ranging from 0.78 to 0.83 for SVR models and from 0.98 to 1.71 for LR models). This indicates higher predictive value and lower prediction error in SVR models compared with LR models. Compared with the reference SVR model estimating the mean score (RMSE=0.86), all SVR models had significantly lower RMSE values, ranging from 0.78 to 0.83. This suggests lower prediction error in estimating individual outcome prediction compared with estimating a group average. The best performing model was the SVR model including all variable subsets. This model had the highest predictive value (R^2=0.19) and the lowest prediction error (RMSE=0.78) of all the models.

DISCUSSION

In this study, advanced methods were explored to study the correlation between intraoperative vital function parameters and early motor outcome in infants undergoing surgery.

Our findings indicate that on a group level, patients with surgical congenital malformations after infant surgery have small impairments in early motor outcome compared with a Dutch normative sample. This finding is in line with previous meta-analytic findings on medium-sized impairments in motor development in patients with surgical congenital malformations.[5,43]. In the meta-analysis of Roorda et al., the number of surgeries was associated with impairments in motor outcome, also indicating a negative influence of surgical procedures on motor outcome. The broader literature shows inconsistent findings about the effects of surgical procedures in infants on motor development. General anesthesia[2,7], abdominal of thoracic insufflation of CO2 as is used in laparoscopic surgery[44], blood loss and the size of the resection surface are hypothesized to be of negative influence on neurodevelopmental outcome.[45] Possibly these effects are moderated by the their influence on intraoperative hemodynamics and oxygenation.

The current study assessed whether this negative influence could be explained by intraoperative hemodynamics during the surgical procedure. Both in the LR and SVR models, the inclusion of vital function parameter data increased the explained variance (6% in LR models and 19% in SVR models) compared with the models that only included clinical background features (3% in LR models and 12% in SVR models). Our findings indicated that static features contributed to the prediction of early motor outcome, whilst for dynamic features this was not demonstrated. This suggest that aspects of intraoperative hemodynamics and oxygenation may have a negative impact on motor development.

What specific aspects of intraoperative hemodynamics and oxygenation are explanatory for the possible negative impact on early motor outcome remains unclear from the current study. Previous studies in preterm patients and patients with low-birth-weight indicate that the risk of impaired motor outcome is related to prolonged episodes of hypoxemia[18]. Moreover, studies in patients with cardiac malformations have suggested that episodes of hypoperfusion and ischemia are of even greater negative influence to the brain compared with episodes of hypoxemia.[46,47] Patients with cardiac malformations and preterms or low-birthweight infants differ from patients with surgical congenital malformations with regard to the prevalence of comorbidity,[48] procedural aspects of surgical treatment, and a longer duration of exposure to sedatives, mechanical ventilation and extracorporeal membrane oxygenation and subsequently potentially more frequent alterations in vital function parameters [13,19,23,49] This may explain differences in the extent to which they exhibit impairments in motor outcome.[50,51] Despite these differences, the negative effects of hypoxemia, hypoperfusion and ischemia on early motor outcome described in these patients are in line with our findings and may also translate to patients with surgical congenital malformations.

In the current study, dynamic features did not significantly add to the predictive performance of the LR and SVR models compared with static features. There were no significant differences in explained variance and prediction error between models including the static features variable subset and models including the dynamic features variable subset. This is contrary to what other have described about the predictive potential of dynamic features.[27] However, the correlation between dynamics in vital functions and sepsis is different from the correlation between dynamics in vital functions and motor outcome. Sepsis leads to changes in hemodynamic and oxygenation processes, whereas impact on early motor outcome may be a consequence of changes in hemodynamic and oxygenation processes.

The findings in the current study further suggest that the predictive value of intra-operative vital function parameter features to estimate motor outcome was highly dependent of the type of model that was used. With the use of machine learning algorithms an innovative approach was applied in the current study. The findings in our study indicate that the machine learning algorithms (SVR models) were able to explain a significantly greater percentage of the variance in motor outcomes compared with traditional linear regression models. Moreover, prediction errors were lower in SVR models compared with SVR models predicting the groups' average and traditional linear regression models.[19] This shows the promising potential of machine learning algorithms to capture complex correlations between predictors and outcome even in small-sized samples of patients with rare conditions such as surgical congenital malformations.[39,40,52]

Strengths and Limitations

This study shows the potential of the use of device data reflecting potentially pathological intraoperative hemodynamic and oxygenation processes, but had some limitations. First, the resolution of the vital function parameter time series and retrospective collection of the intraoperative vital function data. Prospective collection of data with higher resolution would decrease the need for artefact deletion and interpretation of missing values that in turn would influence the accuracy of static and dynamic features. Second, this study had a small sample size. Although a sample size of 137 is not unusual in clinical studies, especially in studies on rare diseases, it is somewhat small for training machine learning algorithms, and to examine dependencies and relationships between many different variables. A larger sample sizes would improve prediction performance and generalizability of findings, because adding more observations increases statistical power and makes a model more sensitive to discover complex relations between predictors and outcome. Third, although predictive performance of the SVR models was better compared to traditional statistical models, clinical interpretation is more challenging. The SVR models used in the current study did not provide insight in the contribution of individual variables on the predictive performance, because of the use of subsets. Although the LR models are able to do so, no factors could be identified that were significantly associated with early motor outcome,

possibly because overall predictive performance of the models was small and statistical power was limited. Subsequently, the current study was unable to address the question which specific aspects of hemodynamics and oxygenation have the greatest influence on early motor outcome in patients with surgical congenital malformations Fourth, in this study the intraoperative data of the corrective surgical procedure only was used, whereas some patients undergo multiple surgical procedures (including creation or reversal of a stoma or redo surgery). Fifth, although early motor outcome was measured using a widely accepted and valid instrument, that allows for a comparison with age- and sex-adjusted normative Dutch data, the outcome data may have been influenced by the time interval between exposure to the surgical intervention (event) and the outcome measure (early motor outcome in follow-up). In this time period, children who underwent surgery may also be exposed to other factors that may influence their early motor outcome (both factors with a negative impact, including the effects of admittance to the ICU, or postoperative complications, as well as factors with a positive impact, including physical therapy, stimulation of motor development by parents)[53]. A last limitation is that although the models were externally validated in unseen test data to assess generalizability, the test data consisted of patients from the same patient population. Our data was therefore not validated in other patient populations undergoing infant surgery.

Future work

In the current study a moderate predictive potential of intraoperative vital function parameter data on early motor outcome in patients undergoing infant surgery was found. Future studies should be aimed at the validation of the predictive potential of intraoperative vital function parameter data for prediction of patient outcome in other patient population undergoing infant surgery. Moreover, future studies should focus on further elucidating what aspects of intraoperative hemodynamics and oxygenation have a negative impact on patient outcome. The predictive potential of other types of vital function parameters should also be further explored, including near-infrared-spectrometry of the brain[17]. Future prospective studies in larger samples that elucidate the predictive potential of intraoperative hemodynamic and oxygenation parameters for patient outcome can contribute to identifying parameters that can be used for intraoperative direction of vital functions by the anesthetist.

With regard to feature extraction from vital function parameter time series, unsupervised machine learning methods are also interesting to explore when larger quantities of vital function parameter observations are available. Rather than using supervised methods in which features are based on literature and medical insights, unsupervised feature extraction could absorb more abstract patterns and variability from time-series measurements, which could provide a more complete (numerical) picture on the vital function parameter dynamics. This may help us to identify patterns in data that contribute to prediction of outcome and that can be considered pathological patterns.

Identifying pathological patterns may help us to prevent them and thus help to improve patient outcome.[54]

Conclusions

Our findings suggested impaired early motor outcome in patients with surgical congenital malformations, a potential correlation between static and dynamic features of intraoperative vital function parameters and early motor outcome, but awaits validation in a larger prospective study. SVR models showed better predictive performance compared to traditional linear regression models, emphasizing the promising potential of machine-learning algorithms to capture complex correlations between predictors and outcome compared with traditional statistical models.

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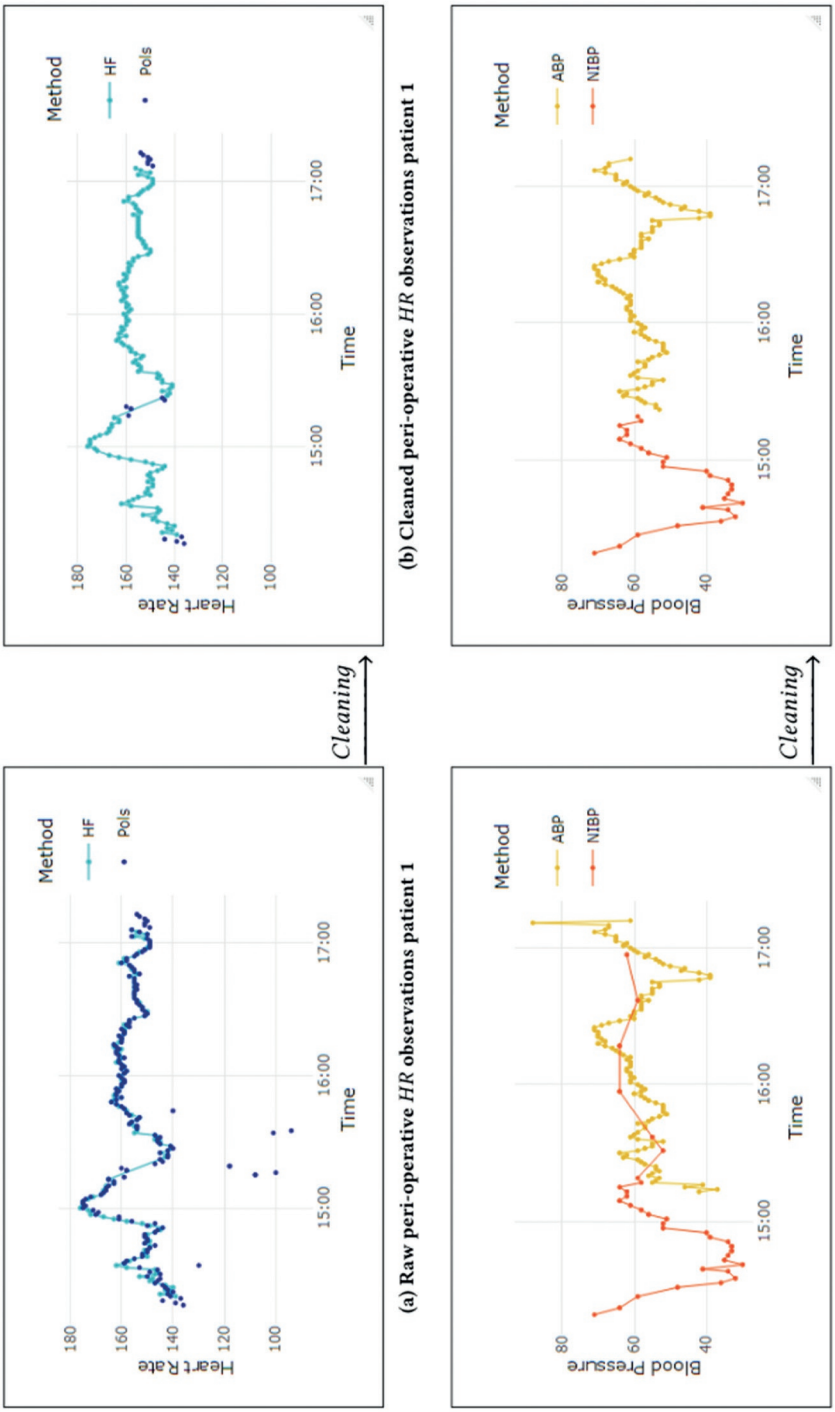
SUPPLEMENTARY MATERIAL



sFigure 1 Visual example of how data cleaning in terms of artefact removal and combining data from multiple devices (invasive and non-invasive) of heart rate (A;B) and Blood Pressure (C;D) was achieved on a patient level

sTable 1 Included features of vital function parameter time series, with corresponding functions and references

Feature	Function	Vital function parameters	Reference
Time Under Threshold (TUT)	$\sum_{i=1}^{N}(x_i < T)$	BP, SpO2	Cornelissen 2010, Ya 2019, Alderliesten 2014, Kim 2018, Goldstein 1995, Lamer 2016
Area Under Threshold (AUT)	$\sum_{i=1}^{N}\frac{1}{2}(yi-1+y_i)(x_i-xi-1)$	BP, SpO2	
Sample Entropy (SaEn)	$\Phi^m(r)-\Phi^{m+1}(r)$	HR, BP	Shaffer 2017, Kumar 2019, Addison 2009, Goulding 2015, Temko 2015, Semenova 2019, Oliveira 2019, Griffin 2007, Lee 2014
Sample Asymmetry (SaAs)	$\frac{\frac{1}{N}\sum_{i=1}^{N} r_1(x_i)^2}{\frac{1}{N}\sum_{i=1}^{N} r_2(x_i)^2}$	HR, BP	Shaffer2017, Kumar 2019, Addison 2009, Goulding 2015, Temko 2015, Semenova 2019, Oliveira 2019, Griffin 2007, Lee 2014
Minimum (min)	$Max(x)$	HR, BP, SpO2	Ya 2019, Bloch 2019, Birajdar 2017
Maximum (max)	$Min(x)$	HR, BP	Ya 2019, Bloch 2019, Birajdar 2017
Mean (mean)	$\frac{1}{N}\sum_{i=1}^{N} x_i$	HR, BP	Ya 2019, Bloch 2019, Birajdar 2017, Fanaroff 2006
Standard deviation (σ)	$\sqrt{\frac{\sum(x-\mu)^2}{N}}$	HR, BP, SpO2	Lee 2014, Ya 2019
Variance	σ^2	HR, BP, SpO2	Lee 2014, Ya 2019

CHAPTER 12

General Discussion and Future Perspectives

The survival of patients with surgical congenital malformations has improved over the past decades, however, the postoperative morbidity remains high.[1] Studies on postoperative outcome in patients with surgical congenital malformations have a strong focus on functional outcome and have shown that patients may experience a variety of disease-specific sequelae.[2-5] They also show that heterogeneity in functional outcome is high. Some patients achieve excellent functional outcome, whereas others have poor functional outcome. To advance knowledge on postoperative outcome of patients with surgical congenital malformations, this thesis covered three aims. The first aim was to explore underlying risk factors and treatment strategies for poor gastrointestinal functional outcome in patients with Hirschsprung disease. For patients with Hirschsprung disease (HD) poor functional outcome is characterized by obstructive defecation problems (or constipation), soiling or fecal incontinence and a risk of developing Hirschsprung-associated enterocolitis (HAEC). Impaired postoperative outcome in patients with surgical congenital malformations is not limited to poor gastrointestinal functional outcome, but also may occur in other domains of health and functioning, requiring multidisciplinary follow-up.[6] The second aim of this thesis was therefore to explore other aspects of patient outcome, including health-related quality of life, neurodevelopmental outcome, psychosocial outcome and parental psychosocial outcome, as studies have suggested that patients with surgical congenital malformations may also experience impairments in these domains of health.[7-9] The third aim of this thesis was to explore the value of routine outcome monitoring in standardized prospective multidisciplinary follow-up for the purposes of 1) improvement of patient outcome, 2) evaluation and improvement of quality of surgical care, and 3) contributing to scientific research on outcome in patients with surgical congenital malformations. The first aim was addressed in the first part of this thesis (*chapter 2 to 6*), the other two aims were addressed in the second part of this thesis (*chapter 7 to 11*). In the current chapter, a general discussion of the main findings in this thesis is provided, followed by a discussion of the methodological strengths and limitations of this thesis, and a discussion of the clinical implications of the findings and directions for future research.

DISCUSSION OF MAIN FINDINGS

PART I Gastrointestinal functional outcome in patients with Hirschsprung disease

Postoperative gastrointestinal functional outcome varies largely between patients with HD. He majority of patients will accomplish normal bowel function, some will have problems with obstructive defecation or constipation defecation, soiling, fecal incontinence or HAEC.[10-13] The prevalence of these problems appears to vary with age in follow-up, but the origin of this heterogeneity remains poorly understood.

Poor gastrointestinal functional outcome in patients with Hirschsprung disease is characterized by the inability to adequately and voluntary pass stools. Normal defecation

is a multifactorial process and may be impaired in patients with HD as a result of hypertonia of the internal anal sphincter (due to the absence of the rectoanal inhibitory reflex in patients with HD), injury to the anal sphincter complex, impaired colonic motility (that leads to relative hypertonia of the colonic wall) and stool retention.[14] One of the possible underlying causes for impaired colonic motility or sphincter dysfunction is incomplete resection of the affected bowel segment during pull-through surgery. In that case the proximal side of the anastomosis contains transition zone bowel, which is called transition zone anastomosis (TZA). The transition zone is a bowel segment affected by HD, that is characterized by hypodense distribution of ganglions, ectopic ganglions, hypoganglions and hypertrophic nerve fibers in histopathological examination.[15] The aim of the meta-analysis presented in *Chapter 2* was to study the prevalence of transition zone anastomosis and its clinical impact in terms of gastrointestinal functional outcome. The findings presented in C*hapter 2*, representing 2207 patients in 34 studies, showed that the incidence of TZA after pull-through surgery was an estimated 9%. However, the incidence of TZA varied largely between studies. This heterogeneity in prevalence findings is fueled by heterogeneity in case definitions and challenges in the detection of TZA.[14,16] A previous meta-analysis found a higher incidence of 35%, which can be explained by the sole inclusion of studies with patients who underwent redo surgery, the inclusion of recent studies, and differences in case definition between both meta-analyses.[17] The findings presented in *Chapter 2* further showed that obstructive defecation problems occurred more often in patients with TZA compared to patients without TZA. For other clinical symptoms than obstructive defecation, there is currently not enough evidence available to make this comparison.

Hypertonia of the internal anal sphincter has shown to be another cause for poor gastrointestinal functional outcome in patients with Hirschsprung disease. Intrasphincteric botulinum toxin (BT) injections have been shown to effectively relax the internal anal sphincter, and thus improve defecation in patients with functional constipation.[18] This is why *Chapter 3* aimed to summarize all available evidence on the effectiveness of BT injections to treat obstructive defecation problems and enterocolitis in patients with Hirschsprung disease. The findings of the meta-analysis in *Chapter 3*, including 14 studies representing 287 patients, indicate that in a mean of 66% of patients obstructive defecation problems improved after BT injections. Adverse effects were observed in a mean of 17%. An effect on the incidence of Hirschsprung-associated enterocolitis (HAEC) could not be demonstrated in this meta-analysis. *Chapter 4* of this thesis aimed to further explore what factors determine the need for BT injections in patients with Hirschsprung disease and to identify factors that are associated with clinical improvement after BT injections. The findings presented in this cross-sectional cohort study of 131 patients, show that BT injections effectively treat obstructive defecation problems in 61% after one BT injection, and that 71% of patients achieved spontaneous defecation or defecation supported by laxatives only after treatment with BT injections. Compared to patients who were not

treated with BT injections, patients who were treated with BT injections more often had long-segment disease and had on average a longer postoperative hospital stay and a longer hospital stay due to readmissions in follow-up. This suggests that patients with a more severe form of Hirschsprung disease are more likely to need BT injections during follow-up. Despite satisfactory results in most patients, patients's sex, (syndromal) comorbidity, length of disease, type of operation technique (including approach and whether a stoma was created), type of botulinum toxin and prevalence of complications were not explanatory for differences in response to BT injections. These findings from *Chapter 4* are in line with previous studies that have shown that patient's sex, age at diagnosis, and type of operation were not associated with improvement of defecation after botulinum toxin injections.[18] What factors do explain why some patients respond well to BT injections, whereas others don't, remains unclear from available evidence. The presence of another obstructive cause (including TZA and anastomotic stricture) may be associated with no response to BT injections, because in those patients the primary problem is not an anal outlet obstruction.[19] Furthermore, the use of dietary measures, laxatives or other type of bowel management, and behavioral aspects associated with stool retention, may also play a role. Patients whose stools are not soft enough, may not benefit from relaxation of the internal anal sphincter with BT injection, but need treatment strategies aimed at softening stools.[20]

Obstructive defecation problems and constipation in patients with HD need to be prevented and adequately treated, because recurrent constipation increases the risk of developing HAEC. HAEC is severe form of bowel inflammation that, when treated inadequately, may lead to bowel perforation and can be lethal. The aim of *Chapter 5* was to study the incidence of preoperative and postoperative HAEC in a cross-sectional cohort study of 146 patients with HD. The findings presented in this chapter show that 10% of our patients had preoperative HAEC and 21% had at least one episode of postoperative HAEC. Although the incidence of preoperative HAEC is comparable to previous reports,[12,21] the incidence of postoperative enterocolitis in the cohort of patients studied in this chapter is somewhat higher compared to the reports in a previous meta-analysis.[22] The higher incidence in our findings may be explained by the use of a rather liberal case definition, as we adhered to the clinical conclusion as described in the patient's medical records. Because of the retrospective design of the study, not enough data was available to reconstruct a diagnostic score. However, the diagnosis of HAEC is challenging and based on rather non-specific clinical symptoms. Although there is a clinically validated score available to diagnose HAEC, this score is often not used in currently available studies.[23-25] Standardizing diagnosis and treatment of HAEC would help to gain insight in actual prevalence and also help to prevent hospital admissions.[26] When patients are identified timely and adequately, part of the treatment can be provided in an outpatient setting. On the other hand, this process of identifying patients that develop HAEC or severe forms of HAEC remains a challenge, as there is no consensus what factors are associated with a higher risk of

developing HAEC, in other words: what patients are more at risk. Chapter 5 in this thesis therefore aimed to gain insight in risk factors associated with HAEC in a retrospective cohort study including 146 patients with HD from our center. The findings presented in *chapter 5* further showed that no risk factors for the development of preoperative HAEC could be established. Patients with a history of HAEC had longer length of hospital stay postoperative and longer length of total hospital stay due to readmissions in follow-up, and were on average one month younger at surgery, but age at surgery was not significantly associated with the odds of developing postoperative enterocolitis. For preoperative HAEC, other studies have suggested that associated congenital anomalies and birthweight were associated with higher likelihood of developing preoperative HAEC, or like the current study identified no risk factors.[21,27] For postoperative HAEC, other studies have suggested that constipation, long-segment disease and preoperative enterocolitis were associated with a higher likelihood of developing postoperative HAEC, but this was not confirmed by the findings in the current study.[27-29] The observed association between length of hospital stay in follow-up due to readmissions and risk HAEC is most likely subsequent to HAEC and treatment of HAEC, rather than a predisposing factor for HAEC. The observed association between longer length of postoperative hospital stay and HAEC may indicate that the longer the time from surgery to normal defecation and/or normal oral feeding after surgery, the higher the risk of developing HAEC. It remains unknown from previous studies whether longer time to normal defecation and normal oral feeding, predisposes patients to more obstructive defecation problems in follow-up, but it may influence the consistency of the enteric microbiome of patients. There are emerging insights that the enteric microbiome and the subsequent immune response to fecal stasis plays an important role in the etiology of HAEC.[30,31] Previous studies have found that probiotics did not lower HAEC incidence, whereas rectal irrigations did.[32,33] Because none of the patient and clinical characteristics were found to be predisposing factors for developing HAEC, early recognition and adequate treatment of HAEC remains a challenge. Early recognition of HAEC requires a more standardized diagnostic approach, but also the exploration of advanced diagnostic techniques including the e-nose that detects fecal volatile organic compounds in feces. This type of diagnostic has been shown to help detect early-onset sepsis and necrotizing enterocolitis in preterms.[34]

According to our findings in *Chapter 5 and 6* of this thesis, the higher the patient's age at surgery, the shorter the postoperative enterocolitis free interval (*Chapter 5*) and the higher the risk of getting a temporary or permanent stoma (*Chapter 6*). However, older age at surgery was neither associated with higher rates of mortality, postoperative complications, a redo pull-through, nor with the rate and severity of constipation and fecal incontinence in long term (*Chapter 6*). The evidence about the influence of early or late resection on surgical outcomes shows contradicting results with regard to postoperative complications,[35-39] length of hospital stay,[35,37] readmission rate[37], colostomy rate[40] and functional outcomes.[35,36,38,40-44] Higher rates of complications may

in particular apply to patients with a delayed diagnosis until childhood or adolescence, with subsequent technical challenges that come with operating an adolescent or adult patient or patients with a severely dilated colon.[41,45] Although our results may have been biased by heterogeneity in operation techniques and developments from three-staged to single-staged pull-through over the course of the study. In the earlier years of the study period, a temporary stoma was more often created, not only when clinically indicated, but as standard approach. Moreover, there is a trend in recent years towards earlier resection, so patients may have been somewhat older when resection took place, despite early diagnosis and preoperative adequate treatment with bowel management. This may explain our findings on the increased risk of stoma in older patients at surgery. Differences in findings between previously published studies and our findings may be explained by what age was used to define early or late surgery. Other factors may be more important to take into consideration regarding the optimal timing for pull-through surgery, including the patients general clinical condition (including weight and nutritional status), the extent to which rectal irrigations can be applied successfully, and the extent to which the colon is dilated.[46]

PART II Multidisciplinary outcomes in patients with surgical congenital malformations

Despite the strong focus on gastrointestinal functional outcome in research about postoperative outcome of patients with HD and other surgical congenital malformations, there are several reasons to suggest that morbidity in these patients may extend to other aspects of health and functioning, including health-related quality of life, neurodevelopmental outcome, psychosocial wellbeing and parental psychosocial wellbeing.

Chapter 7 aimed to assess functional outcome and health-related quality of life in follow-up of patients with total colonic aganglionosis, and assess this with patient-reported outcome measures in 35 patients with total colonic aganglionosis. Total colonic aganglionosis is a severe form of HD, in which the whole large intestine is affected and thus is removed. The findings in this chapter show that patients with total colonic aganglionosis had good psychosocial and social health-related quality of life, despite relatively high rates of constipation, diarrhea and fecal incontinence and impaired physical health-related quality of life (*Chapter 7).* These findings are in line with few previous studies that report about normal quality of life in patients with total colonic aganglionosis.[47,48] Disease-specific quality of life assessment showed that mainly fecal incontinence and diarrhea impaired quality of life. This relation between gastrointestinal bowel dysfunction and impaired quality of life has also been demonstrated in patients with rectosigmoid disease.[49-52] However, other studies have shown, normal – not impaired – quality of life in most patients with rectosigmoid Hirschsprung disease despite the occurrence of problems with bowel dysfunction.[50,53,54] Contradictory findings between studies may be explained by the different types of instruments that are used to assess quality of life, but also by

variations in bowel function and quality of life over time. Moreover, quality of life reports may also be influenced by parental care in infants and children, and in adolescent and adult patients by the (in)ability of patients to adjust their life style. Adjustment of life style around functional impairments allows patients to perceive their functioning as satisfactory, despite their bowel dysfunction, thus resulting in normal quality of life. In summary, insight in Health-related quality of life of patients with Hirschsprung disease and determinants of health-related quality of life over the course of growing up await further evaluation in large prospective studies.[7,51,52,55,56]

The meta-analysis in *Chapter 8* aimed to summarize all available evidence on neurodevelopmental outcome of patients with surgical congenital malformations. The findings in this meta-analysis and meta-regression including 47 studies representing 2312 patients, confirm that patients with surgical malformations on average exhibit lower skills on motor, cognitive and language development compared to reference groups. Although the majority of patients exhibit motor, cognitive and language development within the normal range, a relatively larger proportion of patients exhibit delayed development compared to the reference groups. Differences between studies in terms of the observed neurodevelopmental impairment could not be attributed to differences between studies in terms of in the number of male subjects, mean age at follow-up, mean gestational age, and mean birthweight. There is evidence for several factors that may negatively contribute to the development of the central nervous system in patients with surgical congenital malformations, including genetic abnormalities,[57-61] perinatal influences, (including maternal smoking,[62] use of maternal medication,[63-65] preterm birth and low birthweight,[66]) early, long and/or repeated exposure to anesthetics necessary for surgical correction(s),[67,68] perioperative hemodynamics and respiratory functioning,[69-71] postoperative inflammatory challenges,[72] and poor nutritional status leading to an altered microbiome, influencing the developing brain through the gut-brain axis.[73,74] These harmful influences to the central nervous system may lead to neurodevelopmental impairment. Impaired neurodevelopment may negatively influence other important domains of functioning, including academic achievement, and socioeconomic wellbeing.[75,76] These findings therefore emphasize the importance of monitoring neurodevelopmental outcome in follow-up, in order to achieve early recognition of patients at risk for neurodevelopmental delay, which in turn may facilitate to early intervention.

The psychosocial outcomes of patients with surgical congenital malformations vary largely.[8] Although some studies report normal psychosocial functioning,[77] and that psychosocial wellbeing improves when patients are getting older,[7] others have shown that patients with surgical congenital malformations remain at risk for emotional and behavioral problems,[78-81] post-traumatic stress disorder[82] and impaired psychosocial quality of life during follow-up.[83,84] Until the results of large prospective trials evaluating psychosocial outcomes are available, monitoring of psychosocial outcomes is important in order to identify patients with impaired psychosocial wellbeing.

An increasing number of studies also evaluates the psychological impact of diagnosis of congenital malformations, surgical treatment and hospital admission for surgical congenital malformations on parents of patients.[85-90] *Chapter 9* of this thesis aimed to assess the psychosocial wellbeing of parents of patients with surgical congenital malformations during follow-up in a cohort of 97 parents of patients that visited our standardized prospective multidisciplinary follow-up program. The findings presented in this chapter show that although parents of patients with surgical congenital malformations do not show higher rates of clinical distress during follow-up, mothers have a high risk of developing post-traumatic stress syndrome and the majority of parents have intrusions. As mothers are at risk for post-traumatic stress disorder, most parents may experience some symptoms of post-traumatic stress and because post-traumatic stress can negatively influence bonding and the parent-child interaction between parents and children,[88,91] it is important to pay attention at follow-up to parents of patients with surgical congenital malformations.

Unfortunately, current standard practice in follow-up care is highly focused on disease-specific sequelae and most often not multidisciplinary. Patients come for follow-up in case they have functional problems. Few institutions have implemented multidisciplinary follow-up services, but even these programs have a strong focus on somatic functional outcome only. Only few monitor patient outcome in other domains of health than gastrointestinal functional outcome only.[92-95] Although parents and patients are satisfied with such follow-up services,[96] they do not provide a holistic perspective on patient outcome. Health and functioning however, is a multidimensional concept and various aspects of health may mutually influence each other.[97,98] For example, poor somatic functional outcome may influence other domains of functioning, including psychosocial wellbeing.[98-100] It is thus important to use a more holistic perspective on health and functioning in the design of follow-up services and to get a comprehensive picture of a child's health and functioning at follow-up.[8] In 2017 a standardized prospective multidisciplinary follow-up program, called the Follow Me program, was implemented in the Amsterdam UMC, aiming to provide such a holistic multidisciplinary follow-up service. The aim of *Chapter 10* in this thesis was to show an example of how such a standardized prospective multidisciplinary follow-up can contribute to improvement of patient outcome, improvement of health care quality and to scientific research on outcome and prognosis of patients with surgical congenital malformations. This chapter shows how standardized prospective multidisciplinary follow-up facilitates charting of patient outcomes during the course of growing up, early detection of impairments in various domains of functioning, thus facilitating early interventions. In addition, it shows an example of how multidisciplinary team work was established in the context of follow-up care for patients with surgical congenital malformations and how structured data collection in multidisciplinary follow-up facilitates health care evaluation.

Studies have described that multidisciplinary teamwork limits adverse events, improves patient outcome and increases patient and employee satisfaction in various hospital settings.[101] This way the Follow Me program contributes to improvement of health care. Moreover, the use of multiple patient-reported outcome measures (PROMs) are implemented in the program. The use of routine outcome monitoring using has shown to be able to improve aspects of the health care process (including communication between patient and health care provider, early detection of health problems and more shared-decision making), however studies assessing the impact on health care quality improvement and transparency of health care performance are still lacking.[102,103] Although some studies suggest that the use of PROMs may contribute to improvement of individual patient outcome, the current available literature is heterogeneous in its findings and most studies are not able to show an effect or only find weak effects.[103-105] currently available evidence also shows that the value of PROMs is highly depend of the way PROMs are implemented in the health care process, how feedback to health care professionals is provided, how data is presented and how valid and representative the data is perceived to be by health care professionals, whether health care professionals are trained to use PROMs.[106,107]

Standardized collection of outcome data may further contribute to research on outcome and prognosis of patients with surgical congenital malformations. As surgical congenital malformations are rare conditions, most studies are conducted in small-sized cohorts. Establishing standardized outcome measurement in a consecutive cohort of patients, will help us to gain more insight in factors that contribute to the heterogeneity in outcomes, as there is a smaller risk of selection and information bias. Standardized collection of outcome data may further help to develop prediction models predicting patient outcome, thus providing possibilities for improved personalized prognosis. This may contribute to precision medicine in the follow-up of surgical congenital malformations.[108] *Chapter 11* of this thesis aimed to study the potential of machine-learning methods for the development of prediction models, compared to traditional statistical methods. This chapter describes a cohort study about the predictive value of intraoperative hemodynamic features for early motor outcome among 137 patients with surgical congenital malformations who attended the Follow Me program. The findings in this chapter show that hemodynamic features are moderately able to explain variance in early motor outcome, but also that machine learning algorithms exhibited better predictive performance with smaller prediction error compared to traditional statistical methods such as linear regression. Studies in other patient population have also shown promising results of the use of machine-learning algorithms to predict patient outcome.[109-112]

METHODOLOGICAL CONSIDERATIONS

Studies on patient outcome and predictors for patient outcome in patients with rare conditions face methodological challenges including 1) small sample sizes with subsequent statistical limitations,[113] carrying the risk of selection bias (in particular when measuring long term outcome), 2) heterogeneity in outcome measurement and missing data, and 3) a focus on only one or a few single outcomes. It is therefore important to consider some methodological aspects applied in some of the chapters of this thesis, that are promising approaches to improve our insight in patient outcome.

Small sample sizes in cohort studies negatively impact the precision of effect estimates (reflected in large confidence intervals), the statistical power to detect meaningful relationships and the type 1 error rate. One approach in research to increase sample size is (inter)national cooperation in (inter)national cohort studies. *Chapter 6 and 7* are examples of studies conducted in a national cohort. Larger cohort studies are better able to estimate outcomes and have statistical power to detect sources of heterogeneity in outcome findings. Large-scale studies and (inter)national collaboration in research projects is necessary aimed at identifying (subgroups of) patients with a high risk of adverse outcomes. International collaboration would benefit generalization of study findings, as international cohort studies are less likely to be confounded by specific sample characteristics. A second approach is to minimalize the risk of selection or attrition bias that occurs often in cohort studies on patient outcome in patients with surgical congenital malformations, in particular studies on long term outcome. Selection bias is a bias introduced by the fact that some patients are less likely to participate in studies compared to others, resulting in a less representative cohort and thereby influencing outcome findings. For example, patients who are functioning well more often withdraw from follow-up and are thus less likely to be included in studies based on medical records. Another example is that parents and patients with higher educational level and socio-economic status are more likely to participate in follow-up studies compared to parents and patients with lower educational level and socio-economic status, whilst lower socio-economic status may be associated with worse outcomes. Prospective standardized outcome measurement in follow-up creates a consecutive cohort and thereby minimalizes the risk of selection bias.

Another approach to the lack of statistical power in studies with a small sample size, next to strategies aimed at increasing sample size, is to use other statistical techniques. Meta-analysis and meta-regression are statistical techniques that aggregate findings from various studies. Meta-analysis offers the most robust estimate of outcome using all available data and meta-regression allows to study factors that explain heterogeneity in outcome between studies, whilst calculating with aggregated data, thus providing a more representable picture of outcome in a patient group. *Chapters 2, 3 and 9* use these techniques. Although meta-analysis offers robust estimates and random-effects meta-analysis corrects to some degree for heterogeneity between studies, estimates from meta-analysis

are negative influenced in terms of precision (reflected in large confidence intervals) when between-study heterogeneity is high.[114] Moreover, meta-regression is a useful and widely used tool to explore sources of heterogeneity in outcome findings between studies, but it does not allow for conclusions on relations between clinical characteristics and outcomes on a patient level. Studies' average values of clinical characteristics and outcome data are used on a study level as covariates in the analysis, thus creating a risk of aggregation bias. This risk applies especially in case of large variation between individuals in a study (reflected in the variance) and little variation in aggregated outcomes between studies, as well as in meta-regression with a small number of studies. Hence, effects detected with meta-regression are likely to be large and important effects, but the absence of an effect in meta-regression does not exclude an effect in an individual patient.[115]Another approach compared to traditional statistical models, that often need adequate statistical power to detect risk factors or predictors for outcome, is the use of machine learning algorithms, as was done in *Chapter 11*. The methodological strength of a machine learning algorithm, such as Support Vector Machine regression, is its ability to model more complex relations between factors (by also calculating support vectors) and thus to identify more complex, non-linear relations that traditional regression models cannot detect. The findings in C*hapter 11* confirmed the hypothesis that machine learning algorithms show better predictive performance compared to traditional statistical methods.

Second, heterogeneous outcome measurement is a challenge, in particular when studies have a retrospective design and use data from medical records. Standardized outcome measurement using validated instruments offers a solution to this challenge. In studies using data from medical records, data may be subject to reporting bias in terms of missing data or large inter-observer variability in outcome definition. Validated (patient reported) outcome measurements and clinical scores offer solutions to this challenge. This is why within the Follow Me program validated outcome measures are used to assess outcome in patients, for every outcome for which a validated measure is available, as described in *Chapter 10*. Also *Chapter 8, 9 and 11* use validated instruments for outcome measurement. In multiple studies in this thesis patient- or parent-reported outcomes were used to measure bowel function and quality of life of patients and psychosocial wellbeing of parents. Although there is a variation in specific psychometric properties across different instruments, patient-reported outcome measures (PROMs) have shown to play an important role in improving quality of care, despite practical challenges in collecting and interpreting PROMS.[106,116,117] PROMs are also a critical aspect of value-based healthcare because they monitor experiences and outcomes from a patients perspective and help engage patients in the health care process, thus contributing to patient-centered care.[118-120] Implementation of standardized outcome reporting can be challenging. Clinicians may question the clinical usefulness of standardized outcome measures, standardized outcome measures may be time-consuming, there can be a lack of agreement on what instruments to use, there may be challenges in the availability of appropriate information technology systems, or lack of time, financial resources and compliance.[121-124]

Third, most studies on patient outcomes in patients with surgical congenital malformations focus on one single or a few outcomes. One of the strengths of this thesis is the assessment of a large variety of outcomes, in multiple domains of functioning, to chart a comprehensive picture of outcome in patients with surgical congenital malformations. This thesis integrated insights from pediatric surgery, gastroenterology, pediatrics, neuropsychology, developmental psychology and clinical psychology to provide a broad perspective on the outcomes of patients with congenital gastrointestinal malformations and their parents in follow-up. This approach contributes to insight in how patients with congenital gastrointestinal malformations are functioning and shifts the focus from short term somatic outcomes to a more holistic view on the long term functioning of patients with congenital gastrointestinal malformations.

IMPLICATIONS AND FUTURE DIRECTIONS

In the following paragraphs implications and future directions for research on patient outcome in patients with surgical congenital malformations and implications for clinical practice will be discussed.

Research implications and future directions

The findings in this thesis demonstrate that although some patients with Hirschsprung disease have poor bowel function, including obstructive defecation problems, HAEC and fecal incontinence, others have normal bowel function. The origin of these differences remains poorly understood. The studies conducted in this thesis were also not able to identify patient or clinical characteristics that were risk factors for impaired gastrointestinal functional outcome. Our findings did suggest that patients with total colonic aganglionosis have poorer functional outcome and impaired physical health-related quality of life. Our findings further suggest that transition zone anastomosis is associated with impaired functional outcome. But for other patient and clinical characteristics including gender, birthweight, gestational age, age at diagnosis, type of surgery, open or laparoscopic surgery, complication rate and length op post-operative hospital stay no association with functional outcome was demonstrated. Higher age at surgery was also not associated with impaired functional outcome, although it was associated with a shorter enterocolitis free interval in patients who had enterocolitis and with a higher temporary stoma rate. Future studies should be aimed at further understanding the determinants of bowel function during follow-up and to develop clinical prediction models for impaired gastrointestinal bowel function in patients with Hirschsprung disease.

Another direction for future studies subsequent to our findings in Chapter 2 is the improved detection, and in turn prevention, of TZA. Despite that it is standard practice in most hospitals treating patients with HD, to examine the proximal resection plane

for the presence of ganglions with histopathological examination, TZA is still frequently missed directly after pull-through surgery. In a substantial number of patients a transition zone anastomosis or residual aganglionosis was detected by repeated rectal biopsy after pull-through. This emphasizes the need to extend the histopathological examination of the complete resection specimen and conduct a more detailed examination of the distribution of ganglions, the presence of hypoganglions and hypertrophy of nerve fibers.[125,126] Or to improve the detection of transition zone bowel in frozen point biopsies that are done intraoperatively. Future studies should also aim at providing better insight in the histopathological features of a transition zone bowel and thus generate improved diagnostic criteria for TZA. Future studies should also focus on improved perioperative detection of transition zone bowel and determination of the level of resection. Either by improving techniques for intraoperative histopathological examination (now often done by single point frozen biopsy),[127] for example by studying hypertrophic nerve fibers in frozen sections, or by developing new perioperative visualization techniques,[128-130] or by developing prediction models with digital photographs of frozen sections using visual machine learning algorithms.

The risk of getting HAEC also remains poorly understood and future studies should focus on a better understanding of why some patients develop HAEC, while other do not. In particular the fecal microbiome is an interesting focus point for future studies. Disbalance in the microbiome may be related to the risk of HAEC and future studies should focus at improved diagnostics for HAEC, including strategies as the e-nose that is able to detect fecal volatile compounds that reflect the microbiome of the gut.[34] The microbiome may in turn be related to dietary intake, the use of breastmilk, bowel passage and perhaps bowel irrigations.[131-134] Therefore also optimization of bowel passage and nutritional status before pull-through surgery, as well as postoperative bowel management strategies, may influence the risk of developing HAEC and are interesting points of focus for future studies. Optimization of bowel passage may be done by temporary laxatives, creating an ileostomy or rectal irrigations, but future studies should further elucidate the influence of such strategies on functional outcome and the risk of HAEC. Patients with Hirschsprung disease may exhibit feeding problems subsequent to obstructive defecation problems. Nutritional status has shown to be related to postoperative complications in children undergoing surgery and in infants undergoing cardiac surgery.[46,135] Lastly, future studies should focus on elucidating the influence of different operation techniques and the optimal timing for pull-through surgery for short segment aganglionosis and for total colonic aganglionosis.[136] Clinical practice in terms of type of operation and optimal timing for pull-through surgery is to date very heterogeneous and based on surgeons preference.

For outcome studies in patients with surgical congenital malformations, not just patients with Hirschsprung disease, future studies should be aimed at studying patient outcome and parental outcome in broader aspects of functioning than somatic functional outcome only. This includes generic and disease-specific health-related quality of life

outcome, psychosocial outcome including behavioral abnormalities, including attention and hyperactivity behavior, socio-emotional development, symptoms of post-traumatic stress disorder, and neurodevelopmental outcome during the course of growing up. Longitudinal trends in patient outcome and long term outcome are much lesser described compared to short term outcome. Future studies should focus at longitudinal trends in patient outcome to allow for improvement of providing accurate prognosis. This includes the influence of important transitions over the course of growing up (such as the start of the academic trajectory and puberty) on patient outcome. Also the relations between various aspects of functioning during follow-up are interesting points of focus for future studies. For example the relation between the occurrence of disease-specific sequelae and quality of life, or the relation between parental wellbeing and psychosocial wellbeing of patients, or the relation between impairments in neurodevelopmental outcome and quality of life. For some congenital malformations disease-specific quality of life questionnaires exist, for others they are still in development or need to be developed.

Standardized prospective outcome monitoring in follow-up from childhood up to adulthood can yield insight in longitudinal trends in various aspects of patient outcome during follow-up. In standardized prospective follow-up outcome measurement is integrated in standard follow-up care, instead of integrated in additional voluntary research projects. Next to the creation of a consecutive cohort, standardized prospective outcome monitoring also offers the benefit of being able to study both patients with favorable outcome and impaired outcome and thus create a more comprehensive picture of determinants of outcome compared to only studying risk factor for poor outcome.

Ultimately insight in patient outcome and factors that determine patient outcome may help us to develop valid clinical prediction models to predict patient outcome and improve individualized prognostic prediction. Although there are currently no studies that have published a prediction model for patient outcome in patients with surgical congenital malformations, there have been some efforts in other pediatric patient groups, including patients in the emergency room, patients with traumatic brain injury and patients with congenital cardiac malformations.[137-140] To increase generalizability and clinical usability of prediction models, it is important that models are externally validated in unseen data.[141,142] In the development of valid and usable clinical prediction models, future studies should explore more advanced statistical techniques to develop prediction models of patient outcome in patients with surgical congenital malformations, including the use of machine learning algorithms.[143]

A more comprehensive picture of determinants of patient outcome may also help to provide leads for interventions to improve patient outcome. Another point of focus for future studies should be to evaluate the effects of such interventions aimed at improving patient outcome. Prospective outcome monitoring also offers the opportunity to evaluate the effect of interventions, by comparing outcome of patients during follow-up that did or did not receive a specific intervention. This could be all kinds of interventions, such

as changes in current surgical treatment strategies (including for example minimally invasive approaches, operation techniques), interventions in follow-up aimed at improving disease-specific functioning (including botulinum toxin injections, dietary interventions, probiotics and specific types of bowel management), interventions to stimulate motor, cognitive and language development, psychosocial intervention including treatment for childhood trauma or behavioral problems, or interventions in parents, including treatment for trauma. Future studies can help to assess whether interventions are effective and which patients may benefit from what intervention, thus improving evidence-based practice.

Clinical implications

Treatment of obstructive defecation problems and HAEC in patients with Hirschsprung disease

The findings in part 1 of this thesis on bowel function and treatment strategies for patients with Hirschsprung disease with obstructive defecation problems have the following implications for clinical practice: 1) they support the importance of early diagnosis of transition zone anastomosis, 2) they show the benefit of botulinum toxin injections for patients with Hirschsprung disease, and 3) they emphasize the need to standardize diagnosis of HAEC and transition zone pull-through. Based on the findings in this thesis we implemented a standardized protocol for further diagnostics and treatment in patients with obstructive defecation problems that do not respond to laxatives and rectal irrigations (Figure 1). The results of this thesis demonstrate that even from findings in retrospective cohort studies improvements in health care can be made. The protocol is an adapted version of the guidelines recommended by Langer et al.[13]

First, a standardized approach to exclude TZA was added. It is important to exclude a transition zone anastomosis in all patients with Hirschsprung disease, as the findings in this thesis *(Chapter 2)* have shown that the current prevalence of transition zone anastomosis is rather high despite postoperative histopathologic examination of the resection specimen. Second, the indication to administer BT injections was formulated more clearly and standardized moments for effect evaluation and evaluation of the need to repeat BT injections were agreed upon (*based on findings in Chapter 4*). Third, the role of colonic manometry to assess mobility disorders as a cause for obstructive defecation problems in follow-up was emphasized.[144]

Following the insights in *chapter 5* on the challenges of diagnosing HAEC, another protocol was implemented in our hospital. In this protocol, diagnostic criteria for HAEC were formulated based on the clinically validated score of Pastor et al.[23,24] The protocol aims to standardize the diagnosis and treatment of HAEC and improve homogeneity in registration. This will allow improved evaluation of treatment and risk factors of HAEC in the future. Based on the diagnostic clinical score, HAEC is graded as mild or severe in this protocol. For mild HAEC, oral antibiotics and rectal irrigation at home are recommended,

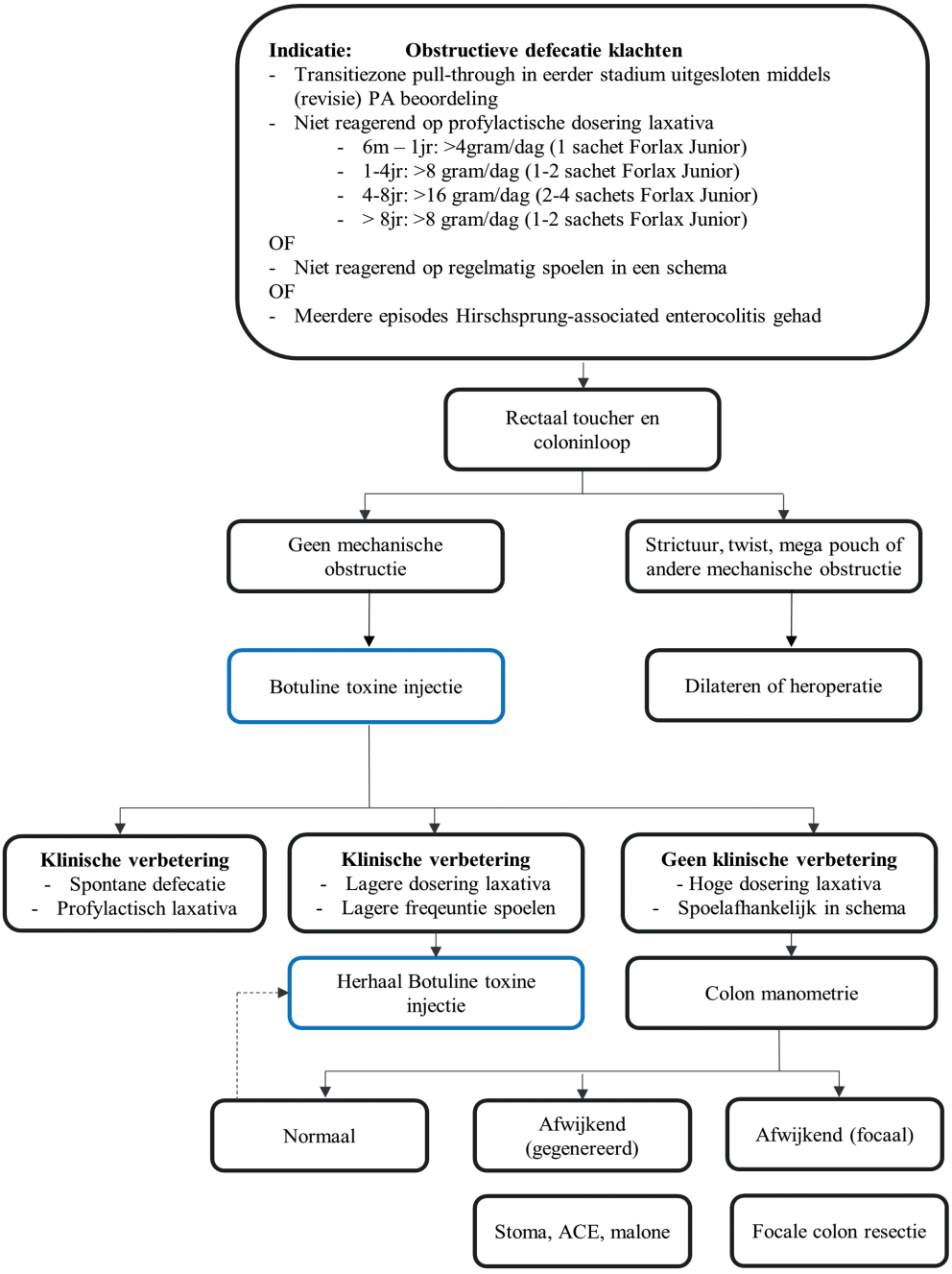


Figure 1 Flowchart of diagnostic strategies and treatment strategies for patients with Hirschsprung disease who have obstructive defecation problems, adapted from the guideline published by Langer et al.[13]

whereas severe HAEC is treated with hospital admission, intravenous antibiotics, rectal irrigations and dietary restrictions or rehydration when indicated.

Long term multidisciplinary follow-up and health care improvement

In this thesis the importance of standardized prospective monitoring of outcomes of patients with surgical congenital malformations in follow-up was demonstrated. A standardized multidisciplinary follow-up program is was implemented in our hospital in 2017. As described in *Chapter 10*, standardized prospective multidisciplinary follow-up of patient outcome is recommend for multiple reasons: 1) it allows for direct adjustments in treatment which may lead to direct improvement of functioning of patients in follow-up (personalized medicine) and functioning and wellbeing of their parents, 2) it allows for early identification of infants at risk for poor outcomes in the long term, 3) it allows for improving our understanding of factors that contribute to heterogeneity in outcome, which in turn may help to adapt clinical practice and clinical decisions to improve functioning of patients, 4) it allows for the use of e-health in follow-up, by using digital patient reported outcome monitoring prior to consultation, and 5) it allows the use of outcome monitoring for health care quality improvement in a multidisciplinary team. Quality evaluation of health care should not only be an internal evaluation within the multidisciplinary team, but through external evaluation and benchmarking an attempt should be made to include outcome evaluation in national and international quality registries. (Inter)national quality registries and (inter)national cooperation in registry-based research are needed to aggregate sufficient data to answer research questions and allow adequate benchmarking. However, current registries are highly focused on 30-day mortality and complication rates. We recommend that an effort should be made to also include long term outcome indicators in such registries. Outcome indicators have shown to be important indicators for quality of care, beside process indicators.[145-147]

CONCLUDING REMARKS

This thesis shows the importance of research aimed at studying patient outcome in patients with surgical congenital malformations. Although there is still a world to win, standardized prospective multidisciplinary follow-up offers a promising route towards further insight in patient outcome of patients with surgical congenital malformations, identification of determinants of outcome and subsequent possibilities to improve patient outcome and health care quality.

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CHAPTER 13

Summary

Surgical congenital malformations are birth defects that require surgical treatment in infants. Despite substantial improvement in survival of patients with surgical congenital malformations over the past decade, patients may experience disease-specific or surgery-related sequelae that cause morbidity during follow-up.

In the general introduction, *Chapter 1*, the context and background of research on patient outcome in patients with surgical congenital malformations is described. In particular that of Hirschsprung disease, a congenital gastrointestinal malformation. Research on outcome and prognosis in patients with surgical congenital malformations is often focused on functional outcome, such as gastrointestinal functional outcome in patients with Hirschsprung disease. The available evidence indicates that although most patients achieve normal bowel function after surgery, about 33% of patients with Hirschsprung disease have poor gastrointestinal functional outcome. This is reflected by complaints of constipation, fecal incontinence or developing Hirschsprung-associated enterocolitis (HAEC). The origin of this heterogeneity in gastrointestinal functional outcome between patients with Hirschsprung disease remains poorly understood. Insight in factors that explain poor outcome may contribute to improvement of patient outcome. To this end, the first objective of this thesis was to elucidate factors explaining poor gastrointestinal functional outcome and treatment strategies for poor gastrointestinal functional outcome in patients with Hirschsprung disease.

The narrow focus on somatic functional outcome is illustrative for research on outcome and prognosis of patients with surgical congenital malformations. However, health and functioning is a multidimensional concept that also describes other aspects of health and functioning. Besides somatic functioning, also psychosocial functioning, quality of life and family functioning are aspects of health and functioning of children. These various of health and functioning have mutual influence on each other. Research on patient outcome and prognosis in patients with surgical congenital malformations should therefore have a broader focus than only on somatic functional outcome. To this end, the second aim of this thesis was to explore outcome of patients with surgical congenital malformations in other aspects of health and functioning, including health-related quality of life, neurodevelopmental outcome and psychosocial wellbeing of parents.

This narrow focus on somatic functional outcome is not only present in research on patient outcome, but is also reflected in clinical follow-up of patients with surgical congenital malformations. Although there are a few exceptions in the Netherlands, Australia and Italy, standardized prospective multidisciplinary follow-up with a broad perspective on health and functioning of patients with surgical congenital malformations is rare. The third aim of this thesis was to explore the possibilities of standardized prospective multidisciplinary follow-up to improve patient outcome, improve quality of care and contribute to scientific research on outcome and prognosis in patients with surgical congenital malformations after surgery. Part I covers the first aim and Part II covers the second and third aim.

PART I Gastrointestinal functional outcome in patients with Hirschsprung disease

Among the factors that may explain poor gastrointestinal functional outcome in patients with Hirschsprung disease is a transition zone anastomosis. In that case the proximal part of the anastomosis contains transition zone, Transition zone is colon between normal ganglionic and aganglionic bowel. The findings from the meta-analysis in *Chapter 2* suggest that transition zone anastomosis is prevalent in about 10-25%, and that prevalence estimates were dependent of whether patients underwent redo pull-through and the type of anastomotic technique. Furthermore, a transition zone anastomosis was associated with high rates of obstructive defecation problems.

One of the treatment strategies for obstructive defecation problems is the use of botulinum toxin injections. The findings from the meta-analysis in *Chapter* 3 based on 14 studies with 278 patients with Hirschsprung disease, suggest that obstructive defecation problems are effectively treated with botulinum toxin injections. In an average of 66% of the patients clinical improvement of obstructive defecation problems was achieved. This percentage was independent of type of botulinum toxin used, dosage, mean age at injection and the proportion of syndromal patients. In on average of 17% of patients adverse effects were observed. In *Chapter 4* the factors that influence effectivity of botulinum toxin injections were explored in a cross-sectional study with 131 patients with Hirschsprung disease. In this study 61% of the patients exhibited clinical improvement after the first injection, whilst 29% experienced mild adverse effects. The majority of patients (71%) achieved spontaneous defecation after treatment with botulinum toxin injections, or defecation supported by laxatives only. In this study no patient-related or clinical characteristics were associated with the effectiveness of botulinum toxin injections.

Another reflection of impaired gastrointestinal functional outcome in patients with Hirschsprung disease is the development of HAEC. HAEC is a severe form of bowel inflammation, potentially resulting in bowel perforation, sepsis and death. In *Chapter 5* the prevalence and risk factors for developing HAEC are studied in a cross-sectional study of 146 patients with Hirschsprung disease. The study shows that the prevalence of preoperative HAEC (10%) was lower than the prevalence of postoperative HAEC (21%). Although patients who developed HAEC were younger at surgery and had longer length of hospital stay, no other risk factors for developing HAEC were identified in this study. Higher age at surgery was negatively associated with the postoperative enterocolitis free interval. In *Chapter 6* the relation between age at surgery ad patient outcome was further explored. The findings from this national cohort study of 830 patients suggest that age at surgery is not associated with the risk of postoperative complications, redo surgery, mortality and long term gastrointestinal functional outcome, only with the risk of a temporary stoma.

PART II Multidisciplinary outcome in patients with surgical congenital malformations

An important outcome in patients with surgical congenital malformations is health-related quality of life. Health-related quality of life is someone's subjective evaluation of their physical, mental and social health. A national cohort study in 35 patients with total colonic aganglionosis, a rare form of Hirschsprung disease in which the whole large intestine is affected, described in *Chapter 7*, shows that patients with total colonic aganglionosis often report constipation (65%), soiling (53%) and fecal incontinence (47%). Despite these findings on functional gastrointestinal outcome, patients report normal psychosocial and social health-related quality of life compared to normative data. Physical health-related quality of life and general perception of health were evaluated worse compared to normative data. The study further showed that physical complaints and diarrhea impaired health-related quality of life in patients with total colonic aganglionosis.

Findings from other studies suggest that beside health-related quality of life, also neurocognitive and motor development in patients with surgical congenital malformations may be negatively influenced during follow-up. The findings from the meta-analysis including 47 studies with 2312 patients with congenital gastrointestinal malformations in *Chapter 8,* suggests that patients with on average exhibit small-sized cognitive impairment, medium-sized motor impairment and medium-sized language impairment compared to normative data. Patients with short bowel syndrome had worse neurodevelopmental impairment compared to other types of congenital malformations. Neurodevelopmental impairment was associated with the mean length-of-hospital stay and median number of surgeries. These findings emphasize the need for outcome monitoring of neurodevelopmental outcome of patients with surgical congenital malformations during follow-up.

Not just patients with surgical congenital malformations may experience disease-specific sequelae during follow-up, also the psychosocial wellbeing of their parents may be negatively influenced. A cross-sectional study in *Chapter 9* in 97 parents of patients with surgical congenital malformations, shows that parents exhibit comparable rates of clinical distress compared to normative data, but higher rates of post-traumatic stress. In particular mothers more often had post-traumatic stress disorder. Post-traumatic stress disorder is characterized by symptoms of intrusion (involuntary memories inducing a stress response), avoidance behavior and feelings of hyperarousal. Of all included parents, 75% reported symptoms of intrusion. The longer the total length of child's hospital stay the more severe symptoms of intrusion, avoidance and hyperarousal in parents were. The longer a child was in follow-up, the less severe symptoms of intrusion in parents were. The findings from this study emphasize the need for monitoring of psychosocial wellbeing of parents during follow-up of patients with surgical congenital malformations.

To monitor a broad range of patient outcomes of patients with surgical congenital malformations and their parents during follow-up, a standardized prospective

multidisciplinary follow-up program was introduced in the Amsterdam UMC in 2017: the Follow Me program. In this program a broad range of outcomes are monitored using validated and standardized outcome measurements. In *Chapter 10* the design of this follow-up program is described, including the developed protocols, the used instruments for outcome measurements and the implemented data-cycle designed for the evaluation and improvement of quality of care. Furthermore it is explained and argued how such a design for follow-up can contribute to improving patient outcome, to improving quality of care and to research on patient outcome.

Standardized routine outcome monitoring in prospective multidisciplinary follow-up can not only be used for improving patient outcome and quality of care. It can also be used to gain further insight in long term patient outcome and determinants of patient outcome and the subsequent development of clinical prediction models of patient outcome. In the study in *Chapter 11* the data of 85 patients that were collected in the standardized prospective multidisciplinary follow-up program were used to develop a clinical prediction model for the prediction of early motor outcome based on clinical characteristics and intra-operative oxygenation and hemodynamics. The study shows that intraoperative oxygenation and hemodynamics were able to explain 12-19% of variance in early motor outcome. Machine learning algorithms further exhibited better predictive performance compared to traditional statistical models. This study emphasizes the potential of standardized routine outcome monitoring and the value of machine learning for the development of clinical prediction models.

In conclusion, this thesis emphasizes the value of routine outcome monitoring of a broad range of patient outcomes in standardized prospective multidisciplinary follow-up for the improvement of patient outcome, quality of care and research.

Main findings

- TZA is prevalent in 10-25% of patients with Hirschsprung disease after pull-through surgery and is associated with obstructive defecation problems
- Botulinum toxin injections are effective in treating obstructive defecation problems
- There are no factors identified that are associated with better effects of botulinum toxin injections
- Hirschsprung-associated enterocolitis is prevalent in 8% of patients before pull-through surgery and in 21% of patients after pull-through surgery
- There are no factors identified that are associated with a higher risk of Hirschsprung-associated enterocolitis
- Higher age at surgery was associated with a higher risk of a temporary stoma
- Age at surgery was not associated with variation in gastrointestinal functional outcome in long term
- Patients with total colonic aganglionosis have impaired gastrointestinal functional outcome and physical health-related quality of life compared to healthy peers

- Patients with congenital gastrointestinal malformations are at risk for impaired motor development, cognitive development and language development
- Mothers of patients with congenital gastrointestinal malformations more often have post-traumatic stress disorder compared to the general population
- Routine outcome monitoring in standardized prospective multidisciplinary follow-up can contribute to improving patient outcome, improving quality of care and to research on outcome and prognosis in patients with surgical congenital malformations
- Early motor outcome of patients with surgical congenital malformations could be moderately predicted with intra-operative oxygenation and hemodynamics
- Machine learning algorithms had better predictive performance in the prediction of early motor outcome compared to traditional statistical models

APPENDICES

NEDERLANDSE SAMENVATTING

Chirurgische aangeboren aandoeningen zijn aangeboren lichamelijke defecten die operatieve behandeling vereisen. Ondanks dat de overleving in patiënten met chirurgische aangeboren aandoeningen sterk is verbeterd over de afgelopen jaren, kunnen patiënten tijdens follow-up klachten blijven ondervinden ten gevolge van de aangeboren aandoening en de chirurgische behandeling.

In de algemene inleiding, *Hoofdstuk 1*, wordt de context en achtergrond van onderzoek naar de uitkomsten van patiënten met chirurgische aangeboren aandoeningen beschreven. In het bijzonder die van de Ziekte van Hirschsprung, een aangeboren aandoening van het maagdarmstelsel. Onderzoek naar uitkomst en prognose van patiënten met chirurgische aangeboren aandoening is vaak gericht op functionele uitkomsten, zoals de darmfunctie bij patiënten met de ziekte van Hirschsprung. Uit onderzoeken blijkt dat hoewel de meeste patiënten na de operatie een normale darmfunctie hebben, ongeveer 33% van de patiënten een verminderde darmfunctie heeft. Dit uit zich in klachten als obstipatie, incontinentie voor ontlasting en Hirschsprung-geassocieerde enterocolitis (HAEC) krijgen. De oorsprong van deze verschillen in darmfunctie tussen patiënten met de Ziekte van Hirschsprung blijft echter beperkt begrepen. Inzicht in factoren die een verminderde darmfunctie kunnen verklaren, kan bijdragen aan verbetering van de uitkomst van patiënten. Het eerste doel van dit proefschrift was dan ook om onderzoek te doen naar factoren die een slechte darmfunctie bij patiënten met de ziekte van Hirschsprung verklaren en behandelingsstrategieën voor een slechtere darmfunctie te evalueren.

De nauwe focus op lichamelijk functioneren is illustratief voor onderzoek naar uitkomst en prognose van patiënten met chirurgische aangeboren aandoeningen. Gezondheid en functioneren is echter een multidimensionaal concept dat ook andere aspecten van gezondheid en functioneren beschrijft. Naast lichamelijk functioneren zijn ook psychosociaal functioneren, kwaliteit van leven en het functioneren van een gezin onderdeel van de gezondheid en het functioneren van kinderen. Deze diverse aspecten van gezondheid en functioneren beïnvloeden elkaar ook wederzijds. Onderzoek naar uitkomsten van patiënten met chirurgische aangeboren aandoeningen zou dan ook een bredere focus moeten hebben dan alleen op darmfunctie of longfunctie. Het tweede doel van dit proefschrift was dan ook om onderzoek te doen naar de uitkomst van patiënten met chirurgische aangeboren aandoeningen in andere aspecten van gezondheid en functioneren, zoals gezondheidsgerelateerde kwaliteit van leven, motorische en neurocognitieve ontwikkeling en het psychosociaal welbevinden van ouders.

Niet alleen in het wetenschappelijk onderzoek, maar ook in de follow-up van patiënten met chirurgische aangeboren aandoeningen is de nauwe focus op lichamelijk functioneren terug te zien. Hoewel er enkele uitzonderingen zijn in Nederland, Australië en Italië, is gestandaardiseerde prospectieve multidisciplinaire follow-up die in brede zin kijkt naar de gezondheid en het functioneren van patiënten met chirurgische aangeboren aandoeningen

zeldzaam. Het derde doel van dit proefschrift was dan ook om te onderzoeken welke mogelijkheden gestandaardiseerde prospectieve multidisciplinaire follow-up biedt in het verbeteren van uitkomsten van patiënten, verbetering van de kwaliteit van zorg en een bijdrage leveren aan wetenschappelijk onderzoek naar de uitkomst en prognose van patiënten met chirurgische aangeboren aandoeningen na de operatie. Deel I van dit proefschrift behandelt het eerste doel en deel II behandelt het tweede en derde doel.

Deel 1: Gastro-intestinale functionele uitkomsten bij patiënten met de ziekte van Hirschsprung

Een van de factoren die een slechte darmfunctie bij patiënten met de Ziekte van Hirschsprung kan verklaren, is de aanwezigheid van een overgangszone-anastomose. In dat geval bevat het proximale deel van de anastomose die bij de doorhaaloperatie wordt gecreëerd de overgangszone. De overganszone is een segment van het colon tussen de gezonde en volledig aganglionaire darm. De bevindingen van de meta-analyse in *Hoofdstuk 2* suggereren dat de prevalentie van een overgangszone-anastomose in patiënten met de Ziekte van Hirschsprung varieert tussen de 10 en 25% is, en afhankelijk was van of patiënten een heroperatie moesten ondergaan en van de gebruikte techniek voor de anastomose. Een overgangszone blijkt in deze meta-analyse geassocieerd te zijn met het vaker voorkomen van obstructieve defecatieklachten.

Een van de behandelstrategieën bij obstructieve defecatieklachten is het gebruik van botox injecties in de interne anale kringspier. De bevindingen van de meta-analyse in *Hoofdstuk 3* op basis van 14 onderzoeken met 278 patiënten met de ziekte van Hirschsprung, suggereert dat obstructieve defecatieklachten effectief te behandelen zijn met botox injecties. In gemiddeld 66% van de patiënten werd een klinische verbetering van de obstructieve klachten waargenomen. Dit percentage was onafhankelijk van het type botox dat werd gebruikt, de dosering, de gemiddelde leeftijd ten tijde van de injectie en hoeveel patiënten een syndroom hadden. In gemiddeld 17% van de patiënten werden bijwerkingen waargenomen. In *Hoofdstuk 4* is onderzocht welke factoren bepalend zijn voor de effectiviteit van botox injecties, in een cross-sectionele studie met 131 patiënten met de Ziekte van Hirschsprung. In deze studie werd een klinische verbetering waargenomen na de eerste botox injecties in 61% van de patiënten, terwijl 29% milde bijwerkingen ondervond. De meerderheid van de patiënten (71%) bereikte spontane defecatie na de botox injectie, of defecatie met alleen laxeermiddelen. In deze studie konden geen patiëntgerelateerde of klinische kenmerken worden aangetoond die de effectiviteit van botox beïnvloedden.

Een andere uiting van een verminderde darmfunctie bij patiënten met de Ziekte van Hirschsprung is het ontstaan van HAEC. HAEC is een ernstige vorm van darmontsteking die in potentie kan lijden tot darmperforatie, sepsis en overlijden. In *Hoofdstuk 5* zijn de prevalentie en risicofactoren voor het ontwikkelen van HAEC onderzocht in een cross-sectionele studie van 146 patiënten met de ziekte van Hirschsprung. Uit deze studie

blijkt dat de prevalentie van preoperatieve HAEC (10%) lager was dan de prevalentie van postoperatieve HAEC (21%). Hoewel patiënten die enterocolitis kregen gemiddeld jonger waren ten tijde van de operatie, en langer opgenomen lagen in het ziekenhuis, werden in deze studie geen andere risicofactoren voor het ontwikkelen van HAEC geïdentificeerd. Wel was een hogere leeftijd tijdens de operatie negatief geassocieerd met het postoperatieve enterocolitisvrije interval. In *Hoofdstuk 6* is verder gekeken naar de invloed van leeftijd tijdens de operatie op patiëntuitkomsten. De bevindingen in deze nationale cohortstudie van 830 patiënten suggereren dat leeftijd tijdens de operatie niet geassocieerd is met het risico op postoperatieve complicaties, heroperatie, overlijden en lange termijn darmfunctie, alleen met het risico op een tijdelijk stoma.

Deel 2: Multidisciplinaire uitkomsten van patiënten met chirurgische aangeboren aandoeningen

Een belangrijke uitkomst van patiënten met chirurgische aangeboren aandoeningen is hun gezondheidsgerelateerde kwaliteit van leven. Gezondheidsgerelateerde kwaliteit van leven is de subjectieve evaluatie van iemands lichamelijke, mentale en sociale gezondheid. Een nationale cohortstudie in 35 patiënten met totale colon aganglionose, een zeldzame vorm van de ziekte van Hirschsprung waarbij de hele dikke darm is aangedaan, beschreven in *Hoofdstuk 7*, laat zien patiënten met totale colon aganglionose regelmatig obstipatie (65%), vochtverlies (53%) en incontinentie van ontlasting (47%) hebben. Ondanks deze bevindingen met betrekking tot hun darmfunctie rapporteerden patiënten een normale psychosociale en sociale gezondheidsgerelateerde kwaliteit van leven in vergelijking met een referentiegroep. Lichamelijke gezondheidsgerelateerde kwaliteit van leven en algemene perceptie van gezondheid werden als slechter ervaren in vergelijking met een referentiegroep. Deze studie toonde verder aan dat vooral lichamelijke klachten en diarree de gezondheidsgerelateerde kwaliteit van leven beperkten in patiënten met totale colonaganglionose.

Onderzoeken suggereren dat behalve gezondheidsgerelateerde kwaliteit van leven, ook de neurocognitieve en motorische ontwikkeling in patiënten met chirurgische aangeboren aandoeningen negatief beïnvloed kan blijken in follow-up. De bevindingen van de meta-analyse met 47 onderzoeken en 2312 patiënten met aangeboren gastrointestinale aandoeningen in *Hoofdstuk 8*, suggereren dat patiënten met aangeboren gastrointestinale malformaties gemiddeld een kleine cognitieve achterstand, een middelgrote motorische achterstand, en een middelgrote taalachterstand hebben in vergelijking met referentiegroepen. Achterstand was het meest nadrukkelijk in patiënten met het korte darm syndroom. De mate van achterstand in cognitieve, motorische en taalontwikkeling was geassocieerd met de gemiddelde opnameduur in het ziekenhuis en het mediane aantal operaties. Deze bevindingen benadrukken het belang van het monitoren van de hersenontwikkeling van patiënten met chirurgische aangeboren aandoeningen gedurende follow-up.

Niet alleen patiënten met chirurgische aangeboren aandoening zelf kunnen klachten ondervinden in follow-up, ook het psychosociaal welbevinden van hun ouders kan negatief beïnvloed worden. Een cross-sectionele studie in *Hoofdstuk 9* in 97 ouders van patiënten met chirurgische aangeboren aandoeningen, laat zien dat ouders in vergelijkbare mate last ervaren in follow-up in vergelijking met een referentiegroep, maar in hogere mate van symptomen van posttraumatische stress vertonen. In het bijzonder moeders hadden vaker een post-traumatische stress stoornis. Een post-traumatische stressstoornis wordt gekenmerkt door symptomen van intrusie (onwillekeurige herinneringen die een stressreactie opwekken), vermijdingsgedrag en gevoelens van hyperactiviteit. Van alle ouders rapporteerden 75% symptomen van intrusie. Hoe langer de totale duur van ziekenhuisopname van het kind, hoe ernstiger de symptomen van intrusie, vermijding en hyperactiviteit waren bij ouders. Hoe langer een kind in follow-up was, hoe minder ernstige de symptomen van intrusie bij ouders waren. Deze bevindingen in deze studie benadrukken het belang van het monitoren van het psychosociaal welzijn van ouders in de follow-up van patiënten met chirurgische aangeboren aandoeningen.

Om een breed scala aan patiëntuitkomsten van patiënten met chirurgische aangeboren aandoeningen en hun ouders zorgvuldig te monitoren gedurende follow-up, is in 2017 in het Amsterdam UMC een gestandaardiseerd prospectief multidisciplinair follow-up programma geïntroduceerd: het Follow Me programma. Binnen dit programma worden middels gevalideerde en gestandaardiseerde metingen uitkomsten gemonitord in allerlei aspecten van gezondheid en functioneren. In *Hoofdstuk 10* wordt het ontwerp van dit follow-up programma beschreven, inclusief de ontwikkelde protocollen, gebruikte instrumenten voor de diverse uitkomstmetingen en de geïmplementeerde data-cyclus ten behoeve van kwaliteitsverbetering. Ook wordt uiteengezet hoe een dergelijke inrichting van follow-up kan bijdragen aan het verbeteren van de uitkomst van de patiënt, aan het verbeteren van de kwaliteit van zorg en aan wetenschappelijk onderzoek naar de patiënt uitkomsten.

Gestandaardiseerde routinematige uitkomstmonitoring in prospectieve multidisciplinaire follow-up kan niet alleen worden gebruikt voor verbetering van uitkomsten van patiënten en kwaliteitsverbetering. Het kan ook worden gebruikt voor het verwerven van inzicht in lange termijn uitkomsten, determinanten van uitkomsten en de ontwikkeling van klinische voorspelmodellen van patientuitkomsten. In de studie in *Hoofdstuk 11* werden de binnen het Follow Me programma verzamelde gegevens van 85 patiënten gebruikt om een klinisch voorspelmodel te ontwikkelen voor de voorspelling van vroeg motorische ontwikkelingsuitkomsten op basis van klinische kenmerken en intra-operatieve kenmerken van de oxygenatie en hemodynamiek. Deze studie toont aan dat intra-operatieve oxygenatie en hemodynamiek zo'n 12-19% van de variatie in vroege motorische uitkomst kon verklaren. Machine learning-algoritmen lieten bovendien betere voorspellende prestaties zien in vergelijking met traditionele statistische modellen. Deze studie benadrukt de potentie van gestandaardiseerde dataverzameling en de meerwaarde

van machine learning algoritmes voor de ontwikkeling van klinische voorspelmodellen.

Concluderend benadrukt dit proefschrift de meerwaarde van routinematige uitkomstmonitoring van een breed scala aan patiëntuitkomsten in gestandaardiseerde prospectieve multidisciplinaire follow-up voor de verbetering van patiëntuitkomsten, kwaliteit van zorg en wetenschappelijk onderzoek.

Belangrijkste bevindingen

- TZA komt voor bij 10-25% van de patiënten met de Ziekte van Hirschsprung na een doorhaaloperatie en is geassocieerd met obstructieve defecatieproblemen
- Botox injecties zijn effectief in de behandeling van obstructieve defecatieproblemen
- Er zijn geen factoren geïdentificeerd die geassocieerd zijn met een beter effect van botox injecties
- Hirschsprung-geassocieerde entercolitis komt voor bij 8% van de patiënten met de Ziekte van Hirschsprung voor de doorhaaloperatie en bij 21% van de patiënten na de doorhaaloperatie
- Er zijn geen factoren geïdentificeerd die geassocieerd zijn met een hoger risico op Hirschsprung-geassocieerde enterocolitis
- Een hogere leeftijd tijdens de operatie was geassocieerd met een hoger risico op een tijdelijk stoma
- Leeftijd tijdens de operatie was niet geassocieerd met verschillen in darmfunctie op lange termijn
- Patiënten met totale colon aganglionose hebben een verminderde darmfunctie en lichamelijke gezondheidsgerelateerde kwaliteit van leven in vergelijking met gezonde leeftijdsgenoten
- Patiënten met aangeboren gastro-intestinale aandoeningen lopen risico op een achterstand in motorische ontwikkeling, cognitieve ontwikkeling en taalontwikkeling
- Moeders van patiënten met aangeboren gastro-intestinale aandoeningen hebben vaker een post-traumatische stress stoornis in vergelijking met de algemene bevolking
- Routinematige uitkomstmonitoring in gestandaardiseerde prospectieve multidisciplinaire follow-up kan bijdragen aan verbetering van de uitkomst van de patiënt, verbetering van de kwaliteit van zorg en aan onderzoek naar uitkomst en prognose bij patiënten met chirurgische aangeboren afwijkingen
- Vroege motorische ontwikkelingsuitkomsten van patiënten met chirurgische aangeboren aandoeningen kunnen in beperkte mate worden voorspeld op basis van intra-operatieve oxygenatie en hemodynamiek
- Machine-learning algoritmes presteerden beter in het voorspellen van vroeg motorische ontwikkelingsuitkomsten in vergelijking met traditionele statistische modellen

SUMMARY TABLE

Chapter	Methods	Sample size *n*	Outcome variables	Main findings
2	Systematic review and meta-analysis	34 studies 2207 patients with Hirschsprung disease	Prevalence of transition zone anastomosis; Clinical impact of transition zone anastomosis (Rate of obstructive defecation problems; rate of Hirschsprung-associated enterocolitis; Rate of soiling; Rate of fecal incontinence; Rate of redo-surgery)	· Prevalence of TZA is 25% · Prevalence was 9% after excluding studies with patients after redo surgery · Prevalence of TZA is significantly higher after straight anastomosis compared to after pouch · TZA associated with higher rates of obstructive defecation problems
3	Systematic review and meta-analysis	14 studies 278 patients with Hirschsprung disease	Proportion of patients with improvement of obstructive defecation problems; Proportion of patients with improvement of Hirschsprung-associated enterocolitis; Rate of adverse effects	· BTI effectively treats obstructive defecation problems in 66% of patients · Effect of BTI was not dependent of type of BTI, dose, age at injection and the presence of associated syndromes · Adverse effects were observed in 17% of patients
4	Cross-sectional cohort study	131 patients with Hirschsprung disease	Rate of botulinum toxin injection use; clinical response to first injection; rate of patients with spontaneous defecation with laxatives after botulinum toxin injection treatment; adverse effects; predictors of clinical improvement after botulinum toxin injection	· 31% of all patients were treated with BTI · Clinical improvement of obstructive defecation was achieved in 61% of patients after first injection · 71% of patients achieved spontaneous defecation or treatment with laxatives only · 29% of patients had adverse effects after BTI · No clinical factors were associated with clinical improvement after BTI
5	Cross-sectional cohort study	830 patients with Hirschsprung disease	Short term surgical outcome (Complication rate, redo-surgery rate, stoma rate, mortality rate); Long term functional outcome (Constipation; Fecal incontinence) (DEFEC-P)	· Age at surgery is not associated with rates of complications, redo-surgery, or mortality · Higher age at surgery was associated with higher rates of a temporary stoma · Age at surgery is not associated with higher rates of constipation or fecal incontinence in long term
6	Cross-sectional cohort study	146 patients with Hirschsprung disease	Prevalence of preoperative and postoperative Hirschsprung-associated enterocolitis; Pre- and postoperative enterocolitis free interval	· Prevalence of preoperative HAEC was 10% · Prevalence of postoperative HAEC was 21% · No clinical factors were identified that were associated with higher risk of HAEC · Patients with HAEC were on average younger at surgery and had longer length of total in-hospital stay · Higher age at surgery was associated with shorter postoperative enterocolitis free interval in patients who had enterocolitis

7	Cross-sectional cohort study	35 patients with total colonic aganglionosis	Gastrointestinal functional outcome (rates of constipation, fecal incontinence, soling and use of bowel management); generic health-related quality of life (CHQ); disease-specific health-related quality of life (HAQL)	· Functional outcome in long term was relatively poor with 65% reporting constipation, 47% fecal incontinence and 53% soiling, 18% used bowel management on a daily basis · General perception of health and physical health-related quality of life was impaired in patients with total colonic aganglionosis compared to normative data · Disease-specific health-related quality of life is mainly impaired by physical complaints and diarrhea
8	Systematic review, meta-analysis and meta-regression	47 studies 2312 patients with congenital gastrointestinal malformations	Overall neurodevelopmental outcome; Motor development; Cognitive development; Language development	· Patients with CGIM show small-sized cognitive, medium sized motor and medium sized language impairment compared to normative data · Patients with SBS have worse neurodevelopmental outcomes compared to other CGIM · Number of surgeries and length-of-hospital stay were associated with worse neurodevelopmental outcome
9	Cross-sectional cohort study	97 parents of patients with surgical congenital malformations	Rate of clinical distress and severity of distress (DT-P); Rate of PTSD and severity of PTSD symptoms (SRS-PTSD)	· Mothers of patients with CGIM are at risk for PTSD · Parents of patients had no higher rate of distress in follow-up compared to parents of healthy children or children with a chronic illness · Symptoms of intrusion were commonly reported by all the parents (75%). · Longer total length of child's hospital stay was associated with more severe symptoms of intrusion, avoidance and hyperarousal. · Child's length of follow-up was negatively associated with severity of intrusion.
10	Design paper	-	-	· Standardized prospective multidisciplinary follow-up with routine outcome monitoring offers a promising model for data driven improvement of patients outcome, quality of health care and research on outcome and prognosis
11	Cross-sectional cohort study	85 patients with surgical congenital malformations	Early motor development (BSID); predictive performance of prediction models	· Patients had on average lower early motor outcome compared with normative data · 12-19% of variance in early motor outcome could be explained by features of intraoperative vital function parameters, suggesting a correlation between intraoperative hemodynamics and oxygenation and early motor outcome · Machine learning algorithms showed better predictive performance compared to traditional statistical methods

ACKNOWLEDGEMENTS

List of authors and affiliations

Z. A. Abeln - *Amsterdam UMC, Emma Children's Hospital, Department of Pediatric Surgery, Amsterdam, the Netherlands*

L. Beltman - *Amsterdam UMC, Emma Children's Hospital, Department of Pediatric Surgery, Amsterdam, the Netherlands*

M.A. Benninga - *Amsterdam UMC, Emma Children's Hospital, Department of Pediatric Gastroenterology, Amsterdam, the Netherlands*

I. de Blaauw - *Radboud UMC, Amalia Children's Hospital, Department of Pediatric Surgery, Nijmegen, the Netherlands*

P.M.A. Broens - *UMC Groningen, Department of Surgery, Groningen, the Netherlands*

J.P.M. Derikx - *Amsterdam UMC, Emma Children's Hospital, Department of Pediatric Surgery, Amsterdam, the Netherlands*

M. van Dijk - *Amsterdam UMC, Emma Children's Hospital, Department of Pediatric Psychology, Amsterdam, the Netherlands*

L.S. Eeftinck Schattenkerk - *Amsterdam UMC, Emma Children's Hospital, Department of Pediatric Surgery, Amsterdam, the Netherlands*

W.G. van Gemert - *MUMC, Department of Surgery, Maastricht, the Netherlands*

R.R. Gorter - *Amsterdam UMC, Emma Children's Hospital, Department of Pediatric Surgery, Amsterdam, the Netherlands*

J.B. van Goudoever - *Amsterdam UMC, Emma Children's Hospital, Amsterdam, the Netherlands*

L. Haverman - *Amsterdam UMC, Emma Children's Hospital, Department of Pediatric Psychology, Amsterdam, the Netherlands*

L.W.E. van Heurn - *Amsterdam UMC, Emma Children's Hospital, Department of Pediatric Surgery, Amsterdam, the Netherlands*

V.F. Huizer - *Amsterdam UMC, Emma Children's Hospital, Department of Pediatric Surgery, Amsterdam, the Netherlands*

M. Königs - *Amsterdam UMC, Emma Children's Hospital, Department of Pediatrics, Amsterdam, the Netherlands*

H. Labib - *Amsterdam UMC, Emma Children's Hospital, Department of Pediatric Surgery, Amsterdam, the Netherlands*

J. Last - *University of Amsterdam, Data Science, Amsterdam, the Netherlands*

R.J. Meinds – *Medisch Spectrum Twente, Department of Gastroenterology, Enschede, the Netherlands*

J. Oosterlaan - *Amsterdam UMC, Emma Children's Hospital, Department of Pediatrics, Amsterdam, the Netherlands*

J. Rotteveel - *Amsterdam UMC, Emma Children's Hospital, Amsterdam, the Netherlands*

D.V. Schulten – *Uniclinic Köln, Department of Pediatric Surgery, Germany*

C.E.J. Sloots - *Erasmus MC, Sophia Children's Hospital, Department of Pediatric Surgery, Rotterdam, the Netherlands*

A.F.W. van der Steeg - *Princess Máxima Center for Pediatric Oncology, Department of Pediatric Surgery, Utrecht, the Netherlands*

M.F. Stevens - *Amsterdam UMC, Department of Anesthesiology, Amsterdam, the Netherlands*

T. Thijssen - *University of Amsterdam, Data Science, Amsterdam, the Netherlands*

M. Trzpis - *UMC Groningen, Department of Surgery, Groningen, the Netherlands*

S.J. Verkuijl - *UMC Groningen, Department of Surgery, Groningen, the Netherlands*

J.P. van der Voorn - *Amsterdam UMC, Department of Pathology, Amsterdam, the Netherlands*

L.M. Wellens - *Princess Máxima Center for Pediatric Oncology, Department of Pediatric Surgery, Utrecht, the Netherlands*

M. J. Witvliet - *UMC Utrechts, Wilhelmina Children's Hospital, Department of Pediatric Surgery, Utrecht, the Netherlands*

Author's contributions per chapter

Chapter 2: *The prevalence and clinical impact of transition zone anastomosis in patients with Hirschsprung disease: a systematic review and meta-analysis*
Authors: H. Labib, D. Roorda, J.P. van der Voorn, J. Oosterlaan, L.W.E. van Heurn, J.P.M. Derikx
DR, JO, LVH, and JD created the concept and design of the study. HL, DR and JD were involved in data acquisition and data analysis. All authors were involved in interpreting the data. HL and DR drafted the article, whilst JV, JD, LH and JO critically revised the manuscript. All authors gave final approval of this version of the manuscript to be published.

Chapter 3: *Botulinum toxin injections after surgery for Hirschsprung disease: Systematic review and meta-analysis*
Authors: D. Roorda, Z.A. Abeln, J. Oosterlaan, L.W.E. van Heurn, J.P.M. Derikx
Roorda D, van Heurn LWE and Derikx JPM designed the research; Roorda D and Abeln ZAM performed the systematic review and data-extraction. Roorda D and Derikx JPM analysed the data. Roorda D, Abeln ZAM, Oosterlaan J, van Heurn LWE and Derikx JPM wrote and revised the paper

Chapter 4: *Intrasphincteric botulinum toxin injections for post-operative obstructive defecation problems in Hirschsprung disease: A retrospective observational study*
Authors: D. Roorda, J. Oosterlaan, L.W.E. van Heurn, J.P.M. Derikx
Study conception and design: J. Derikx, L.W.E. van HeurnData acquisition: D. RoordaAnalysis and data interpretation: D. Roorda, J. DerikxDrafting of the manuscript: D. RoordaCritical revision: J. Derikx, J. Oosterlaan, L.W.E. van Heurn

Chapter 5: *Risk factors for enterocolitis in patients with Hirschsprung disease: a retrospective observational study.*
Authors: D. Roorda, J. Oosterlaan, L.W.E. van Heurn, J.P.M. Derikx
DR and JD designed the study. DR collected and analysed the data. All authors collectively interpreted the data. DR drafted the article and JO, LWEvH and JD revised the article critically. All authors (DR, JO, LWEvH and JD) gave final approval of the version to be published.

Chapter 6: *Did age at surgery for Hirschsprung disease influence surgical outcomes ? A nationwide cohort study*
Authors: D. Roorda, S.J. Verkuijl, J.P.M. Derikx, M. Trzpis, R.J. Meinds, C.E.J. Sloots, M.J. Witvliet, I. de Blaauw, W.G. van Gemert, L.W.E. van Heurn, P.M.A. Broens
DR, SV, LVH and PB created the concept and design of the study. JD, MT, RM, CS, MW,

IB, and WG were involved in data acquisition and data analysis. DR, SV, MT, and PB were involved in interpreting the data. DR, SV, MT and PB drafted the article, whilst JD, MT, RM, CS, MW, IB, WG and LVH critically revised the manuscript. All authors gave final approval of this version of the manuscript to be published.

Chapter 7: *Long-term outcome and quality of life in patients with total colonic aganglionosis in the Netherlands*
Authors: D. Roorda, M.J. Witvliet, L.M. Wellens, D.V. Schulten, C.E.J. Sloots, I. de Blaauw, P.M.A. Broens, J. Oosterlaan, L.W.E. van Heurn, A.F.W. van der Steeg
MW and AS created the concept and design of the study. DR, MW, LW, DS, CS, IB, PB and AS were involved in data acquisition and data analysis. DR, MW, LW and AS were involved in interpreting the data. DR and MW drafted the article, whilst DS, CS, IB, PB, JO, LH and AS critically revised the manuscript. All authors gave final approval of this version of the manuscript to be published.

Chapter 8: *Neurodevelopmental outcome of patients with congenital gastrointestinal malformations: a systematic review and meta-analysis*
Authors: D. Roorda, M. Königs, L.S. Eeftinck Schattenkerk, A.F.W. van der Steeg, L.W.E. van Heurn, J. Oosterlaan
DR, MK and JO designed the concept of the study; DR and LE were involved in data collection; DR analyzed the collected data under supervision of MK and JO. DR, MK and JO interpreted the data. DR drafted the initial manuscript, that was critically revised by all other authors (MK, LE, AS, LH and JO). All authors approved with publication of the final manuscript.

Chapter 9: *Parental distress and symptoms of PTSD in parents of patients with congenital gastrointestinal malformations: a cross-sectional cohort study*
Authors: D. Roorda, A.F.W. van der Steeg, M. van Dijk, J.P.M. Derikx, R.R. Gorter, J. Rotteveel, J.B. van Goudoever, L.W.E. van Heurn, J. Oosterlaan, L. Haverman, Emma Children's Hospital Amsterdam UMC Follow-Me program consortium
DR, AS, MD, JO, and LH designed the concept of the study; DR; AS; JD; RG; EvH were involved in data collection; DR analyzed the collected data under supervision of AS, JD, EvH, JO,and LH. Data interpretation was done by DR, MD and LH. DR drafted the initial manuscript, that was critically revised by all other authors (AS, MD, JD, RG, JG, JR, LvH, JO, LH). All authors gave final approval of the version to be published.

Chapter 10: *Standardized Prospective Multidisciplinary Follow-Up of Patients with Surgical Congenital Malformations: A Model for Continuous Data Driven Improvement of Health Care*
Authors: D. Roorda, A.F.W. van der Steeg, J.P.M. Derikx, R.R. Gorter, L.W.E. van Heurn, J.

Oosterlaan, Emma Children's Hospital Amsterdam UMC Follow-Me program consortium
DR, AS, LH and JO designed the concept of the study; There was no data collection or data analysis done in this descriptive study of the follow-up protocols; DR drafted the initial manuscript, that was critically revised by all other authors (AS, JD, RG, LH and JO). All authors gave final approval of the version to be published.

Chapter 11: *Predicting early motor development after infant surgery under general anesthesia based on intraoperative vital functions: A machine learning approach*
Authors: D. Roorda, T. Thijssen, J. Last, M.F. Stevens, L.W.E. van Heurn, J.P.M. Derikx, M. Königs, J. Oosterlaan, Emma Children's Hospital Amsterdam UMC Follow-Me program consortium
DR, MK and JO designed the concept of the study; DR, MS and JD were involved in data collection; TT and JL analyzed the collected data under supervision of DR and MK; DR, TT, JL, MK and JO interpreted the data. DR, TT and JL drafted the initial manuscript, that was critically revised by all authors. All authors gave final approval of the version to be published.

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haalde door hardop te denken. Marsh, toch een beetje de pater familias, wat was het fijn zo'n hulplijn ter plaatse te hebben en ook om mee te maken hoe je trotse vader werd van Sacha. Nanette en Noor, het is niet voor niets dat ik jullie als paranimfen heb gevraagd. Menne en Alice, we hebben elkaar korter meegemaakt, maar jullie draaiden met evenveel gemak mee in de H8-roulatie en het klikte goed, leuk om samen gewerkt te hebben.

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CURRICULUM VITAE

Daniëlle Roorda was born on June 24, 1988 in Amersfoort, the Netherlands. In 2006 she obtained her high school degree (VWO Atheneum) at the Guido de Bres in Amersfoort. After high school she studied Health and Life Sciences at the Vrije Universiteit in Zwolle and Amsterdam and obtained her bachelor degree in 2009. After obtaining this bachelor degree, she studied Medicine at the VU Medical Centre in Amsterdam and obtained her bachelor degree in 2012 and her master degree in Medicine in 2015. After obtaining her master degree she worked as a clinical resident (ANIOS) at the department of general surgery of the Zaans Medisch Centrum in Zaandam for 16 months under supervision of dr. Frank den Boer. During her clinical residency Daniëlle also worked as a student research assistant for the Pediatric Surgery department of the VU Medical Centre in Amsterdam, studying quality of life in patients with Hirschsprung disease under supervision of dr. Marieke Witvliet and dr. Lideke van der Steeg. She started her PhD in 2017 under supervision of prof. dr. Jaap Oosterlaan and prof. dr. Ernst van Heurn at the Pediatric Surgery department of the Amsterdam University Medical Centre and implemented the Follow Me program for the Pediatric Surgery department, next to her research activities focus on multidisciplinary outcomes in patients with surgical congenital malformations.

After her PhD, Daniëlle worked as a clinical resident (ANIOS) at the department of general surgery of the TergooiMC under supervision of dr. Nanette van Geloven. She currently works as a clinical resident (ANIOS) at the department of general surgery of the ETZ Hospital in Tilburg under supervision of prof. dr. Patrick Vriens. During her PhD, Daniëlle married to Arjan. They live in in the Augustanahof, a living community of the Lutheran Diaconie in Amsterdam.

PHD PORTFOLIO

Name PhD student: Danielle Roorda
PhD period: May 2017 – December 2021
Name PhD supervisor: Jaap Oosterlaan and Ernst van Heurn

1. PhD training

	Year	Workload (Hours/ ECTS)
General courses		
- AMC World of Science (AMC Graduateschool)	2017	0.7
- E-BROK (AMC Graduateschool)	2017	1.5
- Research Data Management (AMC Graduateschool)	2018	0.7
- Scientific Writing for Publication (AMC Graduateschool)	2018	1.5
- Practical Biostatistics (AMC Graduateschool)	2019	1.1
- Advanced Topics in Biostatistics (AMC Graduateschool)	2020	2.1
- Computing in R (AMC Graduateschool)	2020	0.4
- Entrepeneurship in Health & Life Science (AMC Graduateschool)	2020	1.5
Seminars, workshops and master classes		
- Two-weekly Research Meeting Emma Neuroscience Group	2017-2021	4
- Monthly Research Meeting Kinderchirurgie	2017-2021	2
- Masterclass AKS	2018	0.25
(Inter)national conferences		
Oral presentations		
Patiëntenvereniging Hirschsprung, Utrecht	2017	0.2
- Introductie Follow Me polikliniek		
Najaarsdag Heelkunde Regio 1	2017	0.25
- "Long-term outcome and quality of life in patients with total colonic aganglionosis in the Netherlands"		
Meet&Greet Citrienfonds, Zeist, 2017	2017	0.25
- Workshop ValueBasedCare		
Patiëntenvereniging Anorectale Malformaties, Arnhem	2018	0.2
- Introductie Follow Me polikliniek		
19th Annual European Paediatric Surgeons Association Congress, Paris, 2018	2018	1.0
- "Long-term outcome and quality of life in patients with total colonic aganglionosis in the Netherlands"		

Wetenschapsdag Heelkunde Regio 1 - "Botulinum toxin injections for treating obstructive symptoms in Hirschsprung Disease: a systematic review"	2018	0.25
Patientenvereniging Hirschsprung, Hilversum - Botox, enterocolitis en leeftijd bij operatie	2019	0.25
Nederlandse Vereniging voor Kindergeneeskunde (NVK) Congres 2019, Arnhem - Symposium "Lange termijn follow-up als motor achter innovatie in de kindergeneeskunde"	2019	0.25
Wetenschapsdag Heelkunde Regio 1&2 - "Neurodevelopmental outcome of patients with congenital gastrointestinal malformations: a systematic review and meta-analysis"	2019	0.25
22nd Annual European Paediatric Surgeons Association (EUPSA) Congress, Athens, 2021 - "Parental distress and PTSD in parents of patients with congenital gastrointestinal malformations" - "Prevalence and clinical impact of a transitionzone anastomosis in patients with Hirschsprung disease: a systematic review and meta-analysis"	2021	1.0
Wetenschapsdag Heelkunde Regio 1&2 - "Prevalence and clinical impact of a transitionzone anastomosis in patients with Hirschsprung disease: a systematic review and meta-analysis"	2021	0.25

Poster presentations

20th edition European Paediatric Surgeons Association (EUPSA) European Congress, Belgrade, 2019 - "Neurodevelopmental outcome of patients with congenital gastrointestinal malformations: a systematic review and meta-analysis" - "Botulinum toxin injections for treating obstructive symptoms in Hirschsprung Disease: a systematic review"	2019	1.0

Attendance

- NVVH Chirurgendagen 2017	2017	0.5
- NVVH Chirurgendagen 2018	2018	0.5
- NVVH Chirurgendagen 2019	2019	0.5
- Slotmanifestatie NFU Programma E-health, Amsterdam	2018	0.25
- Patientenvereniging Hirschsprung, ledencontactdag Amersfoort	2018	0.2
- Patientenvereniging Hirschsprung, ledencontactdag Harderwijk	2019	0.2
- DCEA meetings	2017-2019	0.5
- AG&M Phd-retreat	2018	0.25
- Bunkerretreat (KCH + KMDL)	2018	0.5

2. Teaching

	Year	Workload (Hours/ ECTS)
Lecturing		
- Onderwijs Bsc: Evidence Based Beleidsvoorstel	2019	0.25
- Onderwijs Bsc: Journal Club Systematic review	2020	0.25
Supervising		
Bachelortheses		
- Lisa van Adrichem – Bachelorthesis Geneeskunde	2017	1.0
- Hosnieya Labib – Bachelorthesis Geneeskunde	2018	1.0
Mastertheses		
- Zarah Abeln - Masterthesis Geneeskunde	2017	1.0
- Lieke Beltman – Masterthesis Geneeskunde	2018	1.0
- Yvonne van der Plas – Masterthesis Psychologie	2019	1.0
- Paulieke Oosterwijk – Masterthesis Geneeskunde	2019	1.0
- Veerle Huizer – Masterthesis Geneeskunde	2020	1.0
- Jop Last – Masterthesis Data Science	2020	1.0
- Tim Thijssen – Masterthesis Data Science	2020	1.0

3. Parameters of Esteem

	Year
Grants, awards and prizes	
- Selected for Masterclass Amsterdam Kinder Symposium	2018
Other	
- Organizing committee Annual Research Retreat Amsterdam Reproduction and Development Research Institute	2019
- Member Digital Patient Journey Lab	2018-2019
- Development of patient information (videos, online content)	2017-2018
- Organizing committee Parent Evening for parents of patients with Hirschsprung disease	2019

LIST OF PUBLICATIONS

This thesis

Botulinum toxin injections after surgery for Hirschsprung disease: Systematic review and meta-analysis
World Journal of Gastroenterology. 2019 Jul 7;25(25):3268-3280. doi: 10.3748/wjg.v25.i25.3268.
D. Roorda, Z.A. Abeln, J. Oosterlaan, L.W.E. van Heurn, J.P.M. Derikx

Intrasphincteric botulinum toxin injections for post-operative obstructive defecation problems in Hirschsprung disease: A retrospective observational study
Journal of Pediatric Surgery. 2021 Aug;56(8):1342-1348. doi: 10.1016/j.jpedsurg.2020.11.025
D. Roorda, J. Oosterlaan, L.W.E. van Heurn, J.P.M. Derikx

Risk factors for enterocolitis in patients with Hirschsprung disease: A retrospective observational study
Journal of Pediatric Surgery. 2021 Oct;56(10):1791-1798. doi: 10.1016/j.jpedsurg.2021.04.020.
D. Roorda, J. Oosterlaan, L.W.E. van Heurn, J.P.M. Derikx

Long-term outcome and quality of life in patients with total colonic aganglionosis in the Netherlands
Colorectal Disease. 2018 Aug;20(8):719-726. doi: 10.1111/codi.14095.
D. Roorda, M.J. Witvliet, L.M. Wellens, D.V. Schulten, C.E.J. Sloots, I. de Blaauw, P.M.A. Broens, J. Oosterlaan, L.W.E. van Heurn, A.F.W. van der Steeg

Neurodevelopmental outcome of patients with congenital gastrointestinal malformations: a systematic review and meta-analysis
Archives of Disease in Childhood – Fetal and Neonatal Edition. 2021 Nov;106(6):635-642. doi: 10.1136/archdischild-2021-322158.
D. Roorda, M. Königs, L.S. Eeftinck Schattenkerk, A.F.W. van der Steeg, L.W.E. van Heurn, J. Oosterlaan

Other international peer-reviewed publications

Redo surgery with longitudinal resection for dilated bowel in Hirschsprung disease: an illustrative case series
International Journal of Colorectal Disease. 2019 Nov;34(11):1983-1987. doi: 10.1007/s00384-019-03399-8.
D. Roorda, T.J. Surridge, R.G.J. Visscher, J.P.M. Derikx, L.W.E. van Heurn

Risk factors for short-term complications graded by Clavien-Dindo after transanal endorectal pull-through in patients with Hirschsprung disease.
Journal of Pediatric Surgery. 2021 Aug 1:S0022-3468(21)00533-9. doi: 10.1016/j.jpedsurg.2021.07.024.
L. Beltman, D. Roorda, M. Backes, J. Oosterlaan, L.W.E. van Heurn, J.P.M. Derikx

Publications in Dutch

De beste zorg creeër je samen. De rol van een multidisciplinair team in kwaliteitsverbetering: ervaringen uit de kinderchirurgie
Kwaliteit in Zorg; Online available at: https://www.qruxx.com/multidisciplinair-team-speelt-grote-rol-bij-kwaliteitsverbetering/
D. Roorda, A.F.W. van der Steeg, L.W.E. van Heurn, J. Oosterlaan

Work under review

This thesis

The prevalence and clinical impact of transition zone anastomosis in patients with Hirschsprung disease: a systematic review and meta-analysis
H. Labib, D. Roorda, J.P. van der Voorn, J. Oosterlaan, L.W.E. van Heurn, J.P.M. Derikx

Did age at surgery influence outcome in patients with Hirschsprung disease? a nationwide cohort study in the Netherlands
D. Roorda, S.J. Verkuijl, J.P.M. Derikx, M. Trzpis, R.J. Meinds, C.E.J. Sloots, M.J. Witvliet, I. de Blaauw, W.G. van Gemert, L.W.E. van Heurn, P.M.A. Broens

Parental distress and symptoms of PTSD in parents of patients with congenital gastrointestinal malformations: a cross-sectional cohort study
D. Roorda, A.F.W. van der Steeg, M. van Dijk, J.P.M. Derikx, R.R. Gorter, J. Rotteveel, J.B. van Goudoever, L.W.E. van Heurn, J. Oosterlaan, L. Haverman, Emma Children's Hospital Amsterdam UMC Follow-Me program consortium

Standardized Prospective Multidisciplinary Follow-Up of Patients with Surgical Congenital Malformations: A Model for Continuous Data Driven Improvement of Health Care
D. Roorda, A.F.W. van der Steeg, J.P.M. Derikx, R.R. Gorter, L.W.E. van Heurn, J. Oosterlaan, Emma Children's Hospital Amsterdam UMC Follow-Me program consortium

Predicting early motor development after infant surgery under general anesthesia based on intraoperative vital functions: A machine learning approach
D. Roorda, T. Thijssen, J. Last, M.F. Stevens, L.W.E. van Heurn, J.P.M. Derikx, M. Königs, J. Oosterlaan, Emma Children's Hospital Amsterdam UMC Follow-Me program consortium

Other work

Generic health-related and disease-specific health-related quality of life in patients with Hirschsprung disease: a systematic review and meta-analysis
V. Huizer, N. Wijekoon, D. Roorda, J. Oosterlaan, L.W.E. van Heurn, M.A. Benninga, S. Rajindrajith, J.P.M. Derikx

Implementing structured follow-up of neonatal and paediatric patients: an evaluation of three university hospital case studies using the functional resonance analysis method
V.L.L.C. Bos, D. Roorda, E.S.V. De Sonnaville, M.R. Van Boven, J. Oosterlaan, J.B. Van Goudoever, N.S. Klazinga, D.S. Kringos