Anorectal malformations and Hirschsprung disease
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Introduction and outline of this thesis
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Anorectal malformations and Hirschsprung disease are two relatively common congenital disorders seen in the pediatric surgical practice. The incidence of anorectal malformations is approximately 1 in 1000 to 1 in 5000, and for Hirschsprung disease this is 1 in 5000 to 1 in 10000 live births.\(^1,2\) Although these are two different disorders, they are often mentioned together because of the similar problems and complaints patients can experience during (long-term) follow-up. These problems and complaints can influence the daily life of our patients.\(^3,4\) Furthermore, the parents of our patients can experience psychosocial burdens because of the disorder of their child.\(^5,6\) In recent years, many studies have been performed concerning the surgical treatment of anorectal malformations and Hirschsprung disease and we have established good surgical techniques to improve the outcome after surgery.\(^4\) Therefore, this is the time to start looking at both psychosocial factors and functional problems that can be the result of these disorders. As doctors, we must become more aware of these factors so that our patients and their parents can receive the complete treatment they need and deserve.

Anorectal malformations

The human digestive system derives from the formation of the foregut, midgut and hindgut. Eventually the hindgut will differentiate into the distal third of the transverse colon, the descending colon, the sigmoid, rectum and anus. The development of the anorectum can be described in three phases: (1) The cloacal period (3\(^{rd}\) to 5\(^{th}\) week), (2) the development of a urogenital sinus and anorectum (5\(^{th}\) to 7\(^{th}\) week), and (3) the development of the anus and perineum (8\(^{th}\) week and later).\(^7\) The normal development of the hindgut depends primarily on the normal formation of the cloacal membrane. In normal embryos the future anal orifice can be identified in the dorsal part of the cloacal membrane close to the tail groove. In abnormal cloacal development, we see absence of the dorsal cloaca, and therefore a short cloacal membrane and an abnormal junction between the proximal hindgut and the cloaca (Figure 1).\(^8\) As a consequence of these embryological abnormalities a wide variety of anorectal malformations can occur. So far no single gene or chromosomal locus has been identified, that causes the development of an anorectal malformation. These malformations are likely caused by a combination of multiple genetic and environmental factors.\(^9\)

Anorectal malformations comprise of a wide spectrum of anomalies of the distal anus and rectum, as well as the urinary and genital tracts. The malformation can be as little as an anal membrane, but it can also involve rectourethral, rectovesical, rectovestibular fistulae or even a cloacal malformation. In 2005 an international classification system (Krickenberg) was reached by consensus, allowing everyone to talk the same language.
and to enable comparable follow-up of patients with anorectal malformations. The most prevalent types of anorectal malformations can be seen in Figure 2 (males) and Figure 3 (female).

For the treatment of anorectal malformations, the preferred approach for many surgeons around the world has become the posterior sagittal anorectoplasty (PSARP) introduced by Peña and De Vries in 1982. A midline incision from the sacrum to the perineum is made, extending through the sphincteric musculature to the terminal bowel and fistula. With this approach the muscle complex and the sphincter are damaged less by staying in the exact midline. Eventually the appropriate anal site is determined by using the electrostimulator. Ninety percent of the anorectal malformations can be surgically corrected using this approach. In recent years other techniques, such as laparoscopy, have been introduced to facilitate the repair of high malformations. Also a more limited perineal dissection has been introduced for rectoperineal fistulae (anterior sagittal anorectoplasty).

The main long-term outcome patients and parents are concerned about, is (in)continence for stool. Many studies have reported soiling, constipation and incontinence for gas, liquid- or solid stool as long term problems after the treatment of an anorectal malformation. Also sexual dysfunction has been described in literature.
Figure 2: Drawings of male anorectal malformations. From left to right: rectoperineal fistula; rectourethral fistula (bulbar); rectourethral fistula (prostatic).

Figure 3: Drawings of female anorectal malformations. From left to right: rectoperineal fistula; rectovestibular fistula; cloacal malformation.

Hirschsprung disease

The ability of the normal bowel to have normal and good functioning peristalsis depends on the development of the enteric nervous system (ENS). Neurons and glia of the ENS are organised into ganglia, which form the outer myenteric plexus (Auerbach) and an inner submucosal plexus (Meissner). The cells of the ENS are originally derived from the neural crest. Correct migration, proliferation, differentiation and survival of these cells within the gastrointestinal tract is essential for normal gut development. Any disruptions in this process, will result in the absence of enteric ganglion cells in a variable length of the distal gastrointestinal tract. This absence of enteric ganglion cells is defined as Hirschsprung disease.17,18 This disease commonly occurs sporadically, however it can also be familial in up to 20% of the cases.19 We know that siblings of affected patients are more often affected (4%) and also long segment Hirschsprung disease seems more likely to be familial.20 Mutations in several genes have been identified, such as RET, EDNRB, EDN3, SOX10, ZEB2 and PHOX2B.21,22

The aganglionic segment of the bowel will lead to a gastrointestinal obstruction and patients will have the inability to pass meconium, abdominal distention and sometimes bilious vomiting. Hirschsprung disease is most often diagnosed in the neonatal period, however a small number of patients present later in childhood, or even during adolescence or adulthood.23 The most common form of Hirschsprung disease is aganglionosis
limited to the rectosigmoid. Five to twelve percent of the patients are diagnosed with total colonic aganglionosis. A longer aganglonotic segment is associated with a higher morbidity and mortality compared to Hirschsprung disease limited to the rectosigmoid.

Primary treatment for Hirschsprung disease, both short and long segment, is surgical resection of the aganglionic bowel and reconstruction of the intestinal tract. Different techniques and approaches have been developed over time varying in length of aganglionic bowel left in situ, in type of anastomosis and in approach (transabdominal or transanal). In the Netherlands currently the (laparoscopic) Duhamel procedure and the (laparoscopic assisted) transanal endorectal pull-through (TEPT) are performed for patients with short or long segment Hirschsprung disease. The surgical treatment that is chosen per pediatric surgical centre mostly depends on the experience of the operating surgeon.

Obstructive symptoms, soiling, anal achalasia, enterocolitis and failure to thrive are frequently seen problems after surgical treatment. These symptoms may vary for each patient and some patients have more than one problem.

Quality of life
In recent years quality of life (QoL) has become an important outcome measurement in the treatment of anorectal malformations and Hirschsprung disease. Especially because of the chronic character of both diseases, it is important for doctors to become aware of the consequences of our treatment. Both the physical and psychosocial consequences. Throughout this thesis, QoL is the recurrent theme in all chapters. However before we can investigate QoL and draw conclusions we need to have a clear definition of this concept. The WHO Quality of Life Group has defined QoL as “an individual’s perception of his/her position in life in the context of the culture and value systems in which he/she lives and in relation to his/her goals, expectations, standards, and concerns.”

In other words, QoL is one’s evaluation of his/her functioning in a wide range of areas. Thus, QoL is subjective and refers to satisfaction. In the literature a distinction is sometimes made between QoL and health-related QoL, with the latter only concerning those aspects of life that are directly influenced by one’s health. Since QoL refers to (dis)satisfaction with functioning, it can vary over time depending on life-events or due to coping strategies. Coping strategies may change when growing up with a chronic disease such as an anorectal malformation or Hirschsprung disease, and lead to changes in QoL.

Questionnaires
We prefer that questionnaires used for measuring QoL are self-administered, because they ask about satisfaction, a very subjective feeling. A typical questionnaire measuring all aspects of QoL includes six domains: the physical domain, the psychological domain,
the social domain, environment, level of independence and spirituality. In this thesis we used several validated questionnaires. The main questionnaires are discussed here.

Generic QoL was measured with the World Health Organization Quality of Life assessment instrument (WHOQOL-100) or the short version, the WHOQOL-BREF. The WHOQOL-100 contains 100 items together assessing QoL in 24 facets covering 6 domains (physical health, psychological health, level of independence, social relationships, environment, spirituality/personal beliefs) and a general evaluative facet (overall QoL and general health). The reliability and validity of the instrument are good. The WHOQOL-BREF has 26 items in 4 different domains and a general QoL facet. The domains are physical health, psychological health, social relationships and environment. In general, a high score represents a good QoL. The reliability and validity of the short version are also good.

Anxiety was assessed using the Spielberger State-Trait Inventory. The State and Trait Anxiety Inventory (STAI) was used to assess state anxiety and the personality characteristic trait anxiety. State anxiety is a momentary emotional condition characterized by subjective feelings of apprehension and tension, and heightened autonomic nervous system activity. Trait anxiety concerns differences in the disposition of individuals to respond to stressful situations with varying amounts of stress. The short versions of the STAI-Trait and STAI-State were used. The psychometric properties of the short version are well established and considered to be good.

The Pediatric Inventory for Parents (PIP) measures the parental stress caused by the medical treatment of their child. The PIP investigates areas of anxiety and concern experienced by parents caring for an ill child without being limited to a specific illness. It combines disease related measures with generic measures so that these dimensions can be investigated in a quantitative fashion. The Dutch version of the PIP has been validated.

Health related QoL was assessed with the Hirschsprung disease and Anorectal Malformation QoL Questionnaire (HAQL). It consists of 60 items (children) or 63 items (adults) assessing domains of disease-related impact on QoL (laxative diet, constipating diet, diarrhea, constipation, fecal continence, urinary continence, social and emotional functioning, body image, physical symptoms and sexual functioning (from the age of 12). The reliability and validity of this instrument are considered good.

**KLANKbord-study**

In 2012, we started the KLANKbord-study in the Netherlands. A longitudinal, multicentre study on QoL of patients with an anorectal malformation or Hirschsprung disease and
their parents. The hypothesis of this study is that the QoL of patients with an anorectal malformation or Hirschsprung disease can be influenced by their functional complaints. Also having a child with one of these disorders can result in parental stress, anxiety and possibly a lower QoL of parents. This parental stress, anxiety and a lower QoL may lead to more functional complaints in the child. We therefore think that identifying those moments in life when, either our patients or their parents, need more standardized, intensified and possibly multidisciplinary follow-up, will eventually lead to a better treatment of our patients. Especially investigating the psychosocial factors of parents with a child with an anorectal malformation or Hirschsprung disease has not been done longitudinally.

We started the study in three of the six Pediatric Surgical Centers in the Netherlands (Amsterdam, Groningen and Utrecht). In the near future we hope that other centres will join this study as well. Parents are approached within several weeks after the diagnosis has been confirmed. The inability to speak and read sufficient Dutch or English is an exclusion criterion. Parents will receive a set of questionnaires every six months to the age of four, and then the frequency decreases to once every year. When the child turns seven, they will also be asked to join the study and they will also complete questionnaires, especially designed for children, on a yearly basis.

Because this study is longitudinal, in this thesis only the first analyses of some of the questionnaires, is published. In the future more results will be published on topics as generic QoL, anxiety, stress, child development and health-related QoL of both patients and parents.
Outline of this thesis

Different aspects of the treatment of patients with an anorectal malformation or Hirschsprung disease can still be challenging. With this thesis we hope to address those aspects that are not often investigated, but are an essential part of the treatment of the child, the adolescent or an adult with one of these disorders. The aim of this thesis was to identify the functional and psychosocial problems patients with an anorectal malformation or Hirschsprung disease can encounter during life, and to investigate the psychosocial impact these diagnoses can have on parents.

In Chapter 2 we provide an overview of literature performed on QoL of children and adults with an anorectal malformation published in peer-reviewed international medical journals. These studies were all reviewed using a 20 item checklist, based on previous systematic reviews assessing QoL.

Since we started the KLANKbord-study in 2012 we have included many patients and their parents in this longitudinal study. This has so far resulted in three chapters of this thesis. Chapter 3 compares QoL and anxiety of parents of newborns with parents of school going children. In Chapter 4 parents are followed for one year after their child was diagnosed with an anorectal malformation or Hirschsprung disease. We investigated the anxiety level and QoL of the parents and were interested if this changed during the first year.

A child with an anorectal malformation or Hirschsprung disease will be in follow-up with the pediatric surgeon for many years. A constant level of stress because of hospital visits, operations or clinical admittances can be expected. In Chapter 5 we investigated the stress that parents experience using the Pediatric Inventory for Parents. And we were interested if the amount of stress would decrease in time.

The second part of this thesis focuses more on the long-term outcome of our patients. In Chapter 6 we investigated the functional results and QoL of patients with near total colonic aganglionosis. This was a national study.

Our patients are followed during childhood and adolescence on a regular basis, but we see that transfer into adult care is often difficult. Chapter 7 describes the design and start of our transitional outpatient clinic in the Pediatric Surgical Center of Amsterdam. This chapter also assesses the use of questionnaires as an addition to the consult in this clinic.

In Chapter 8 sexual functioning and sexual distress in men and women with an anorectal malformation or Hirschsprung disease was investigated. This was set up as a follow-up of the NAHO study, a national study on QoL of patients with an anorectal malformation or
Chapter 1

Hirschsprung disease performed in 1998. This gave us the opportunity to investigate the influence of psychosocial factors in childhood and adolescence, on sexual distress and functioning as an adult.

Chapters 9 serves as a general discussion and describes the clinical implications of this thesis. Chapter 10 is a summary of this thesis respectively in English and Dutch.
Reference List


