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REVIEW ARTICLE

Long-term outcomes in newborn surgery

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Abstract
This article describes the common methods to study long-term outcomes in patients who have undergone major surgery in newborn period. It also sums up today's knowledge on the long-term outcome of some classic newborn surgical conditions. The analysis of long-term outcomes is important to pediatric surgeons. Knowledge of long-term outcome can guide the patient's management and principles of the follow-up throughout the patient's childhood. It also aims to give the parents of the patient a realistic picture on the development of their child. Recent data have shown that many patients who have undergone major surgery during early childhood have significant functional aberrations at adult age. Some of these have a profound influence on the quality of life of these patients.

Keywords Long-term outcomes · Congenital diaphragmatic hernia · Esophageal atresia · Intestinal failure · Hirschsprung's disease · Anorectal malformations

Introduction

The rapid development of pediatric and neonatal surgery after World War II led to formation of pediatric surgery as an independent specialty. This contributed to rapid change in the mortality of patients with congenital malformations and severe neonatal surgical conditions. During the last 50 years, the mortality of patients with congenital defects, also those with severe malformation complexes has continued to decrease (Figs. 1 and 2). This development is due to improved neonatology and pediatric intensive care and especially due to improved treatment of congenital cardiac defects. The downside of decreased mortality is that a significant percentage of survivors today have permanent morbidities and long-term handicaps.

Until recently, there has been little information about long-term consequences of repaired congenital defects or acquired newborn surgical problems. For pediatric surgeons, the end point and final outcome measure is the functional outcome in an adult patient. Recent research has indicated that a significant proportion of patients suffer from abnormal organ functions during childhood and many of these abnormalities are carried on to adulthood. These have often significant impact on quality of life. Long-term functional results and quality of life are today as important outcome measures as early mortality and morbidity.

Rationale of long-term follow-up in newborn surgery

Long-term outcomes of newborn surgery concerns several interest groups. The patients' parents need to get a realistic picture on what is going to happen to their child who has undergone major surgery. The information has to be as accurate as possible without giving inappropriately positive expectations concerning functional outcomes.

The patient himself/herself requires consistent information, as early as this can be given, of potential problems during later life. The information needs to include clarification of management modalities available to treat these problems. The parents may adopt to the handicaps of the patient and may not consider these as major functional problems. On the other hand, the patients may experience these handicaps to limit their social life. For example, even minor soiling in a teenager with an anorectal malformation may segregate the patient from social activities such as sports and overnight visits to friends, although the parents may consider that

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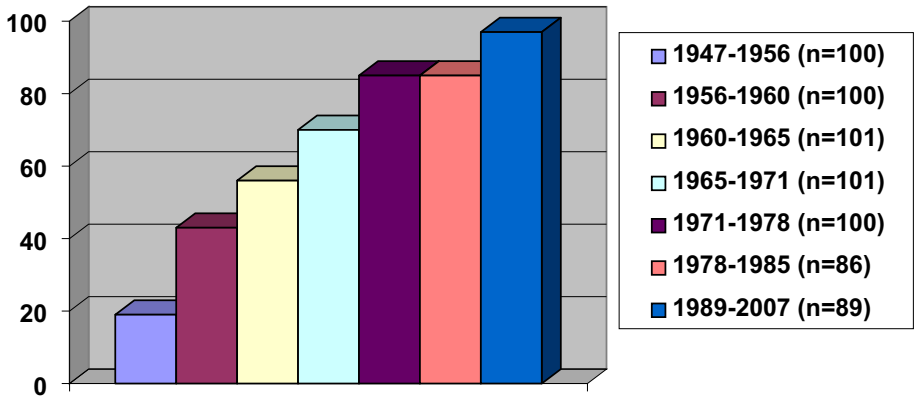

Fig. 1 Survival of 677 oesophageal atresia patients undergoing surgery at Children's Hospital, University of Helsinki from 1947 to 2007

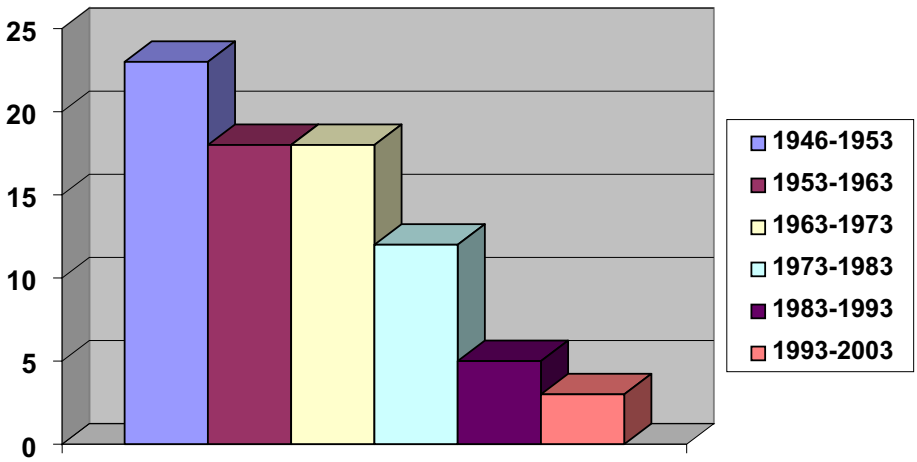

Fig. 2 Overall mortality of patients with anorectal malformations at Children's Hospital, University of Helsinki from 1946 to 2003

the patient's continence has greatly improved since earlier childhood.

The surgical team caring for children needs long-term follow-up data to guide clinical practice. In neonatal surgical conditions, the final functional outcome is not evident until the child has reached adolescence or adulthood. Longitudinal follow-up studies are required to determine the natural history of these disorders. Knowledge of possible complications that may develop during the developmental period of a surgical patient may guide primary treatment and definitely modifies the follow-up of the patient.

Health care administration need to be aware of the consequences and costs of newborn surgery. Although the numbers are not high, the management costs of a newborn surgical patient are very high. There is a need for highly specialized intensive care facilities. In many cases, the intensive care period may be long, especially in patients who have major neonatal surgical defects combined with cardiac abnormalities. On the other hand, the mortality of practically all neonatal surgical conditions has decreased significantly during the last decades. This implicates that more sick children survive with more handicaps. It is likely that these surviving children with serious primary conditions have more needs for medical care during their growth period than those with less stormy start.

How the long-term outcomes are assessed

Although newborn surgical conditions, either congenital or acquired, are usually well defined and classified, a significant issue in assessing long-term outcomes in neonatal surgical patients is the uniform lack of standardization of surgical procedures used to repair these defects. It is likely that the type of surgical procedure plays a significant role but this is very difficult to demonstrate.

The length of the follow-up period is a crucial factor. The most valid endpoint is the outcome beyond childhood. There is, however, paucity of long-term follow-up data in adults with congenital defects, therefore, short-term studies, often with variable age ranges of patients, have been used as measures of long-term outcome. This kind of studies often have significant methodological problems. A lack of a healthy control population is very common. Healthy controls with similar age and sex distribution as the patients are crucial for reliable outcome analysis. Most of the long-term follow-up

studies have been cross-sectional that does not give truly valid data on the natural development of the outcomes of pediatric surgical conditions.

Long-term outcome data, in terms of function and quality of life, is usually based on clinical history and examination. A major problem is the validity and agreement of the information attained from children and parents. Reliable data can be collected only from older children. The parents may not be able to provide truly reliable functional data for several reasons. They may not want to report unfavorable results to a surgeon who has been responsible for the treatment of their child. Therefore, it is important that when functional data are collected personally or by telephone interviews that the person performing the queries has not been involved in the actual management of the patient. The parents may also ignore minor and moderate functional defects in a child who has had a congenital problem from birth or, in the case of smaller children, may consider them to be part of normal functional maturation.

The low incidence of neonatal surgical conditions poses a significant problems for outcome analysis. Institutional series are commonly too small to allow reliable comparisons between different management modalities. Pooling data from multiple centers could be a powerful tool for long-term outcome studies but there is an increased opportunity for bias. Standardized management and follow-up protocols are very difficult to set up and long-term outcome studies commonly require many years of follow-up that are challenging in a multi-center setting.

The study design in the evaluation of long-term outcomes is inherently problematic. Randomized controlled trials with enough power are usually unavailable for long-term outcome studies; the patient series are too small and there are too many confounding factors such as variable surgical skills and techniques, inhomogeneous patient material and problems in recruiting patients for follow-up visit/examinations. Observational studies are more commonly used for analysis of long-term outcomes. Observational studies can be performed prospectively, retrospectively or as a cross-sectional study. Prospective matched, controlled cohort studies are powerful in providing information on natural history of a congenital defect or disease. Case–control studies are useful for cross-sectional studies e.g. gastrointestinal morbidity in adult esophageal atresia patients. The critical point in case–control studies is the matching of controls [1].

Recently, measures to assess the functional status and quality of life have become widely available also for children. These instruments are designed to measure health-related quality of life (HRQoL) and are today validated for many languages and cultural backgrounds. Quality of life instruments can usually be divided in two categories: generic instruments that assess overall HRQoL and disease specific validated instruments. A typical generic HRQoL instrument is SF-36 [2] that has 36 items and assess 7 domains. SF-36 is not validated for children under 16 years of age, therefore, other instruments need to be used. Of the commonly used paediatric HRQoL generic instruments CHQ (Child Health Questionnaire) [1] includes 87 items and 11 dimensions, and PedsQL (paediatric Quality of Life Inventory) [3] that is a very flexible and easy to use tool has 23 items in 4 domains. Both of these come in several forms for different age groups and also for parents/caregivers. A typical disease specific instrument is GIQLI (gastrointestinal quality of life index) that has 36 items in 5 domains [4]. A significant problem with the generic validated instruments is that these are relatively crude and do not consider specific outcome variables of the rare congenital surgical conditions.

Long-term outcomes of specific pediatric surgical conditions

The long-term outcome of defects that are life-threatening in the newborn period is influenced by severity of the anatomy, success of the anatomic reconstruction and occurrence of operative complications. Associated malformations have a significant impact on the outcome, too. In the following section examples of surgical conditions with recent consistent long-term follow-up data are considered, illustrating the factors that are involved in the outcome, especially beyond childhood.

Long-term outcome in children with congenital diaphragmatic hernia

Including abortion, stillbirths and pre-hospital deaths the total mortality caused by congenital diaphragmatic hernia is estimated at close to 50% [5]. Mainly owing to the new ventilatory strategies the survival of congenital diaphragmatic hernia (CDH) has improved considerably from 50% in 1990 to over 85% in high volume centers [6]. Consequently, the group of CDH survivors includes an increasing amount of children with high-risk diaphragmatic hernia and a history of extensive therapeutic measures including vasoactive drugs, advanced ventilatory support and extracorporeal membrane oxygenation with exposition to prolonged periods of reduced brain oxygenation. Long-term morbidity includes chronic respiratory disease, neurodevelopmental problems, gastroesophageal reflux and musculoskeletal disorders. Considering long-term studies in adult CDH survivors, it should be borne in mind that most of the patients may not have been high-risk cases by today's criteria.

Chronic respiratory tract disease

Insufficient airway branching during fetal development of the lungs causes hypoplasia of the ipsilateral and contralateral lungs with reduced gas exchange surface, abnormal sacculo-alveolar maturation and abnormal, muscularized distal arterioles [7]. Lung function can be further compromised during the initial treatment by oxygen toxicity, barotrauma and volume trauma. Many survivors have broncho-pulmonary dysplasia [8] and some require oxygen treatment for longer periods beyond discharge.

Recent studies indicate that in CDH patient's postnatal lung growth is impaired and may not fully compensate the initial lung hypoplasia. When the patients grow into adulthood the total lung volume increases but there is slight deterioration of pulmonary diffusion capacity. Similar long-term deterioration of lung function is also observed in critically ill non-CDH children indicating that the deterioration is attributed not only to sequelae of CDH but also to intensive care treatment [8–10]. Lung function tests in adult CDH survivors show restrictive, obstructive or combined ventilatory impairment in 50% and bronchial hyperreactivity in 35%. The degree of ventilatory impairment and bronchial hyperreactivity correlates with the initial clinical severity of the affliction. Long-term respiratory problems seem to be particularly severe in patients treated with extracorporeal membrane oxygenators (ECMO) and long periods of artificial ventilation and with patch closure of the diaphragm. [8–10]. Approximately 30–40% of the survivors have chronic lung disease, 12% had asthma, and 7% reported increased susceptibility to respiratory infections. Subjective physical performance is below average in 10–13% of patients [10–12]. In Finnish adult CDH survivors, (median age 39 years, mostly low-risk patients), scores in Respiratory Symptoms Related Quality of Life questionnaire were similar than healthy controls and only 2% had decreased quality of life because of respiratory symptoms [12]. Respiratory problems will likely remain a severe issue when high-risk CDH patients surviving today reach their adulthood. In all CDH patients, long-term respiratory follow-up extending into adulthood is warranted.

Gastroesophageal reflux disease

A significant percentage of CDH patients (20–81%) suffer from gastroesophageal reflux disease (GERD) following surgical repair. GERD after CDH repair can cause significant respiratory and nutritional problems and be unmanageable with medical therapy. In 26 Finnish CDH patients, significant early GERD developed in 27% and 15% required anti-reflux surgery within 6 months of the repair. Within 10 years, after the repair 53% of these patients eventually developed significant GERD defined by pathologic 24 h esophageal pH-monitoring, endoscopically diagnosed moderate or severe oesophagitis, or need for anti-reflux surgery [13]. Another Finnish study assessed 60 adult CDH survivors for GERD. Thirty years after the repair 63% had symptomatic GERD or endoscopically diagnosed esophagitis, Barrett´s esophagus was found in 13% of patients [14]. Although CDH survivors were found to have ten-fold more of GERD symptoms compared with a control population, the effect of GERD symptoms on quality of life was limited [12]. Long-term surveillance for CDH-associated GERD should extend beyond childhood, and a targeted endoscopic surveillance program is recommended.

Failure to thrive and growth

Failure to thrive and impaired growth is common among CDH survivors. The etiological factors behind failure to thrive include increased respiratory work, gastroesophageal reflux and aversion to feeding. To obtain adequate caloric intake a substantial number of patients require aggressive nutritional therapy, nevertheless the weight may be below 25th percentile in up to 60% of patients at the age of 3 years [15]. Body mass index (BMI) in two-thirds of 60 adult Finnish CDH survivors has been found slightly below that of general population and in 6% of patients BMI was less than 18 [12].

Skeletal abnormalities

The most common skeletal anomalies are chest asymmetry and pectus deformities followed by vertebral anomalies such as kyphosis and scoliosis. These deformities may originate from abnormal fetal development or be related to surgical management. Among 60 Finnish adult CDH survivors (median age 30 years), 49% had anterior chest asymmetry, 18% funnel chest in and 27% scoliosis. Most of the deformations were mild and rarely require surgical treatment. The skeletal abnormalitis were more common in patients who had large defects and a patch repair [16]. Periodic and regular follow-up is suggested to detect and prevent development of functionally significant deformities.

Neurological deficits

Patients with CDH are susceptible to abnormal brain development and maturation and consequently to impairment or delay in neurocognitive development. The most common neurological deficits include hypotonia, hearing loss and impaired visual-motor integration, oral-motor programming, behavioural attention and lack of concentration. Neuromuscular hypotonicity is common in CDH survivors. The original severity of CDH appears to be predictive of adverse neurodevelopmental outcome [17]. However, the

neurodevelopmental functioning of majority of CDH children is in the average range of normal children at early preschool and preschool age.

There is not much data of neurodevelopmental afflictions in adult CDH survivors. A study of Finnish adult CDH survivors—most of them had not had a high-risk disease found similar psychosocial function outcomes in CDH survivors and in healthy controls. Distribution between low, medium, and high educational levels were similar in CDH patients and control subjects, but a significantly lower percentage of CDH survivors (9%) reached higher academic levels (vocational college or university degree) compared with the controls (21%) [12].

Health-related quality of life

Most reports on the effect of CDH on quality of show relatively subtle differences between patients and healthy. Quality of life of Finnish adult CDH survivors (median age 39 year) and healthy controls was assessed with SF-36 questionnaire. There were no differences in different SF-36 domains or in overall scores between CDH patients and controls. However, the percentage of CDH patients with low SF-36 overall score indicating low quality of life was 1.5 times higher than expected. Medical conditions that were related to low quality of life in CDH patients were GERD, recurrent intestinal obstruction, recurrent abdominal pain, musculoskeletal disorders, and exercise-related shortness of breath [12].

Although the impact of long-term symptoms on the quality of life of CDH patients who mainly have had a low-risk primary condition seem subtle, future studies may disclose still more deleterious effects on quality of life in the growing population of survivors with high-risk CDH.

Long-term outcome in children with esophageal atresia

Since the first successful repair in 1941 the mortality of esophageal atresia (EA) has significantly decreased from 60% in 1960's [18] to 2% during 1991–2012 [19]. Consequently, a significant number of EA survivors have reached their adulthood. The most important issues in the long-term outcome are associated with esophageal morbidity including gastroesophageal reflux (GER), dysphagia and pre-neoplastic mucosal changes of the esophagus and the risk of esophageal cancer. Other major issues of long-term morbidity are respiratory symptoms and morbidity caused by various associated anomalies and syndromes. Long-term endoscopic follow-up of adult EA survivors is recommended for patients with defined risk factors.

Esophageal morbidity

Gastroesophageal reflux in EA is thought to arise from short esophagus and impaired motor function causing poor luminal acid clearance. Gastroesophageal reflux may cause significant problems immediately after EA repair and at a later age. Negative tests for GER in infancy do not rule out significant GER later in childhood [20] and by the age of 10 years significant GER is detected in up to 50% of the EA patients. Over half of these patients require anti-reflux surgery [21]. In a Finnish study of adult EA survivors (median age 36 years), the prevalences of GER symptoms and dysphagia were 34% and 85%, respectively. In 80% of the patients, dysphagia required adaptive eating habits such as slow eating, copious use of fluid during eating and careful chewing. Endoscopy disclosed macroscopic Barrett´s esophagus in 11%, hiatal hernia in 28%, esophagitis in 8% and esophageal stricture in 8% of patients. Mucosal histology of endoscopic biopsies showed esophagitis in 25% of patients. 21% of patients had columnar epithelial metaplasia and 6% intestinal metaplasia. Esophageal manometry showed non-propagating peristalsis and low ineffective distal wave amplitudes in 80% of the patients. The occurrence of columnar metaplasia was strongly related with increased age and ineffective esophageal peristalsis. Other factors strongly associated with the occurrence of columnar metaplasia were long-gap atresia, anastomotic stricture and recurrent tracheoesophageal fistula. Columnar metaplasia and esophagitis were not associated with the severity of GER symptoms or dysphagia [22].

Barrett's esophagus with intestinal columnar metaplasia is a known risk factor for mucosal dysplasia and adenocarcinoma. Among adult EA survivors, the estimated occurrence of Barrett's esophagus is four times higher than in the normal population [22]. Among EA survivors, there are a number of published cases of esophageal carcinoma but the true risk of esophageal cancer after EA repair is not known. A 50–500 fold risk estimates have been proposed [23, 24]. Although the effect of endoscopic follow-up on timely detection and treatment of malignant lesions is not known, an endoscopic follow-up program of EA survivors, especially those with esophagitis or Barrett's esophagus is reasonable.

A proportion of EA patients, mainly those with long-gap, require esophageal reconstruction. The techniques most often used are gastric pull-up, gastric tube, colonic interposition and jejunal interposition. Long-term results of the different reconstruction methods are variable. After gastric pull-up and colonic interposition, good functional results but also significant long-term morbidity such as chronic acid reflux, aspiration pneumonitis, ulceration, deficiency of iron and B12 vitamin and compression of the respiratory tract by the dilated intrathoracic stomach or a redundant colon have been reported, whereas long-term data is unavailable of jejunal interposition [25]. Barrett's esophagus of the remaining

native esophagus and dysplasia of the interposed colonic segment has also been described [26, 27]. Because of many potential long-term problems life-long endoscopic surveillance after esophageal reconstruction is recommended.

Respiratory morbidity

After repair of EA, approximately one-third of patients suffer from respiratory symptoms such as wheezing, asthma, pneumonia and dyspnoea at adolescence and adulthood [28, 29]. Respiratory symptoms are thought to be caused by abnormal structural development of the airways, GERD and chronic aspiration. Comparison of respiratory morbidity in 101 Finnish adult EA survivors (median age 36 years) with healthy controls showed that EA survivors had lower respiratory quality of life and more respiratory symptoms including infections, asthma and allergies. In addition, spirometry, histamine challenge test and exhaled nitric oxide tests disclosed high occurrence of ventilatory defects and bronchial hyperresponsiveness in EA patients [29].

Musculoskeletal morbidity

Esophageal atresia associates typically with various midline defects and skeletal anomalies. Scoliosis may develop to up to 56% of patients as a consequence of vertebral anomalies and thoracotomy-induced rib fusions. Risk of scoliosis is 13-fold compared with the general population. The scoliosis is mostly mild and corrective surgery is seldom needed. Anomalies of the cervical spine are the most common vertebral anomalies occurring in 38% of the patients. These anomalies are often overlooked in infancy and among adult EA survivors remarkably few (11%) were diagnosed during childhood. Radial ray anomalies are found in 25% of the patients, commonly thenar aplasias or hypoplasias. Again, many of these defects were not detected during primary treatment period [30].

Other issues of long-term morbidity

Apart from tracheomalacia, upper airway malformations may occur in 13% of EA patients. Most of the airway malformations such as choanal atresia, tracheoesophageal clefts, cleft palate or subglottic stenosis are diagnosed and treated in early infancy and are likely to cause little long-term morbidity. After successful EA repair or reconstruction, many patients continue to have insufficient oral intake of food. Patients with impaired oropharyngeal function such as those with CHARGE syndrome and patients with mental retardation are at risk of permanent dependency of feeding ostomy [19]. Approximately 10% of EA patients have associated malformations of the gastrointestinal tract such as duodenal atresia, hypertrophic pyloric stenosis and anorectal malformations. Although these conditions are diagnosed and treated in infancy, especially anorectal malformations may have a constant impact on quality of life. Long-term neurodevelopment of children born with EA has been studied by several groups, with contrasting results. Impairments were mostly found not only in motor function, but also in cognitive performance [31]. Long-term neurodevelopmental follow-up is warranted.

Quality of life

Despite high incidence of GER symptoms, dysphagia and respiratory symptoms the general quality of life of EA patients is similar as in general population. The educational and occupational status of EA patients is also similar as in general population. When gastrointestinal and respiratory quality of life is measured, however, EA patients have impaired quality of when compared with general population [32, 33]

Hirschsprung's disease

Hirschsprung's disease (HD) is a rare (1:5000) congenital disease characterized by an absence of enteric neurons and ganglion cells of the distal bowel. Failure of enteric neural crest derived cells to colonize the distal bowel results in functional obstruction at the affected region and secondary bowel dilatation proximal to the aganglionic segment. Clinical manifestations of HD include failure or delayed passage of meconium, severe constipation, intestinal obstruction and failure to thrive and may be even fatal due to HD-associated enterocolitis. Mutations in more than ten genes have been associated with HD, but the majority of identified mutations are in RET explaining around 40% of familial and 20% of sporadic cases. Between 75 and 80% of all patients have rectosigmoid HD in which the aganglionosis is confined the rectosigmoid colon. More extensive colonic or total colonic aganglionosis (TCA) with a variable ileal involvement both occur in about 10% of patients. Aganglionosis extending to the proximal small bowel is exceedingly rare. Overall long-term functional outcome expectancy of HD in terms of fecal and urinary continence is relatively optimistic today. The outcomes have improved significantly due to increasing understanding of the pathological anatomy and physiology of the defect, and modern surgical techniques. Although some degree of bowel dysfunction and defects in fecal continence remain permanent in many patients, great majority of patients reaching adolescence and adulthood are socially continent and live normal lives [34–37]. In some, however, this may require special measures such as bowel management programs. Psychosocial implications of HD in adulthood including quality of life issues have recently gained significant attention [38].

Bowel function—classic rectosigmoid aganglionosis

Outcomes of HD regarding bowel function in childhood and adolescence are well characterized [39–44]. During childhood, different degrees of fecal incontinence and constipation are major functional derangements, whereas enterocolitis is an exceptional problem in the long-term [46]. Controlled follow-up studies that assess long-term outcomes of bowel function among HD patients are still few [34–37, 44]. Comparison with healthy controls carefully matched for demographic variables such age and gender is essential in order to obtain reliable results [34, 45]. Relatively few studies have solely concentrated on adults with operated HD [34, 35, 37, 44, 46]. These studies have mainly included patients who have been operated by Duhamel or Soave procedures for rectosigmoid aganglionosis.

Available controlled follow-up studies extending to adolescence uniformly demonstrate impaired bowel function of variable degree including increased incidence of fecal incontinence and constipation in relation to age-matched controls [34, 35, 39–42, 44]. Table 1 displays controlled studies on bowel function in adolescence after operative treatment of HD. These investigations suggest that approximately half of the patients have impaired bowel function mainly resulting from different degrees of fecal incontinence and constipation. The results of functional assessment of bowel function are very similar among adults with operated HD as shown in Table 2, suggesting that no major alterations in bowel function occur after adolescence. In both age groups, only approximately half of the patients achieved optimal functional outcome defined as bowel function score comparable to that of control population in the absence of fecal incontinence, constipation or stoma.

Long-term bowel function in adulthood was assessed in a Finnish population-based cross-sectional controlled follow-up study including 92 patients, who had been operated for HD in childhood [34]. The great majority (94%) of the patients had rectosigmoid aganglionosis and most (78%) had undergone the Duhamel's procedure. The overall bowel function was significantly inferior to that of controls. Patients reported significantly more often difficulties to hold back defecation, fecal soiling, constipation and social problems related to bowel function. The percentages of patients and controls who reported any degree of respective functional impairment was 40% vs. 17%, 48% vs. 22%, 30% vs. 9%, and 29% vs. 11%. A total of 14% of patients had frank fecal accidents compared to 0% among controls. The proportion of patients with fecal soiling more frequently than once a week, fecal accidents more often than once a week, or constipation treated with laxatives or enemas were 13%, 2.2%, and 10%, respectively. Frequency of bowel actions was like that of controls. In a multivariate analysis, only increasing age was a significant predictor of poor functional

Table 1 Overview of controlled bowel function studies among adolescents with operated Hirschsprung disease

Author	Year	Patients studied	Controls	Follow-up age (year)*	Main operation	Rectosigmoid aganglionosis (%)	Impaired continence† (%)	Constipation (%)	Bowel function score	Optimal outcome‡ (%)
Diseth	1997	22	33	16 (10–20)	Duhamel	64	36	16	Decreased	52
Reding	1997	27	39	12 (5–26)	Swenson	100	NR	NR	Decreased	52
Bai	2002	45	44	11 (8–16)	Swenson	100	45	7	Decreased	49
Baillie	1999	80	22	8 (5–16)	Duhamel	71	NR	NR	Decreased	42

NR not reported

*Median or mean (range)

†Includes any degree of fecal incontinence such as soiling as described by authors

‡Defined as bowel function score comparable to that of controls in the absence of fecal incontinence, constipation or stoma

Table 2 Summary of follow-up studies on bowel function in adults operated for Hirschsprung disease in childhood

Author	Year	Patients studied	Controls	Follow-up age (year)*	Main operation	Rectosigmoid aganglionosis (%)	Impaired continence† (%)	Constipation (%)	Bowel function score	Optimal outcome‡ (%)
Jarvi	2010	92	53	43 (18–68)	Duhamel	94	48	30	Decreased	46
Ieiri	2010	43	No	33 (19–55)	Duhamel	79	36	33	NR	67
Heikkinen	1995	102	81	31 (15–39)	Duhamel	95	45	5	Decreased	54
Conway	2007	49	20	20 ± 3.6	Duhamel	81	NR	NR	Decreased	47
Granström	2015	39	48	28 (20–43)	Soave	37	NR	NR	Decreased	NR

NR not reported

*Median or mean (range/standard deviation)

†Includes any degree of fecal incontinence such as soiling as described by authors

‡Defined as bowel function score comparable to that of controls in the absence of fecal incontinence, constipation or stoma

outcome and age inversely associated with bowel function score. These results are supported by another study demonstrating bowel function comparable to healthy controls in 47% of 49 patients after the Duhamel procedure, with mean age of 20 years using an identical bowel function scoring [46]. A Swedish study on adults with operated HD using mainly Soave procedure found that the patients had significantly worse continence and constipation scores that healthy peers [37]. It is evident that bowel function in adolescence and adulthood are clearly impaired among adults operated for HD. Derangements of bowel function occur in approximately half of the patients. On the other hand, socially disturbing fecal soiling is relatively uncommon in adults and had little impact on their psychosocial functioning [34–37, 39], most likely reflecting more advanced coping methods and efficient adaptation to the problem in adulthood.

Evolution of bowel function with advancing age

Overall bowel function of patients with HD seems to improve with time at least to a certain age [36, 39, 42–44, 46]. The critical age for this improvement is puberty [41]. It is unclear what are the mechanisms behind this age-related improvement and whether bowel function continues to improve after adolescence. Taking into account very similar overall outcomes of bowel function reviewed for adolescents and adults in Tables 1 and 2, it seems unlikely that significant improvement of overall bowel function occurs after puberty. Conversely, bowel function appears to deteriorate along with advancing adult age [34].

Urinary and sexual function

Low pelvic dissection during surgery for HD is associated with a risk of neural damage and may interfere with genitourinary function, the risk being higher when the dissection is performed outside the rectal wall. Day or night-time enuresis have been reported in addition to urodynamic abnormalities in occasional children with operated HD. Urinary and sexual dysfunction occurs also in a small minority of adult and adolescent patients with HD [36, 46, 47]. Controlled long-term follow-up studies specifically designed to investigate urinary and sexual function following surgical treatment of HD are rare but some recent studies have found no differences in the urinary and sexual functions between adults with HD and healthy controls [47]. However, Moore et coworkers found in their detailed analysis of 178 patients with mean age of 10 years that a significant percentage of patients suffer from micturition disturbances, and sexual dysfunction. The respective figures were 9.8% and 11% [48]. Sexual dysfunction included dyspareunia, erectile dysfunction and even infertility. Majority of the patients with

micturition disturbances suffered from different degrees of urinary incontinence.

Total colonic and panintestinal aganglionosis

The usual surgical techniques in TCA are standard procedures for classic HD. Long side-to-side anastomoses between ileum and distal aganglionic bowel have largely been abandoned. Restorative proctocolectomy with J-pouch ileoanal anastomosis is used in some centers. In the long term, no operative method has proven superior to others regarding postoperative morbidity, mortality, occurrence of enterocolitis and functional outcomes.

The long-term outcomes of TCA extending to adolescence are clearly inferior to rectosigmoid HD. A dominant long-term complication associated with TCA is recurrent enterocolitis. The reported rates of post pull-through enterocolitis range from 2 to 27% in rectosigmoid HD and between 20 and 55% in TCA, respectively. Soiling and fecal incontinence are common in TCA patients. At least one third of the patients suffer from frank fecal incontinence in later childhood or adolescence. This has significant psychosocial implications, because the incontinence in many of these patients is a continuous daily problem. Moreover, a significant percentage of these patients require nighttime diapers [49]. Because of intractable incontinence or recurrent enterocolitis some patients opt for permanent or long-term bowel diversion. The percentage of TCA patients ending up with a permanent ileostomy ranges between 5 and 18% [50].

In patients with TCA, stooling frequency significantly decreases over time. The numerous bowel movements during early postoperative years often cause significant discomfort because of defective fecal continence and perianal rash. Typically, stooling frequency decreases from 5 to 6 bowel movements per day at 5 years of age to around 3–4/day at adolescence. Growth retardation during childhood is common extending to adolescence and affecting mainly body weight [51]. In recent reports, long-term severe failure to thrive is, however, uncommon.

Near total or panintestinal aganglionosis represents the most extensive and a rare form of HD with extension of aganglionosis to the proximal small intestine [52]. This condition carries extremely high mortality and uniform permanent dependence on parenteral nutrition without intestinal transplantation. Initially, these patients may be salvaged by myectomy–myotomy of the retained aganglionic proximal jejunum. In addition to providing prerequisite for stable parenteral nutrition without massive stomal fluid losses, the operation may facilitate significant enteral tolerance preventing development of liver disease [53]. The mainstay of treatment is parenteral nutritional support, and every effort should be made to avoid life-threatening complications of long-term parenteral nutrition such as intestinal failure associated liver disease, frequent septicemia and loss of venous access sites. Intestinal transplantation has a role as a salvage therapy.

Syndromic Hirschsprung disease

Down's syndrome (trisomy 21) is the most common syndromic association with HD. Incidence of Down's syndrome in patients with HD ranges from 2 to 15%. Mortality of Down's syndrome combined with HD is increased due to frequent comorbidities. Many of the fatalities are attributed to cardiac problems such as atrioventricular septal defects that are common in Down's syndrome.

Down's syndrome patients are more susceptible to chronic enterocolitis than non-syndromic HD patients, while chronic enterocolitis may lead to development of inflammatory bowel disease-like colonic inflammation. Functional prognosis of HD patients with Down's syndrome is inferior to otherwise healthy patients [54]. They develop bowel control much slower than HD patients without chromosomal aberrations. A significant proportion of them, and especially those with chronic enterocolitis suffer from fecal incontinence as adolescents or adults.

HD is also associated with other more uncommon syndromes and neurocristopathies. Patients with Mowat-Wilson syndrome, resulting from mutations in the SIP 1 gene, have typical dysmorphic features, severe intellectual disability, microcephaly and seizures, and commonly HD. These patients often display frequent bouts of severe enterocolitis and develop bowel control very slowly. Cartilage-hair hypoplasia is a metaphyseal chondrodysplasia associated with growth failure, impaired immunity and high incidence of HD. It is caused by a mutation in the RMRP gene. Cartilage-hair hypoplasia patients with HD have worse prognosis than other HD patients [55]. Due to immune defect, they have extremely high incidence of potentially fatal pre- and postoperative enterocolitis.

Hirschsprung disease and cancer

Phenotype of HD, multiple endocrine neoplasia type 2 (MEN2A) and familial medullary thyroid cancer are all associated with germline mutations of the RET-proto-oncogene. Approximately 2.5–5% of HD patients carry MEN2A RET-mutations with an increased risk of medullary thyroid carcinoma. Incidence of medullary thyroid carcinoma and other cancers was assessed in a population-based cohort of 156 adult patients treated for HD (Table 3) [56]. Among 156 patients and 4816 person years at risk, 2 cases of medullary thyroid cancer were observed giving the standardized incidence ratio of 550 (95% CI 67–2000) [56]. Risk of other cancers than medullary thyroid carcinoma was not increased. Of note, only one patient had been treated for rectal carcinoma.

Table 3 Cancer cases among 156 adults with Hirschsprung disease

Malignancy	*N*
Medullary thyroid cancer	2
Papillary thyroid cancer	1
Adenocarcinoma of the rectum	1
Adenocarcinoma of the prostate	1
Non-Hodgkin's lymphoma	1
Acute lymphocytic leukemia	1
Glioma of the brain	1

N number of cases

To further elucidate risk of thyroid malignancies in adults with HD, a total of 91 of the 156 patients agreed to participate the follow-up part of the study; they underwent ultrasound examination of the neck with a thyroid needle biopsy when indicated, determination of serum calcitonin and extraction of DNA from whole blood samples. These investigations revealed one additional patient with increased serum calcitonin as a sign of medullary thyroid cancer and one patient with papillary carcinoma of the thyroid.

Quality of life

Some earlier reports describing outcome in adult or adolescent patients show very little limitations regarding occupation, social contacts, or physical activities [35, 39]. More recent data suggest that children and adolescents with HD report comparable overall quality of life in relation to healthy reference subjects, although there are individuals with very low level of quality of life [34, 36]. Adults with HD show decreased overall physical quality of life when compared to general population [38]. However, in the same study, all the specific domains of quality of life among adults with HD were comparable to those of general population. Interestingly, psychosocial functioning appears to have stronger effect on quality of life than disease-specific factors such as constipation and fecal incontinence. Adults with operated HD demonstrate only marginally lower gastrointestinal quality-of-life in relation to controls mainly due to lower scores in questions assessing functional bowel symptoms [34]. Lower quality of life domains is related to poor functional outcomes [36, 37, 57]. Furthermore, social problems associated with impaired bowel function are more prevalent among adult patients than controls. A worrying finding is that degree of impairment of bowel function increases by increasing adult age, which may have a significant negative impact on quality of life of older patients with HD [34].

Conclusions

The development of neonatal surgery and improving early outcomes has brought into light a growing group of individuals that in the past would have died or suffered from serious functional defects. Although early outcomes in these patients groups are well recognized, amazingly few reports on long-term outcomes beyond childhood are available. The medical teams taking care of neonatal surgical patients should have a responsibility to follow-up their patients throughout the whole growth period to reveal the true long-term outcomes. The caregivers of the patients have the right to know the effect of the neonatally repaired condition on growth and development, and also the cognitive and psychosocial consequences and the effects on fertility and sexuality. The follow-up should also continue during adult age as aging may impact functional outcome. The potential risks of malignancy and future inheritance need also be addressed. The research on long-term outcomes is facilitated by development of preferably multinational patient registries and tracking systems. Reliable long-term outcome studies require also validated and standardized research tools and healthy control materials.

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Data availability There are no associated data available.

Declarations

Conflict of interest There are no conflicts of interest.

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