ANORECTAL MALFORMATIONS

A Multidisciplinary Approach

Desiree van den Hondel

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Preface and outline of the thesis

Congenital malformations of the anorectum occur in 1 to 3 in every 5000 live borns.[1,2] In the Netherlands, each year approximately 50 to 60 children are born with an anorectal malformation.[3] This may not seem much, but these malformations constitute a considerable part of everyday pediatric surgery practice. Anorectal malformations consist of a wide spectrum of anomalies with different functional results, and are therefore fascinating both to treat and to study.

Historical background

The first description of anorectal malformations goes back to the second century AD, when Soranus, a Greek physician who practiced in Alexandria and subsequently in Rome, was one of the first to describe anorectal malformations in detail.[4] Where newborns with congenital anomalies usually were left to death, Soranus attempted to treat neonates with an anorectal malformation by dividing a thin anal membrane.[5] Paul of Aegina (625-690 AD) further refined the treatment by dilating the anus with bougies and applying wine and salve after the incision.[6] Thereafter, there was stagnation in medical care until the fifteenth century, when Sabuncuoglu from Turkey emphasized the difference between high and low malformations, referring to the amount of tissue between the skin and the rectum. Fig. 1 shows an illustration of Sabuncuoglu of the incision for anorectal malformations.[7]

Fig. 1: Puncture of anal membrane in the 15th century

Illustration from Sabuncuoglu (Figure from Yesildag et al.©[7])

As medical care improved, so did survival. With the introduction of colostomy by Littré in 1710 also patients with more severe anorectal malformations had a -slight- chance for survival.[8] In the 18th century, the German anatomist and surgeon Heister, wrote a treatise 'About how should the anus be opened when it is imperforate' in 1749.[7] He recommended to check all newborns for anorectal malformations. He described the operative technique, placing the infant on the knees of an assistant and making two incisions, as if draining an abscess. This technique is remarkably similar to the operative technique described by Sabuncuoglu two centuries before. The present-day techniques were developed in the 20th century by Dr Browne (V-Y cutback procedure, 1951) and Dr Peña and DeVries (posterior sagittal anorectoplasty, 1982). These techniques will be described later.

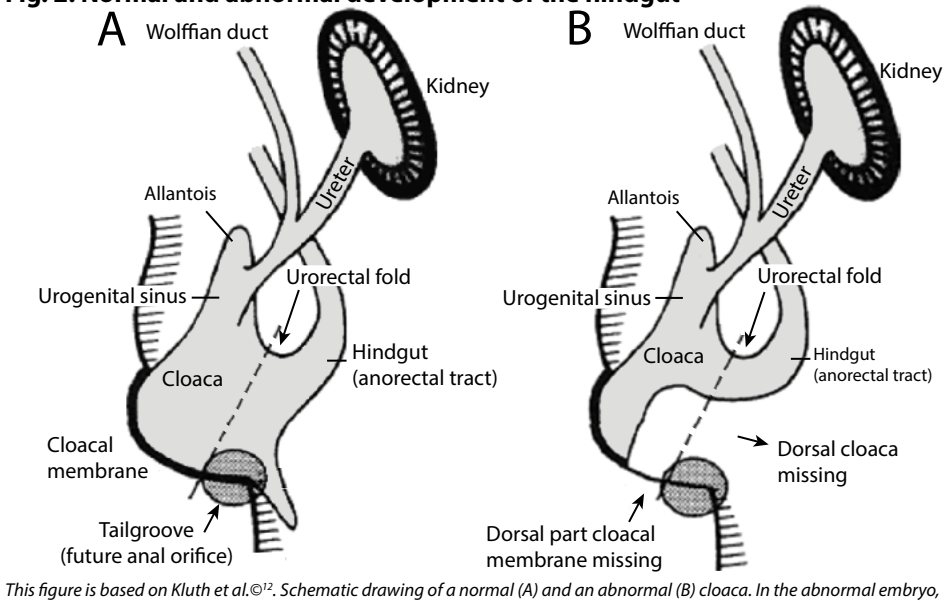
Embryology and definitions

Anorectal malformations are characterized by absence of the anal orifice within the sphincter complex. In most cases, an 'ectopic opening' or fistula is present and the pelvic floor is hypoplastic.[9]

In normal embryonic development, the digestive tract is formed from the foregut, the midgut, and the hindgut. The foregut differentiates into the esophagus, stomach, duodenum, liver, gall bladder, pancreas, and spleen, while the midgut differentiates into duodenum, jejunum, ileum, cecum with appendix, ascending and transverse colon. The hindgut differentiates into the distal third of the transverse colon, descending and sigmoid colon, rectum and anus.[10] The hindgut terminates in the endodermally lined cloaca, which is caudally in direct contact with the ectoderm, forming the 'cloacal membrane'.[10] The cloacal membrane reaches dorsally into the tail groove, which is the future anal orifice. During the sixth and seventh weeks, the cloaca is divided into the urogenital sinus and the anorectal tract by a septum of mesodermal tissue, called the urorectal fold. In this process the cloacal membrane is thought to play an important role for orientation, although exact biomechanisms are unclear (Fig. 2a).[11]

In abnormal development as seen in anorectal malformations, the dorsal cloaca and dorsal part of the cloacal membrane seem to be missing (Fig. 2b).[12] As a consequence, the cloacal membrane does not extend to the tail groove. Now, when the anorectal fold develops, which should divide the cloaca into the urogenital sinus and anorec-

Fig. 2: Normal and abnormal development of the hindgut



This figure is based on Kluth et al.©[12]. Schematic drawing of a normal (A) and an abnormal (B) cloaca. In the abnormal embryo, the cloacal membrane is too short because it does not extend to the region of the tail groove (dark grey area). As a consequence, the dorsal cloaca is missing. These drawings were based on scanning electron microscopy in 80 mice embryos (SD-mice or 'Danforth's short tail mice').

Fig. 3: Most prevalent types of anorectal malformations

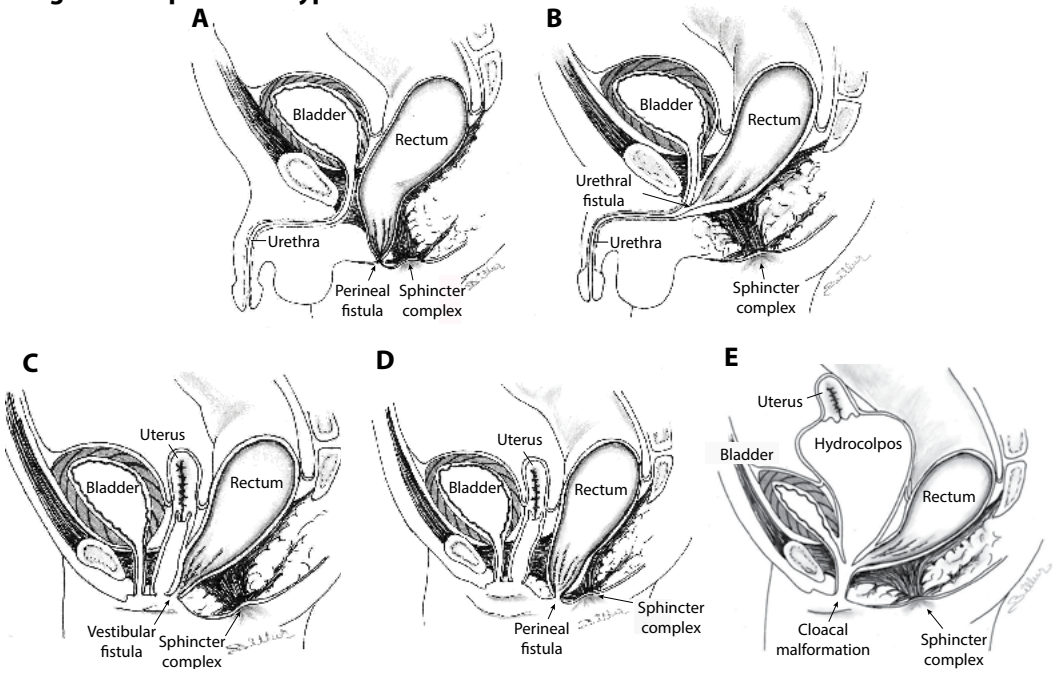


Fig. 3a: Male perineal fistula. Fig. 3b: Rectourethral fistula. Fig. 3c: Vestibular fistula. Fig. 3d: Female perineal fistula. Fig. 3e: Cloacal malformation. These figures were kindly provided by dr Demirogullari, Ankara, Turkey.

tal tract, a wide variety of anomalies can occur. Molecular mechanisms are still under research, but there is evidence that mutations of sonic hedgehog (*SHH*) and its downstream molecules *Gli-2* and *Gli-3*[10,13] as well as *Wnt inhibitory factor 11*[4] and *FGF* signaling pathways[15] have been described to play a role in the pathogenesis of anorectal malformations.

Several classification systems for anorectal malformations have been proposed. The classification system used nowadays, the Krickenbeck classification[5] (Table 1) was developed in 2005 and had two main purposes: first to determine what operative technique would be required for the patient, and second to be able to compare long-term follow up studies more precisely.

The most common types of anorectal malformations (Fig. 3) seen in male patients are perineal fistula (40%) and rectourethral fistula (31%), and in female patients are vestibular fistula (57%), perineal fistula (27%) and cloacal malformation (11%).[16] The different types of malformations require different operative techniques and have different prognoses.

In almost all patients, the anorectal malformation is detected postnatally. Only few cases of antenatally detected anorectal malformations have been reported.[17-19] These cases were detected by ultrasonography at the end of the first trimester, when liquid contents of the dilated distal colon were be detected. This may have been the result of swallowed amniotic fluid or urine that had passed the fistula.

Table 1: Krickenbeck classification for anorectal malformations

Major clinical groups	Rare / regional variants
Perineal fistula	Pouch colon atresia / stenosis
Rectourethral fistula	Rectal atresia / stenosis
Prostatic	Rectovaginal fistula
Bulbar	H-type fistula
Rectovesical fistula	Others
Vestibular fistula	
Cloaca	
Anorectal malformation without fistula	
Anal stenosis	

Neonatal care

The absence or abnormal location of the anal orifice is usually detected on the initial newborn examination, especially when the nurse measures the temperature. In missed cases, the anorectal malformation is detected later in childhood[20] or even in adulthood[21]. The operative techniques are then similar to those in newborns.

When an anorectal malformation is detected in a newborn, the patient is stabilized first, a nasogastric tube is inserted to decompress the upper gastrointestinal tract, the patient is kept nill by mouth, and will be immediately referred to a pediatric surgical center in a tertiary hospital.

Initial management

In the pediatric surgical center, generally 16 to 24 hours (maximum 48 hours) is awaited to see if meconium appears at the pelvic floor.[22,23] From the appearance or lack of meconium, it can be determined what type of anorectal malformation is present. If meconium appears at the pelvic floor, there is a high probability for a perineal or vestibular fistula, in which case an anoplasty or a limited posterior sagittal anorectoplasty (PSARP) operation is performed.[24,25] This can be done either within the first days of life, or later, after resorting to dilatations of the fistula first.[26]

If no meconium appears at the pelvic floor, if the male patients' urine is mixed with meconium or air (in case of a rectourethral fistula), or if a cloacal malformation is present in a female patient, a colostomy is performed to decompress the bowel, because direct reconstruction is too extensive for neonatal period.[25,27] If the colostomy is not or cannot be performed timely, the bowel becomes distended and the patient can become unstable and the colon might perforate.[28,29] In developing countries, where delay in diagnosis is more prevalent, it may even necessary to perform the colostomy operation under local anesthesia, when general anesthesia is too risky because of the patient's hemodynamical instability.[30] In case of a cloacal malformation, drainage of hydro(metro)colpos (Fig. 2e: fluid in the vagina and/or uterus) should be considered, as this was found present in 28% of the cloacal malformation patients.[31]

Associated anomalies

In 49-78% of the cases, anorectal malformations co-occur with other congenital anomalies.[16,32,33] These may be part of a chromosomal disorder such as trisomy 13, 18, or 21, or of a single gene mutation as is in Cat eye syndrome.[34] However, it is not obligate that associated anomalies are part of a genetic disorder. Etiology of nonsyndromic anorectal malformations is not yet clear but probably multifactorial, involving both genetic and nongenetic risk factors. Candidate genes that may be involved in nonsyndromic anorectal malformations are mentioned above.

Considering what types of associated anomalies are present, urogenital anomalies are most prevalent, occurring in more than half of the patients.[35,36] In these patients, special care should be taken to preserve kidney function.[37] Further, present in approximately 10% of the patients are three or more components of the VACTERL-association (an acronym for Vertebral, Anal, Cardiac, Tracheo-Esophageal, Renal, and Limb anomalies).[38] The etiology of VACTERL-association is not clear, but abnormalities in the *Sonic Hedgehog* pathway[39], de novo and rare copy number variants[40], and mitochondrial dysfunction[41] have been described.

Besides the urogenital anomalies and the anomalies part of the VACTERL-association, anorectal malformations can also be accompanied by tethered spinal cord, present in 10-17% of anorectal malformation patients.[42,43] In tethered spinal cord, caudal traction on the conus medullaris may result in symptoms such as gait abnormalities or urinary or fecal incontinence.

In Erasmus MC-Sophia Children's hospital, all anorectal malformation patients are screened for associated anomalies. The screening protocol prescribes special attention to the urogenital system during physical examination. Screening for VACTERL association is performed with x-rays of the chest and spine and with ultrasound of the heart and abdomen. Spinal ultrasound is performed to screen for tethered spinal cord.

Surgical techniques

Colostomy

When primary repair is required but cannot be performed, a colostomy is created to

divert the fecal stream. Two types of colostomy are distinguished: a loop colostomy, in which the bowel is not completely divided, and a split colostomy, in which the bowel is completely divided and both colostomies are placed wide enough so that a stoma cap can be placed on only the afferent loop. The colostomy can be placed virtually anywhere on the colon. Both type and place of colostomy are mostly dependent on the preference of the surgeon. In our hospital, mostly loop transverse colostomies were performed. However some doubt about the performance of this operation remained as prolapses occur quite frequently, up to 17 to 21% described in the literature[44,45], and overflow of fecal material could theoretically occur, causing a potential source of urinary tract infections in case of a rectourethral fistula.[46] Therefore a shift had occurred towards split descending colostomies.

Reconstructive surgery

In cases of anal stenosis in which the fistula is located within the sphincter complex, no reconstructive surgery is required.[22] In other cases, and in patients with vestibular fistula, primary repair can be performed without a diverting colostomy. This can be done either in neonatal period or later, within 6 months of age, with dilatations of the fistula in the bridging period. For perineal fistula, a V-Y cutback procedure or anoplasty can be performed, described by Browne.[47] In patients with a vestibular fistula, the preferred operation is the anterior or posterior sagittal anorectoplasty (ASARP or PSARP) operation, developed and popularized by Peña.[48] In this operation, a sagittal midline incision is used to dissect the fistula (Fig. 4a), special care taken to avoid perforation of the vagina. When sufficient length is reached, the perineal body is built (Fig. 4b) and a neo-anus is created in the center of the sphincter complex (Fig. 4c).

Fig. 4: Posterior sagittal anorectoplasty (PSARP) operation

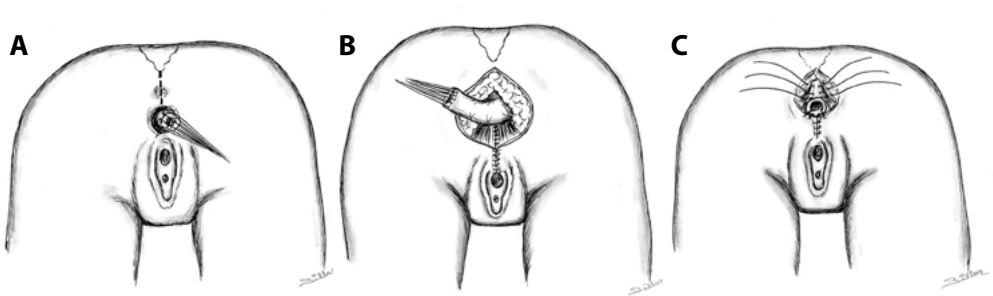


Fig. 4a: Sagittal midline incision and dissection of the fistula. Fig 4b: building the perineal body. Fig 4c: placement of neo-anus in the sphincter complex. These figures were kindly provided by dr Demirogullari, Ankara, Turkey.

The PSARP operation is the operation of choice for rectourethral fistulas as well. Using the sagittal midline incision, the fistula is identified and closed. Then the perineal body is built and the neo-anus is placed in the center of the sphincter complex. Prior to the operation, a distal colostogram can be performed to determine the level of the fistula.[49] If a high fistula is present, e.g. prostatic fistula or bladder neck fistula, an abdominal laparoscopy can help identify the fistula and dissect the rectum so that the neo-anus can be created without tension.[27,50,51]

After the wound is healed, the neo-anus is calibrated to prevent anal stricture.[52,53] This is done either daily by the parents[52] or weekly by the pediatric surgeon[53]. When a sufficient diameter of the neo-anus is reached, and when the anastomosis is proven to be intact by a distal loop contrast radiograph[54], the colostomy will be closed during a third operation.

Long-term outcome

Continence

The main long-term concerns about outcome are fecal and urinary continence. The prognosis of fecal continence is multifactorial -sphincter function, sensory function, and bowel pattern all play a major role in continence- is mainly dependent on type of malformation and the development of the sacrum. That of urinary continence is mainly dependent on associated urogenital anomalies besides sacral anomalies.[55]

The most important prognostic factor for fecal continence is type of malformation, where the less severe malformations have better functional prognosis than the more severe malformations. The functional outcome of anorectal malformation patients can be classified according to the Krickenbeck classification for postoperative results (Table 2). Voluntary bowel movements were found to be present in 80-90% of the patients with a perineal fistula, vs. 34-58% of males with urethral fistula.[56,57] Severe constipation, where diet or laxatives do not provide sufficient treatment, is present in 8-21% of patients with a perineal fistula, vs. 17-42% of the male patients with a urethral fistula.[56,57]

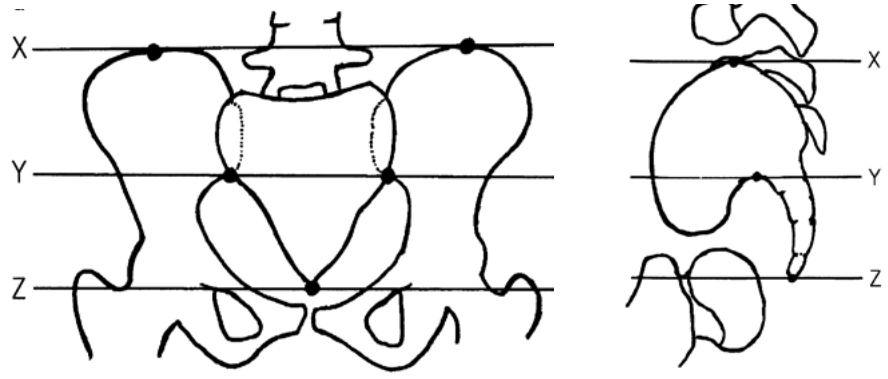
Besides type of anorectal malformation, development of the sacrum is a prognostic

Table 2: Krickenbeck classification for postoperative results

Voluntary bowel movement[1] yes/no
Soiling
No soiling
Grade 1, occasionally
Grade 2, every day, no social problem
Grade 3: constant soiling, social problem
Constipation
No constipation
Grade 1, manageable by changes in diet
Grade 2, requires laxatives
Grade 3, resistant to diet and laxatives

[1] Voluntary bowel movements are defined as presence of a feeling of urge, capacity to verbalize, and ability to hold the bowel movement.

Fig. 5: Sacral ratio



Schematic drawing of sacral ratio in AP (Fig. 5a) and lateral (Fig. 5b) position. (Figures by Warne et al. ©[64]). The sacral ratio is the distance between lines x and y divided by the distance between lines y and z.

factor for fecal continence. Peña proposed the so-called sacral ratio as a measure for the development of the sacrum.[58] To obtain the sacral ratio, three lines are drawn on the radiograph (AP and lateral view, Fig. 5): line (x) between the uppermost aspects the iliac crests; line (y) between lowest points of the sacroiliac joints; and line (z) parallel to the above touching the lowest visible point of the sacrum. The ratio, then, is the distance between lines (x) and (y) divided by the distance between lines (y) and (z).[58] Some studies indicate that patients with a higher sacral ratio would have better prognosis for continence[59-61], possibly because the sacral nerves are better developed.

However, other studies indicate a poor correlation with continence[62] and also healthy peers have a wide variation in sacral ratio[63,64]. Therefore the sacral ratio should not be used as the sole indicator for continence, as the main prognostic factor for fecal continence remains the type of anorectal malformation.[65-67]

Long-term follow up is warranted to best guide patients towards socially acceptable continence. If necessary, dietary changes should be made and oral laxatives should be started.[64] Bowel management, such as daily enemas or rectal washouts, may be needed if these measures are not sufficient to treat constipation and prevent soiling.[69-71] If rectal washouts are not tolerated by the child, a Malone Antegrade Continence Enema (MACE) procedure can be performed.[72-74] In this procedure the appendix is sutured in the abdominal wall, either in the right lower quadrant or in the umbilicus. The appendix then can be used to perform antegrade washouts, which are more comfortable for the patient than rectal washouts. The MACE-procedure can improve quality of life[73-75], although complications directly related to the operation have been reported to occur in 30-43% of the procedures.[72,74,76,77] The high complication rate suggests that the MACE-procedure should be performed only when strictly necessary by specialized teams.

Other modalities to improve fecal continence are individualized biofeedback training[78-80] and multidisciplinary biopsychosocial treatment[81]. A more novel treatment option is sacral nerve stimulation, which was found to be beneficial in 5 adult patients with fecal incontinence.[82] Thomas et al. reported sacral nerve stimulation in two adult anorectal malformation patients: continence improved in one patient.[83] More evidence is lacking so far and further studies are certainly needed before sacral nerve stimulation can be recommended for daily practice.

Psychosocial development and quality of life

The frequent hospital admissions, associated anomalies, and defecation disorders carry a high risk of impaired psychosocial development and quality of life.[84] Because psychosocial development and quality of life are both multidimensional and multifactorial, they are challenging to study.

Concerning psychosocial development, 15 to 19% of anorectal malformation patients

aged 8 to 16 years were diagnosed with internalizing behavioral problems.[85,86] Dissociation disorder has been related to anal dilatations.[87] Twelve to 50% of patients experience social restrictions due to fecal soiling.[86,88] Also, two small studies describe problems with sexual function, mainly erectile dysfunction and dyspareunia.[89,90]

Studies on quality of life show that general quality of life also appears to be impaired.[91,92] Children tend to have more physical symptoms than adolescents, but adolescents more frequently report an impaired quality of life. Furthermore, even negative associations have been shown between physical symptoms and quality of life –i.e. more positive quality of life when more physical symptoms are present-, and therefore the relationship between quality of life and physical symptoms remains unclear.[91]

Multidisciplinary approach

Concluding from the information stated above, multidisciplinary approach is essential in anorectal malformation patients. If other congenital anomalies are present, it is only logical to consult the concerning specialists in question.

Besides the additional care for associated congenital anomalies, multidisciplinary treatment is essential for treating defecation disorders[93], such as behavioral therapy[70,94] or individualized biofeedback training by the pelvic floor physical therapist[81,95]. Multidisciplinary treatment is also necessary to guide the patients and parents psychologically, through a psychologist and a social worker.[86]

Outline of the thesis

As made clear above, the management of anorectal malformations remains challenging, and many questions are still unanswered. This thesis aims to evaluate various aspects that are important in this respect, with the eventual goal of optimizing the multidisciplinary approach in these patients. This thesis consists of two parts:

Part 1 focuses on neonatal care and contains retrospective case studies. Colostomies play a major role in the treatment of anorectal malformations, however complication rates remain high. In *Chapter 1*, the most ideal place and type of colostomy is investigated by a retrospective study and a systematic review of the literature. Further, the clinical geneticist's observation that limb anomalies in anorectal malformation patients might point towards a syndromal disorder was further investigated in *Chapter 2*. *Chapter 3* describes various aspects of screening, management, and outcome of tethered cord syndrome in anorectal malformation patients.

Part 2 focuses on long-term outcome from childhood into adulthood. It contains a cohort study and prospective studies. Because of the multiple operations anorectal malformation patients are subjected to within the first years of life, we hypothesized that they were at risk for developmental problems. Growth, mental development, and motor function development within the first five years of life were prospectively evaluated in *Chapter 4*. *Chapter 5* describes outcomes of neuropsychological evaluation and quality of life at school age, while *Chapter 6* compares the quality of life of patients with the most severe type of anorectal malformation, cloacal malformation, with that of other female anorectal malformation patients. *Chapter 7* reports a large cross-sectional cohort study evaluating psychosexual well-being in adults who underwent colorectal surgery in early childhood. The thesis concludes with a general discussion section.

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PART 1: NEONATAL CARE

Chapter 1

To split or not to split: colostomy complications for anorectal malformations or Hirschsprung's disease

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To split or not to split: colostomy complications for anorectal malformations or Hirschsprung's disease

A single center experience and a systematic review of the literature

Desiree van den Hondel[1], Cornelius EJ Sloots[1], Conny JM Meeussen[1], René MH Wijnen[1]

ABSTRACT

Introduction	The aim of this article is to identify the ideal type and location of colostomy in children with colorectal disease.
Patients and methods	A retrospective case study of children with an anorectal malformation who received a colostomy, born between January 1990 and July 2012. Furthermore, a systematic literature search on colostomies in neonates with an anorectal malformation or Hirschsprung disease. Colostomies were classified as loop or split colostomies in the transverse or sigmoid colon. Outcome measures were mortality and complications such as prolapse, technical difficulties with the reconstruction, urinary tract infections, and others.
Results	The mortality rate in the 180 children with anorectal malformation was 6%, and none of them were directly related to stoma formation or closure. The overall complication rate was 23% and the specific rates for the two types of procedures and the two locations of the colostomy did not differ (p=0.389 and p=0.667, respectively). All prolapses (n=22) occurred in loop colostomies in the transverse colon. One colostomy required revision because of insufficient length for the reconstruction. Urinary tract infections were not documented. A total of eight studies were included in the systematic review (1982–2011; 2,954 patients). Mortality ranged between 0.1 and 11%. Loop colostomies had more complications than split colostomies (63 vs. 45%; p=0.007), mainly prolapse (18 vs. 6%; p<0.001). Overall complication rate differed between transverse en sigmoid colostomies (62 vs. 51%, p=0.006), and prolapse occurred more often in the transverse colon (23 vs. 7%; p<0.001). Revision because of insufficient length during the reconstruction was needed in 0 to 6%. Two studies reported on urinary tract infections which are as follows: One showed no difference between loop or split colostomies, whereas the other showed frequent episodes of urinary tract infections in 64% of the loop colostomies.
Conclusions	The complication to be avoided in transverse colostomies is prolapse and the surgical technique should be modified accordingly. The procedure of split sigmoid colostomy is meticulous, and the risk of insufficient length for the reconstruction remains.

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Introduction

Anorectal malformations and Hirschsprung disease are congenital malformations that show a wide clinical variety. In children with a high anorectal malformation, a colostomy is constructed in the neonatal period when direct reconstruction in the first few days of life is not possible. The colostomy is closed after reconstructive surgery later in life. In children with Hirschsprung disease, a stoma is formed if the bowel cannot be decompressed with the use of rectal washouts. The stoma is closed after the aganglionic bowel has been resected and a pull-through procedure has been performed.[1]

Littré in 1710 undertook the first deliberate colostomy in children after earlier having noticed maldevelopment of the rectum in a deceased 6-day-old neonate.[2] Since then, many publications have addressed the preferred type of colostomy and location of the stoma in different conditions. In our hospital, we have seen a shift from loop transverse colostomies to split colostomies in the descending or sigmoid colon around 2006. Location of the stoma in children with Hirschsprung disease mainly depends on the length of aganglionic colon and the location of the transition zone.

Two varieties of colostomy are generally performed: Loop and split colostomies. In a loop colostomy, the bowel is sutured into the abdominal wall and is not completely divided. In a split colostomy, both colostomies must be placed wide enough apart so that a stoma cap can be placed on the afferent loop without covering the efferent loop. The split colostomy has the advantage of preventing overflow of stool into the mucous fistula. Overflow could lead to bacterial overgrowth and recurrent urinary tract infections if a rectourethral fistula is present. On the other hand, a split colostomy is more meticulous and time consuming compared with a loop colostomy, especially when the bowel is dilated. A Hartmann procedure including sigmoid resection in children with an anorectal malformation or Hirschsprung disease is considered obsolete now.[3]

The colostomy can be placed anywhere between the ascending colon and the sigmoid colon. The most frequently used locations are the transverse and the descending/sigmoid colon. The transverse colostomy carries the greatest risk of prolapse because the transverse colon is more mobile than the sigmoid colon. Identifying the proper location in the sigmoid colon when the bowel is distended may be difficult, however, and placement too distally may result in insufficient length for the reconstruction and

necessitate a revision of the sigmoid colostomy.

In short, the options for colostomy in children with an anorectal malformation or Hirschsprung disease are many; each has its own pros and cons. It would be great to have more information on what type and place of colostomy is most favorable. In this study, we therefore evaluated our own experiences with colostomies in children with an anorectal malformation, and performed a systematic review of the literature on complications of colostomies in children with an anorectal malformation or Hirschsprung disease.

Patients and Methods

Retrospective Case Study

Study Sample

A retrospective case study was performed on all children with an anorectal malfor-ma-tion treated in our center from January 1, 1990, to July 1, 2012, who were treated with a stoma. The study was approved by the Erasmus MC Medical Ethical Review Board. Patient and surgery characteristics were obtained from the medical records, with special interest in the type and location of the stoma and their complications (prolapse, dehiscence, infection, stenosis, revision because of complications, revision because of insufficient length with the reconstruction, and other complications). Anorectal malformations were classified by the Krickenbeck classification.[4] Low-type malformations are anal stenosis, perineal fistula, and vestibular fistula; high-type malformations are rectourethral fistula (bulbar or prostatic), anal atresia without fistula, rectum atresia, and persistent cloaca.

Surgical techniques

Complication rates of the following two surgical techniques are compared: Loop colostomy and split colostomy. In loop colostomy, a loop of the bowel is pulled out onto the abdomen and opened. Both loops are sutured to the skin and/or fascia. In split colostomy, the surgeon first makes an incision in the mesentery adjacent to the bowel wall and then divides the colon. A separate incision of the skin is performed. Both proximal and distal limbs of the colon are passed through the stoma sites, making sure

that there is no twisting or kinking of the blood supply.

The locations of the stomas were classified as follows: ileum/coecum, transverse colon, and descending/sigmoid colon (the latter two were combined and are further referred to as "sigmoid colostomy").

Systematic Review

Search strategy

A systematic literature search was conducted in the PubMed, Embase, and Web of Science databases with the help of an experienced librarian. The general search terms were the same for the three databases, which are as follows: anorectal malformations, Hirschsprung disease, colostomy, and children. The exact search strategies are shown in Appendix 1. Two investigators (D.H. and C.S.) independently screened titles and abstracts of retrieved citations, retrieved full texts of eligible articles, and selected relevant articles matching the selection criteria described below. Disagreements were resolved by discussion.

Inclusion and Exclusion Criteria

Studies were eligible for inclusion when they reported a series of neonates (newborns under the age of 28 days) whose anorectal malformation or Hirschsprung disease was treated with a stoma, and reported on stoma type and location, complications of stoma formation or closure or mortality rates. Studies excluded were the case series of less than 10 patients, articles that were not written in English, and articles that did not provide information on stoma type and location. Studies from developing countries were excluded because of the different setting compared with the developed countries. In case of duplicate publications, the most recent publication was included.

Quality Assessment

Methodological quality was assessed with the checklist proposed by Downs and Black,[5] with a maximum score of 32 for the optimal study quality. Studies were classified as randomized controlled trials, prospective case studies, retrospective case studies, or case-control studies.

Data Extraction

The two investigators selected the articles independently, extracted literature data, and recorded them in purpose designed forms. These data concerned study design, study population, follow-up, survival, complications, and reoperations. Primary outcome measure was complication rate in relation to colostomy type (loop or split colostomy) and location (transverse colon or sigmoid colon). Secondary outcome measures were mortality rate, requirement of stoma revision, and complications after stoma closure.

Statistical Analysis

Results are shown as number (%), mean (95% confidence interval), or median (range) when appropriate. Statistics was performed with SPSS Statistics version 20 for Windows (IBM Corporation, Armonk, New York, United States). Continuous variables were tested using the one sample t-test, categorized with the independent samples t-test (Mann–Whitney U test). Proportions were compared with the chi-square test.

Results

Retrospective Case Study

Between January 1990 and July 2012, 346 children with an anorectal malformation were treated in our center. Among these, 291 neonates had been referred to our center for initial treatment. A total of 180 children (52%) had received a stoma and thus were included in this study. In 18 cases, type and/or location of the stoma could not be retrieved. The baseline characteristics of the 180 children with a stoma are shown in Table 1.

Mortality

A total of 19 children (6%) died. Among the 19 children, 9 of them received palliative treatment because of their severe congenital anatomic malformations other than the anorectal malformation and died in neonatal period. A total of 10 children died after neonatal period because of severe comorbidity; 3 deaths were directly related to cardiac anomalies. In two children, the cause of death remains unknown; the parents did not consent to postmortal examination. There were no deaths due to complications of stoma formation or closure.

Table 1: Sophia Children's Hospital: patient characteristics

Total number of patients	n=180
Type of anorectal malformation; n (%)	
Low	41 (23)
High	136 (76)
Unknown	3 (2)
Male sex; n (%)	127 (71)
Absent or minor associated anomalies; n (%)	76 (42)
At least 1 major associated anomaly; n (%)	104 (58)
Specification of major anomaly[a]; n (%)	
Urogenital	59 (33)
Gastro-intestinal	36 (20)
Central nervous system	33 (18)
Cardiac	28 (16)
Skeletal	24 (13)
Pulmonary	10 (6)
Gestational age (wks); mean (95% CI)	37.8 (37.4-38.2)
Prematures[b]; n (%)	47 (26)
Birth weight (g); mean (95% CI)	2830 (2707-2954)
Small for gestational age; n (%)	16 (9)
Colostomy closure; n (%)	146 (81)
Definitive correction performed; n (%)	163 (91)
Total surgical interventions; median (range)	9 (1-29)
Surgical interventions related to anorectal malformation; median (range)	4 (1-9)

Results are presented as n (%). All included children had an anorectal malformation. [a] Many children had more than one major associated anomaly. [b] Gestational age <37 weeks.

Complications in Relation to Type of Colostomy

A total of 133 loop stomas (74%; three were loop ileostomies, the remaining were loop colostomies) and 19 split colostomies (11%) had been performed. A total of 10 children (6%) primarily received an end stoma, 2 cases because of persistent cloaca, 1 case

Table 2: Sophia Children's Hospital: colostomy complications in children with an anorectal malformation

	n	Total complications, n (%)	Prolapse, n (%)	Infection, n (%)	Stenosis, n (%)	Other complications, n (%)	Revision for colostomy related complications, n (%)
Colostomy type							
Loop	133	31 (23)	21 (16)	2 (2)	2 (2)	6 (5)	23 (17)
Split	19	3 (16)	0	1 (5)	1 (5)	1 (5)	1 (5)
End	10	3 (30)	0	1 (10)	0	2 (20)	2 (20)
Unknown	18	2 (11)	1 (5)	0	1 (5)	0	2 (11)
Colostomy location							
Transverse	121	28 (23)	22 (18)	0	2 (2)	4 (3)	23 (19)
Sigmoid	36	7 (20)	0	2 (6)	1 (2)	4 (11)	3 (8)
Cecum/ileum	4	2 (50)	0	2 (50)	0	0	2 (50)
Unknown	19	2 (11)	0	0	1 (5)	1 (5)	0
Total	180	39 (22)	22 (12)	4 (2)	4 (2)	9 (5)	28 (16)

Results are presented as n (%).

Note: Other complications include: 1 insufficient length for the definitive reconstruction; 1 parastomal fistula; 1 incisional hernia; 1 wound dehiscence; 1 retracted colostomy; 1 child received an end colostomy elsewhere and required revision for further diagnostic workup; 1 too much tension on the colostomy; 1 necrotizing enterocolitis; 1 decompensated heart; 1 infection and stenosis.

because of cloacal extrophia, and the remaining cases because of severe comorbidity (urogenital or neurologic). In 18 children (10%), the type of stoma could not be determined. Overall complication rate was 22% (Table 2).

Complication rates for loop and split colostomies were 23 and 16%, respectively (p=0.389). The most frequent complication was prolapse (n=22). This was documented in 21 loop colostomies; in 1 case the type of stoma was not documented. The prolapse occurred in the efferent loop in 14 cases, in the afferent loop in 4 cases, in both the loops in 1 case, and the location was not documented in 3 cases. The incidence of prolapse did not significantly differ between loop and split colostomies (p=0.053). The other complications are detailed in Table 2.

All children with a rectourethral fistula received prophylactic antibiotics before recon-structive surgery to prevent urinary tract infections. All children with urologic comorbidity were evaluated by a pediatric urologist and received prophylactic antibiotics when indicated. A total of five children had recurrent urinary tract infections, all with severe urologic comorbidity (vesicoureteral reflux with different causes; three children had undergone a loop transverse colostomy, one child had a split stoma of unknown location, and for one child, both type and location was unknown).

Complications in Relation to Location of Colostomy

Most colostomies (n=121, 67%) were placed in the transverse colon; 36 (20%) were placed in the sigmoid colon. A total of four children received a loop ileostomy (2%); the location of the other stomas (n=19) could not be determined. The complication rate for colostomies in the transverse colon was 23 versus 20% for colostomies in the sigmoid colon (p=0.667). All 22 prolapses occurred in the transverse colon, this was statistically significant compared with the sigmoid colostomies (p=0.005) (Table 2).

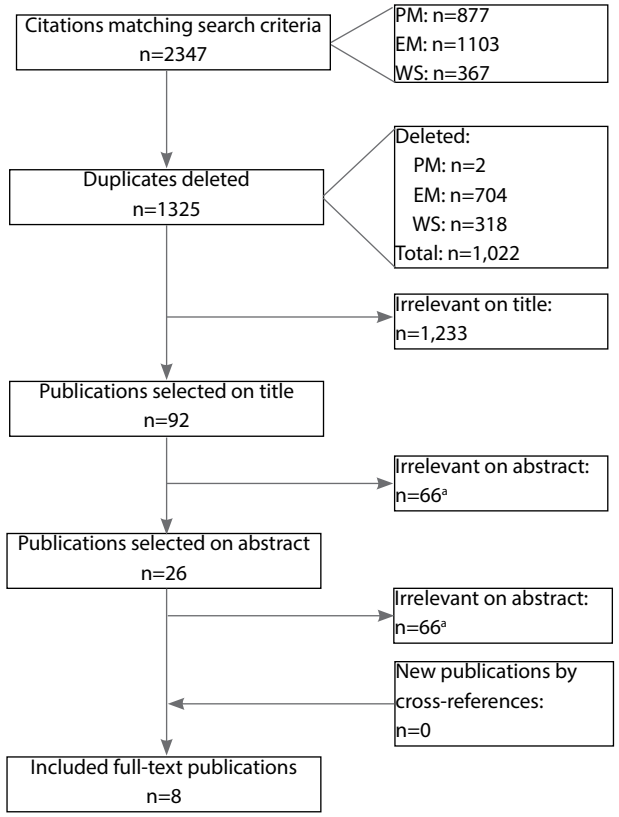
Colostomy Revision

A total of 25 colostomies (14%) were revised for various following reasons. Prolapse in 19 cases, too much tension on the colostomy in 1 case, stenosis in 1 case, parastomal fistula in 1 case, necrotizing enterocolitis in 1 case, and 1 case the stoma was revised for further diagnostics (A mucous fistula of the colon was needed for contrast X-rays of the rectourethral fistula; the child had received an end colostomy before referral to our hospital.). Finally, in one case, stoma revision was needed because insufficient length could be obtained at the reconstruction. The stoma had erroneously been placed on the distal part of the sigmoid colon rather than on the transverse colon (according to the intention to treat this stoma was classified as a transverse colostomy). Types and locations of colostomies that required revision are detailed in Table 2. In addition, six colostomies were converted to end colostomies in view of the severe comorbidity (tethered cord in three cases, very poorly developed pelvic floor in two cases, infarction during the posterior sagittal anorectoplasty operation with hemiparesis in 1 case).

Colostomy Closure

A total of seven complications were registered in relation to colostomy closure. Among the seven complications, one was wound dehiscence, one was incisional hernia, one wound infection, one ileus, one bladder retention, one candida and herpes stomatitis, and one child had severe breath-holding spells with low saturation that prolonged his

Fig. 1: Article selection



PM, Pubmed; EM, Embase; WS, Web of Science.

[a]Specification of articles irrelevant on abstract using the inclusion and exclusion criteria (total n=66): language other than English: n=21, case reports of fewer than five patients: n=8, review: n=5, other disease: n=1, stoma is not main topic: n=17, developing country: n=8, and published before 1980: n=6.

[b]Specification of articles irrelevant on article using the inclusion and exclusion criteria (total n=18): inadequate information: n=13, developing country: n=5.

intensive care admission. All were loop stomas: four in the transverse colon, two in the sigmoid colon, and one in the ileum.

Systematic Review of the Literature

Study Selection

The described search strategy yielded 877 citations in PubMed, 1,103 in Embase, and 367 in Web of Science. After deleting the duplicates, 1,325 publications remained. Eight

Table 3: Systematic review: overview of included studies

	DS, n	Patients, n	Male, n	ARM, n	HD, n	Other, n	Mortality, n (%)	Total complications, n (%)	Total prolapse, n (%)
Ciğdem[6]	13	473	278	252	117	104	50 (11)[a]	381 (81)	97 (21)
Demirogullari[7]	15	157	N/A	157	0	0	2 (1)	24 (15)	7 (4)
Ng et al[8]	13	55	N/A	0	55	0	N/A	9 (16)	9 (16)
Nour et al[9]	15	138	110	53	85	0	9 (7)b	38 (28)	26 (19)
Patwardhan[10]	7	49	31	49	0	0	N/A	19 (39)	8 (16)
Rees[11]	5	340	221	105	202	33	0	138 (41)	66 (19)
Wilkins/Peña[12]	7	272	N/A	272	0	0	1 (0.4)	25 (9)	5 (2)
Peña[13]	3	1,470	N/A	1,470	0	0	2 (0.1)	616 (42)	119 (8)

Abbreviations: ARM, anorectal malformations; DS, Down score as proposed by Downs and Black,[5] maximumscore of 32 for the optimal study quality; HD, Hirschsprung disease; N/A, not applicable, i.e., not mentioned in the study.

[a]Thirty-seven died directly because of major congenital anomalies of cardiac or renal origin. The remaining 13 (3%) had complications of the colostomy.

[b]Eight died directly because of severe comorbidity, and one because of small bowel obstruction, directly related to stoma closure

of these met the inclusion and exclusion criteria (Fig. 1).[3,6–12] These studies had been published between 1982 and 2011, and methodological quality based on the criteria of Downs and Black ranged from 3 to 15, of a maximum score of 32 for the optimal study quality (Table 3). The eight studies included a total of 2,954 patients. In all studies, type and location of the stoma was determined by the discretion of the operating surgeon. Seven were retrospective reviews of hospital records, while Ng compared two methods of split colostomy with or without tethering in preventing prolapse.8

Mortality

Almost all studies reported on mortality (Table 3). Mortality related to the stoma (formation or closure) varied between 0.1 and 3% (Table 3). Ciğdem et al[6] reported 50 deaths (mortality rate 11%). Most were because of severe comorbidity. A total of 3% of the study sample had died of colostomy-related complications. The deaths described in Nour et al[9] (n=1; 1%) and Wilkins and Peña[12] (n=1; 0.4%) occurred after colostomy closure and were caused by small bowel obstruction or sepsis after wound dehiscence. The two deaths (1%) in the series of Demirogullari et al were caused by intestinal perforation and obstruction after multiple laparotomies.[7]

Table 4: Systematic review: main outcomes

	Colostomy type n (%)		Total complications n (%)		Prolapse n (%)		Colostomy type n (%)		Total complications n (%)		Prolapse n (%)	
	Loop	Split	Loop	Split	Loop	Split	Transverse	Sigmoid	Transverse	Sigmoid	Transverse	Sigmoid
Ciğdem[6]	364 (77)	109 (23)	316 (88)	65 (61)	85 (23)	12 (11)	341 (72)	132 (28)	280 (82)	101 (78)	79 (23)	18 (14)
Demirogullari[7]	79 (50)	58 (23)	9 (11)	9 (16)	6 (8)	0	84 (53)	66 (42)	6 (7)	14 (21)	N/A	N/A
Ng[8,a]	55 (100)	0	9 (16)	0	9 (16)	0	55 (100)	0	9 (16)	0	9 (16)	0
Nour[9]	91 (66)	45 (33)	27 (30)	18 (40)	20 (22)	6 (13)	95 (69)	43 (31)	29 (61)	9 (21)	23 (24)	3 (7)
Patwardhan[10]	39 (80)	10 (20)	12 (31)	7 (70)	5 (13)	3 (30)	7 (14)	32 (65)	N/A	N/A	3 (43)	N/A
Rees[11]	244 (72)	71 (20)	N/A	N/A	51 (5)	10 (14)	266 (78)	49 (14)	N/A	N/A	60 (23)	1 (2)
Wilkins/Peña[12]	57 (19)	250 (81)	N/A	N/A	4 (7)	1 (0.4)	80 (26)	112 (36)	N/A	N/A	2 (3)	3 (3)
Peña[3]	351 (24)	755 (51)	N/A	N/A	55 (16)	42 (6)	391 (27)	483 (33)	N/A	N/A	N/A	N/A
Total (% of data known)	1,280	1,298	393/628 (63)	99/222 (45)	255/1280 (18)	74/1298 (6)	1,319	917	356/575 (62)	124/24 (51)	196/844 (23)	25/336 (7)
Chi-square test			p=0.007		p<0.001				p=0.006		p<0.001	

Abbreviation: N/A, not applicable, i.e., not mentioned in the study. Note: Children with an anorectal malformation and children with Hirschsprung's disease were combined. Cases not included in the table are other locations or types of stomas (e.g., ileostomies) and unknown types or locations of the stoma.

[a]Ng and coworkers compared conventional loop colostomy with the method using tethering of the distal loop. There was no significant difference in the incidence of prolapse.

Type of Colostomy

Five studies presented complications broken down for type of colostomy (Table 4). Complications were seen in from 11 to 88% for loop colostomies and from 16 to 70% for split colostomies. The mean complication rate was 63% for loop colostomies and 45% for split colostomies (p=0.007). Prolapse was reported in all studies and it was more common in loop colostomies than in split colostomies (18 vs. 6%, p<0.001).

Two studies reported on urinary tract infections. Patwardhan et al10 reported urinary tract infections in 14 patients (29%); 10 of 14 patients had a renal abnormality and used prophylactic antibiotics. The incidence did not differ significantly between loop or split colostomies, and the skin gap in split colostomies did not prevent urinary tract infections in two children. Peña et al reported frequent episodes of urinary tract infections in 64% of the children with a loop colostomy.[3] Furthermore, they found that 116 split colostomies were located too close to each other, resulting in urinary tract infections in 42 children (36%) without urologic comorbidity.

Location of Colostomy

Four studies[6–9] reported complications broken down for location of colostomy. Complications were seen in from 7 to 82% (mean 62%) of colostomies in the transverse colon and in from 9 to 78% (mean 51%) of colostomies in the sigmoid colon (p=0.006). Prolapse was more common in the transverse colon than in the sigmoid colon (23 vs. 8%, p<0.001).

Colostomy Revision

Five studies[3,6,9–11] provided information on stoma revision. This was done in 304 of 2,470 (12%) cases. The main reasons for stoma revision were prolapse, bowel obstruction, and insufficient length for the definitive reconstruction (further specified in Table 5). Nour et al showed that the number of revisions did not significantly differ between sigmoid loop versus transverse loop colostomy.[9] Peña et al[3] reported 91 revisions for prolapse. Of the 91 revisions, 40 cases were of split colostomies; 14 cases occurred in the transverse colon, 10 cases occurred in the sigmoid colon, and 8 cases occurred in the descending colon. The prolapse tended to occur in the mobile part of the colostomy. Some colostomies were improperly placed in view of the definitive reconstruction. Wilkins and Peña described 12 such cases.[12] Of the 12 sigmoid colostomies, 9 sigmoid colostomies were placed too distally, and in 3 cases, the surgeon erroneously performed a right upper quadrant sigmoid colostomy. All patients required an abdomi-

nal approach or revision before the definitive reconstruction. Peña et al described 137 mislocations; in 97 of them, the colostomy was located too distally in the rectosigmoid colon, thereby complicating the reconstruction.[3]

Colostomy Closure

Four studies reported data on colostomy closure (Table 5).[3,7,9,11] Only two studies reported the actual number of colostomy closures and their complication rates, the latter being 7 and 11%, respectively. Complications described were generally wound infection, intestinal obstruction, and incisional hernia. Only Nour et al[9] also reported complications in relation to type and location of the colostomy. Three complications occurred in loop transverse colostomies, two complications in loop sigmoid colostomies, and five complications occurred in split sigmoid colostomies.

Discussion

Neonates born with an anorectal malformation or with Hirschsprung disease often need a stoma. This will divert the fecal stream until the exact anatomy of the anomaly is known and a reconstruction is performed. In Hirschsprung disease, it is needed if the aganglionic segment of the colon is too long and the colon cannot be rinsed by rectal washouts. The location of the stoma on the colon (or ileum) is determined by the position of the transition zone. In children with an anorectal malformation or Hirschsprung disease, the ideal type (split or loop) and location of the stoma is not clear; different types and colonic locations are propagated in the literature. Therefore, we evaluated our experience and in addition performed a systematic review of the literature.

Fortunately, mortality directly related to colostomy formation or closure in children with an anorectal malformation or Hirschsprung disease is low, but still up to 3% and not to be neglected. It is independent of the type and location of the stoma. However, complications may occur, and complication rates from 9 to 91% have been reported. Our retrospective study revealed an overall complication rate of 23%, with no significant difference in respect between loop and split colostomies, and between transverse and sigmoid colostomies. From the systematic review, it appeared however that loop colostomies had a significantly higher complication rate than split colostomies, and transverse colostomies had more complications than sigmoid colostomies. The most frequent complication noted in the literature review besides skin excoriation was

prolapse, which occurred mostly in loop and/or transverse colostomies.

The wide range of complication rates in the systematic review may be because of the inconsistency in defining complications. This is particularly in the definition of skin excoriation. For example, Ciğdem et al mentioned a high incidence of skin excoriation, 47%.[6] Only 8% of these children required hospital admission, the other cases were mild and did not require hospital admission. It is probable that the latter percentage is the incidence of skin excoriation mentioned in the other studies. Skin excoriation in colostomies could occur when stoma management is insufficient and loose stools come into contact with the skin. The risk is greater in the case of a transverse colostomy compared with a sigmoid colostomy because in the former less colon is available for absorption of salts and bile acids. In our clinic, gel capsules are administered to bind the stool and to prevent leakage. Dedicated stoma nurses advise parents on good stoma management and materials for their children. The retrospective study revealed few cases of skin excoriation. This is probably under documented; however, the question remains whether those mild cases of skin excoriation are of clinical importance.

Our retrospective study revealed that all prolapses occurred in loop transverse colostomies, but that the overall complication rate did not differ between loop and split colostomies. From the systematic review, it appears that both the total complication rate and the prevalence of prolapse are higher in loop colostomies. The small number of split colostomies could explain this discrepancy. With regard to urinary tract infections, it has been suggested that a split colostomy may prevent these because there is no fecal contamination of the mucous fistula and thus no contamination of the urinary tract via the rectourethral fistula. Besides, a contaminated and filled rectum could obstruct the urine outflow, leading to incomplete bladder emptying. Only two studies reported information on urinary tract infections, with contradictory results. Patwardhan et al[10] reported no difference in incidence of urinary tract infections between loop and split colostomies; however, Peña et al[3] reported a prevalence of 64% in loop colostomies and of 36% of the split colostomies that were placed too close to each other. They did not report the incidence of urinary tract infections in the properly placed split colostomies. In our series, five children had recurrent episodes of urinary tract infections, all with explanatory urologic comorbidity. Our hospital protocol provides for administration of prophylactic antibiotics to all children with a rectourethral fistula even after colostomy formation (in addition to the children with urologic comorbidity that receive prophylactic antibiotics from the pediatric urologist). Furthermore, after

the colostomy formation the distal colon is flushed clean during a few days so that less fecal spill is to be expected in the rectum and into the urinary tract. Considering the closure of the stoma, loop colostomies could have an advantage over split colostomies because the procedure is less complicated; however, in our series, there were more complications in closing loop colostomy as compared with split colostomy.

Loop colostomies could be the procedure of choice in a severely distended distal colon because the procedure is less meticulous than split colostomies; however, it remains a delicate procedure and should be performed with great precision in each patient to prevent prolapse. A trick to prevent prolapse—while flushing the distal colon and performing a colostogram are still possible—is tethering of the distal loop to the peritoneum.[8] Suturing the afferent and efferent loop to the abdominal wall is likewise advised to prevent prolapse.[13] The opening in the abdominal wall should be reduced, because wide openings can lead to prolapse or parastomal herniation. This is especially important in distended colon, when the tendency is to make the abdominal opening for the stoma too wide. A new technique is umbilical loop colostomy, 14 in which a double barreled loop colostomy is created with a high chimney of more than 2 cm above the skin. Only a small scar at the base of the belly button remains after closure. However, this relatively new technique is not generally accepted; further studies should prove its worth.

Transverse colostomies have a higher overall complication rate compared with sigmoid colostomies. Transverse colostomies prolapse more often, as appears from our retrospective and from the literature. As Peña et al pointed out, the prolapse was more likely to be found in the mobile part of the colon, that is, the transverse colon.[3] The preferred location for the stoma, therefore, seems to be the descending or sigmoid colon, because this part of the colon is more attached to the abdominal wall and the mesocolon is less mobile. It could be necessary to mobilize the colon from the splenic ligaments if this location is chosen. Furthermore, later reconstruction could be hampered by placing the stoma too distally, which in our series occurred once. Therefore, when constructing a sigmoid colostomy the surgeon must ensure that the stoma is placed in the optimal location, especially in distended bowel.

Timing of colostomy construction is very important because the colon distends after birth and the procedure becomes more difficult when time passes. Our hospital protocol prescribes that the child is treated conservatively for 48 hours in expectation of

meconium appearance. However, in most cases, it is clear whether it is a high malformation and/or whether there is a rectourethral fistula, as can be seen by a greenish aspect of the urine. In those cases, it is favorable to perform the colostomy within 24 hours, when the procedure easier. Some complications can become more apparent when a stoma is longer in situ. Examples are skin problems, overflow of fecal material in the distal rectum resulting in urinary tract infections, and prolapse. Thus, timing of the reconstruction and afterward closure of the colostomy can influence the complication rate. It is recommended to perform the definitive construction in early life —within 6 months of age—and to close the stoma soon after the reconstruction is proven intact.

In the systematic review of the literature, studies from developing countries were excluded. In developing countries, it often takes more time for the child to receive proper care and the bowel often gets pathologically dilated. Sometimes, it is even necessary to place a colostomy under local anesthesia, because general anesthesia is too risky or not available.[15] In those cases, it is necessary to adapt to the possibilities in that setting, and thus to perform an emergency loop colostomy. Still, in each case, also in the developed countries, to prevent complications the surgical technique should be geared to the individual patient.

Conclusion

A relatively high complication rate is described in colostomy formation in children with an anorectal malformation or Hirschsprung disease. The preferred location of the stoma is the descending or sigmoid colon to avoid prolapse and to leave enough length for the reconstruction. When transverse colostomy is preferred because of severely distended bowel, the complication to be avoided is prolapse and surgical technique should be modified accordingly. In answer to our question, splitting of the stoma is advised; however, evidence for overflow and contamination of the distal rectum resulting in episodes of urinary tract infections is not present. Whether tethering of the efferent loop is sufficient is unknown. The procedure of colostomy formation in anorectal malformations and Hirschsprung disease is meticulous and should be performed with great care.

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Appendix 1: Exact search strategies of the systematic review

Pubmed:
(((anorect*[tw] OR anal[tw] OR anus[tw]) AND (malformat*[tw] OR anomal*[tw] OR imperforat*[tw] OR inperforat*[tw] OR atre*[tw])) OR hirschsprung*[tw] OR agangli-on*[tw]) AND (ostom*[tw] OR stoma[tw] OR stomas[tw] OR stomata[tw] OR stomy[tw] OR artificial anus*[tw] OR colostom*[tw] OR cecostom*[tw] OR coecostom*[tw] OR caecostom*[tw] OR anus praet*[tw] OR anus pret*[tw]) AND (child*[tw] OR infan*[tw] OR newborn*[tw] OR neonat*[tw] OR pediatr*[tw] OR paediatr*[tw]).

EMbase:
('anorectal malformation'/exp OR ((anorect* OR anal OR anus) NEAR/3 (malformat* OR anomal* OR imperforat* OR inperforat* OR atre*)):ti,ab,de OR hirsch-sprung*:ti,ab,de OR aganglion*:ti,ab,de) AND (ostom* OR stoma OR stomas OR stomata OR stomy OR 'artificial anus' OR colostom* OR cecostom* OR coecostom* OR caecostom* OR (anus NEAR/2 (praeter* OR preter*))):ti,ab,de AND (child* OR infan* OR newborn* OR neonat* OR pediatr* OR paediatr*):ti,ab,de.

Web of Science:
(((anorect* OR anal OR anus) NEAR/3 (malformat* OR anomal* OR imperforat* OR inperforat* OR atre*)) OR hirschsprung* OR aganglion*) AND (ostom* OR stoma OR stomas OR stomata OR stomy OR 'artificial anus' OR colostom* OR cecostom* OR caecostom* OR coecostom* OR (anus NEAR/2 (praeter* OR preter*))) AND (child* OR infan* OR newborn* OR neonat* OR pediatr* OR paediatr*).

Chapter 2

Patients with anorectal malformation and upper limb anomalies: genetic evaluation is warranted

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Provisionally accepted

Patients with anorectal malformation and upper limb anomalies

Genetic evaluation is warranted

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ABSTRACT

Objective	Objective was to compare the prevalence of genetic disorders in anorectal malformation (ARM) patients with upper limb anomalies to that in ARM patients with other associated anomalies.
Methods	A retrospective case study was performed in two pediatric surgery centers. All patients born between 1990 and 2012 were included. VACTERL was defined as at least three components present.
Results	We included 700 ARM patients: 219 patients (31%) had isolated ARM, 43 patients (6%) had a major upper limb anomaly, and 438 patients (63%) had other associated anomalies. Most prevalent upper limb anomalies were radial dysplasia (n=12) and hypoplastic thumb (n=11). Ten of the 43 patients (23%) with an upper limb anomaly were diagnosed with a genetic disorder –nine also met VACTERL criteria-, vs. 9% of ARM patients with other anomalies (p=0.004, Chi squared test).
Conclusion	Genetic disorders are twice as frequently diagnosed in ARM patients with upper limb anomalies than in those with other anomalies. As they also frequently meet the VACTERL criteria, it is important to consider VACTERL as a diagnosis per exclusionem. Genetic counseling is certainly warranted in these patients.

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Introduction

Anorectal malformations (ARMs) are rare congenital anomalies that occur in approximately 1 to 3 in every 5000 live births.[1] 43 to 71% of the ARM patients have additional congenital anatomical anomalies.[2-6] These include a great variety of upper limb anomalies, from a mild hypoplastic thumb to severe radial dysplasia.[4,7-13]

Some types of upper limb anomalies are associated with specific syndromes. For example, thumb anomalies may indicate Townes-Brocks syndrome, given the fact that 89% of the patients with Townes-Brocks syndrome have a thumb anomaly[14]; or they may even indicate Fanconi anemia (prevalence of thumb anomalies 50%[15]). Ulnar deficiencies may be suggestive of for example ulnar-mammary syndrome.[16] Once evaluation has excluded known syndromes, VACTERL association can be considered, which refers to the non-random co-occurrence of vertebral defects (V), anal atresia (A), cardiac malformations (C), tracheoesophageal fistula with esophageal atresia (TE), renal dysplasia (R), and limb anomalies (L). VACTERL association is mainly associated with preaxial limb defects.[17]

Naturally, patients with more than one congenital anatomical anomaly are more likely to be diagnosed with a syndrome than are patients with a single congenital anomaly. However in our experience ARM patients with an upper limb anomaly –with or without other congenital anomalies- are more frequently diagnosed with a syndrome than are non-isolated ARM patients without upper limb anomalies. The aim of this study is to answer the following questions: 1. What is the prevalence of upper limb anomalies in ARM patients? 2. What upper limb anomalies are most frequently seen in ARM patients? 3. Are syndromes more prevalent in ARM patients with a major upper limb anomaly –with or without other additional congenital anomalies- compared to non-isolated ARM patients without an upper limb anomaly?

Materials and methods

Study sample

A retrospective case study was performed on all patients with an ARM born between

1 January 1990 and 1 July 2012 and treated in one of the participating university pediatric surgery centers (Erasmus MC - Sophia Children's Hospital, Rotterdam, the Netherlands and Amalia Children's Hospital, Radboudumc, Nijmegen, the Netherlands). Patient characteristics were obtained from the medical records, with special attention to the presence of upper limb anomalies. This study was approved by the Erasmus MC Medical Ethical Review Board.

Two main groups were distinguished: isolated ARM patients and non-isolated ARM patients. The latter group was subdivided into patients with and without major upper limb anomalies (Fig. 1). The prevalence of genetic disorders was determined in these two subgroups.

Classification systems

ARMs were classified by the Krickenbeck classification.[18] VACTERL association was considered to be present if three or more components of the acronym were identified.[19,20] In our centers, all patients with ARM are screened for VACTERL association as follows: x-rays of the spine (V), echocardiogram of the heart (C), x-ray of the chest after insertion of a nasogastric tube (TE), ultrasound of the abdomen (R), and physical examination of the limbs (L).

Upper limb anomalies were classified as major or minor by the clinical geneticists (YB and CM). Examples of major anomalies are radial or ulnar dysplasia and polydactyly, and of minor anomalies are single palmar crease, long fingers, or long, coarse hands. As the minor anomalies are subjective anomalies, especially since this is a retrospective study, these were not included in the main analysis but mentioned separately.

Most major upper limb anomalies had been classified by the plastic surgeon as part of regular care (radial dysplasia and thumb hypoplasia were classified according to James et al., 1999[21] and Abdel-Ghani et al., 2004[22], respectively). Polydactyly was classified as pre-axial or post-axial. Major upper limb anomalies in patients who had not been seen by the plastic surgeon were classified as type unknown (n=4) and described according to the medical charts.

Patients with multiple congenital anomalies who had a pure clinical diagnosis, for

which the underlying genetic defect is unknown, such as Goldenhar syndrome, were classified as 'Multiple Congenital Anomalies (MCA) syndrome' and not as 'genetic disorder'.

Statistical analysis

Results were shown as number (%) or as median (range). Continuous variables were compared using the Mann-Whitney U test, whereas proportions were compared using the Chi-squared test.

The prevalence of genetic disorders was compared between ARM patients with a major upper limb anomaly –with or without other associated congenital anomalies- and non-isolated ARM patients without an upper limb anomaly. This was also done for organ systems, being lower limb, cardiac, central nervous system (CNS), urogenital, other gastro-intestinal, and vertebral anomalies. Further, Phi analysis was conducted to determine whether anomalies in different organ systems were associated with each other.

Results

In total 219 of the evaluated 700 patients (31%) had an isolated ARM and were excluded from further analyses (Fig. 1). A major upper limb anomaly had been documented in 43 patients (6%). Radial dysplasia was the most prevalent major upper limb anomaly (n=12; 28%), followed by thumb hypoplasia (n=11; 26%). Table 1 provides details of all major upper limb anomalies. Four patients were not classified by the plastic surgeon and were therefore classified as type unknown. The remaining 438 patients all had an ARM with other associated anomalies.

In 10/43 patients who had a major upper limb anomaly –with or without other congenital anomalies- a genetic disorder had been diagnosed (23%; Table 2). Nine of these patients also met the criteria of VACTERL association. Of the remaining 33/43 patients, 24 had been diagnosed with VACTERL association per exclusionem (that is 56% of patients with major upper limb anomaly) and one with Goldenhar syndrome; of the other eight patients, four had additional congenital anomalies but did not meet

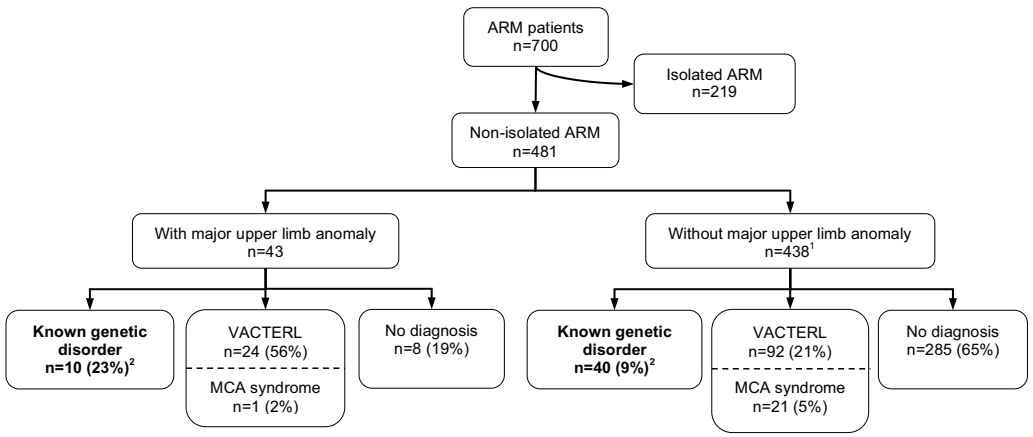
the VACTERL criteria, and four had no other anomalies besides the ARM and upper limb anomaly.

Forty of the 438 patients with other associated anomalies (9%) had been diagnosed with a genetic disorder: 23 (5% of patients with non-isolated ARM without a major upper limb anomaly) with a numerical chromosomal disorder (mostly trisomy 21, n=17; others were Turner syndrome, trisomy X) and 17 (4%) with a microdeletion or duplication,. Of these 40 patients, 14 (35%) met the criteria for VACTERL association. Of the 398 remaining patients, 21 were diagnosed with an MCA syndrome and 92 patients met the criteria for VACTERL association.

The prevalence of genetic disorders (thus excluding VACTERL association and MCA syndromes) in the group of ARM patients with a major upper limb anomaly –with or without other anomalies- was significantly higher than that in the group of ARM patients with other associated anomalies: 23% vs. 9%, respectively; p=0.004, Chi squared test.

The patient characteristics of the non-isolated ARM patients with and without major upper limb anomalies are shown in Table 3. The prevalence of urogenital anomalies did not differ between both groups (60% and 62%), but cardiac anomalies (varying

Fig. 1 Flow chart of patient selection



Abbreviations: ARM, anorectal malformations; MCA syndrome, multiple congenital anomalies syndrome. VACTERL was defined as three or more components present. [1] Including 15 patients with a minor upper limb anomaly. As the minor anomalies, as classified by the clinical geneticists, are subjective anomalies, these were not included in the main analysis. [2] p=0.004, Chi squared test. Isolated ARM patients were excluded from analysis. The patients who had an upper limb anomaly were significantly more frequently diagnosed with a genetic disorder than those with other associated anomalies.

from atrial or ventricular septal defect to coarctation of the aorta or Fallot tetralogy) occurred more frequently in the patients with a major upper limb anomaly than those without (60% and 33%, respectively; p<0.001). The same was true for gastro-intestinal anomalies (44% vs. 18%, respectively; p<0.001). Most common gastro-intestinal anomaly was esophageal atresia (with or without fistula), occurring in 13 patients of the major upper limb anomaly group (30%). Others were duodenal atresia, small bowel atresia, and choledochal cyst.

We included 15 patients with a minor upper limb anomaly in the non-upper limb anomaly group. These minor anomalies were single palmar crease, long fingers, or large, coarse hands. Five of these patients (33%) had been diagnosed with a genetic disorder: two patients had trisomy 21, one had 47,XY,+der(22) (Cat eye syndrome; OMIM #607575), one had deletion 17p13.3 (Miller-Dieker syndrome; OMIM #247200), and one had duplication of chromosome band 3p12.2 (no reference available).

The prevalence of genetic disorders in patients with associated anomalies other than upper limb anomalies are shown in the Online Supplemental Table 4. The associations between the different associated anomalies were all poor (Online Supplemental Table 5).

Discussion

The prevalence of major upper limb anomalies in this cohort of 700 ARM patients was 6%. The most prevalent anomalies were radial dysplasia and thumb hypoplasia. Of the patients with a major upper limb anomaly, 23% had a genetic disorder versus 9% of other non-isolated ARM patients.

An extensive literature search yielded eight publications describing the prevalence of upper limb anomalies in ARM patients.[4,7-13] The prevalence ranged from 2 to 12% in study cohorts varying from 99 to 1417 ARM patients, which is in concurrence with the present study. However, none of these studies provided details of types of anomalies or numbers of syndromes diagnosed in this patient group. In present study, we found that the most prevalent upper limb anomalies were radial dysplasia and thumb hypoplasia.

Table 1: Detailed findings in 43 anorectal malformation patients with a major upper limb anomaly

		Additional description	Disorder
Radial dysplasia; n=12			
Type 0	Unilateral	With thumb hypoplasia type 3	VACTERL (trisomy X)
	Bilateral	With thumb hypoplasia type 2	22q11 microduplication (maternal)
Type 2	Unilateral	With thumb hypoplasia type 4; other hnd radial dysplasia type 1 with thumb hypoplasia type 1	Goldenhar syndrome
	Unilateral	Unilateral radial dysplasia type 2	[a]
	Bilateral	With thumb hypoplasia type 4	VACTERL
Type 4	Unilateral	With micromelia of 3 digits	VACTERL [b]
	Unilateral	With thumb hypoplasia type 5 and syndactyly 2nd and 3rd digit; other hand thumb hypoplasia type unknown	VACTERL [b]
	Unilateral	Other hand radial dysplasia type 1	VACTERL
	Bilateral	Bilateral radial dysplasia type 4	VACTERL
	Bilateral	With thumb hypoplasia type 5	VACTERL
	Bilateral	With thumb hypoplasia type 5; syndactyly 2nd and 3rd digit, hypoplasia 2nd digit, camptodactyly all digits	Fanconi anemia (no mutation known)
Type unknown	Bilateral	Bilateral radial dysplasia, type unknown	Trisomy 18[b]
Thumb hypoplasia without apparent radius involvement; n=11			
Type 2	Unilateral	Unilateral thumb hypoplasia, type 2	VACTERL[a]
	Unilateral	Unilateral thumb hypoplasia, type 2	VACTERL[c]
	Unilateral	Unilateral thumb hypoplasia, type 2	VACTERL
	Unilateral	Other hand thumb hypoplasia type 1	VACTERL
Type 3	Unilateral	Unilateral thumb hypoplasia, type 3	VACTERL [b]
	Bilateral	One hand triphalangeal thumb	VACTERL
Type 4	Bilateral	Bilateral thumb hypoplasia type 4	VACTERL [b]
Type 5	Unilateral	Other hand thumb hypoplasia type 2	VACTERL
	Unilateral	Other hand thumb hypoplasia type unknown	VACTERL [b]
Type unknown	Unilateral	Unilateral thumb hypoplasia, type unknown	(16q12.1) polymorphism
	Unilateral	Unilateral thumb hypoplasia, type unknown	[a]

Table 1: Continued

	Additional description	Disorder
Ulnar dysplasia; n=1		
Unilateral	Unilateral longitudinal ulnar growth arrest (1 thumb, 3 digits, floating 4th digit). Other hand cleft hand between 4th and 5th digit	Ulnar mammary syndrome, heterozygous *TBX3* mutation (maternal)
Preaxial polydactyly; n=5		
Unilateral	Extra thumb	VACTERL
Unilateral	Extra thumb	VACTERL
Bilateral	Extra thumb	[a]
Bilateral	Extra thumb	[a]
Bilateral	One hand extra thumb, other hand 7 digits; both hands syndactyly thumb and 2nd digit and triphalangeal thumb	Townes Brocks syndrome, *SALL1* mutation
Postaxial polydactyly; n=2		
Bilateral	6 fingers; bilateral camptodactyly 2nd-4th digit	Trisomy 13[b]
Bilateral	Extra 6th metacarpal	[a]
Thumb hyperplasia; n=2		
Unilateral	Same hand single palmar crease	VACTERL
Unilateral	Both hands also clasped thumb	VACTERL
Other; n=10		
Unilateral	Triphalangeal thumb	Blackfan-Diamond anemia (no mutation known)
Bilateral	Syndactyly 3rd-5th digit; other hand syndactyly 3rd-4th digit	Trisomy 21
Bilateral	Syndactyly 3rd-5th digit; other hand absence of 5th digit; bilateral nail dysplasia	VACTERL[b,d]
Unilateral	Brachymesophalangy 5th digit	[a]
Unilateral	Clasped thumb	[a]
Bilateral	Clasped hands	VACTERL
Unilateral	Deviating implantation of the thumb	VACTERL[a]
Bilateral	Deviating implantation of the thumb	VACTERL
Unknown	Clino/brachydactyly not further specified	del(1)(q23q25) [b]
Bilateral	Clubbing hand, long fingers	Cri du Chat syndrome, der(5).t(5;14) [b]

[a]No known genetic disorder, does not meet criteria VACTERL association; [b]Patient deceased; [c]SALL-1 mutation (Townes Brocks syndrome) still needs to be excluded.; [d]GLI-3 mutation (Pallister Hall syndrome) still needs to be excluded.

Table 2: Details of 10 patients with a major upper limb anomaly and a genetic disorder

Genetic anomaly	Disorder (OMIM)	Associated anomalies
Numerical chromosomal disorders		
Trisomy 13[a]	Patau syndrome	Typical dysmorphic features, possible esophageal atresia, ASD, VSD, overriding aorta, absent external auditory canal, micropenis, non-descended testes.
Trisomy 18[a]	Edward syndrome	Typical dysmorphic features, VSD, intra uterine growth retardation.
Trisomy 21	Down syndrome	Typical dysmorphic features.
Microdeletions/duplications		
22q11 duplication	22q11 microduplication syndrome (#608363)	Kidney agenesis, caudal regression syndrome, esophageal atresia, VSD; mother had same duplication.
Heterozygous mutation *TBX3*	Ulnar mammary syndrome (#181450)	Congenital subglottic stenosis, ASD, non-descended testes, mother had same mutation.
SALL 1 mutation	Townes Brocks syndrome (#107480)	Bilateral dysplastic kidneys, hemivertebrae, club foot, hearing loss.
Diagnosis confirmed by hematologic investigations	Blackfan-Diamond anemia (#105650)	VSD.
del(1)(q23q25)[a]	No reference available	Dysmorphic features, kidney agenesis, dextrocardia, esophageal atresia, abnormal hearing.
Diagnosis confirmed by chromosomal breakage tests[b]	Fanconi anemia	Esophageal atresia, ADS, open ductus Botalli, hypospadia, hearing loss, non-descended testes. Familial.
der(5)t(5;14) [a]	Cri du Chat syndrome (#123450)	Dysmorphic features, VSD, bicuspid aortic valve, uterus didelphys, enlarged kidney.

Abbreviations: OMIM, Online Mendelian Inheritance in Man; ASD, atrial septal defect; VSD, ventricular septal defect; AVSD, atrioventricular septal defect. [a] Patient deceased. Due to treatment withdrawal these patients were not all fully screened for other congenital anomalies; [b] Parents did not consent for mutation analysis.

Unfortunately because of the retrospective nature of this study, we were unable to determine at what ages the upper limb anomalies had been diagnosed. The prevalence of subtle upper limb anomalies such as thumb hypoplasia -in our study sample one of the most prevalent upper limb anomalies- could very well be underestimated in newborns. It might not only because of the mere size of the hand and thumb, but also when for example a plaster for a peripheral intravenous line covers the hand. Early recognition of the thumb anomaly is not only wanted for optimal treatment of the thumb[22,23], but also even more for early recognition of syndromes such as Fanconi anemia. Even though Fanconi anemia is a rare disorder, the clinical consequences for the child warrant early recognition, and this will also permit appropriate counseling of the parents. Unfortunately we were unable to determine whether Fanconi syndrome had been excluded in all patients with radial limb deficiencies, but chromosomal breakage tests were available in our country from the beginning of the study period.

Furthermore, the prevalence of other genetic diagnoses may have been underestimated because the possibilities for genetic testing have advanced rapidly since 1990. In the 1990s, diagnostic investigations in medical genetics mostly consisted of karyotyping. In the Netherlands, Townes-Brocks syndrome could be confirmed by Sanger sequencing from the late 1990s and 2005, respectively. Nowadays, the widespread application of affordable microarray approaches provides improved screening for genetic disorders.[24] In the Netherlands, arrays were used for screening since 2011. Further improvements in genetic diagnostics are to be expected with Next Generation Sequencing, where even smaller events can be detected and an absolute copy number prediction is possible.[24,25]

It is important to consider VACTERL association as a diagnosis per exclusionem and to have a keen eye for specific genetic disorders in this patient group, not only for the clinical consequences for the child, but also to adequately counsel the parents in the case of an inheritable disorder. Ten of the 43 patients (23%) with a major upper limb anomaly were diagnosed with a genetic disorder. This prevalence is higher than in patients without a major upper limb anomaly (9%), and also higher than reported in patients with an upper limb anomaly without an ARM (7-17%).[26,27]

Besides the major upper limb anomalies, 15 patients had a minor upper limb anomaly, mostly large, coarse hands or deviating implant of the thumb. Compared to the major limb anomalies, a larger proportion of this group was diagnosed with a genetic disorder (33%). This might be biased, as clinicians may tend to more actively search for small anomalies when a disorder is suspected based on dysmorphic features or a specific

Table 3: Background characteristics of non-isolated anorectal malformation patients

	Non-isolated ARM with major upper limb anomaly	Non-isolated ARM without upper limb anomaly
Number of patients	n=43	n=438
Type of ARM		
Perineal fistula	12 (28%)	139 (32%)
Rectourethral fistula		
Bulbar	2 (5%)	31 (7%)
Prostatic	5 (12%)	46 (11%)
Unknown	5 (12%)	38 (9%)
Rectovesical fistula	0	15 (3%)
Vestibular fistula	7 (16%)	62 (14%)
Cloaca	3 (7%)	34 (8%)
Other	2 (5%)	55 (13%)
Unknown	7 (16%)	18 (4%)
Male sex	22 (51%)	276 (63%)
Gestational age (wks)	38.5 (29-43)	38.0 (26-42)
Birth weight (g)	2610 (1020-3920)	2980 (625-4760)
Associated anomalies[a]		
Urogenital	26 (60%)	272 (62%)
Cardiac	26 (60%)*	145 (33%)*
Other skeletal[b]	20 (47%)	202 (46%)
Gastro-intestinal	19 (44%)*	77 (18%)*
CNS	8 (19%)	96 (22%)
Pulmonary	4 (9%)	28 (6%)

*Results are presented as n (%) or as median (range). Abbreviations: ARM, anorectal malformation. [a]Several patients had more than 1 associated anomaly; [b]Skeletal anomalies other than upper limb anomalies; *p<0.001, Chi squared test.*

pattern of congenital anomalies, compared to the situation in which there is an isolated ARM without apparent associated anomalies. However, we recommend to consult a geneticist specialized in dysmorphology in all ARM patients, as these minor features can be hard to recognize while they still might hint towards a specific genetic disorder.

Cardiac and gastro-intestinal anomalies were documented almost twice as much in patients with a major upper limb anomaly compared to other non-isolated ARM patients. Still, Phi analysis showed only poor associations between these anomalies and upper limb anomalies. These anomalies in part are inherent to the syndromes these patients were diagnosed with, but they can also be part of VACTERL association.[28] VACTERL screening in the neonatal period is internationally recommended for all ARM patients.[29] Preoperative cardiac screening by ultrasound should strongly be considered especially in ARM patients with an upper limb anomaly in order to minimize anesthesiologic risks.

This study provides new insights for the work up of a neonate with an ARM. When an upper limb anomaly is present, the pediatrician should be alert to genetic disorders. We propose an algorithm for genetic work up for ARM patients (Fig. 2). This algorithm includes the most relevant syndromes in order to provide a general approach. A clinical geneticist specialized in dysmorphology should be counseled when an ARM co-occurs with an upper limb anomaly, because of the great diversity of genetic disorders present in this patient group.

Concluding, the prevalence of major upper limb anomalies in ARM patients is 6%. The most frequent anomalies were radial dysplasia and thumb hypoplasia. ARM patients with a major upper limb anomaly are twice as frequently diagnosed with a genetic disorder compared to ARM patients with other associated anomalies. Ninety percent of patients with a major upper limb anomaly and genetic disorder met the criteria for VACTERL association; it is therefore important to consider VACTERL association as a diagnosis per exclusionem and to be conscious of genetic disorders in patients with ARM and an upper limb anomaly. Consultations by a clinical geneticist specialized in dysmorphology in all ARM patients could help optimize screening for other syndromes.

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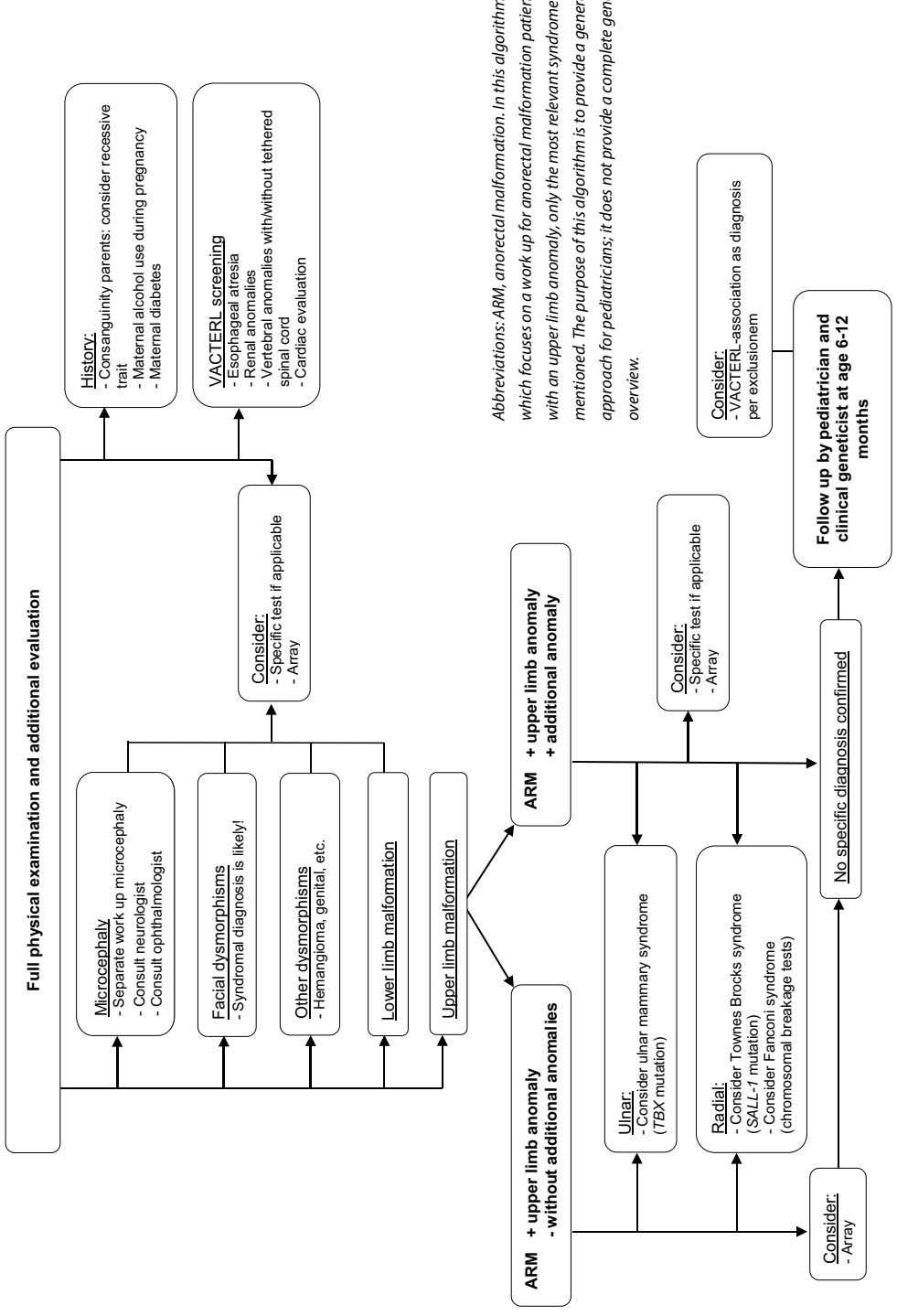
Fig. 2 Algorithm for work-up of a patient with an anorectal malformation, with special attention to upper limb anomalies



Abbreviations: ARM, anorectal malformation. In this algorithm, which focuses on a work up for anorectal malformation patients with an upper limb anomaly, only the most relevant syndromes are mentioned. The purpose of this algorithm is to provide a general approach for pediatricians; it does not provide a complete genetic overview.

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Online supplementary Table 4: Prevalence of genetic disorders in anorectal malformation patients with associated anomalies in different organ systems

Associated anomaly		Genetic disorder present
Lower limb	Yes	13/46 (28%)
	No	53/438 (12%)
Cardiac	Yes	34/171 (22%)
	No	32/310 (10%)
CNS	Yes	23/104 (22%)
	No	43/377 (11%)
Urogenital	Yes	28/298 (9%)
	No	38/183 (21%)
Other GI	Yes	11/89 (12%)
	No	55/384 (14%)
Vertebral	Yes	12/168 (7%)
	No	54/313 (17%)

Abbreviations: CNS, central nervous system; GI, gastro-intestinal. Total number of non-isolated ARM patients: n=481.

Online supplementary Table 5: Correlation for associated anomalies in anorectal malformations

		Upper limb	Lower limb		Vertebral		Other GI		Cardiac		Urogenital		CNS			
			Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No		
Upper limb	phi		8	35	21	22	19	24	26	17	26	17	8	35	Yes	Upper limb
			38	400	147	291	78	360	145	293	272	166	96	342	No	
Lower limb	phi	0.096			15	31	12	34	11	35	31	15	19	27	Yes	Lower limb
					153	282	85	350	160	275	267	168	85	350	No	
Vertebral	phi	0.091	0.016				40	128	53	115	110	58	42	126	Yes	Vertebral
							57	256	118	195	188	125	62	251	No	
Other GI	phi	0.188	0.048		0.067				45	52	53	44	24	73	Yes	Other GI
									126	258	245	139	80	304	No	
Cardiac	phi	0.163	0.079		0.061		0.114				85	86	33	138	Yes	Cardiac
											213	97	71	239	No	
Urogenital	phi	0.010	0.036		0.053		0.076		0.187				66	232	Yes	Urogenital
													38	145	No	
CNS	phi	0.023	0.155		0.060		0.038		0.042		0.016				Yes	CNS
															No	

Phi-values are shown on the left side, and numbers of patients on the right side. The phi value is the correlation coefficient based on chi-squared analysis. It measures the association in which two anomalies tend to co-occur, regardless of occurrence of other anomalies. 0-0.25 represents poor association, 0.50 moderate association, 0.75 strong association, 1 represents complete association.

Chapter 3

Screening and treatment of tethered spinal cord in anorectal malformation patients

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Screening and treatment of tethered spinal cord in anorectal malformation patients

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ABSTRACT

Introduction	To evaluate diagnosis and treatment of tethered spinal cord (TSC) in anorectal malformation (ARM) patients.
Material and methods	A retrospective case study was performed on patients with an ARM born between 2004 and 2011 and treated at the Erasmus MC - Sophia Children's Hospital.
Results	In the study period 110 neonates with ARM were treated. Spinal ultrasonography was performed in 94 (85%) patients. Ultrasonography findings were abnormal in 17 patients (18%): 16 had evidence for TSC and 1 for caudal regression. These findings were confirmed by MRI in 8 patients. Six of the other 76 patients developed neurologic symptoms and MRI revealed evidence for TSC in 2 of those 6 patients. Thus, sensitivity of spinal ultrasonography was 80%, specificity was 89%, the positive predictive value was 47% and the negative predictive value was 97%. The prevalence of TSC, as confirmed by MRI, was 9%. Three patients underwent untethering surgery: one patient developed neurologic symptoms and two patients were asymptomatic at time of surgery (MRI showed progressive syringomyelia in one and the other had a dermal sinus with TSC). All operations were without complications and the symptoms resolved in the first patient. A relationship between TSC and a specific type of ARM or syndromal disorder could not be found.
Conclusions	Tethered cord occurs in 9% of ARM patients. Neonatal spinal ultrasonography has a sensitivity and specificity of 80 and 89%. Not in all patients an MRI was performed, but the vast majority remained clinically asymptomatic concerning TSC. Ultrasound screening seems an effective screening method, however when ultrasonography is negative and the patient becomes symptomatic later in life, an MRI should be performed to exclude TSC. In our series only one of 110 ARM patients had symptomatic tethered cord syndrome, and symptoms resolved postoperatively.

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Introduction

Anorectal malformations (ARMs) are rare congenital anomalies that occur in approximately 1 to 3 in every 5,000 live births[1] and are associated with other congenital anomalies in up to 43-71% of the cases.[2-4] These associated anomalies are often part of the VACTERL association, which refers to a non-random co-occurrence of vertebral defects (V), anal atresia (A), cardiac malformations (C), tracheoesophageal fistula with esophageal atresia (TE), renal dysplasia (R), and limb anomalies (L). Therefore, all ARM patients are screened for components of the VACTERL association. In addition they are screened for tethered spinal cord (TSC)[5], which is reported in up to 35% of patients.[6] Screening for TSC is by spinal ultrasonography or Magnetic Resonance Imaging (MRI).[7]

TSC refers to an anatomical disorder of a low-lying spinal cord, e.g. caused by loss of the viscoelasticity of the filum terminale or by fatty infiltration or abnormal thickening of the filum. Caudal tension and traction may cause undue stress upon the conus medullaris. This may be a causative agent for a low-lying conus, which is a hallmark of this disorder. TSC can develop into symptomatic tethered cord syndrome, with symptoms such as musculoskeletal abnormalities, limb weakness, gait abnormalities, pain in the back or legs, sensibility disorders of the legs, and orthopedic deformities. Urologic abnormalities may be present, too, mainly bladder dysfunction and urinary incontinence.[8,9] There is a clear consensus that patients with tethered cord syndrome should be surgically untethered to prevent further deterioration, as a clinical response has been reported in 44 to 67%.[8,10]

In view of the high occurrence of TSC in ARM patients and because the fact that early symptoms of tethered cord syndrome such as urinary incontinence may be difficult to recognize in ARM patients due to associated anomalies of urogenital or renal origin, all ARM patients in our hospital are screened for TSC in the neonatal period using spinal ultrasonography. The aim of this study was to evaluate diagnosis and treatment of TSC in ARM patients by determining the sensitivity and specificity of spinal ultrasonography with MRI as golden standard. In addition, outcome after untethering surgery was evaluated.

Patients and Methods

All ARM patients born between January 2004 and December 2011 and treated in the neonatal period at the Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands, were included in this retrospective study. ARMs were classified according to the Krickenbeck classification[11] as perineal fistula, vestibular fistula, rectourethral fistula, vesical fistula, cloacal malformation, and others. Associated anomalies were classified according to the VACTERL-association: vertebral, cardiac, tracheo-esophageal, renal, limb, and other anomalies. This study was approved by the Erasmus MC Medical Ethical Review Board.

Radiographic studies and definitions

In our hospital it has been protocol to screen all neonates up to 4 months of age with ARM for TSC using spinal ultrasonography. All ultrasound images had been evaluated and reported by a pediatric radiologist. MRI images were obtained using a 1.5-T magnet. Images included T1- and T2-weighted images in the sagittal and axial planes with a slice thickness of 3 to 6 mm. All MRI images had been evaluated and reported by a pediatric neuroradiologist who was not blinded for the spinal ultrasonography outcome.

Evidence for TSC, either on ultrasonography or on MRI, was a conus below the level of the L3 vertebra with or without other evidence of spinal dysraphism, such as lipomeningocele, spinal lipoma, meningo(myelo)cele, diastematomyelia, or a thickened and/or fatty filum.[12] MRI was considered as the golden standard. In the case of normal ultrasonography findings without subsequent MRI, the patient was considered not to have TSC. If ultrasonography findings in an asymptomatic patient were abnormal, but no subsequent MRI had been performed, this patient was also considered not to have clinically relevant TSC.

Outcome tethered spinal cord surgery

The patient charts were further reviewed for indications of untethering surgery, age at untethering surgery, postoperative complications, and clinical outcome in terms of neurologic outcome and continence.

Analysis and statistics

Results are shown as number (%) or as median (range). Sensitivity, specificity, positive predictive value, and negative predictive value of screening spinal ultrasonography were calculated using MRI as the golden standard. The patients who had not undergone an MRI were classified as not having clinically significant TSC.

Sensitivity was calculated as the number of patients with abnormal ultrasonography confirmed by MRI, divided by the total number of patients with an abnormal MRI. Specificity was calculated as the total number of patients with normal ultrasonography -that was either confirmed by MRI or who did not undergo an MRI-, divided by the total number of patients who either had a normal MRI or did not undergo an MRI. Positive and negative predictive values were calculated likewise.

Results

In total 110 neonates with ARM were treated at Erasmus MC - Sophia Children's Hospital between January 2004 and December 2011. Table 1 shows background characteristics of these patients. Ninety-four (85%) were screened for TSC by ultrasonography in the neonatal period.

Two of the 16 patients (15%) who were not screened by ultrasonography in neonatal period had severe additional anomalies and died in neonatal period. For the other 14, reasons for not screening were not noted in the charts. These were patients with ARM type perineal fistula (n=8), vestibular fistula (n=3), vesical fistula (n=2), and ARM without fistula (n=1). In 5 patients the ARM was treated conservatively (perineal fistula n=4, vestibular fistula n=1). Median follow up time of all 16 patients who were not screened was 8.5 years, range 4.5 to 10.4 years. None had developed symptoms of TSC.

Table 1: Patient characteristics

	Patients without TSC n=100	Patients with TSC n=10
Type of anorectal malformation		
Perineal fistula	45 (45%)	3 (30%)
Rectourethral fistula	21 (21%)	2 (20%)
Vesical fistula	4 (4%)	0
Vestibular fistula	16 (16%)	2 (20%)
Cloacal malformation	5 (5%)	2 (20%)
Other	6 (6%)	1 (10%)
Unknown	3 (3%)	0
Males	58 (58%)	5 (50%)
Associated anomalies		
None	31 (31%)	0
Vertebral	22 (22%)	9 (90%)
Cardiac	41 (41%)	4 (40%)
Tracheo-esophageal	7 (7%)	1 (10%)
Renal	23 (23%)	3 (30%)
Limbs	12 (12%)	2 (20%)
Other	34 (34%)	10 (100%)

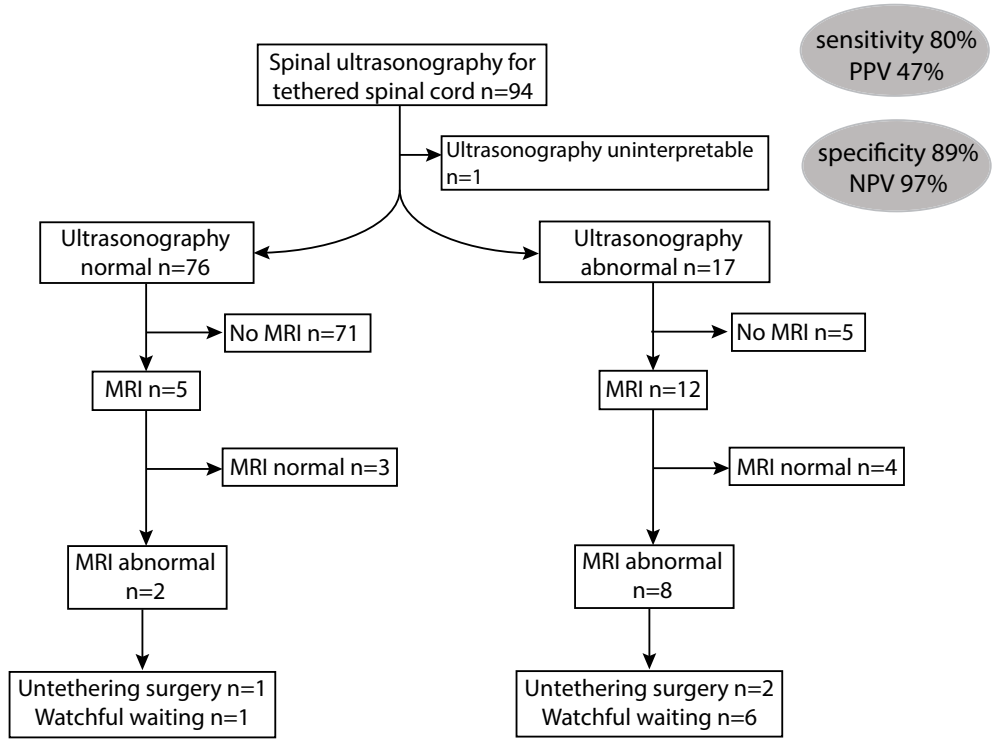
Abbreviations; TSC, tethered spinal cord.

Spinal ultrasonography

Spinal ultrasonography showed normal position of the conus medullaris in 76 (81%) of the 94 screened patients (Fig. 1). Regarding the other 18 patients, the ultrasound in a 4-month-old infant was uninterpretable, 16 showed signs of TSC and 1 showed signs of caudal regression (Table 2). Abnormal ultrasonography findings were confirmed by MRI in 8 patients and not confirmed in 4 patients. Subsequent MRI had not been performed in 5 patients, who all remained asymptomatic after median follow up age 6.3 years (range 5.0 to 8.2 years)).

Five (7%) of the patients in whom ultrasonography revealed normal position of the myelum underwent an MRI because of neurologic symptoms. These symptoms included gait abnormality in one, weakness of both legs in one, urologic symptoms in two, and a dermal sinus –undetected by the screening ultrasonography- in one. MRI

Fig. 1: Flow chart of screening and treatment of tethered spinal cord in anorectal malformation patients



Abbreviations; MRI, magnetic resonance imaging; PPV, positive predictive value; NPV, negative predictive value

revealed evidence of TSC in one patient with urologic symptoms and in the patient with dermal sinus.

The sensitivity and specificity of spinal ultrasound were 80% and 89%, and the positive and negative predictive value were 47% and 97%, respectively. In total 10 patients were diagnosed with TSC, i.e. confirmed by MRI, which was 9% of our total study sample. Three had an ARM type perineal fistula, 2 with a rectourethral fistula, 2 with a vestibular fistula, 2 with a cloacal malformation, and 1 an ARM without fistula. None had a syndromal disorder.

Outcome of tethered spinal cord surgery

Untethering surgery was performed in three of the 10 patients with TSC. The other

Table 2: Characteristics of 18 patients with abnormal ultrasound

Patient charactieristics	n=18
Male sex	9 (50%)
Type of anorectal malformation	
Perineal fistula	8 (44%)
Vestibular fistula	2 (11%)
Urethral fistula	5 (27%)
Cloacal malformation	2 (11%)
Unknown	1 (6%)
Associated anomalies*	16 (89%)
Vertebral	10 (56%)
Urogenital	9 (50%)
Cardiac	9 (50%)
Esophageal atresia	3 (17%)
Limb	4 (22%)
Other	8 (44%)
Ultrasound and MRI findings	
Ultrasound findings*	
Conus ends under L2	13 (72%)
Lipoma	5 (28%)
Thickened filum terminale	4 (22%)
Syringomyelia	1 (6%)
Caudal regression	1 (6%)
Other	5 (27%)
MRI findings*	
MRI performed	12 (67%)
Confirmation of ultrasound findings	6 (33%)
Normal MRI	4 (22%)
Other anomalies	2 (11%)

seven patients are seen by the neurosurgeon once a year. Six of those patients remained asymptomatic at median follow up time of 5 years (range 2 to 9 years). MRI was performed in the seventh patient at 4 years of age because of a small bladder capacity with detrusor overactivity. This was a girl with ARM type cloacal malformation who had recurrent urinary tract infections and a vesicostomy, among other things. The MRI

Table 2: Continued

Outcome**	
Follow up time (years)	6.6 (4.8 to 10.1)
Urinary	
Continent	15 (83%)
Normal urodynamic studies	16 (89%)
Intermitting catheterizations	1 (6%)
Defecation	
Voluntary bowel movements	14 (78%)
Soiling grade 2 or higher	6 (33%)
Constipation grade 2 or higher	13 (72%)
Neurologic	
Normal	14 (78%)
Intellectual disability	4 (22%)

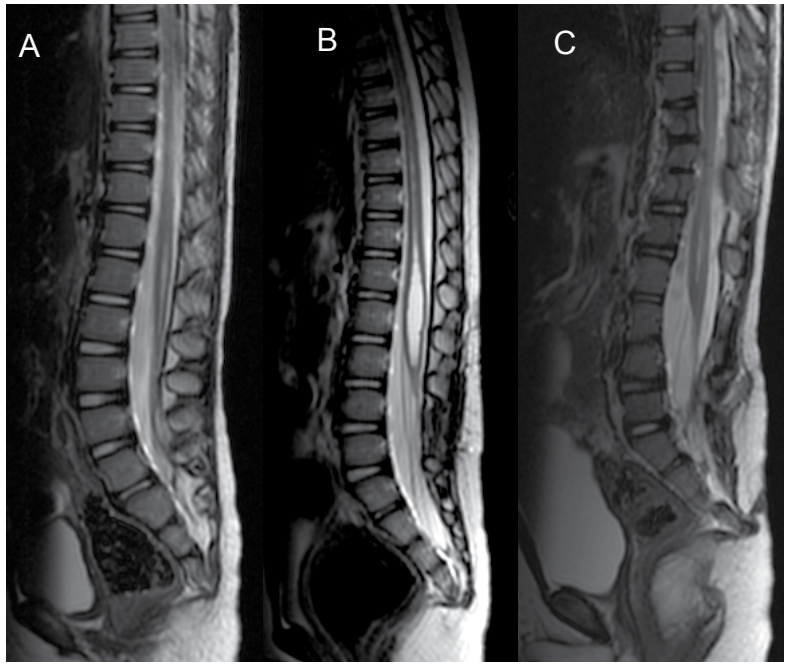
*Results are presented as number (%) or as median (range). * Many patients had more than one associated anomaly or more than one abnormal finding at spinal ultrasound or MRI. ** One patient diseased in neonatal period.*

revieled a conus ending at level L4 with a small lipoma in the filum terminale. Because she had no other symptoms of TSC, the small bladder capacity was thought to be subsequent to the urinary tract infections and vesicostomy, and untethering surgery was therefore not performed. She regularly underwent urodynamic investigations – with stable outcome. She is now 8 years old and did not develop other symptoms of TSC.

One of the three patients who underwent untethering surgery, Patient #1 had ARM type vestibular fistula. Spinal ultrasonography showed a conus ending at L2 and fatty infiltration of the filum terminale. MRI showed an intradural lipoma and hydromyelia at level L4-S1. At age 2 years, she developed progressive gait abnormalities caused by weakness in the left foot and pain in both legs. On the second MRI, a syringomyelia was visible at the level of the conus medullaris (Fig. 2a). The surgery consisted of laminectomy from L3 to S1 with excision of the lipoma. Urodynamic studies showed stable large bladder capacity with normal compliance and vesicoureteral reflux grade 2. The gait abnormalities and pain in the legs resolved after the operation and complications did not occur.

Patient #2 had ARM type vestibular fistula and agenesis of the os coccygis. She underwent untethering surgery at 3 years of age. The ultrasonography showed a conus

Fig. 2: MRI images of patients operated for tethered spinal cord



2a: Patient #1: syringomyelia at the level of the conus medullaris
2b: Patient #2: MRI images of the second MRI, which showed progressive syringomyelia
2c: Patient #3: dermal sinus and conus medullaris ending at L3

ending at L4 and a thickened filum terminale. She remained asymptomatic but had progressive syringomyelia on a second MRI (Fig. 2b), for which a release of the filum terminale was performed. Urodynamic studies remained normal and the operation was uncomplicated.

Patient #3 underwent untethering surgery at 2 years of age. He had ARM type perineal fistula, thoracolumbal vertebral anomalies resulting in scoliosis, agenesis of the os coccygis, and a persistent foramen ovale that closed spontaneously. The spinal ultrasonography was normal, but at 1.5 years of age a dermal sinus was discovered. MRI confirmed the dermal sinus and showed evidence for tethered spinal cord with a conus ending at L3 (Fig. 2c). The boy was asymptomatic at time of surgery. At surgery, the dura was found attached to a dermoid cyst. The cyst, the dermal sinus, and the filum terminale were resected. There were no complications related to the operation and the patient remained asymptomatic.

Discussion

The aim of this study was to evaluate diagnosis and treatment of TSC in a series of ARM patients. In 17 of 94 patients, ultrasonography revealed signs of TSC, which were confirmed by MRI in 8 patients. In 2 patients, TSC was discovered with MRI while ultrasonography showed normal position of the conus medullaris. Therefore the sensitivity and specificity of screening spinal ultrasonography were 80% and 89%, respectively. The prevalence of TSC, confirmed by MRI, was 9% in our study population. Three patients underwent untethering surgery because of symptomatic tethered cord syndrome, development of syringomyelia, or dermal sinus with tethering of the spinal cord.

The prevalence of TSC in this population is low, at 9%, in comparison with other series ranging from 10 to 46%.[6,13-17] This can best be explained by the diagnostic methods used. In the studies that detected a higher prevalence, up to 35 to 46%[6,17], patients were screened for TSC using MRI. In contrast, we primarily screened with ultrasonography and only performed an MRI on indication, either based on ultrasonography findings or based on clinical symptoms. It is possible that we underestimated the 'true prevalence' of TSC. However, considering the regular clinical evaluations and the relatively long follow up times, it is unlikely patients with symptomatic tethered cord syndrome were missed.

The present study showed a sensitivity and specificity of spinal ultrasonography for the detection of TSC in ARM patients of 80% and 89%. It should be noted that an MRI was not performed in all patients and that the radiologists were not blinded. However, all patients remained in follow up as part of standard of care and remained clinically asymptomatic. In addition, two comparable earlier studies showed a sensitivity of 15 and 71% and a specificity of 90 and 100%.[15,18] Further, Azzoni and co-workers reported on a large cohort of 436 neonates who underwent screening spinal ultrasonography for different reasons such as hip dysplasia, a diabetic mother, or congenital anomalies. They found a sensitivity of 37% and a specificity of 97%.[19] The widely ranging results for sensitivity suggest that screening ultrasonography is protocol- or operator-dependent. The main advantages of ultrasonography are that it is easy available, that it is quick and that it does not require sedatives. False-negative results, as was the case in 2 patients in our study sample, cannot be excluded however. Therefore, when an ARM patient presents with symptoms suggestive for tethered cord syndrome, such as pain

or weakness of the legs, an MRI is indicated, even if spinal ultrasonography was normal. Still, because of the high specificity found both in the literature as well as in our study, we think that screening ultrasonography is of value in ARM patients.

The aim of this study was not only to evaluate screening for TSC, but also to evaluate treatment of TSC in ARM patients. In the literature, there is an ongoing discussion on whether the spinal cord should be untethered prophylactically in non-symptomatic TSC patients. In two studies, which used MRI as screening method for TSC in ARM patients, untethering surgery was performed in all patients with TSC.[6,17] Although this operation has very low direct complication rates (0-6%[6,8,15]), retethering requiring surgical revision occurs in 9-25%.[6,20] Therefore, some authors advocate untethering only when symptoms of TSC are present.[16,21] Routine MRI screening as a separate investigation should strongly be reconsidered because of the costs and need of sedation in most children. Selectively screening for TSC with MRI solely in the more complex cases only should be advised against, as TSC is just as frequently seen in patients with ARM types perineal or vestibular fistula.[6,16]

The rationale behind untethering surgery in symptomatic patients is not only to prevent further deterioration, but also to relieve the symptoms of TSC. In occult tethered cord syndrome, thus without an ARM, patients present with neurologic symptoms such as pain or weakness in the legs, orthopedic deformities, and symptoms such as fecal incontinence and bladder dysfunction[8,9] at approximately 4.6 to 5 years of age.[9,20] In ARM patients, it is often unclear whether fecal incontinence and bladder dysfunction are the consequence of either the congenital urogenital or anorectal malformation or of TSC. Several studies in ARM patients show no improvement of fecal continence or bladder dysfunction by untethering surgery.[15-17,22] However, neurologic symptoms such as pain, sensibility disorders, and gait abnormalities can be improved by untethering surgery[16,17], which was confirmed in our study. In summary, untethering surgery is especially of benefit in patients with neurologic symptoms such as pain or weakness in the legs, and improvement of urinary and fecal continence is less likely. Whether symptoms can be prevented by prophylactic untethering surgery remains unsure, but could be investigated in a randomized multicenter trial.

Conclusion

TSC occurs in 9% of the patients with an ARM. Neonatal spinal ultrasonography has a sensitivity and specificity of 80 and 89%. Not in all patients an MRI was performed, but the vast majority remained clinically asymptomatic concerning TSC. Ultrasound screening seems an effective screening method for TSC in ARMs. False-negative results cannot be excluded completely, however, and an MRI is still recommended when a patient presents with symptoms of TSC. Whether symptoms can be prevented by prophylactic untethering surgery remains unsure, but could be investigated in a randomized multicenter trial. In our study sample one patient had symptoms of TSC, which resolved after untethering surgery.

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PART 2: LONG-TERM OUTCOME

Chapter 4

Prospective long-term follow up of children with anorectal malformation: growth and development until 5 years of age

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Prospective long-term follow up of children with anorectal malformation

Growth and development until 5 years of age

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ABSTRACT

Background/ purpose	To evaluate growth and development in children with anorectal malformations and to analyze effects of type of malformation and comorbidities.
Methods	Non-syndromal children with anorectal malformations were prospectively evaluated at 0.5, 1, 2, and 5 years. Biometrics were obtained at all visits. Mental and psychomotor function development was determined.
Results	108 children (59% male) were included. 49% had a high malformation, and 46% had ≥1 additional major comorbidity. All growth parameters were below the norm at all ages ($p<0.01$), irrespective of type of malformation. Children with ≥1 additional major anomaly had lower height at all ages; at 5 years, mean (95% CI) height was −1.83 (−2.7 to −1.1) and −0.70 (−1.3 to −0.1) in children with and without comorbidities, respectively ($p=0.019$). Mental development was normal, irrespective of the type of malformation or comorbidities. Motor development was delayed at all ages. At 5 years, motor development (n=30) was normal in 70%, borderline in 23%, and 7% had definitive motor problems ($p=0.043$).
Conclusion	Non-syndromal children with anorectal malformations are at risk for growth impairment, especially those with additional major comorbidity. Mental development is normal. Motor development is slightly impaired. Supportive care should focus on growth, dietary man-agement, and motor development besides defecation problems.

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Introduction

Anorectal malformations are congenital malformations varying from minor to very complex malformations. They occur in approximately 1 in 5000 live births. It is well-known that children with anorectal malformations have many surgical challenges, such as pelvic floor dysfunction[1], but little is known on the general health issues involved, such as growth and development. The only study on growth was a cross-sectional study in 34 children with anorectal malformations (mean age 11 years); these children showed a normal growth.[2] To date, long-term motor function development of children with anorectal malformations has not been studied or described. Three studies dealt with intelligence and educational performance.[2-4] One described a normal intelligence, the other two described learning problems and lower completed educational level.

Gischler and co-workers have shown that in newborns with severe anatomical malformations[5], factors such as number of associated anomalies, duration of hospital admission, and number of surgical interventions may negatively influence growth and development within the first two years of life.[6] Long-term multidisciplinary follow-up is important in these children, aiming at monitoring growth and development, and providing, when indicated, early intervention.

We hypothesized that children with anorectal malformations are at risk for impaired growth and development at the long-term, notably those with serious comorbidity. To test this hypothesis, we prospectively evaluated physical growth and mental and motor development in children with anorectal malformations, treated in our hospital at various ages, until the age of 5. In addition, we analyzed possible effects of the type of malformation and the presence of comorbidity on the growth and development.

Patients and methods

All children with an anorectal malformation born between January 1999 and March 2011 who participated in our structured follow-up program for congenital malformation survivors were included in this study. This program aims to regularly assess growth, developmental parameters, and lung function when appropriate, until 18 years of age.[6] The assessment protocol is the standard of care at the Erasmus MC-So-

phia Children's Hospital. The Erasmus MC Medical Ethical Review Board (IRB) ruled that the "Medical Research in Human Subjects Act" does not apply to this research proposal, since subjects are not being submitted to any handling, nor are there rules of human behavior being imposed. Therefore, IRB approval was waived. All parents were informed about the study and provided permission to use the data for research purposes. Data were evaluated at the end of 2011. For the purpose of this study, we evaluated data at the ages of 0.5, 1, 2, and 5 years.

The following data were retrieved from the medical records: sex, gestational age, birth weight, type of malformation, number and type of associated anomalies, presence of a syndromal disorder, and number and type of surgical interventions. We classified the malformations as low and high, according to Rintala and co-workers.[1] Low malformations include anal stenosis, perineal fistula, and vestibular fistula. High malformations include rectourethral fistula, rectovesical fistula, anal atresia without fistula, rectum atresia, and persisting cloaca.

We classified the comorbidity as major or minor. Ravitch' pediatric surgical index diagnoses[5] (e.g. esophageal atresia), cardiac malformations requiring operative correction or follow-up by a pediatric cardiologist, other congenital malformations requiring major surgical interventions, or malformations seriously affecting normal function (e.g. tethered cord with neurogenic bladder function) were considered major. All other anomalies were considered minor (e.g. a small atrial septal defect closing spontaneously). Children with urologic problems were referred to a pediatric urologist to follow-up renal and bladder function. For patients with urologic comorbidity, serum creatinine levels were administrated and compared with reference values.[7,8] Prematurity was defined as a gestational age of less than 37 weeks. Small for gestational age was defined as a birth weight for gestational age of <–2 SD from the Dutch reference values.[9]

Physical growth

Children with a syndromal or chromosomal disorder with known influence on physical growth were excluded for the evaluation of physical growth and development. Children with an unconfirmed but suspected syndromal diagnosis (as established by the clinical geneticist) were included.

At each contact moment, we calculated the standard deviation scores (SDS) for height, weight for height, and head circumference (the latter until 2 years of age), and corrected for ethnicity.[10-12] The Dutch normative data have been collected cross-sectionally in a total of 14,500 children. For Dutch children of Turkish or Moroccan origin, normative data were collected in 2904 and 2880 children of Turkish and Moroccan origin, respectively, living in the largest four cities in the Netherlands. Further, we corrected for prematurity until 2 years of age.[10] Target height (TH) is structurally recorded since January 2011; in earlier years it was recorded on indication only.[13] The target height range (THR) was defined as TH in SDS ±1.3. A persisting growth problem was defined as two contact moments with SDS height <–2 or below the THR, and lack of a normal growth at a later contact moment.

Development

Within the framework of the follow-up program, the Dutch translation of the Bayley Developmental Scales (BOS 2–30) had been administered until the age of 2 years. This standardized instrument assesses both mental and motor development of 2 to 30-month-old children.[14] From December 2003 onwards, a new version of the BOS 2–30 was used: the Bailey Scales of Infant Development-Second Edition-Dutch version (BSID-II-NL).[15] The BOS 2–30 and the BSID-II-NL share the same background and are substantially related to each other.[16] Both tests provide a mental developmental index (MDI) and a psychomotor developmental index (PDI) with a mean (SD) of the normative population of 100 (15). We clustered the results into normal (>–1 SD), mild developmental delay (–2 to –1 SD), and severe developmental delay (<–2 SD). We identified the children with a developmental delay (mild or severe) at any contact moment, and lack of a score in the normal range at a later contact moment, and clustered them as such.

At 5 years of age, both the short version of the Revised Amsterdam Intelligence Test (RAKIT) and the Movement Assessment Battery for Children (MABC) were administered, as described previously.[17] For the RAKIT[18], the mean (SD) score of the normative population is 100 (15). The MABC[19] presents a total impairment score (TIS) and three subtest scores: manual dexterity, ball skills, and balance skills. The MABC test results are expressed in percentiles, which we clustered into normal (>p15), borderline (p6-p15), and definite motor problem (≤p5). The maximal exercise capacity was tested

with the Bruce treadmill protocol at 5 years of age. This yielded a maximal endurance time which was converted to SDS using recently published Dutch reference values.[20]

Data analysis

The distribution of the numerical data was tested with the Shapiro–Wilk test. Numerical data are presented as mean scores and 95% confidence intervals (CI), or as median and range when appropriate. Categorical data are presented with numbers (n) and percentages. Numerical data were tested with the reference population with the one-sample t-test, means between groups were compared using the independent samples t-test. Proportions were compared to the normative population using the Chi-square test. Groups with categorical data were compared with the Mann–Whitney test. Statistical analysis was performed using SPSS 17.0 for Windows, with the significance level set at $p<0.05$.

Results

In the study period, 152 children were treated for anorectal malformations in our hospital; treatment of 8 of them had been initiated elsewhere. Eleven children died at a young age due to severe comorbidity: 3 patients had a complex cardiac malformation and died of postoperative cardiac complications, 3 patients with multiple malformations (including cerebral abnormalities) died from sepsis, and only supportive care was given in 3 patients with a cloacal exstrophy; 2 of these patients had trisomy 18 and one patient had Pallister Hall syndrome. Twenty-seven children were lost to follow-up, and parents of 6 did not enter the child in the follow-up program, resulting in 108 children included for this study. The baseline characteristics of the 33 children not seen in follow-up did not differ from those included in this study (not shown). The baseline characteristics of the 108 included children are shown in Table 1. Note the almost equal distribution of the type of malformation: 51% had a low malformation. At least one additional major comorbidity was documented in 46%. Other GI-disorders related to persisting growth problem were mainly esophageal atresia (n=9), and the need of a gastrostomy for serious feeding disorders (n=4). Twenty-two children did not undergo correcting surgery: 18 had a low malformation requiring Hegar dilatation only; 4 had a high malformation for which a permanent colostomy was done. Four patients had

Table 1: Baseline characteristics

Total number of patients	n=108
Type of ARM[a]; n (%)	
Low	55 (51)
High	53 (49)
Male sex; n (%)	65 (59)
Absent or minor associated anomalies; n (%)	58 (54)
At least 1 major associated anomaly; n (%)	50 (46)
Specification of major anomaly[b]; n (%)	
Urogenital	28 (26)
CNS	19 (18)
Gastro-intestinal	14 (13)
Cardiac	12 (11)
Skeletal	7 (7)
Pulmonary	7 (7)
Gestational age (wks); mean (95% CI)	38.4 (37.9-38.8)
Prematures[c]; n (%)	23 (21)
Birth weight (g); mean (95% CI)	3010 (2880-3150)
SGA; n (%)	8 (7)
Surgically corrected[d]	86 (80)
Total surgical interventions; median (range)	3 (0-15)
Surgical interventions related to ARM; median (range)	1 (0-7)

Data shown are mean (95% confidence interval) or median (range), when appropriate. Abbreviations: ARM, anorectal malformations; CNS, central nervous system; SGA, small for gestational age; CI, confidence intervals.

[a] ARM classified parallel to Rintala as follows: low malformations were anal stenosis, covered anus, perianal fistula, and vestibular fistula. High malformations were rectourethral fistula, anal atresia without fistula, rectum atresia, and persisting cloaca.

[b] Percentages shown are of the total study sample. Because many children had more than 1 associated major anomaly, the total percentage exceeds 46%.

[c] Gestational age <37 weeks.

[d] 22 children had not undergone surgical correction of ARM: 18 had a low malformation requiring Hegar dilatation only, 4 had a high malformation and permanent colostomy

a suspected syndromal diagnosis: 2 Cat eye syndrome, 1 Townes–Brocks syndrome, 1 Bardet–Biedl syndrome, they had all been included because the diagnosis was not confirmed.

4

Physical growth

In the children whose malformation was not part of a syndrome, SDS height was significantly lower than in the normative population at all contact moments (p<0.01, one sample t-test, Fig. 1). In total, 26 children (24%) had a persisting growth problem — 12 based on the SDS scores; 14 based on the THR. Growth failure was suspected in 12 other children (11%). Of the children with a persisting growth problem, 16 (62%) had at least one additional major comorbidity. Most of these comorbidities were of urogenital origin (n=10, 63%) and of CNS origin (n=10, 63%). Four of 30 children (13%) with major urogenital comorbidity had mildly impaired renal function: in 2 children serum creatinine levels were only elevated during urinary tract infections (maximum levels never exceeding 1 mg/dL), whereas both other children had one functioning kidney and chronically elevated creatinine (maximum levels never exceeding 0.8 mg/dL). One child with chronic renal dysfunction, who was also born small for gestational age, suffered from impaired growth.

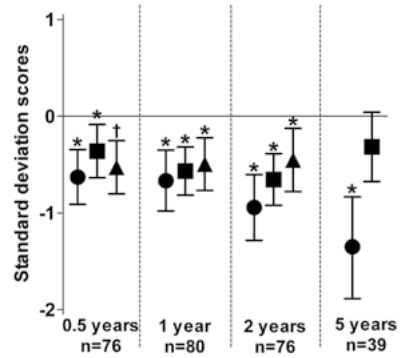
SDS weight for height was impaired until 2 years of age (at 0.5 years p=0.015, at 1 year and 2 years p<0.01, one sample t-test). Also, SDS head circumference (measured until 2 years of age) was smaller than expected (p<0.01, one sample t-test).

SDS height, SDS weight for height, and SDS head circumference did not differ signifi¬cantly between children with a high malformation and children with a low malformation at any of the contact moments (independent samples t-test, data not shown).

In contrast, the presence of additional major comorbidity significantly influenced height at all ages (0.5 and 1 year p<0.01, 2 and 5 years p=0.01, and 0.02, respectively, independent samples t-test), and weight for height until 1 year of age (p<0.01); Fig. 2.

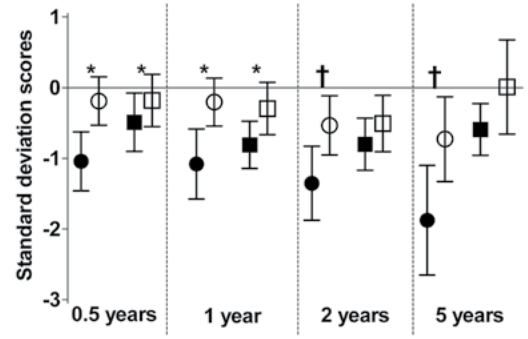
In 54 children (50%) enterostomy was performed after birth. Nineteen of 26 children (73%) with a persisting growth problem had had an enterostomy, vs. 35/82 children (43%) without a persisting growth problem (p=0.007, Chi-Square test). Children with a persisting growth problem had a median (range) length of time with enterostomy of 529 (10 to 895) days vs. 470 (168 to 3622) days in the children without a persisting growth problem (p=0.403, Mann-Whitney test). Seven of 25 children with spinal anomalies had scoliosis; in four of them the severity of scoliosis might have impaired growth.

Fig. 1: Physical growth until 5 years of age



*Presented are the means (symbols) and 95% confidence intervals (whiskers). Circles represent height, squares represent weight for height, and triangles represent head circumference (measured until 2 years of age). *p<0.01, † p<0.05; tested with the one sample t-test (SDS=0).*

Fig. 2: Difference of growth in children with comorbidity



Presented are the means (symbols) and 95% confidence intervals (whiskers). Circles represent height; squares represent weight for height. Closed symbols represent children with at least 1 additional major comorbidity, open symbols represent children without or only minor additional comorbidity. At 0.5 year: with major comorbidity n=37, without n=39; at 1year n=40 with major comorbidity and n=40 without; at 2 years n=36 with major comorbidity and n=40 without; and at 5 years n=20 with comorbidity and n=19 without.
**p<0.01, † p<0.05; tested with the independent sample t-test, with grouping variable presence of additional major comorbidity.*

The median (range) number of operations in children with a persisting growth problem was 8 (1 to 29), vs. 6 (0 to 29) in the children without a persisting growth problem (p=0.147, Mann–Whitney Test). Two of 9 children who underwent major cardiac surgery had a persisting growth problem. The median (range) number of operations related to the anorectal malformation in children with a persisting growth problem was 3 (0 to 6), vs. 1 (0 to 8) in the children without (p=0.052, Mann–Whitney Test).

Development

Development had been evaluated in 102 children within the first 2 years of life. Seven of these had a syndromal disorder. Thus, 95 children were included for analysis of development within the first two years of life.

Mental development

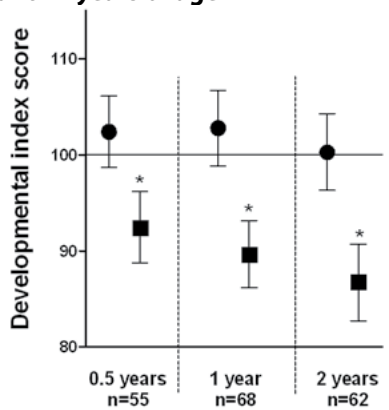
The mean (95% CI) mental developmental index (MDI) was not significantly lower than expected at 0.5, 1, and 2 years of age (Fig. 3). Five children (5%) had severe mental

developmental delay; 8 children (8%) had mild mental developmental delay (i.e. between –1 and –2 SD).

IQ was tested in 25 of the 37 children (68%) who were seen at 5 years of age. Ten children were not tested for organizational reasons (they were seen after March 2011, when tests were only performed in case of suspected developmental delay); one child was visually impaired and one was severely retarded. The latter two were thought to have impaired intelligence. The baseline characteristics of the children tested did not differ from those not tested (data not shown).

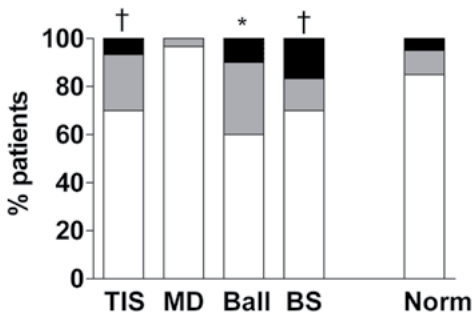
The mean IQ (95% CI) was 102 (94 to 109). One child had a definitive cognitive delay (IQ<70; 4%), 4/25 children (16%) had a mild cognitive delay (–1 to –2 SD); and 20 (80%) had normal intelligence (IQ>85). The child that scored <70 (i.e. 60) had a high malformation and multiple major comorbidities. The MDI and IQ scores were neither significantly different between the children with a high malformation and those with a low malformation, nor between the children with additional major comorbidity and those without (data not shown, Mann–Whitney test).

Fig. 3: Development in children with an anorectal malformation until 2 years of age



Presented are the means (symbols) and 95% confidence intervals (whiskers) of the Bayley Developmental Scales 2–30 and the Bailey Scales of Infant Development-Second Edition-Dutch version. Circles represent mental developmental indexes, squares represent psychomotor developmental indexes.
** p<0.01; tested with the one sample t-test (compared to the normative population).*

Fig. 4: Results of the Movement Assessment Battery for Children (MABC) at 5 years of age



Abbreviations: TIS, total impairment score; MD, manual dexterity; Ball, ball skills; BS, balance skills; Norm, normative population. Black represents the percentage of children that scored in the definitive motor problem range (≤p5); gray represents that of the borderline range (p6– p15); white represents that of the normal range (>p15).
**p<0.01, † p<0.05; tested with the Chi square test (compared to the normative population).*

Motor function development

At all contact moments within the first 2 years of life, the mean PDI of the 95 children tested was significantly lower than that of the normative population (p<0.01, one sample t-test; Fig. 3). Fourteen (15%) children showed severe motor devel-opmental delay (PDI<70); 20 children (21%) had PDI scores between –1 and –2 SD. The PDI was significantly influenced neither by the type of malformation nor by the presence of additional major comorbidity (data not shown, Mann–Whitney test). Major CNS comorbidity was found in 5/14 children with a PDI<70 (4 tethered cord and 1 caudal regression syndrome).

At 5 years of age, reliable MABC results were obtained in 30/37 children. Four were not tested because of logistic reasons; these children were not suspected to have an impaired motor development. Three children who could not be tested had already physical therapy at home: 2 children suffered from severe neurological impairment; and 1 child was visually and auditorily impaired. Another four children who had physical therapy at home at time of assessment scored either normal (n=3) or within the borderline range (n=1). High type of malformation was significantly more frequent among the children not tested than among the children who did complete the MABC test (p<0.01, Mann–Whitney test). The other baseline characteristics did not differ between these two groups.

The total impairment score (TIS) distribution differed significantly from that of the normative population (p=0.043, Chi-square test; Fig. 4), with significantly more children in the borderline range (7/29; 24%). A definitive motor problem was observed in only 2/29 children (7%). Many children had problems with the gross motor function (i.e. ball skills and balance skills); only few children had problems with the fine motor function (i.e. manual dexterity) (Fig. 4). Three children were referred to a physical therapist based on their poor motor function performance.

Maximal exercise capacity

At 5 years of age, 25/30 children successfully completed the Bruce protocol. The mean (SD) SDS endurance time was –0.49 (1.17) (p=0.047, one sample t-test). Two children, both with a low malformation, scored <–2 SDS for the maximal exercise capacity. One child had 2 major comorbidities (none neurological) and the other had no significant comorbidity.

Discussion

This longitudinal evaluation of physical growth and development within the first 5 years of life in non-syndromal children with an anorectal malformation, which we believe is the first of its kind, points to risk for growth impairment, especially when the child has one or more major comorbidities. Mental development up to age 5 did not differ significantly from that in the normative population. More than a third showed impaired motor function development within the first 2 years of life; 15% of all children had a severe motor developmental delay; 21% had a mild motor developmental delay. At 5 years of age, 7% had a definitive motor function problem, while another 24% scored borderline. Accounting for the children that could not be tested because they were severely neurologically impaired; a total of 13% of the study sample has a definitive motor function problem at the age of 5. The maximal exercise tolerance was slightly, but significantly lower than in the normative population.

Analysis revealed that growth impairment was not related to the type of malformation (low or high). It was, however, related to the presence of comorbidity, notably of urogenital origin. Ginn-Pease and co-workers[2] found impaired growth in 9% of their study sample (n=34; mean age 11 years), while we found that 35% had a (possible) growth problem. There are two possible explanations for this difference. First, Ginn-Pease and co-workers described that most of the children did not have any chronic medical disorder, although they failed to provide a number. In our study, more than half of the children had at least one additional major comorbidity, which is in concurrence with the literature.[21] The comorbidity found in the children with growth impairment was mainly of urogenital origin. Renal function was normal in the majority of the patients. Only 4 children had mild renal dysfunction, of whom one had a persisting growth problem. Growth retardation resulting from a partial insensitivity to growth hormone, even if renal function is normal, has been reported in children with urological morbidity (i.e. vesicoureteral reflux).[22]

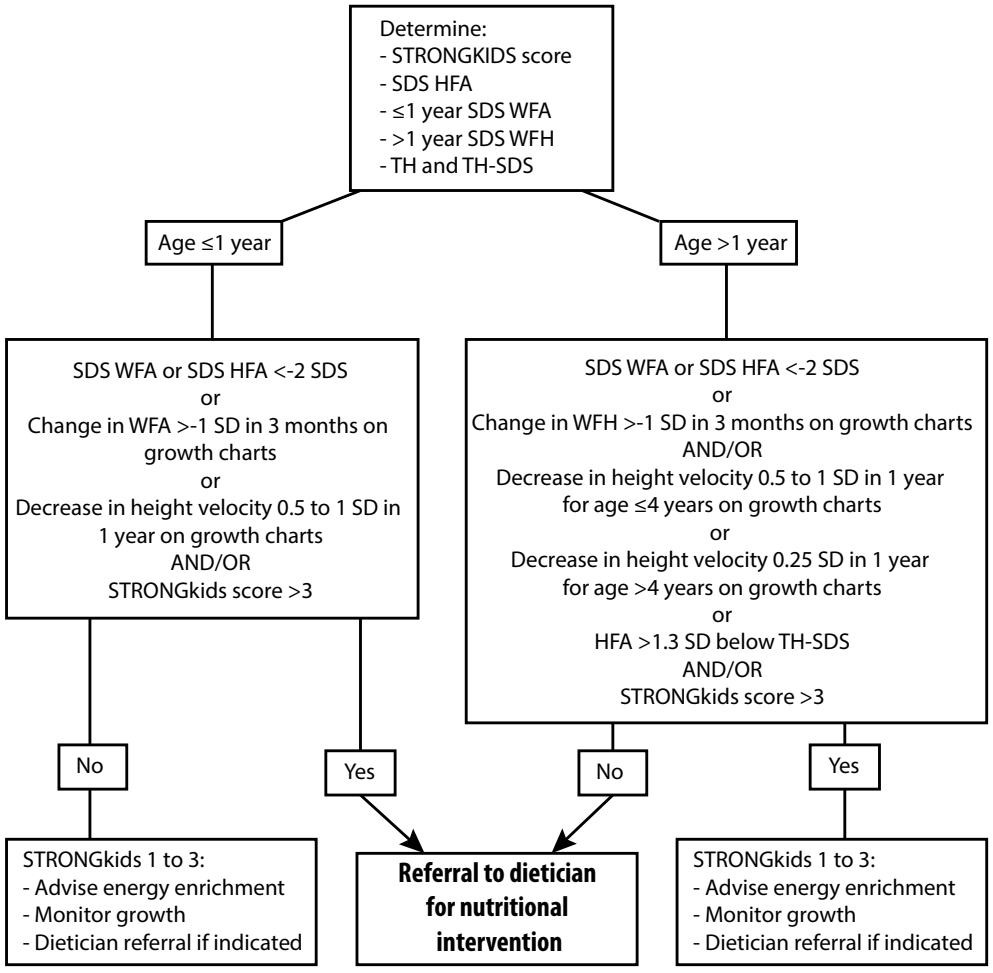
Secondly, Ginn-Pease and coworkers used another definition for growth impairment: they based their conclusions solely on height percentiles, while we also used the target height range. Using height percentiles only, we would have missed 14/26 children with a persisting growth problem (46%). Therefore, we advocate the use of the target height range, to avoid missing children at risk who could be adequately treated.

Growth retardation may result from either acute or chronic malnutrition. Recurrent hospitalizations and surgical procedures for additional major malformations may result in episodes of acute malnutrition. The chronic constipation with lack of appetite, which is inherent to anorectal malformations, may lead to chronic malnutrition. However, Rintala and coworkers described an up to 60% prevalence of constipation[1], and Chao and coworkers reported that healthy children with adequate treatment of functional constipation gained more height and weight than the non-responsive constipated children.[23] In addition, loss of appetite may be due to nausea and abdominal pain as a consequence of intensive bowel management. Because treatment of constipation is still an everyday challenge, pediatric surgeons and pediatricians should pay special attention to adequate bowel management and educating the parents and child. Further studies could make clear whether intensive bowel management in combination with tailor-made advice on daily caloric requirements may enhance physical growth in children with anorectal malformations. Screening all children with the STRONGkids score[24] – a nutritional risk screening tool – in combination with a practical algorithm (Fig. 5) can identify those in need for early referral to a dietician to prevent a persisting growth delay.[25]

We found normal IQ in the children whose malformation was not part of a syndrome. Ginn-Pease and co-workers also found normal IQ in a cross-sectional cohort of 34 children with an anorectal malformation, mean age 11 years.[2] Hassink and co-workers reported a lower completed educational level in comparison to the normal Dutch population in a group of 58 adults with a corrected high malformation (median age 26 years, range 18 to 57 years).[3] They suggested that fecal continence problems may have kept some patients away from school. The children in our study population were too young to experience such problems. Based on the scarce studies, we assume that in spite of normal mental capacity, underlying physical problems may give rise to educational problems. Both child and caregivers should receive adequate guidance, and additional guidance throughout the school career is needed.

We showed that non-syndromal children with anorectal malformations – especially those with additional major comorbidity – are at risk for motor function problems within the first 5 years of life. Based on previous observations by our group[6] in young children with abdominal wall defects, congenital diaphragmatic hernia, small intestinal anomalies, and esophageal atresia, we assume that factors indicative for severity of disease – e.g. the number of associated anomalies, but also duration of hospital admis-

Fig. 5: Practical algorithm for dietetic intervention.



STRONGkids score: screening tool for risk of nutritional status and growth for children (Hulst et al.[24]). Abbreviations: SDS, standard deviation score; HFA, height for age; WFA, weight for age; WFH, weight for height; TH, target height.

sion and number of surgical interventions – also negatively influence development of children with an anorectal malformation. As test results within the first years of life well predict development at 5 years of age[26], we advocate screening at a young age with early referral to a physical therapist, if indicated, to prevent delayed motor function development at a later age. This will improve the child's physical activity and diminish the risk of impaired exercise tolerance.

These are the first results of a prospective longitudinal study in children with anorectal malformations. Regrettably, due to the small sample size at 5 years of age and the large number of possibly predictive factors, we could not perform a regression analysis to predict long-term morbidity. Future studies – preferably with a multicenter design – are needed to further define risk factors for delayed growth and development in non-syndromal anorectal malformation patients.

Conclusion

Non-syndromal children with an anorectal malformation are at risk for physical growth problems, especially when major comorbidity is involved. Thus, the nutritional status and bowel management should be optimized individually to prevent stunting. Mental development is generally not impaired, but attention should be paid to school performance and absenteeism secondary to persisting physical problems. Children with an anorectal malformation are at risk for gross motor function problems, especially those with additional major comorbidities. These findings are of importance in counseling parents. Longitudinal evaluation by a multidisciplinary team, including a pediatric surgeon, a pediatrician, a physical therapist, a dietician, a stoma nurse, and a pediatric urologist, is advocated during childhood and adolescence. In this way, optimal growth and development can be achieved.

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4

Chapter 5

Children with congenital colorectal malformations often require special education or remedial teaching, despite normal intelligence

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Children with congenital colorectal malformations often require special education or remedial teaching, despite normal intelligence

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ABSTRACT

Aim	To prospectively evaluate neuropsychological functioning in eight-year-old anorectal malformation (ARM) and Hirschsprung's disease (HD) patients.
Methods	School functioning and behavior were assessed in a standardized interview. Intelligence, attention, self-esteem, and quality of life were evaluated with validated tests and questionnaires. Assessed risk factors were social economic status, number of episodes of general anesthesia, type of laxative treatment, and premature birth. Patients with severe intellectual disability were excluded.
Results	23 ARM and 20 HD patients were included, of whom 12 and 11 (52% and 55%) respectively received special education or remedial teaching. Full scale IQ of both was normal (mean (SD) 98 (17) and 96 (17) respectively), but in both groups sustained attention was below the norm (mean (SD) Z-score -1.90 (1.94) and -1.43 (1.98) for ARM and HD, both $p<0.01$). Self-esteem was normal: mean (SD) z-score 0.10 (1.29) and -0.20 (1.11) for ARM and HD patients, respectively. Quality of life was normal in ARM patients and slightly impaired in HD patients. No predictors for neuropsychological outcome were identified.
Conclusion	Despite normal intelligence, half of ARM and HD patients received special education or remedial teaching. In addition, problems with sustained attention were found. These findings are important for long-term care.

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Introduction

Anorectal malformations (ARM) and Hirschsprung's disease (HD) are the most prevalent congenital colorectal malformations, each occurring in approximately 1 to 3 in every 5000 live births. Both often require pelvic floor surgery in early childhood and postoperative anal dilatations to prevent anastomotic stenosis.[1] On the long-term, continence problems and constipation occur in up to 40%.[2,3] These events, as well as childhood anesthesia, might negatively affect development.[4]

Neuropsychological functioning of these children has received little attention. Our group has found normal intelligence in 5 year old children with non-syndromal ARM patients.[5] In a study from another group 5 of 25 children with ARM were considered as intellectually disabled, although only intelligence was assessed.[6] Lastly, a prospective longitudinal study reported specific language problems at three years of age and learning problems at adolescent age.[7]

There is also evidence that of risk for internalizing behavioral problems between the ages of 8 to 16 years[8], especially when fecal continence is poor[6]. The usually necessary anal dilatations have been related to dissociation disorder in adolescent ARM patients.[9] In addition, quality of life (QoL) in children with ARM or HD patients of all ages is lower than in healthy reference groups[10], notably social and psychosocial aspects[11]. Several studies have tried to link this with disease-specific symptoms, such as constipation, incontinence, and bowel management; however a clear relationship is not proven in current literature.[10]

The aim of this study was to prospectively evaluate neuropsychological functioning in eight-year-old children with ARM or HD, as an indication for long-term development. Neuropsychological outcome was assessed, including the following main outcome measures: intelligence, attention, memory, behavior, education, self-esteem, and QoL.

Patients and Methods

Study population

5

This study is part of a structured long-term follow-up program offered to patients with congenital malformations treated at the department of paediatric surgery of the Erasmus MC-Sophia Children's Hospital since 1999. These children's physical and psychological development is regularly assessed until 18 years of age.[12] All patients with ARM or HD born between 1999 and 2006 who participated in this follow-up program were eligible for inclusion. Exclusion criteria were: intellectual disability (unable to test or intelligence quotient (IQ) <50), inability to complete the psychological tests due to severe neurological impairments, or refusal.

The Erasmus MC Medical Ethical Review Board ruled that the "Medical Research in Human Subjects Act" does not apply to this research, since subjects are not being submitted to any handling, nor are there rules of human behavior being imposed. Therefore, IRB approval was waived. All parents were informed about the study and provided permission to use the data for research purposes.

Classification systems

Patient characteristics were obtained from the medical records. ARMs were classified according to the Krickenbeck criteria.[13] Hirschsprung's disease was classified as short segment (aganglionosis up to the descending colon), long segment (aganglionosis extending beyond the splenic flexure, up to the ascending colon), or total colonic aganglionosis.

Laxative treatment was classified as non-invasive (either no treatment, laxative diet, or oral laxatives) or as bowel management (daily enemas or rectal washouts). Continence was classified according to the Krickenbeck criteria for postoperative results.[13]

Further characteristics obtained from the medical records were: major comorbidity, genetic anomalies, and episodes of general anesthesia. Socio-demographic variables included native (mother) language and the parents' socioeconomic status (SES) of the

parents. The latter was based on educational level of the mother and classified as low, moderate, or high.[14]

Neuropsychological assessment

5

All children had undergone neuropsychological assessment at eight years of age, performed by a developmental psychologist and supervised by a paediatric neuropsychologist. Assessment included a standardized interview addressing academic skills and previous behavioral problems, and validated tests assessing intelligence, memory, and attention. Self-esteem and QoL were assessed with validated questionnaires.

Standardized interview

Education Current academic skills were established as 'attends regular education', or 'attends regular school, but needs remedial teaching' (i.e. extra help at school, often from a teacher), or 'attends a school for special education'. Parents-reported problems with academic skills were classified as pertaining to reading, spelling, mathematics, or writing.

Behavior In a standardized interview, previous behavioral problems diagnosed by a psychologist or psychiatrist, if any, were inventoried.

Cognitive development

Intelligence For children born before 2001, the short version of the Revised Amsterdam Intelligence Test (RAKIT) and the short version of the TVIQ scale of the WISC-III-NL were used. For children born after 2001, the Dutch version of the Wechsler Intelligence Scale for Children (WISC-III-NL) was used to assess Full Scale Intelligence Quotient (FSIQ), Total Verbal Intelligence Quotient (TVIQ), Total Performance Intelligence Quotient (TPIQ), Verbal Organization Index (VOI), Perceptual Organization Index (POI), and Processing Speed Index (PSI). This version had been validated for the Netherlands in 2001. Both intelligence tests have been validated and normed for the Dutch population.[15,16] For both tests, the intelligence quotient has a mean (SD) of 100 (15) in the normative population.

Memory Memory was assessed with the subtest Digit Span of the WISC-III. This test measures verbal short-term memory and working memory and has been validated

and normed for the Dutch population.[16] The test has a mean (SD) of 10 (3) in the normative population.

Attention Attention was assessed with the Dot Cancellation test. This test is a continuous performance paper-and-pencil test that measures sustained attention and concentration in terms of speed, attention fluctuations, and accuracy. It has been validated for the Dutch population.[17] Speed and attention fluctuations are continuous variables respectively expressed in Z-score and raw score. Accuracy is classified as below average or average/above average.

Social-emotional development

Self-esteem Self-esteem was measured with the Dutch version of the Self Perception Profile for Children (SPPC). This self-reporting questionnaire assesses children's sense for global self-worth and their perception of themselves in specific domains e.g. scholastic competence and social acceptance. Internal consistency has been proven and results were converted to Z-scores using the Dutch manual and reference norms.[18]

Quality of life QoL was assessed with the self-report and/or the proxy-report forms of the Paediatric Quality of life Inventory 4.0 (PedsQL). Self-reports were administered by a psychologist at the outpatient clinic, while proxy-reports were completed by the parents at home. The PedsQL encompasses a total of 23 items on four scales: physical, emotional, social, and school functioning scale.[19] Also the summarizing psychosocial score was calculated. All scale scores were converted to Z-scores using Dutch reference data for self-reports[20] and proxy-reports[21].

Statistical analysis

Results are presented as n (%), as mean (SD), or as median (IQR), as appropriate. The test and questionnaire results were converted into Z-scores with exception of the attention fluctuations score on the Dot Cancellation test. This raw score was compared to the mean raw score of attention fluctuations at eight years of age (mean raw score = 2.3).

Data were compared with the normative data using the two-sided student's t-test or Chi-squared test as appropriate. Proportions of children receiving special education or remedial teaching were compared to the national averages of 5% (special education) and 20% (remedial teaching), respectively.[22] ANOVA analysis was used to determine if the data of the intelligence tests could be pooled, as data of both tests were normally distributed.

A two-sided correlation matrix was computed to determine predictors for neuropsychological outcome. Backward stepwise linear regression, based on highest partial correlations obtained in the correlation matrix, served to identify parameters predicting significantly lower scores on the neuropsychological test scores in the entire group. Included risk factors were SES, number of episodes of general anesthesia, type of laxative treatment, and premature birth.

Data were stored in and analyzed with SPSS 21.0 software (SPSS Inc., IBM Corp., Somers, NY, USA) and significance level was set at $p<0.05$.

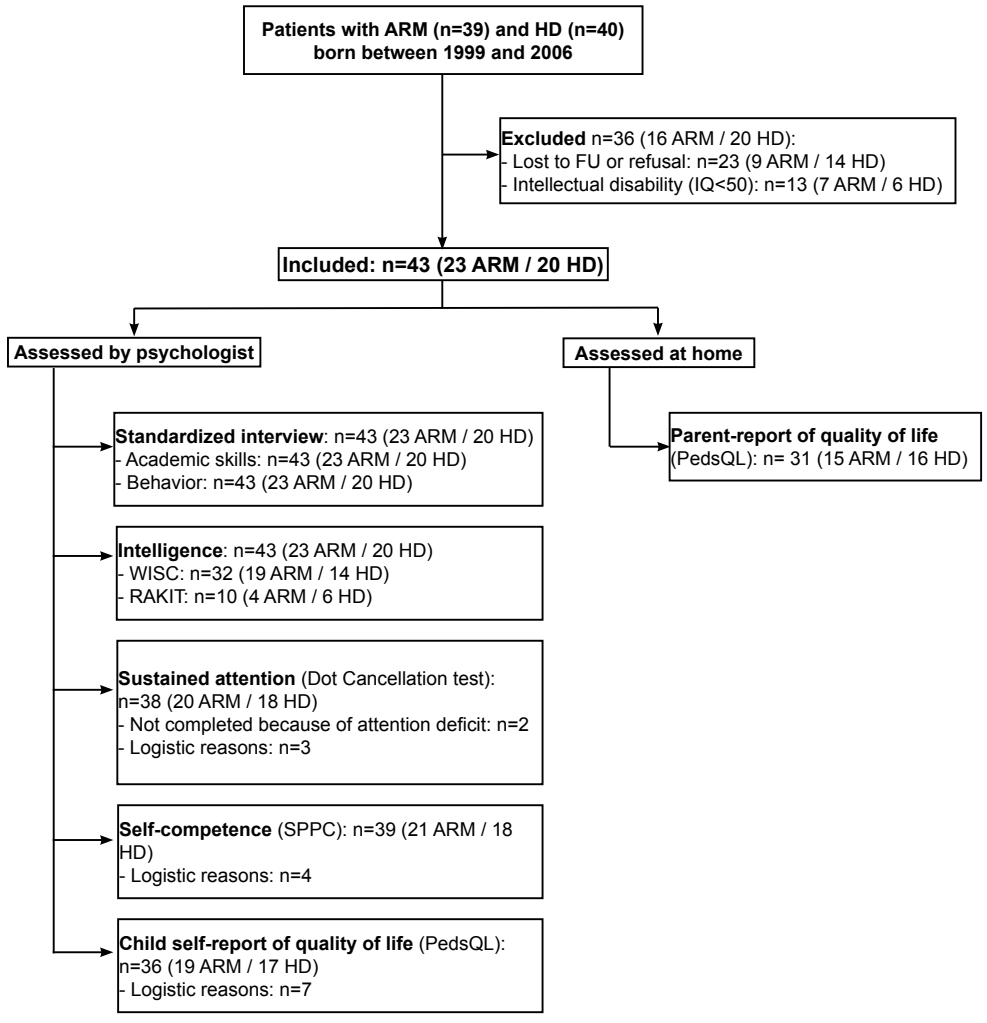
Results

Patient selection and characteristics

Patient selection is shown in Fig. 1. Of 79 eligible patients, 13 were excluded because of intellectual disability (IQ<50): 12 Down's syndrome and one OEIS-complex (omphalocele-exstrophy-imperforate anus-spinal defects). Of the remaining 66 patients, 43 (65%) were tested according to our standard clinical follow-up protocol for 8-year-olds (23 ARM and 20 HD patients). The other 23 either were not willing to participate or had been lost to follow up since the previous assessment.

Table 1 shows the background characteristics of included patients. These characteristics did not differ from those lost to follow up or who did not consent (data not shown). Bowel management was necessary in 14 ARM (61%) and seven HD (35%) patients (including some patients who did have voluntary bowel movements). Continence results, specified for the different types of ARM and lengths of aganglionosis are shown in Online supplemental Table 1. Twelve ARM patients (52%) and 16 HD patients (80%) had voluntary bowel movements. Thirteen ARM patients (56%) and 15 HD patients (75%) had no or grade 1 soiling.

Fig. 1: Flowchart of patient inclusion



Abbreviations: ARM, anorectal malformation; HD, Hirschsprung's disease; FU, follow up; IQ, intelligence quotient; WISC, Wechsler Intelligence Scale for Children; RAKIT, Revised Amsterdam Intelligence Test; SPPC, Self Perception Profile for Children; PedsQL, Paediatric Quality of Life Inventory.

Neuropsychological assessment

Standardized interview

Education In total 52% and 55% of ARM and HD patients received special education services (special education: 13% and 25%; remedial teaching: 39% and 30%, respectively). This was significantly higher than the national average of 5% for special edu-

Table 1: Patient characteristics of included patients

	ARM; n=23	HD; n=20
Males	12 (52%)	17 (85%)
Type of ARM		
Perineal fistula	6 (26%)	
Recto urethral fistula	6 (26%)	
Rectovesical fistula	0	
Vestibular fistula	5 (22%)	
Cloaca	3 (13%)	
Other	3 (13%)	
Type of HD		
Short segment		8 (40%)
Long segment		8 (40%)
Total colonic aganglionosis		4 (20%)
Major comorbidity present1	16 (70%)	1 (5%)
Urologic	10 (44%)	1 (5%)
Skeletal	7 (30%)	1 (5%)
Sacral	4 (17%)	0
Esophageal atresia	2 (9%)	0
Cardiac	1 (4%)	0
Genetic anomalies present	2 (9%)2	4 (20%)3
Episodes of general anesthesia	9 (2-20)	4 (1-42)
Before 2 years of age	6 (2-15)	3 (2-18)
Premature (<37 weeks)	4 (17%)	2 (10%)
Mother language		
Dutch	19 (83%)	14 (70%)
Other	4 (17%)	6 (30%)
Social economic status		
Low	7 (30%)	5 (25%)
Middle	9 (39%)	10 (50%)
High	4 (17%)	3 (15%)
Unknown	3 (13%)	2 (10%)
Laxative treatment at 8 yrs		
No / laxative diet	4 (17%)	13 (65%)
Oral laxatives	3 (13%)	0
Bowel management4	14 (61%)	6 (30%)
Permanent stoma	2 (9%)	1 (5%)

Data are shown as n (%) or as median (range). Abbreviations: ARM, anorectal malformation; HD, Hirschsprung's disease.
[1]Some patients had >1 comorbidity.
[2]One patient had Townes-Brocks syndrome and one patient had Cat eye syndrome.
[3]One patient had Bardet Biedl syndrome, and 3 patients had RET mutation.
[4]Bowel management included daily enemas or rectal washouts

cation and 20% for remedial teaching (p<0.01 for both). Parents of 11 children (five ARM and six HD patients) reported problems with academic skills (seven children had problems with reading, two with mathematics, and two with spelling). No writing disorders were reported.

Behavior Five patients had previously been diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) (one ARM and four HD patients). Two of them in addition had been diagnosed with Oppositional Defiant Disorder (ADHD and ODD) and one with Pervasive Developmental Disorder Not Otherwise Specified (ADHD and PDD-NOS). In one other ARM patient an Anxiety Disorder not otherwise specified had been diagnosed and two other patients (one ARM and one HD patient) had been diagnosed with Reactive Attachment Disorder of Infancy or Early Childhood. Five children underwent psychological counseling at home. Academic skills did not differ between children with and without a psychiatric disorder.

Cognitive development

Intelligence Intelligence was assessed in all children (Fig. 1). The data on total intelligence were pooled because there was no significant difference between the RAKIT and WISC-III-NL full-scale intelligence scores (p=0.316). Mean (SD) full scale IQ for ARM and HD patients was 98 (17) and 96 (17), respectively, both within the reference norm (Table 2). Also verbal IQ and performance IQ were within the norm for both ARM and HD patients. Perceptual Organization Index for ARM patients was below the norm (mean (SD) POI=91 (16), p=0.02).

Memory Verbal short-term memory and working memory was measured in 30 children. All patients assessed with the short version of the TVIQ scale of the WISC-III-NL did not perform the subtest Digit span of the WISC-III-NL. For both ARM and HD patients the mean score on this subtest was conform the Dutch norm.

Attention Sustained attention was measured 38 children using the Dot Cancellation test (Fig. 1). Three were not tested as they were too late for the appointment, and two others could not complete the test (one was too tired and one could not count dots due to a mild intellectual disability). Sustained attention was significantly lower than that in the normative population (speed and attention fluctuation p<0.01 for both ARM and HD). However accuracy was normal in both groups (Table 2).

Table 2: Neuropsychological outcome

	ARM; total n=23		HD; total n=20	
	n	outcome	n	outcome
Education (standardized interview)				
Normal	11	48%[1]	9	45%[1]
Remedial Teaching	9	39%[1]	6	30%[1]
Special education	3	13%[1]	5	25%[1]
Intelligence (WISC-III / RAKIT)				
Full scale IQ	23	98 (17)	20	96 (17)
Verbal IQ	23	101 (15)	20	97 (15)
Performance IQ	19	92 (17)	14	95 (20)
Verbal Organization Index	23	101 (15)	20	97 (15)
Perceptual Organization Index	19	91 (16)[2]	14	94 (19)
Processing Speed Index	18	95 (28)	14	101 (20)
Memory (WISC-III)				
Digit span	18	10.67 (3.01)	13	9.62 (3.62)
Attention (Dot Cancellation-test)				
Working speed, z-score	20	-1.90 (1.94)[1]	18	-1.43 (1.98)[1]
Attention fluctuation, raw score	20	4.80 (2.68)[1]	18	4.37 (2.00)[1]
Accuracy				
Below average	5	25%	6	33%
Average or above	15	75%	12	66%
Self-esteem (SPPC), z-score				
Scholastic competence	21	0.09 (1.32)	18	-0.04 (1.12)
Social acceptance	21	0.10 (1.02)	18	-0.04 (1.04)
Athletic competence	21	0.55 (1.03)[2]	18	0.29 (1.01)
Physical appearance	21	-0.02 (0.99)	18	-0.10 (0.91)
Behavioral conduct	21	0.38 (1.29)	18	0.15 (1.63)
Global feeling of self-worth	21	0.10 (1.29)	18	-0.20 (1.11)

Results are presented as mean (SD). Abbreviations: n, number; WISC-III, Wechsler Intelligence Scale for children third version; RAKIT, Revised Amsterdam Intelligence Test; IQ, intelligence quotient; SPPC, Self-Perception Profile for Children.
[1]p<0.01; [2]p<0.05; significantly different from the reference population.

Predictors for outcome of neuropsychological tests Regression analysis performed on the neuropsychological tests showed that SES, number of episodes of general anesthesia, type of laxative treatment, and premature birth did not significantly predict

Table 3: Quality of life – Results of the PedsQL

	ARM patients		Hirschsprung's disease patients	
	Self-report; n=19	Proxy-report; n=15	Self-report; n=17	Proxy-report; n=16
Total score	-0.7 (-1.0 to 0.4)	-1.3 (-2.8 to -0.7)[1]	-1.0 (-2.1 to 0.4)[1]	-0.6 (-2.2 to 0.6)[1]
Physical health	-0.1 (-1.5 to 0.6)	-2.0 (-4.1 to -0.6)[1]	-1.5 (-2.0 to 0.1)[1]	-0.1 (-2.9 to 0.7)
Psychosocial health	-0.6 (-1.0 to 0.6)	-0.7 (-1.7 to -0.2)[1]	-0.6 (-1.8 to 0.7)	-0.6 (-1.6 to 0.5)[1]
Emotional functioning	-0.9 (-0.9 to 0.6)	-0.6 (-1.8 to -0.1)[1]	-0.1 (-1.0 to 1.0)	-0.5 (-1.2 to 0.7)
Social functioning	-0.1 (-1.3 to 0.7)	-1.1 (-1.5 to 0)[1]	-0.5 (-0.9 to 0.1)[1]	-0.4 (-1.7 to 0.7)
School functioning	0.1 (-0.7 to 0.7)	-0.8 (-1.4 to 0.2)[1]	-0.3 (-2.2 to 0.3)	-1.1 (-1.9 to 0.2)[1]

Quality of life was assessed with the PedsQL. Data are shown as Z-score median (IQR). Abbreviations: ARM, anorectal malformation.

[1]p<0.05, all others not significantly lower than reference values. (Wilcoxon signed-rank test)

scores on tests measuring intelligence, speed, memory, or attention (data not shown). No relationship could be identified between attention and academic skills (data not shown).

Social-emotional development

Self-esteem Thirty-nine children completed the SPPC. Four others were either too tired (n=1) or had r language comprehension problems (n=3). The mean Z-score was higher (i.e. more positive functioning) for athletic competence in ARM patients compared to the reference norm (p=0.03). For both ARM and HD patients, the other domains did not differ from the reference norm.

Quality of life The self-report form for QoL was completed by 36 children, and the parents of 31 children completed the proxy-report form (Fig. 1). For 28 patients both self-report and proxy-report was available.

For children with ARM, the summarizing scores of self-reported QoL did not differ from those of the reference population (Table 3). The parents of ARM patients rated their child significantly lower than the reference population on all summarizing scores, i.e. total score, physical health, and psychosocial health (median Z-scores -1.3, -2.0, and -0.7, p=0.005, 0.003, and 0.012, respectively).

For children with HD, the self-reported total score and physical health score were significantly lower than the norm (median Z-scores -1.0 and -1.5, p=0.035 and 0.010, respectively). Also the parent-reported total score and psychosocial health score were significantly lower than those of the reference population (median Z-scores -0.6 for both and p=0.044 for both).

Discussion

The aim of this study was to prospectively evaluate neuropsychological functioning in eight-year-old ARM or HD patients, as an indication for long-term development. The most surprising finding of this study was that, despite normal intelligence and memory, about half of children in both groups received remedial teaching or special education. Moreover, problems with sustained attention were found in both groups, but we were unable to identify determinants for these problems. Both groups reported normal self-esteem; ARM patients reported normal QoL, but HD patients slightly impaired QoL.

The finding that many of these children received remedial teaching or special education is in line with a study by Ludman et al.[7], who found that at 11 to 13 years of age, children who had undergone major neonatal surgery performed worse at school (particularly in mathematics, and science) that age and gender matched controls. It is unfortunate that the number of patients receiving remedial teaching was not reported. In the present study, possible determinants were sought for the problematic sustained attention, and for the high prevalence of ADHD (11%, vs. 5% in the normative population[23]). Firstly, a relationship between the problems with academic skills and sustained attention problems or psychiatric disorders could not be supported by our data. Secondly, we hypothesized that the problems could be associated with bowel management, as a relationship between attention deficit disorder and constipation has been described in the literature.[24] However, this hypothesis could not be confirmed with regression analysis. Intelligence and SES also have been described as risk factors for ADHD[25]; however both were normal in this study. Neither could we find a relationship between sustained attention and other determinants such as associated comorbidities, possibly due to the relatively small patient samples. Factors such as absence from school were not evaluated in this study.

The children's problems with visual-spatial sustained attention and perceptional organization could point to maldevelopment of the right hemisphere[26], as this hemi-

sphere is important in all visual-(spatial) functions. Causes for abnormal development of the right hemisphere should be sought in early life. It has been suggested that early relational trauma can be a causative factor.[27] The extensive medical treatment most patients must undergo to obtain the best possible anorectal function could very well be a risk factor for early relational trauma. Often the parents perform these dilatations. This could influence the attachment style, and result in insecure attachment or even attachment disorders (attachment theory of Bowlby). Naturally these hypotheses are highly speculative and this study was not designed to provide evidence for this. Nevertheless it is remarkable that in this small patient sample 5% were diagnosed with Reactive Attachment Disorder (vs. 1% in the normative population[28]).

Hartman et al. studied QoL in 316 ARM and HD patients, both children (8-11 years of age) and adolescents (12-16 years of age), and found that the QoL (measured with the TACQOL, The Netherlands Organization for Applied Scientific Research Academic Medical Center Leiden Child Quality of Life Questionnaire) was similar to the reference population.[29] In our study this was also the case for ARM patients, but QoL for HD patients was lower than that of the reference population. Comparison of child and parent reports on quality of life was not within the scope of our study. Still it was clear that the parents of ARM patients reported more problems on each domain for their child than parents of healthy peers. This was also the case for psychosocial domains in HD patients. Further, self-reported self-esteem was within the normal range. This suggests that the coping strategies of the children are sufficient at this age, even of the HD patients, who experienced more physical and social problems than their peers. However, self-esteem of both groups at adolescent age has been reported to be lower than that at childhood age.[29] This aspect should be addressed in the follow up.

The main limitation of this study is the relatively small study sample. Therefore our data are inconclusive regarding determinants of academic skills and neuropsychological outcome. Still the fact that so many of children needed extra help at school, despite normal intelligence, is reason for caution because this may affect their professional careers later in life. Moreover, the question can be raised whether our study group is a representative population. Patients with severe intellectual disability (mostly Down's syndrome) were excluded. Further, compared to other patient groups in our follow-up program a substantial proportion of patients was lost to follow-up: 35% compared to 13 and 15%.[30] It is likely that they represent ARM patients with less complex malformations, considering that of included ARM patients a much higher proportion required bowel management than reported in the literature (i.e. 61%, vs. 17-42% grade 3 constipation[2]). Moreover, a higher proportion of HD patients had total aganglionosis compared to the literature.[3] Lastly, the data on anal dilatations were unfortunately not recorded prospectively, and a relationship with behavioral problems could therefore not be tested reliably.

Still, we find the results of this study important, because it appeared that, even when excluding children with intellectual disability, half of the children need extra services at school. Although highly speculative, we suggest this might be influenced by the invasive medical treatment required, and the consequent interference in the parent-child relationship. Thus, apart from provision of necessary medical care, early socio-emotional development should be carefully monitored, so that any problems are timely recognized.

Conclusion

Half of the anorectal malformation and Hirschsprung's disease patients required remedial teaching or special education despite normal intelligence. Further, significant problems with sustained attention were found, however no relationship could be found with the need for special education services. Self-esteem was normal in both patient groups. Besides necessary paediatric surgical care more attention should be paid to early socio-emotional development and problems should be timely recognized.

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Chapter 6

Cloacal malformation patients report similar quality of life as female patients with less complex anorectal malformations

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Cloacal malformation patients report similar quality of life as female patients with less complex anorectal malformations

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ABSTRACT

Purpose	Cloacal malformations are the most complex type of anorectal malformation in females. This study aimed to report quality of life (QoL) of patients with a cloacal malformation for the first time in literature.
Materials and Methods	Female patients with an anorectal malformation participating in a follow-up program for congenital malformation survivors aged 5 or older were eligible for this study. QoL was assessed with the PedsQL™ 4.0 inventory. Scores of patients with a cloacal were compared with those of female patients with rectoperineal or rectovestibular fistulas and with reference data.
Results	A total of 59 patients (67% response rate; 13 patients with cloacal malformation) were included, QoL was assessed by patient self-report at median age of 12 years (8-13), and by parent proxy-report at median age of 8 years (5-12). Scores of the cloacal malformations group were similar to those of the comparison group, except the proxy-reported scores on school functioning (60.0 vs. 80.0, p=0.003). Proxy-reported scores of cloacal malformation patients were significantly lower than reference values on total QoL-score, psychosocial health, and emotional and school performance. Patients (irrespective of type of ARM) who suffered from fecal soiling reported significantly lower scores with regard to psychosocial health (71.7 vs. 81.7, p=0.034) and its subscale school performance (65.0 vs. 80.0, p<0.001). QoL-scores reported by cloacal malformation patients did not differ significantly from the reference values of the healthy population. Parents of cloacal malformation patients reported significantly lower total QoL, emotional and school performances, as well as a lower general psychosocial health for their children relative to reference data of healthy children.
Conclusion	Patients with cloacal malformations and females with less complex anorectal malformations report similar QoL. Parents of cloacal malformation patients report more problems on several psychosocial domains relative to the healthy reference group. To monitor these matters, long-term follow-up protocols should contain multidisciplinary treatment including periodical assessment of psychosocial wellbeing.

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Introduction

In patients born with a cloacal malformation the anus is absent and the rectum, vagina and urethra confluence in one common channel. Cloacal malformations are considered more complex than other types of anorectal malformations (ARM) in females, such as rectoperineal or rectovestibular fistulas.[1] Most ARM patients will undergo multiple surgical procedures in the first years of life, which aim to achieve the best possible bowel function, urological function, and gynecological function. However, the majority of cloacal malformation patients will still suffer from long-term impairments in one or more of these functions.[2] These impairments may have an impact on QoL. On the other hand, a study in patients with ARM – but not including patients with cloacal malformations – found that impairments such as fecal incontinence or constipation had almost no effect on QoL and that psychosocial functioning was more important.[3] In another study by Hartman et al., however, poorer QoL was reported for female patients and for patients suffering from associated congenital anomalies.[4] Thus, as a cloacal malformation obviously occurs in females only, and considering that in up to 88% of cases it is associated with other congenital anomalies[5], there is reason to expect that QoL in the latter patients will be lower than that in female patients with other ARM. We are not aware of studies that have addressed this assumption. With this study, therefore, we aimed to report QoL in patients with cloacal malformations during childhood and adolescence for the first time in literature and to compare outcomes with those in female patients born with a rectoperineal or a rectovestibular fistula. We furthermore compared them with reference values of the general Dutch population.

Methods and materials

All ARM patients treated in our institution (Erasmus MC-Sophia Children's Hospital) are invited to join a prospective, structured follow-up program for congenital malformation survivors.[6,7] The assessment protocol for this program is standard of care at our institution. The Erasmus MC Medical Ethical Review Board (IRB) ruled that the "Medical Research in Human Subjects Act" does not apply to this study, since subjects are not being submitted to any handling, nor are there rules of human behavior being imposed. Therefore, IRB approval was waived. All parents were informed about the study and provided permission to use the data for research purposes. Included in the program is a periodical assessment of QoL using proxy-reports from the age of 5 years

and self-reports from 8 years onwards. All female ARM patients with a cloacal malformation, or a rectoperineal or rectovestibular fistula aged 5 years and older whose QoL was assessed were eligible. Severe mental or neurological impairment was an exclusion criterion (Fig. 1).

QoL was assessed with the PedsQL™ 4.0 inventory[8,9], which was constructed to test health-related QoL in children and adolescents. Validated, age-appropriate versions are available for children aged 5 to 18 years as a parent proxy-report and children/adolescents aged 5 to 25 as patient self-report. The questionnaire assesses both physical health (8 items) and psychosocial health, divided in emotional, social, and school performance (5 items each). All 23 items scored will generate a total QoL-score with a maximum possible score of 100. Parent proxy-reports were completed by the parents at home, self-reports were completed with the help of a psychologist at the outpatient clinic (without parents).

If a patient (and/or her parents) had completed the questionnaire more than once, only data from the most recent self-report and proxy-report were included in the analysis. Data regarding associated anomalies, surgical procedures, and functional outcome such as colorectal function and urinary continence were obtained in the same outpatient clinic with the use of structured interviews. Colorectal function was classified according to the Krickenbeck criteria.[10] Dysfunctional voiding was defined as either urinary incontinence or need for intermittent catheterization.

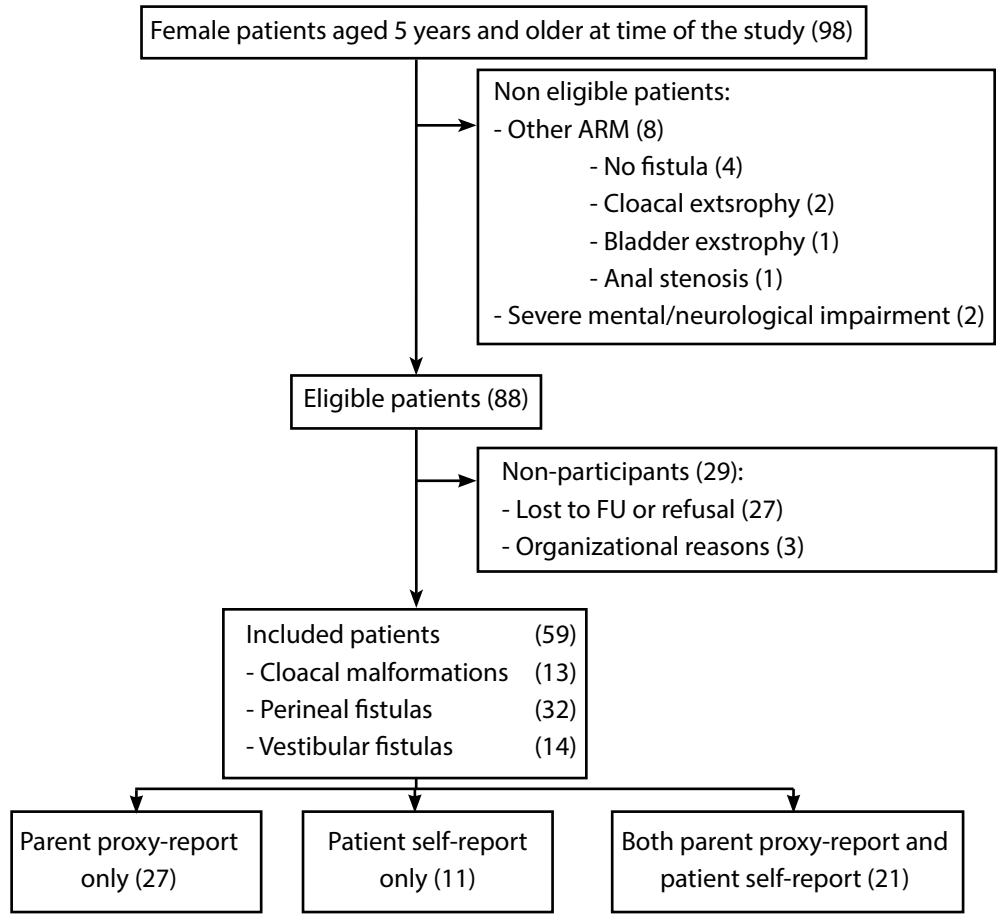
Data were stored and analyzed using SPSS version 21 (SPSS Inc, Chicago, Ill). QoL-scores are expressed as median (IQR) unless otherwise stated. Mann-Whitney U non-parametric tests and one-sample Wilcoxon signed rank tests were used to compare QoL-scores of different types of ARM and to compare these scores with Dutch reference data previously obtained in 74 children aged 7.4 – 18.2 years.[11]

Results

Patient characteristics

Since the introduction of the follow-up program in 1999, 88 female patients with ARM

Fig. 1: Flow chart of patient inclusion



aged five or older were seen at outpatient appointments and met all inclusion criteria. Fifty-nine (67%) of them – or their parents – completed at least one PedsQL™ 4.0 (Fig. 1). QoL was assessed by patient self-report at a median age of 12 (8-13) years , and by parent proxy-report at a median age of eight (5-12) years. Self-reporting patients in the cloacal malformation group were older than the Rectoperineal/Rectovestibular (RP/RV) comparison group at time of the study (14 [12-19] vs. 12 [8-13] years, p=0.009), ages for the proxy-reporting group were not significantly different from each other (Table 1A-B). Associated anatomical anomalies were seen in 32 (54%) of the patients, the most common being (sacro)vertebral anomalies in 16 patients (27%) and renal anomalies in 11 (19%), with no differences between the two study groups. Median (IQR) age at ARM repair was 10 (4-18) months. Thirty-eight (64%) patients underwent

Table 1A: Clinical characteristics: Patient self-report group (n=32)

	CM (11)	RP/RV (21)	Total (32)	p-value
Median age (years)	14 (12-19)	12 (8-13)	12 (8-13)	0.009
Associated anomalies	6 (55%)	12 (57%)	18 (56%)	1.000
Voluntary bowel movements	4 (36%)	18 (86%)	22 (69%)	0.013
Soiling	6 (55%)	7 (33%)	13 (41%)	0.283
Grade 1	3 (27%)	1 (5%)	4 (13%)	
Grade 2	3 (27%)	5 (23%)	8 (25%)	
Grade 3	0	1 (5%)	1 (3%)	
Constipation	5 (45%)	11 (52%)	16 (50%)	1.000
Grade 1	0	1 (5%)	1 (3%)	
Grade 2	0	4 (19%)	4 (13%)	
Grade 3	5 (45%)	6 (28%)	11 (34%)	
Colostomy	3 (27%)	1 (5%)	4 (13%)	0.106
Urological outcome				
Spontaneous voiding	6 (55%)	15/20 (75%)	21/31 (68%)	0.423
Clean intermittent catheterization	2 (18%)	3/20 (15%)	5/31 (16%)	
Incontinence	2 (18%)	2/20 (10%)	4/31 (13%)	
Diversion	1 (9%)	0	1/31 (3%)	

Table 1B: Clinical characteristics: Parent proxy-report group (n=48)

	CM (8)	RP/RV (40)	Total (48)	p-value
Median age (years)	12 (6-12)	8 (5-12)	8 (5-12)	0.306
Associated anomalies	4 (50%)	21 (53%)	25 (52%)	1.000
Voluntary bowel movements	4 (50%)	35 (88%)	39 (81%)	0.031
Soiling	4 (50%)	18 (45%)	22 (46%)	1.000
Grade 1	1 (12%)	7 (17%)	8 (17%)	
Grade 2	3 (38%)	10 (25%)	13 (27%)	
Grade 3	0	1 (3%)	1 (2%)	
Constipation	6 (75%)	20 (50%)	26 (54%)	0.260
Grade 1	0	2 (5%)	2 (4%)	
Grade 2	1 (12%)	8 (20%)	9 (19%)	
Grade 3	5 (63%)	10 (25%)	15 (31%)	
Colostomy	1 (12%)	1 (3%)	2 (4%)	0.364
Urological outcome				
Spontaneous voiding	5 (62%)	28/36 (78%)	33/44 (75%)	0.391
Clean intermittent catheterization	3 (38%)	3/36 (8%)	6/44 (14%)	
Incontinence	0	5/36 (14%)	5/44 (11%)	

CM cloacal malformation group; RP/RV rectoperineal/rectovestibular group.

surgical reconstruction by either posterior sagittal approach (42%) or anterior sagittal approach (16%); a cutback procedure was carried out in three patients (5%); and the surgical procedure was unknown in one other patient, who was adopted from China. Twenty-one patients (36%) with rectoperineal fistulas underwent anal dilatations only without surgical correction. At follow-up, fewer patients with cloacal malformations had voluntary bowel movements (VBM) relative to patients with other types of ARM.

Quality of life questionnaires

Patients with cloacal malformations and patients from the RP/RV comparison group had similar median (IQR) scores (81.5 [75.0-87.0] vs. 76.1 [69.0-87.0], p=0.551, Table 2A). QoL subscores reported by patients themselves did not significantly differ between the two study groups. Parents of patients with a cloacal malformation reported a median total QoL-score of 80.4 (73.4-84.0), which was not different from the RP/RV comparison group (82.1 [69.0-91.6], p=0.554, Table 2B). However, parents of patients with a cloacal malformation did report significantly lower scores on school performance than parents of patients with a rectoperineal or a rectovestibular fistula (60.0 [56.3-75.6] vs. 80.0 [68.1-95.0], p=0.003, Table 2B).

Effects of fecal continence and voiding dysfunction on QoL

Patients (irrespective of type of ARM) who suffered from fecal soiling reported significantly lower scores than patients who do not soil with regard to psychosocial health (71.7 [65.8-80.0] vs. 81.7 [73.3-86.7], p=0.034) and its subscale school performance (65.0 [57.5-70.0] vs. 80.0 [75.0-90.0], p<0.001). The parents of patients who suffered from dysfunctional voiding (either urinary incontinence or need for intermittent catheterization, irrespective of type of ARM) reported significantly lower scores than the parents of patients without urological disturbances on: total score (68.2 [57.6-80.4] vs. 82.6 [73.9-93.7], p=0.005), overall psychosocial health (61.7 [56.7-76.7] vs. 80.0 [70.0-92.5], p=0.002), emotional performance (55.0 [50.0-70.0 vs. 77.5 [65.0-90.0], p=0.005), and social performance (70.0 [50.0-80.0] vs. 85.0 [75.0-100.0], p=0.004).

Table 2A: Quality of life in female ARM patients by patient self-report

	CM (11)	RP/RV (21)	p-value**	Reference values[11]
Total	81.5 (75.0-87.0)	76.1 (69.0-87.0)	0.551	84.2 (10.4)
Physical health	84.4 (75.0-90.6)	81.3 (70.3-92.2)	0.631	88.8 (9.7)
Psychosocial health	78.3 (70.0-86.7)	75.0 (68.3-84.2)	0.604	81.7 (12.2)
Emotional performance	70.0 (65.0-85.0)	75.0 (62.5-82.5)	0.836	78.0 (17.3)
Social performance	85.0 (80.0-95.0)	75.0 (70.0-95.0)	0.388	86.0 (13.4)
School performance	75.0 (65.0-85.0)	75.0 (65.0-85.0)	0.945	81.4 (13.0)

Table 2B: Quality of life in female ARM patients by parent proxy-report

	CM (8)	RP/RV (40)	p-value**	Reference values[11]
Total	80.4 (73.4-84.0)*	82.1 (69.0-91.6)	0.554	87.6 (11.0)
Physical health	92.2 (90.6-98.4)	89.1 (63.3-99.6)	0.260	93.2 (9.1)
Psychosocial health	71.7 (62.8-78.0)*	80.0 (65.4-91.7)	0.124	84.6 (13.2)
Emotional performance	69.1 (57.5-73.8)*	76.3 (57.5-90.0)	0.258	81.1 (17.4)
Social performance	78.8 (66.3-92.5)	81.3 (70.0-98.8)	0.696	90.3 (14.0)
School performance	60.0 (56.3-75.6)*	80.0 (68.1-95.0)	0.003	82.5 (16.3)

CM cloacal malformation group; RP/RV rectoperineal/rectovestibular group.
** Significant difference between cloaca group and reference value, p < 0.05.*
*** p-value describing CM group vs. RP/RV group.*
Data are reported as median (IQR), except for reference values, which are expressed as mean (SD).

Comparison with reference values from the Dutch general population

Reference values were obtained for the Dutch population in a previous study at a mean age of 12.1 years (±3.1), which was not significantly different compared to the cloacal malformation group. Scores obtained from cloacal malformation patients themselves did not differ significantly from the reference values (Table 2A). Parents of cloacal malformation patients reported significantly lower total QoL (p=0.012), emotional (p=0.025) and school performances (p=0.011), as well as a lower general psychosocial health (p=0.012, Table 2B) for their children relative to reference data.

Discussion

To date our study is the first assessing QoL in patients with a cloacal malformation in particular, and the results suggest that self-reported QoL may not differ from that of female patients with less complex ARM. Long-term impairments in colorectal, urological, and gynecological function are common in patients with cloacal malformations.[2] The same impairments are known in female patients with other types of ARM, albeit in lower rates.[1] Still, in the present study QoL-scores in cloacal malformation patients were comparable to those of female patients with other types of ARM and to the Dutch reference population, despite the worse functional outcome in the cloacal malformation group. A possible explanation is that in view of the poor long-term prognosis for patients with a cloacal malformation, coping strategies of both parents and patients have focused on better life quality as was suggested in another study.[12]

Parents of patients with a cloacal malformation perceived lower school performance, but this does not hold for the children involved themselves. The question is whether the proxy-reported scores on school performance reflect actual schooling problems leading to lower educational outcomes, as was suggested in a study of patients with high anorectal malformations[13], or rather parental concern regarding the effect of the child's illness on school performance.[14] Our data do not allow for such conclusions. Not frequent absence from school, but rather the items concerning 'forgetting things' and 'keeping up with schoolwork' scored below average for the patients with a cloacal malformation. Furthermore, school performance and other psychosocial health related outcomes were lower in patients suffering from fecal soiling and dysfunctional voiding, as was found in previous study regarding QoL in ARM patients.[15,16] Thorough, multidisciplinary follow-up is therefore mandatory in these complex patients in order to optimize the treatment of functional bowel and urinary symptoms (e.g. with the use of bowel management and pelvic floor physiotherapy) and to address their effects on psychosocial wellbeing and school performance. The results reported by proxy in this study suggest that familiar involvement in the therapy is essential and that family of patients might also benefit from being offered psychosocial support for coping with the child's illness.

Scores on several domains reported by parents were lower than the Dutch reference data, which, however, was not reflected in the patients' self-reported scores. A large study assessing QoL in chronically ill children with gastrointestinal conditions showed

that patients with functional conditions (such as chronic constipation) reported a worse QoL than patients with organic disease (such as Crohn's and ulcerative colitis).[17] Total QoL-scores reported by cloacal malformation patients in the present study (80.4-81.5) are comparable to those of patients with organic disease (75.6-78.0), but higher than those of patients with functional conditions in that study (70.2-70.5). Possibly, this difference is a consequence of the fact that for both ARM and organic disease anatomical and/or inflammatory substrate can be found, whereas benign functional disorder more than once stay without a clear cause and sometimes even are diagnosed as partially psychological of origin. Conform this, a study by Hartman et al. concluded that QoL in ARM patients is more influenced by psychosocial functioning.[3] This again emphasizes the need for a low threshold for psychosocial guidance throughout (early) childhood and adolescence in these patients and their parents.

The limited sample size of our study may have influenced outcomes in this assessment and may have increased the risk on type II error. This also contributed to the fact that median age of the cloacal malformation group was higher than in the RP/RV comparison group, which may have influenced the results. Unfortunately, the rarity of cloacal malformations makes the reporting of larger samples difficult. A multi-center assessment similar to our study may show other results. A study with a larger group of patients with cloacal malformations would also make it possible to compare patient from different ages groups with each other, as well as patients with different types of cloaca. For instance, patients with long common channels seem to have poorer functional outcome, as well as patients with severe associated anomalies to sacrum and spine.[18] These patients may, therefore, very well have an impaired QoL compared to patients with short common channels and no associated anomalies.

Unfortunately, although our series is one of the largest published, it still gives too limited data to draw such conclusions. Another limitation of our study is the fact that some patients have been lost in follow-up and one may assume that patients who have no long-term complications may not show up anymore. This may explain high rates of associated anomalies and soiling in the group of patients with a rectoperineal or a rectovestibular fistula which we used as a comparison. Also, our study did not assess sexual function as a possible influence for QoL, while it is known that impaired sexual function may lead to severe disturbances in life quality.[19] A future study in a more adult patient population should focus on this matter as well. Lastly, the choice of questionnaire may be questioned. Many different generic questionnaires are available to score

QoL. For example, the HAQL is a questionnaire constructed to score disease-specific QoL in patients with Hirschsprung's disease and anorectal malformations.[20] However, we preferred the PedsQL™ 4.0 as it is easier and less time-consuming than the HAQL questionnaire. Furthermore, the HAQL is not specifically validated for this group of complex patients.

Conclusions

In this study, patients with a cloacal malformation reported similar quality of life as female patients with less complex types of anorectal malformations. Parents of cloacal malformation patients reported comparable QoL compared to parents of RP/RV patients, but lower emotional performance, school performance and psychological health in their child in comparison to data from the Dutch general population. Female patients with ARM reported lower scores when suffering from fecal soiling; lower scores on psychosocial domains were reported by parents of patients suffering from dysfunctional voiding. The long-term assessment of these patients should include a multidisciplinary approach to assess functional problems (with an emphasis on therapeutic strategies such as bowel management programs) as well as periodical assessment of the psychosocial well-being of these patients and their parents.

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Chapter 7

Psychosexual well-being after childhood surgery for anorectal malformation or Hirschsprung's disease

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Psychosexual well-being after childhood surgery for anorectal malformation or Hirschsprung's disease

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ABSTRACT

Introduction	Anorectal malformations (ARM) and Hirschsprung's disease (HD) are congenital malformations requiring pelvic floor surgery in early childhood, with possible sequelae for psychosexual development.
Aims	To assess psychosexual well-being in adult ARM and HD patients related to health-related quality of life.
Methods	Eligible for this cross-sectional two-center study were all patients aged ≥18 years who had been operated for ARM or HD. Exclusion criteria were intellectual disability, comorbidity affecting sexual functioning, and cloacal malformation.
Main outcome measures	Participants completed the International Index of Erectile Functioning (IIEF-15), Female Sexual Functioning Index (FSFI), Female Sexual Distress Scale (FSDS), Hirschsprung and Anorectal Malformation Quality of Life Questionnaire (HAQL), and sexual education questionnaire.
Results	Response rates were 32% and 37% for ARM and HD patients, respectively. We studied 70 participating ARM and 36 HD patients (median age 26 years). We excluded 10 patients with sexual inactivity in the past four weeks. Six of 37 men with ARM (16%) reported moderate to severe erectile dysfunction, versus 2 of 18 men with HD (11%). Thirteen and 10 of 26 women with ARM (50% and 38%) reported sexual dysfunction or sexual distress, respectively, versus 8 and 3 of 15 women with HD (53% and 20%). Quality of life, and type of malformation or operation was not associated with self-reported psychosexual problems. Addressing sexuality with special interest to the congenital anomaly during medical care was reported to be insufficient by 42 ARM (60%) and 22 HD patients (61%).
Conclusion	Approximately 13% of male ARM and HD patients reported erectile dysfunction, while 50% female ARM and HD patients reported sexual dysfunction not related to quality of life or type of malformation. Both ARM and HD patients felt a need for better addressing sexual concerns during medical care. Further research is needed to optimize form and timing of this education.

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Introduction

Anorectal malformations (ARMs) and Hirschsprung's disease (HD) are rare congenital colorectal anomalies. Almost all children with these anomalies require pelvic floor surgery in early childhood. In ARM patients, the pelvic floor is hypoplastic[1] and often a fistula is present from the rectum to perineum or to the urogenital tract. Associated anomalies are frequently of urogenital origin, such as hypospadias -present in 26 to 40% of the male ARM patients[2-4]-, or of the internal reproductive system in females.[5] In HD the distal colon is functionally obstructed due to aganglionosis of the last part of the colon and associated congenital anomalies are less prevalent.[6]

Children operated upon for congenital anomalies are now usually being followed into adolescence. In ARM and HD patients, this follow up generally focuses on continence, because constipation and soiling are still everyday problems (7-40% and 5-45%, respectively).[7,8] However, ARM and HD patients might also be at risk for experiencing psychosexual problems as well, considering the pelvic floor surgeries in both diseases and considering the hypoplastic pelvic floor and urogenital comorbidity in ARM patients. Three studies indeed indicate some form of impaired sexual functioning, e.g. erectile dysfunction, vaginal stenosis or dyspareunia, both in ARM and HD patients.[9-11] These studies were however conducted in small patient groups and results were mostly obtained through self-developed questionnaires, so these results cannot be unequivocally extrapolated. It is important to obtain more detailed information on psychosexual well-being so that we can anticipate in current treatment of psychosexual problems, and so we can improve education and counseling of future ARM and HD patients and their parents.

Aims

The aims of this study were threefold: (1) to investigate whether ARM and HD patients experience sexual dysfunction or sexual distress in adulthood; (2) to investigate whether these problems are related to the type of malformation or to the quality of life; and (3) to determine whether ARM and HD patients in their follow up period missed that their caregiver addressed sexuality and sexual concerns with special interest to the congenital anomaly during medical care.

Methods

Study sample

All patients treated for ARM or HD in one of the two participating university pediatric surgery centers (Erasmus MC – Sophia Children's Hospital, Rotterdam and Amalia Children's Hospital, Radboudumc, Nijmegen, the Netherlands) who were at least 18 years of age at time of the study (i.e. born in 1995 or before) were eligible for inclusion. Excluded were patients with a cloacal malformation, intellectual disability (as documented in the medical records) or severe comorbidity affecting sexual functioning, for example malignancies that required chemotherapy. Patients were identified by a systematic search in the electronic patient files and in databases of patients with congenital anomalies kept by the pediatric surgeons. Patient characteristics were obtained from the medical records. This study was approved by the Erasmus MC Medical Ethical Review Board and the Radboudumc Medical Ethical Review Board. Patients with ARM and HD were analyzed separately because of the great difference in etiology and associated anomalies.

Classifications and procedures

ARMs were classified according to the Krickenbeck classification.[12] Surgical techniques were described as mentioned in the medical records: anoplasty, posterior sagittal anorectoplasty (PSARP), abdominosacroperineal pull through operation (i.e. with laparotomy), and other/unknown operations.

In HD, the length of the aganglionic segment was retrieved from the surgical records and pathology reports and was classified as short (rectosigmoid), long (descending, transverse, and ascending colon), or total colonic aganglionosis. The surgical techniques were described as mentioned in the records and included Rehbein operation, Duhamel operation, and other operations.

Chronic urogenital comorbidity or complications (both further referred to as chronic urogenital comorbidity) that could have a negative influence on sexuality were documented. These included hypospadias, recurrent urinary tract infections, neurogenic

bladder requiring intermittent catheterization, and other congenital anomalies of the genital tract (excluding non-descended testes and phimosis).

Questionnaires

A letter was sent to the patient's last known address with general information on the purpose of this study and the patients were invited to return a reply-card. Those who returned the reply-card were sent more detailed study information, the patient consent form, and questionnaires. The latter two could be returned in a pre-stamped envelope. The following questionnaires were used:

International Index of Erectile Functioning (IIEF-15): The IIEF-15 contains 15 questions covering five domains: erectile function (EF), orgasm, desire, intercourse satisfaction, and overall satisfaction.[13] Reported moderate to severe erectile dysfunction was defined as IIEF-EF score <16.14 The IIEF-15 is cross-culturally normed and linguistic validated for the Dutch language. The reference group compiled 109 men, mean age 55 years.[14]

Female Sexual Functioning Index (FSFI): The FSFI contains 19 questions covering six domains: desire, arousal, lubrication, orgasm, satisfaction, and pain.[15] Sexual dysfunction was defined as a FSFI total score <26.55 (out of a maximum score of 36), normed for the Dutch population The reference population consisted of 198 women with mean age 27 years.[16]

Female Sexual Distress Scale (FSDS): The FSDS contains 12 items solely about sexual distress.[17] Sexual distress was defined as a FSDS score >15 (out of a maximum score of 48), normed for the Dutch population. The reference population consisted of 198 women with mean age 27 years.[16]

Hirschsprung's Disease and Anorectal Malformation Quality of Life Questionnaire (HAQL): The HAQL is a general quality of life questionnaire for ARM and HD patients of both sexes. It contains 51 and 33 questions for patients with and without a stoma, respectively. The HAQL covers the following domains: diet, diarrhea, fecal incontinence, urinary incontinence, social, emotional, body image, physical complaints, and sexuality (the latter covered by only 4 questions about interference of the congenital anomaly

with sexual activity, desire or satisfaction). For each question the responses were linearly transformed to a scale from 0 to 100, higher scores indicating more positive levels of functioning. The domain scores were calculated by averaging the transformed scores of all items belonging to that domain. The HAQL has shown good reliability in Dutch ARM and HD patients.[18] There are no cut-off values available for this questionnaire, as it was meant for comparison between two groups.

Sexual education questionnaire (SEQ): We developed an additional questionnaire for both sexes with the following questions: 1. Did a doctor ever discuss with you sexual issues related to your condition? 2. If yes, was the information enough? 3. If not, would you have liked to receive information? 4. We think it is necessary to educate young people with a condition like yours about sexual issues involved. We can only do this based on experience of adults. Would you be willing to think along with us, for example in an interview, either in person or by telephone? 5. Would you appreciate that we inform your family doctor that you participated in this study? This might make it easier for you to ask questions, or discuss problems with him or her. Note that we will not inform your doctor about your results of this study." These questions could be answered by yes or no. Finally, patients were invited to write additional remarks. This questionnaire was not validated with a control group, as its administration was purely meant as an inventory.

Main outcome measures

Results are given as number (%), mean (standard deviation), or median (interquartile range) as appropriate. Patient characteristics of responders and non-responders were compared with the unpaired t-test, Mann-Whitney U test, or the Chi-squared test, as appropriate. Data of ARM and HD patients were analyzed separately. Because the sexual functioning questionnaires use a four-week period to assess self-reported psychosexual problems, the patients who were not sexually active in the past four weeks were not included in the analyses but are described separately.

The results of the sexual functioning questionnaires (IIEF-15, FSFI, and FSDS) were compared to the reference values using the Wilcoxon signed rank test because the data were not normally distributed. The prevalences of reported erectile dysfunction, sexual dysfunction, and sexual distress were determined using the cut-off values for

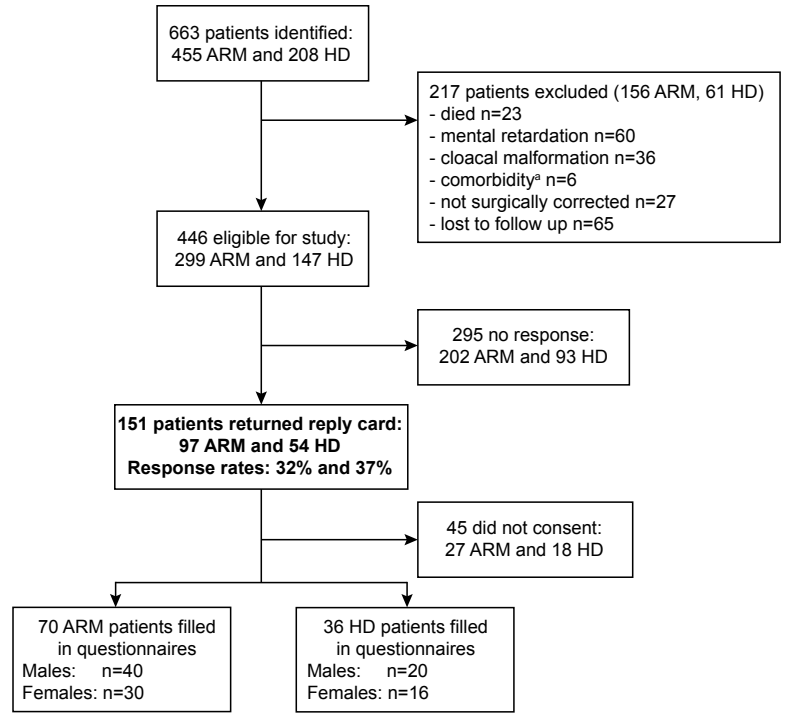
the questionnaires as described above.[14,16] Furthermore, scores below -1.96 SD or above +1.96 SD of the reference population mean (i.e. outside the 95% confidence interval) were considered abnormally low or high and patients with such abnormal scores were recorded.

Correlation between scores of the sexual functioning questionnaires and the domains of the HAQL was explored with Spearman correlation analysis. The results of the SEQ were described as numbers and percentages. All statistical tests were performed with SPSS v. 21 software (SPSS Inc., IBM Corp., Somers, NY, USA) and significance level was set at $p<0.05$.

Results

Of the 455 ARM and 208 HD patients identified, in total 446 patients were eligible for the study (Fig. 1). The characteristics of those who were lost to follow up (n=65) did not

Fig. 1: Flowchart showing inclusion of participants



Abbreviations; ARM, anorectal malformations, HD, Hirschsprung's disease.

[a]these included age>70 yrs at time of study, chemotherapy, meningomyelocele.

Table 1A: Characteristics of anorectal malformation patients

	Responders; n=97	Non-responders; n=202
Male sex	60 (62%)	140 (69%)
Age at time of study (yrs)	26 (23-34)[a]	25 (21-29)[a]
Type anorectal malformation		
Perineal fistula	28 (29%)	81 (40%)
Vestibular fistula	26 (27%)	38 (19%)
Urethral fistula	26 (27%)	61 (30%)
Bladder neck fistula	6 (6%)	7 (3%)
Other	5 (5%)	7 (3%)
Unknown	6 (6%)	8 (4%)
Type of operation		
Anoplasty	28 (29%)	76 (38%)
Abdominosacralperineal pull through	9 (9%)	11 (5%)
Posterior sagittal anorectoplasty (PSARP)	33 (34%)	78 (39%)
Other / unknown	27 (28%)	37 (18%)
Chronic urogenital comorbidity[b]	28 (29%)	41 (20%)

Table 1B: Characteristics of Hirschsprung's disease patients

	Responders; n=54	Non-responders; n=93
Male sex	33 (61%)[c]	81 (87%)[c]
Age at time of study (yrs)	26 (22-33)[d]	24 (22-26)[d]
Type Hirschsprung's disease		
Short segment	27 (50%)	55 (59%)
Long segment	9 (17%)	18 (19%)
Total colonic aganglionosis	4 (7%)	8 (9%)
Unknown	14 (26%)	12 (13%)
Type of operation		
Rehbein operation	41 (76%)	75 (81%)
Duhamel operation	1 (2%)	4 (4%)
Other / unknown	12 (22%)	14 (15%)
Chronic urogenital comorbidity[b]	0	0

Results are presented as n (%) or as median (IQR).

[a] p=.013, Mann-Whitney U test. [b] Chronic urogenital comorbidity comprised mainly hypospadias (n=29), recurrent urinary tract infections (n=19), neurogenic bladder requiring intermittent catheterization (n=7), and congenital anomalies of the genitalia (excluding non-descended testes). [c] p=.000, Chi-squared test. [d] p=.027, Mann-Whitney U test.

differ from those who could be traced (n=446, data not shown). The reply-cards were returned by 32% and 37% of the ARM and HD patients, respectively. Tables 1a and 1b show the characteristics of responders and non-responders. Twenty-seven ARM patients and 18 HD patients responded but did not give consent to participate in the study. In total 70 ARM patients (40 men and 30 women) and 36 HD patients (20 men and 16 women) participated and completed the questionnaires.

Anorectal malformation patients

Thirty-nine of 40 participating male ARM patients completed the IIEF-15, the remaining patient did not because he was not sexually active (an 18 year old man operated for ARM type urethral fistula, associated anomalies were unilateral radius aplasia and urethral duplicature). Two additional male ARM patients were not sexually active in the past four weeks (age 21 and 50 years, both had ARM type perineal fistula, associated anomalies were duodenal atresia and kidney agenesis, respectively). The scores of the IIEF-15 of the sexually active patients were comparable to the reference scores, except for the sexual desire score, which was higher (i.e. more positive; p=.001; Table 2a). Six men (16%) reported moderate to severe erectile dysfunction; two of them (5% of the study group) scored under -1.96 SD of the IIEF-EF. Concerning ejaculation, 4 men answered the question "how often did you ejaculate in the last 4 weeks" with "almost never/never" or "a couple of times". Overall, male ARM patients scored relatively high on the HAQL, as all median domain scores were over 80 out of maximum 100. A significant positive correlation between total score of the IIEF-15 and the scores on the HAQL was found for the domains: constipating diet (rs=.330, p=.046), fecal continence (rs=.402, p=.018), urinary continence (rs=.370, p=.024), body image (rs=.364, p=.027), physical symptoms (rs=.345, p=.046), and sexual functioning (rs=.436, p=.007).

Of the 30 participating female ARM patients, one did not complete the sexual functioning questionnaires because she was not sexually active (an 18 year old woman operated for ARM type vestibular fistula without significant associated anomalies). Three additional female ARM patients were not sexually active in the past four weeks (two had ARM type perineal fistula, one ARM type vestibular fistula, ages 21, 34, and 54 years, the last patient also had esophageal atresia). Of the sexually active patients all domain scores of the FSFI except the domain orgasm were significantly lower than the reference scores (Table 2b), indicating that these women experience sexual dys-

Table 2A: Results of questionnaires – male patients

	ARM; n=40		HD; n=20		Reference
	Score	p-value[a]	Score	p-value[a]	
Not sexually active in past four weeks[b]	n=3		n=2		
International Index of Erectile Functioning (IIEF-15)[c]					
Erectile functioning	29 (4)	0.208	29 (1)	0.026	*25.8 ± 7.6*
Orgasmic functioning	10 (2)	0.093	10 (1)	0.001	*8.8 ± 2.9*
Sexual desire	8 (1)	0.001	8 (2)	0.006	*7.0 ± 1.8*
Intercourse satisfaction	12 (3)	0.036	12 (3)	0.047	*10.6 ± 3.9*
Overall satisfaction	9 (3)	0.578	8 (2)	0.098	*8.6 ± 1.7*
Hirschsprung and Anorectal malformation Quality of Life questionnaire (HAQL)[c]					
Laxative diet	100 (0)	-	100 (16.7)	-	-
Constipating diet	100 (16.7)	-	83.3 (33.3)	-	-
Presence of diarrhea	100 (16.7)	-	66.7 (50.0)	-	-
Fecal continence	95.8 (8.3)	-	100 (12.5)	-	-
Urinary continence	100 (8.3)	-	100 (16.7)	-	-
Social functioning	100 (11.1)	-	88.9 (22.2)	-	-
Emotional functioning	90.5 (22.6)	-	81.0 (19.1)	-	-
Body image	91.7 (33.3)	-	83.3 (33.3)	-	-
Physical symptoms	83.3 (21.1)	-	70.8 (22.2)	-	-
Sexual functioning	100 (16.7)	-	100 (16.7)	-	-

Results are presented as median (IQR). Reference scores are presented as mean (SD). Abbreviations: ARM, anorectal malformations; HD, Hirschsprung's Disease.

[a]Tested to the reference values, Wilcoxon's Signed rank test.

functioning. The median FSDS score was significantly higher than the reference score, indicating more experienced sexual distress. Thirteen women (50%) reported sexual dysfunctioning, of whom 9 (35% of the study group) scored under -1.96 SD of the normative population. Ten women (38%) reported sexual distress, of whom all 10 scored over +1.96 SD. Nine women reported both sexual dysfunctioning and sexual distress. Median HAQL score for female ARM patients for the domain physical symptoms was 70.4 (22), while the other median domain scores all were over 80. The total score of the FSFI did not correlate significantly with any of the HAQL domains (data not shown). The FSDS score had a significant negative correlation with the HAQL domains body image (rs=-.410, p=.037) and sexual functioning (rs=-.415, p=.039).

Table 2B: Results of questionnaires – female patients

	ARM; n=30		HD; n=16		Reference
	Score	p-value[a]	Score	p-value[a]	
Not sexually active in past four weeks[b]	n=4		n=1		
Female Sexual Functioning Index[c]	26.2 (10.9)	0.000	26.5 (10.7)	0.030	*31.2 ± 3.9*
Desire	3.6 (1.9)	0.023	3.6 (1.2)	0.170	*4.0 ± 0.8*
Arousal	4.8 (1.3)	0.012	5.1 (1.5)	0.393	*5.3 ± 0.8*
Lubrication	5.4 (1.0)	0.002	5.7 (1.5)	0.059	*5.7 ± 1.0*
Orgasm	4.8 (1.7)	0.096	5.2 (1.2)	0.531	*5.1 ± 1.1*
Satisfaction	4.6 (3.9)	0.002	5.2 (2.8)	0.049	*5.4 ± 0.8*
Pain	4.0 (4.0)	0.000	5.2 (3.6)	0.026	*5.7 ± 0.8*
Female Sexual Distress Scale (FSDS)[d]	13.5 (18)	0.000	5.0 (14)	0.495	*5.1 ± 6.4*
Hirschsprung and Anorectal malformation Quality of Life questionnaire (HAQL)[c]					
Laxative diet	100 (29.2)	-	83.3 (50.0)	-	-
Constipating diet	100 (12.5)	-	100 (16.7)	-	-
Presence of diarrhea	83.3 (16.7)	-	83.3 (33.3)	-	-
Fecal continence	91.7 (20.8)	-	95.8 (8.3)	-	-
Urinary continence	100 (22.9)	-	100 (8.3)	-	-
Social functioning	100 (30.1)	-	100 (33.3)	-	-
Emotional functioning	83.3 (23.8)	-	76.2 (28.6)	-	-
Body image	83.3 (50.0)	-	83.3 (50.0)	-	-
Physical symptoms	70.4 (22.2)	-	66.7 (37.0)	-	-
Sexual functioning	91.7 (33.3)	-	100 (33.3)	-	-

Results are presented as median (IQR). Reference scores are presented as mean (SD). Abbreviations: ARM, anorectal malformations; HD, Hirschsprung's Disease.

[a]Tested to the reference values, Wilcoxon's Signed rank test.

In both male and female ARM patients, the type of malformation and type of operation did not differ between the patients who reported psychosexual problems and who did not (Online Supplemental Table 3a). In 5/70 ARM patients (7%) sexuality and sexual concerns with special interest to the congenital anomaly were addressed during medical care (Fig. 2). Four of those five found the education sufficient. Of the other 65 ARM patients, 42 felt a need for education (60%). This was the case for 5/6 (83%) men who reported erectile dysfunction, 10/13 (77%) women who reported sexual functioning problems, and 7/10 (70%) women who reported sexual distress. In addition, 18/31 (58%) men without erectile dysfunction, and

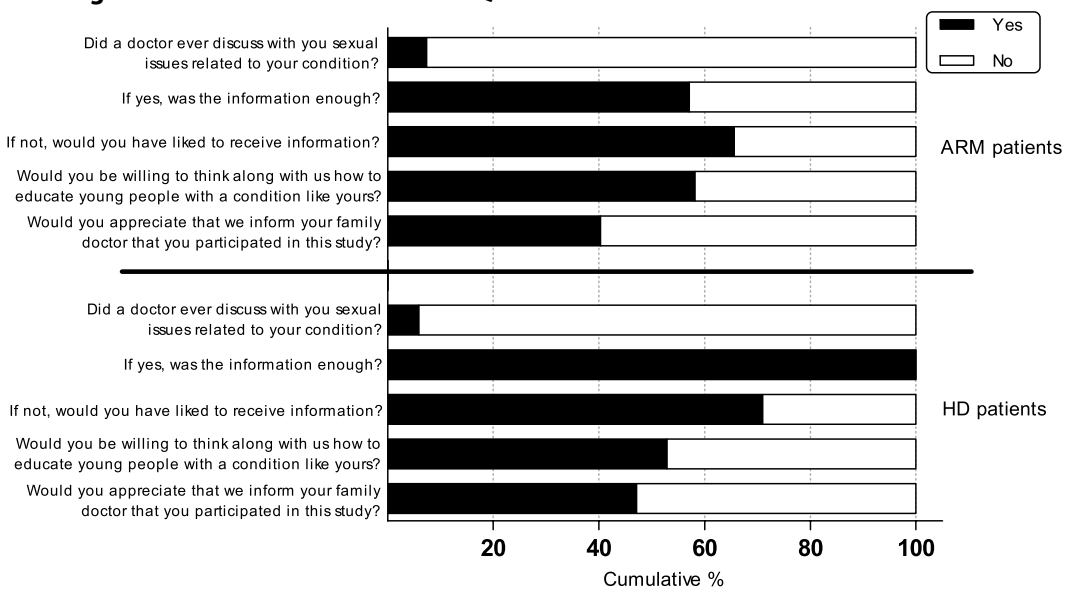
7/13 (54%) and 10/16 (63%) women without sexual functioning problems and without sexual distress, respectively, also felt a need for addressing sexuality and sexual concerns with special interest to the congenital anomaly during medical care. Thirty-eight patients (59%) offered to help find out what sexual education would be best suited for new ARM patients.

Hirschsprung's disease patients

Twenty male HD patients completed the questionnaires. Two patients were not sexually active in the past four weeks (age 19 and 28 years, the first had short segment and the latter long segment HD, neither had associated anomalies). Overall, the scores of the IIEF-15 of the sexually active patients were higher than the reference scores, indicating more positive functioning (Table 2a). Moderate to severe erectile dysfunction was reported by two men (11%; one had Svenson procedure, and one unknown), of whom one (6% of the male HD patients) scored under -1.96 SD. None reported ejaculation difficulties. Male HD patients scored under 80 on the HAQL domains presence of diarrhea and physical symptoms (median scores 66.7 and 70.8, respectively). The other median domain scores were all above 80. There was no significant correlation between the IIEF-15 total score and any of the HAQL domains (data not shown).

Sixteen women with HD completed the questionnaires. One patient was not sexually active in the past four weeks (she was 22 years of age and had short segment HD without associated anomalies). Of the sexually active patients, the total score of the FSFI and the scores on the domains satisfaction and pain were significantly lower than the reference scores (Table 2b). The median FSDS score did not differ from the reference score. Eight women (53%) reported sexual functioning problems, of whom 6 (40% of the study group) scored under -1.96 SD. Three women (20%) reported sexual distress; two of them scored over +1.96 SD. Female HD patients scored under 80 on the HAQL domains emotional functioning and physical symptoms (median scores 76.2 and 66.7, respectively). The other median domain scores were all above 80. There was no significant correlation between the FSFI and any of the domains of the HAQL (data not shown). There was a significant negative correlation between the FSDS score and the scores on the HAQL domains social functioning (rs=-.712, p=.004) and sexual functioning (rs=-.573, p=.026).

Fig. 2: Results of Sexual Education Questionnaire



Abbreviations; ARM, anorectal malformations, HD, Hirschsprung's disease.

In both male and female HD patients, both aganglionic length and type of operation did not differ between those who reported psychosexual problems and those who had not (Online supplementary table 3b). Two of the 36 HD patients had received sexual education (6%), while 22/36 patients (61%) did not but felt a need for this education (Fig. 2). This was the case for both men who reported erectile dysfunction, 7/8 (88%) women who reported sexual dysfunctioning, and all three women who reported sexual distress. In addition, 8/16 (50%) men without erectile dysfunction, and 3/7 (43%) and 7/12 (58%) women without sexual functioning problems or sexual distress also felt a need for addressing sexuality and sexual concerns with special interest to the congenital anomaly during medical care. In total 18 patients (50%) offered to help find out what education would be best for new HD patients.

Discussion

The hypothesis of this study was that ARM and HD patients are at risk for self-reported psychosexual problems. Sixteen percent of the male ARM patients and 11% of the male HD patients reported moderate to severe erectile dysfunction. Sexual dysfunction was reported by 50% and 53% of the female ARM and HD patients, respectively;

and sexual distress by 38% and 20%, respectively. Overall, quality of life was reported as being good and correlated with the total IIEF-15 score of ARM patients, but less convincingly with the other self-reported psychosexual scores. More than half of the patients missed addressing sexuality and sexual concerns with special interest to the congenital anomaly during medical care.

In this study we aimed to determine the prevalence of self-reported psychosexual problems in ARM and HD patients. The reported prevalence of moderate to severe erectile dysfunction of approximately 16 and 11% for ARM and HD patients is higher than the 5% prevalence in 40-year-olds in the normative Australian population.[19] However, there is a discrepancy when comparing the continuous data (i.e. the median scores) to the reference scores, because it then appears that self-reported erectile function in ARM and HD patients is comparable or even better than the reference population. Concerning female patients, Witting and co-workers aimed to determine the prevalence of reported female sexual distress (FSDS<26.55) in a healthy study population, and found this to be 33%. However, they found a natural cut-off limit of FSDS<13, and with this new cut-off value the prevalence of sexual distress was 5%.[20] Because of this discussion on the cut-off limits, we additionally analyzed how many participants scored under -1.96 SD, so that only 2.5% of the study population should score under this value. In this case, 5% and 6% of the men with ARM and HD reported erectile dysfunction. It should be noted however that the median age of our study population was lower than that of the reference population (26 years vs. 55 years), which might explain the fair results found on erectile function. Using the 1.96 SD cut off limit, women with ARM and HD reported sexual dysfunction in 35% and 40%, respectively, and sexual distress in 38% and 13%, respectively, which all are still higher than the reference population.

Concerning ARM patients, the findings of this study are in line with the literature, as the prevalence of erectile dysfunction in ARM patients has been described to be 6-41%, depending on number of patients and definitions.[11,21,22] For female ARM patients, dyspareunia has been described in up to 63% in patients with vestibular fistula or cloacal malformations.[11] Concerning HD, compared to the study of Moore and co-workers, who found that 5% (14/175) of the HD patients had some form of sexual dysfunction including erectile dysfunction, dyspareunia, and infertility (mean age 10 years)[9], our findings are less favorable for both male (11% reported erectile dysfunction) and female HD patients (53% reported sexual dysfunctioning). Besides the difference in mean age of the study population, a reason for this difference could be the methodological differences, as we collected the data from questionnaires filled in at home, while the above studies used personal interviews or interviews by phone. This may have caused that interviewees felt embarrassed to report psychosexual problems. There also may have been an inclusion bias as they did not clearly specify the inclusion process. In this study we aimed to overcome these biases so that the results can be extrapolated more freely.

In this study we related self-reported psychosexual problems to the type of malformation and type of operation; however a clear relationship could not be found. Other possible causes for experiencing psychosexual problems in this patient group could be: (1) abnormal anatomy of the pelvic floor and reproductive organs, (2) abnormal innervation, either congenital or as a consequence of reconstructive surgery, or (3) abnormal psychosexual development.

First, the cause could lie in associated genitourinary anomalies, as hypospadias occurs in 26-40% of the male ARM patients[2-4] and a vaginal septum in 5% of the female ARM patients.[5] Besides these congenital anomalies, dyspareunia may be caused by scarring of the vagina during the correction of the rectovestibular fistula or of the vaginal septum. Most of the ARM patients underwent anoplasty or the PSARP operation, which are still the preferred operations for this condition. There has been a shift, however, in the preference of the operative technique for Hirschsprung's disease, i.e. from the Rehbein operation, performed in 76% of the patients, to the currently preferred transanal pull through. The transanal pull through, often with laparoscopy to mobilize the rectum[23,24], is less invasive and involves dissection closer to the colon, and therefore minimizes damage to innervation of the pelvic floor and reproductive organs. Further studies are needed to determine if psychosexual well-being is indeed more favorable with the transanal pull through operation. Further studies are needed to determine if psychosexual well-being is indeed more favorable with the transanal pull through operation.

A second cause for experiencing psychosexual problems could lie in abnormal innervation of the pelvic floor. Female ARM and HD patients scored significantly lower on all domains of the FSDS than the normative population, and the lowest score was for pain. It could be that the perineal branches of the pudendal nerve are hypoplastic, the sacrum is hypoplastic, or a tethered spinal cord may be present. Another possibility is

that the perineal branches are damaged during final repair, causing pain or problems with lubrication. Especially in HD the cause of self-reported psychosexual problems could have an iatrogenic component, as the pelvic floor is not thought to be hypoplastic. In contrast to the reported psychosexual problems in female patients, problems with ejaculation was reported by only four ARM patients. It appears that the internal urethral sphincter -and its afferent sympathetic nerves- that closes the proximal urethra during ejaculation remains intact in most cases, although we did not perform actual diagnostic tests to detect retrograde ejaculation or other ejaculation disorders.

Besides the anatomical abnormalities, either due to congenital anomalies or due to reconstructive surgery, the self-reported psychosexual problems could be the result of abnormal psychosexual development. Most children with ARM and HD require frequent anal dilatations to prevent anal stenosis after reconstructive surgery. These dilatations, sometimes combined with an intensive bowel management program -e.g. daily rectal washouts- or accompanied by recurrent urinary tract infections, can result in repetitive negative attention to the genital area. Although this was beyond the scope of this study, it can become a source of tension between parents and child and interfere with and possibly delay sexual development.[25] In addition, fear of pain in the genital region can cause problems with arousal and so create a vicious circle. The anal dilatations have even been associated with dissociative disorder.[26] It remains speculative if dissociation is a causative agent for the absence of correlation between reported psychosexual impairment and quality of life. Other psychosocial comorbidity could be of influence on sexuality, too, for example feelings of depression or anxiety.[27] Further studies are needed to determine the exact cause of reported psychosexual problems in ARM and HD patients.

The main limitation of this study is a selection bias, which is inherent to the cross-sectional nature of this study. Firstly, patients with many post-operative complications are usually followed longer, and are therefore easier to trace than patients without complications or continence problems. Secondly, patients who experience more psychosexual problems and patients who have missed addressing sexual issues related to their anomaly could be more willing to participate than those who had not missed the education. Lastly, patients without any problems who do not recognize the need to educate future patients on this subject may have been less inclined to participate. Nevertheless, considering that type of ARM and HD did not differ between the responders and non-responders, and that initial response rates were respectively 32 and 37%, we think that the results of this study can be extrapolated. Other factors that are of influence on psychosexual well-being such as age of first sexual experience, homosexuality, and influential lifestyle factors, such as smoking habit, hypertension, obesity, religion, relationship status, and educational level –although those with intellectual disability were excluded from the study- were beyond the scope of this study.[28]

A most surprising finding was that more than half of the patients did not receive information on sexual issues related to their condition from a medical doctor, but would have liked. This concerned not only patients who reported psychosexual problems, but also those who did not report psychosexual problems. We would like to plea for addressing sexuality and sexual concerns with special interest to the congenital anomaly during medical care in relation to the malformation for all ARM and HD patients. Because this is a delicate subject, especially for teenagers, the most ideal timing and form of education and by whom it should be provided should be determined in collaboration with the study participants who consented to be part of this process.

Conclusion

Up to one sixth of the men and up to half of the women with ARM and HD reported some form of self-reported psychosexual problems. This was not related to the type of ARM or the length of aganglionosis. More than half of the patients did not receive information on sexual issues related to their condition by a medical doctor, but would have appreciated this. Therefore appropriate education is systematically required so patients know who to consult in case of problems. Further research is needed to determine the optimal form and timing of this education, and by whom it is best provided.

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Online supplementary Table 3a: Characteristics of anorectal malformation patients with psychosexual dysfunction

	Men with ED n=6	Men without ED n=31	Women with sexual functioning problems n =13	Women without sexual functioning problems n =13	Women with sexual distress n =10	Women without sexual distress n =16
Age at time of study (yrs)	28 (9.8)	28 (11.8)	24 (16.2)	25 (8.2)	23 (6.8)	27 (13.2)
Type anorectal malformation						
Perineal fistula	2 (33%)	10 (32%)	0	2 (15%)	1 (10%)	1 (6%)
Vestibular fistula	-	-	10 (77%)	10 (77%)	7 (70%)	13 (81%)
Urethral fistula	4 (67%)	12 (39%)	-	-	-	-
Bladder neck fistula	0	4 (13%)	-	-	-	-
Other	0	2 (7%)	2 (15%)	1 (8%)	1 (10%)	2 (13%)
Unknown	0	3 (10%)	1 (8%)	0	1 (10%)	0
Type of operation						
Anoplasty	1 (17%)	9 (29%)	3 (23%)	3 (23%)	2 (20%)	4 (25%)
Abd. sacralperineal pull through	2 (33%)	5 (16%)	0	1 (8%)	0	1 (6%)
PSARP	2 (33%)	7 (23%)	4 (31%)	8 (62%)	6 (60%)	6 (38%)
Other / unknown	1 (17%)	10 (32%)	6 (46%)	1 (8%)	2 (20%)	5 (31%)
Chronic urogenital comorbidity	3 (50%)	10 (32%)	3 (23%)	4 (31%)	2 (20%)	5 (31%)

Results are presented as n (%) or as median (IQR). Abbreviations: ED, erectile dysfunction.

None of the characteristics was significantly different between men with and without erectile dysfunction nor between the women with and without sexual functioning problems and sexual distress (Chi-squared test and independent samples t-test, data not shown). Two patients (one male and one female) did not complete the questionnaire because he / she was not yet sexually active.

Online supplementary Table 3b: Characteristics of Hirschsprung's disease patients with psychosexual dysfunction

	Men with ED n=2	Men without ED n=16	Women with sexual functioning problems n =8	Women without sexual functioning problems n =7	Women with sexual distress n =3	Women without sexual distress n =12
Age at time of study (yrs)	60 (59 and 61 yrs)	25 (5.9)	31 (10.2)	28 (14.0)	33 (range 32 to 40 yrs)	28 (16.3)
Type Hirschsprung's disease						
Short segment	1 (50%)	9 (56%)	6 (75%)	3 (43%)	2 (67%)	7 (58%)
Long segment	1 (50%)	3 (19%)	1 (13%)	0	0	1 (8%)
Total colonic aganglionosis	0	1 (6%)	1 (13%)	1 (14%)	1 (33%)	1 (8%)
Unknown	0	3 (19%)	0	3 (43%)	0	3 (25%)
Type of operation						
Rehbein operation	0	12 (75%)	7 (88%)	6 (86%)	2 (67%)	11 (92%)
Duhamel operation	0	0	0	1 (14%)	0	1 (8%)
Other / unknown	2 (100%)	4 (25%)	1 (13%)	0	1 (33%)	0
Chronic urogenital comorbidity	0	0	0	0	0	0

Results are presented as n (%) or as median (IQR). Abbreviations: ED, erectile dysfunction.

Only the age at time of study was significantly different between women with and without sexual distress (p=.044a, independent samples t-test), the other characteristics between men with and without erectile dysfunction or between the women with and without sexual functioning problems and sexual distress did not differ significantly (Chi-squared test and independent samples t-test, data not shown).

PART 3: DISCUSSION AND SUMMARY

Chapter 8

General discussion and recommendations

One of the most alluring aspects of the pediatric surgery practice is the long-term follow up of patients with congenital anomalies. It is a good opportunity –and an obligation as well- to actually see the results of your work and to see how the children develop, not only physically but also psychosocially, and to see how they finally participate in society. Therewith presents the unique opportunity to combine research of short-term outcomes with that of long-term outcomes, even into adulthood. In this thesis, we aimed to optimize care of anorectal malformation patients with a multidisciplinary approach, and pioneered in the long-term follow up of this patient group.

Neonatal care

Upon birth of a child with an anorectal malformation, the neonate is first stabilized and transferred to a pediatric surgery center, then the appearance of meconium at the pelvic floor is awaited for 16 to 24 hours.[1,2] If meconium appears at the pelvic floor, which means there is a perineal or vestibular fistula, primary reconstruction can be performed either in the neonatal period or later in life.[3,4] Otherwise, a colostomy must be created to decompress the bowel.[4,5] This procedure is essential, but it is associated with a high complication rate up to 50%. The most frequent complications are being excoriation and prolapse.[6] The type and location of the colostomy are mainly surgeon-dependent. Therefore the following research question was formulated:

What is the ideal type and place for colostomy creation in anorectal malformation patients?

From a retrospective case study and systematic review of the literature (*Chapter 1*) it was concluded that split colostomies in the descending or sigmoid colon are associated with the lowest complication rate. However, a great limitation of this study was that all studies included in the systematic review were retrospective case studies and that type and location remained surgeon-dependent. In addition, description of complications differed between the included studies, which was reflected by the wide range of complication rates reported -how severe must an excoriation be to be called a complication? A randomized controlled trial might seem an obvious solution, but this is not achievable because of the rarity of anorectal malformations and because the circumstances during the surgery differ for each patient, requiring a patient-centered approach with expert-based decisions of the surgeon. A more workable alternative

is international registration of anorectal malformation patients, including colostomy complications. For example through ARM-Net, which is an international web-based anonymized meta-registry of anorectal malformations.[7,8] Then, complications can be registered in a structured manner and the complication rates can be determined more precisely. All in all, colostomy complications remain prevalent in anorectal malformation patients, and there are some aspects of the creation of a colostomy that require special attention.

The first aspect is that orientation might be difficult when the bowel is distended. When creating a sigmoid colostomy, there is a risk that the stoma is placed too distally on the sigmoid colon, and consequently there might be insufficient bowel length left to create the neo-anus during the posterior sagittal anorectoplasty (PSARP), making colostomy revision inevitable.[9,10] It therefore appears to be safer to perform a descending colostomy. However, whenever it is not clear what part of the colon is descending or sigmoid, a transverse colostomy is a reasonable alternative.

When it is necessary to perform a transverse colostomy, one complication that must be prevented is prolapse. It is important to make the opening in the abdominal wall not too wide when the bowel is distended. A second trick is tethering of the distal loop –the most mobile part of the colon- to the peritoneum, as well as suturing the afferent and efferent loop to the abdominal wall.[11,12] Umbilical loop colostomies are still under research, but it is reassuring that the first case series show promising results in terms of complication rate and cosmetic outcome.[13,14]

The best method to prevent colostomy complications is primary repair of the anorectal malformation, which is safe in patients with perineal or vestibular fistula.[3,4] Furthermore, a small case series from a developmental country documented good functional results of primary repair of 'high malformations', including rectourethral fistula, rectovaginal fistula, and anorectal malformation without fistula.[15] However, awaiting confirmation in a larger case series, we still need to perform a colostomy in many anorectal malformation patients. From the currently available evidence, it can be concluded that the most ideal colostomy in anorectal malformation patients is split descending colostomy. As it is a meticulous procedure requiring great expertise, we recommend that only pediatric surgeons who are experienced in this field should perform this procedure.

Screening for associated anomalies

More than half of the anorectal malformation patients have associated anomalies[16-18], which can be part of a syndrome in 4-11% of cases[19] or part of the VACTERL-association (Vertebral, Anal, Cardiac, Tracheo-Esophageal, Renal, Limb) in 10-17% of cases[20,21] when VACTERL-association is defined as three or more components present while no other genetic disorder is present.[22,23] It is important that in VACTERL-association other possible genetic disorders are excluded by a clinical geneticist.

All anorectal malformation patients are screened for anomalies that are part of the VACTERL-association. The screening consists of an x-ray of the spine (V), an ultrasound of the heart (C), insertion of a nasogastric tube and x-ray of the chest (TE), and an ultrasound of the abdomen (R).[24,25] Limb anomalies are initially clinically diagnosed, followed by further examinations (e.g. x-ray) if indicated. In our practice, we had the impression that upper limb anomalies were frequently associated with a genetic disorder, and therefore the following question was raised:

Are anorectal malformation patients with an upper limb anomaly more frequently diagnosed with a syndromal disorder than are anorectal malformation patients with other associated anomalies?

To find the answer to this question, we performed a large retrospective case study in 700 patients from two pediatric surgery centers (*Chapter 2*). The results suggest that the answer to this question is yes; approximately twice as many patients with an upper limb anomaly were diagnosed with a genetic disorder –excluding VACTERL association.

One of the most prevalent upper limb anomalies seen in anorectal malformation patients is thumb hypoplasia. Thumb hypoplasia is of special importance because it can be associated with Fanconi anemia[26], which was detected in one patient of our study sample. Fanconi anemia should be detected in early life, not only in view of the clinical consequences for the child, but also to allow genetic counseling of the parents as it often is an autosomal recessive or x-linked recessive disorder.[27] Thus, it is highly important not to overlook upper limb anomalies during VACTERL screening. Furthermore, a clinical geneticist should always be consulted to detect any facial dysmorphisms, subtle limb anomalies, and to determine if further genetic investigations are necessary. A

flow chart for genetic work up of anorectal malformations was proposed in *Chapter 2*, but diagnosing a genetic disorder nowadays still requires a patient-centered approach because of the great number of different genetic disorders that can be diagnosed.

In the future, with detailed registration of anorectal malformation patients, for example through ARM-Net, a more specific genetic workup may be proposed and become more evidence-based. In addition, with the rapid advances in genetics in the last decades and the coming of Next Generation Sequencing, the prevalence of detected syndromes and their genetic etiology may rise further and provide new insights.[28] A disadvantage of the rapid advances is that secondary variants will also be detected, and health care costs could rise dramatically. It seems appropriate to use Next Generation Sequencing in research and in patients with multiple congenital anomalies in whom the clinical geneticist can detect no syndromal disorder, although detailed informed consent procedures for the parents must be in place.[29]

Besides forthright vertebral anomalies, anorectal malformations are also associated with tethered spinal cord in 10-17% of cases.[20,21] In tethered spinal cord, caudal traction on the conus medullaris may result in symptoms such as motor weakness or gait difficulties, lower limb deformities, bowel or bladder dysfunction, and pain in the lower back or legs. Tethered cord syndrome refers to symptomatic tethered cord. Because the possibility of this association, screening for tethered spinal cord is often performed parallel to the VACTERL screening[28,30], either with ultrasound or MRI[28]. The advantages of ultrasound over MRI are that it is easily available, cheaper, and that it can be performed in the awake patient without need for a specific setting, although it is less sensitive and specific than MRI. However, questions remained on the clinical relevance of screening for tethered cord:

What is the use of screening for tethered spinal cord in anorectal malformation patients, and what is the outcome of these patients?

A retrospective case study was performed (*Chapter 3*), describing the test parameters of spinal ultrasound as screening tool for tethered spinal cord. Sensitivity was found to be 80%, specificity 89%, and positive and negative predictive values were 47% and 97%, respectively. However, the results could have been strongly influenced by the fact that not all patients with an abnormal ultrasound subsequently underwent an MRI. It remains unknown if it would have had a positive or negative effect on the sensitivity

and specificity. Other studies show a varying sensitivity of 15-71%, but all reported a high specificity of 90-100%.[20,31,32] Therefore, ultrasound seems a fairly effective screening method, but the possibility of false-negative results should be kept in mind, especially when a child develops symptoms suggestive for tethered spinal cord syndrome.

8

The value of screening with spinal ultrasound does not primarily lie in the parameters of the diagnostic test, but more in the clinical consequences of the tethered spinal cord. Clear indications are needed when to perform an MRI and when to surgically untether the spinal cord, which indications both the present study and the current literature do not provide. Concerning continence problems, we may ask ourselves: are continence problems the consequence of the tethered spinal cord or of the anorectal malformation and associated urogenital anomalies? Fecal and urinary continence have been described not to improve after untethering surgery in anorectal malformation patients[21,33,34], while they did improve in 20-70% of occult tethered cord syndrome patients –thus without an anorectal malformation- depending on the definition of continence problems.[35,36] Thus, it remains speculative whether fecal and urinary continence problems are the consequence of the tethering of the spinal cord, the anorectal malformation, or perhaps both.

In contrast to the opinion that only patients with symptomatic tethered spinal cord should be operated on[37], prophylactic untethering has also been advocated[34,38]. Low direct complication rates have been described (0-6%), although retethering requiring surgical revision was needed in 9-25% of the patients.[35,38] The mean age of the patients at untethering surgery in these studies was 3.5 to 4.6 years (mean follow up 2.3 years), while retethering occurred mostly within two years. The most important motivation for prophylactic untethering surgery is the conviction that tethered spinal cord is a progressive disorder and deterioration is inevitable. However, this conviction has been proved wrong as no more than 18-25% of the patients develop tethered cord syndrome[37] –although this still is a considerable proportion- while spinal lipomas have been described to regress spontaneously.[39] A randomized controlled trial of occult tethered cord syndrome has been proposed to shine light on this issue.[40] Although anorectal malformations are rare, and tethered spinal cord occurs in 9% of the anorectal malformation patients, it would be interesting to also include anorectal malformation patients as a separate group in such a study –as tethered cord is usually detected in earlier life and associated congenital anomalies complicate the measurement of continence problems- to find out if a wait and see approach is indeed justified.

Seeking alternatives or supplements to spinal ultrasound screening, three come to mind. The first is to educate the parents, since mainly gait abnormalities and pain in the legs tend to improve after untethering surgery. In that case, education should be provided timely, as most patients already become symptomatic at approximately three to five years of age. However, since parents of anorectal malformation patients are already burdened by aspects of the malformation itself[41,42], continence and bowel management, and often also by associated anomalies, additional education for tethered spinal cord might not be efficient. The second is to perform follow-up neurologic examinations at regular intervals. However, the right timing of these examinations must be determined first, as it is not yet clear when patients will develop symptoms. This could be done with the study proposed above. Third, consistent MRI screening of all anorectal malformation patients could be considered, as this is seen as the gold standard for diagnosing tethered cord. Recently, MRI has been described as an accurate method to visualize the type of anorectal malformation[43] and when an MRI is considered, spinal cord anomalies can also be visualized. However, it should be noted that only screening patients with a rectourethral or vesical fistula does not seem appropriate, as an equal proportion of patients with perineal or vestibular fistula have tethered cord.[38]

8

Concluding, screening ultrasound for tethered spinal cord seems a fairly effective method, however it should be kept in mind that the result might be false-negative. When a patient develops symptoms such as gait abnormalities or lower limb deformities, an MRI should be performed to exclude tethered spinal cord. A prospective multicenter study in which the criteria for performing an MRI and untethering surgery are clearly defined is needed before more definite conclusions can be drawn.

Surgical treatment and continence

An anorectal malformation is surgically corrected either primarily or secondarily –i.e. after creation of a colostomy. The current surgical technique is the PSARP procedure for all types of anorectal malformation.[44] In case of a high fistula (a prostatic or bladder neck fistula) the PSARP procedure can be combined with an abdominal laparoscopy (LAARP, laparoscopic assisted anorectoplasty) to help identify the fistula and dissect the rectum.[45-47] This procedure was not further investigated in the thesis as international consensus has already been established.[48]

In the past, different scoring systems for bowel function were applied, e.g. Kelly score[49], Holschneider score[50], Rintala score[51], and Rome III criteria[52], making it difficult to compare different studies. Most recently, the Krickenbeck score has been adopted to measure postoperative results.[53] The Krickenbeck score was used in our studies and described in *Chapter 5*.

All in all, the prognosis concerning continence of anorectal malformation patients seems mainly dependent on the type of malformation[54] and sacral agenesis[55]. Voluntary bowel movements have been reported for 80-90% of patients with a perineal fistula vs. 34-58% of patients with a urethral fistula, while severe constipation, resistant to diet and laxatives, has been described in 8-21% of patients with a perineal fistula and in 17-42% of patients with a urethral fistula.[54,56] As bowel function and continence have received great attention in the literature[55,57-60], this was not the main scope of this thesis and an overview of other prognostic factors for continence is presented in the Preface section of this thesis.

Preschool age

It can be hypothesized that physical and mental development of anorectal malformation patients is at risk, as many patients require repetitive hospital admissions and episodes of general anesthesia in early childhood, either because of the anorectal malformation or the associated anomalies.[60,61] Further, mother-child interaction has been shown to be non-optimal in children with major birth defects requiring newborn surgery.[62] Anorectal malformation patients are no exception, because of the home care that parents need to provide, for example anal dilatations to prevent stricture of the neo-anus[63,64] and regular rectal washouts to treat constipation[54,56]. Disturbances in mother-child interaction could also lead towards problems with growth[65], mental[66], and motor[67] development. Therefore, the following question was raised:

Are anorectal malformation patients at risk for impaired growth and development?

In the Erasmus MC – Sophia Children's Hospital, a long-term follow up program for congenital malformation survivors was initiated in 1999. Inclusion gradually started at the intensive care unit, and since 2004-2006 all patients are offered participation as

standard of care. In this follow up program, growth and development are assessed at regular intervals with validated tests. One might argue that the initial gradual inclusion at the intensive care unit had created an inclusion bias, i.e. that relatively more patients with severe anorectal malformations and with more associated anomalies had been included, but the distribution of types of anorectal malformation and the proportion of patients who had associated anomalies are comparable with other case series[17,68-70], so the results of this study can be extrapolated.

From the results of this follow up program growth appeared to be impaired in anorectal malformation patients, even when excluding the patients with syndromes affecting growth (*Chapter 4*). As growth is a reflection of the general well-being of the child, and as growth impairment is associated with impaired general development[71-73], this is an important finding and possible causative factors should be sought.

As both weight and height were impaired, it is likely that both acute (influencing weight) and chronic malnutrition (influencing height) play a role in the etiology. Considering acute malnutrition, the first episode can occur within the first week of life, which is alarming because nutritional status in the first eight weeks of life could influence mental development later in life.[74] In anorectal malformations the first days are generally awaited to determine if primary repair is possible or if a colostomy has to be created. Either way, surgery has to be performed often within the first days of life, which increases energy expenditure while the neonate is already in a katabolic state.[75] An obstacle to early feeding especially after primary repair is that it is thought to be associated with increased incidence of wound infections. However, a recent systematic review of the literature has shown that early enteral feeding is safe in patients with perineal or vestibular fistula, and that it is even associated with fewer wound complications.[76]

Besides acute malnutrition, chronic malnutrition could also play a role in growth impairment in anorectal malformation patients. Especially children with associated congenital anomalies, mainly urogenital anomalies, are at risk for impaired growth, even with normal renal function. This could be the result of partial insensitivity to growth hormone, as has been reported in children with vesicoureteral reflux.[77] Besides associated anomalies, chronic malnutrition could also be a consequence of chronic constipation, which is prevalent in up to 60% of anorectal malformation patients.[78] In patients with functional constipation, it has been shown that adequate treatment results

in weight and height gain.[79] Bowel management is already an important factor in management of anorectal malformation patients, and it speaks for itself that it should be optimized individually in all patients.

Fortunately, we found that cognition up till the age of five years was normal, when excluding patients with syndromal disorders affecting mental development. However, motor development was impaired at all ages. At 5 years of age, 7% had a definitive motor problem and another 23% borderline motor problems according to the Movement Assessment Battery for Children (MABC), affecting mainly gross motor skills. This may be due to the repetitive hospital admissions the children had to undergo, offering less opportunity to develop gross motor skills, but it has also been linked to growth impairment.[80] Furthermore, trunk stability has been shown to play a role in constipation.[81] It is therefore recommended to monitor gross motor function, balance, and trunk stability, especially in constipated anorectal malformation patients, preferably by a (pelvic floor) physical therapist.

Concerning intervention to optimize the chances for normal development, a window of opportunity lies in the early development of the child and the parent-child interaction. So far no research has been performed on this subject in anorectal malformation patients. Long-term cost benefit analysis, including direct and indirect costs, could help determine if assessment and treatment of disturbances in parent-child interaction are lucrative. However, first a pilot study is necessary as the assessment of parent-child interaction is quite laborious and time-consuming.[82,83] However, as a training program might improve the mother-child interaction[66] and subsequently the development of the child, it appears to be worthwhile investigating.

School age

Because of the growth and motor function impairment found in the previous study and contradictory results in the literature concerning mental development[84], questions were raised on the neuropsychological development of anorectal malformation patients on the longer term:

What neuropsychological problems do anorectal malformation patients experience at school age?

A small case series of in total 43 eight-year-old anorectal malformation (n=23) and Hirschsprung's disease patients (n=20), excluding intellectual disabled patients, was described (*Chapter 5*). Despite normal intelligence, half of the patients in both groups received special education or remedial teaching, and also problems with sustained attention were identified. Even though an inclusion bias was present, i.e. compared to other case series[54,56] relatively more patients with severe anomalies and associated anomalies were included, this study still provides new insights, notably that possible attention problems, school problems, and behavioral problems deserve attention in the long-term follow up.

In *Chapter 5*, a hypothesis was proposed, linking the sustained attention problems to maldevelopment of the right hemisphere of the brain[85], which in the literature has been linked to early relational trauma[86]. Although this theory remains highly speculative, further research is needed to determine if there are disturbances in the parent-child relationship, as this provides an excellent point for intervention[82] with many possible beneficiary aspects concerning both physical and psychosocial development.

As has been stated, a larger patient sample is required in order to determine prognostic factors for neurodevelopmental outcome. When prognostic factors have been determined, neuropsychological examination can be administered to the patients at risk instead of screening all anorectal malformation patients. Furthermore, screening for behavioral problems is ideally performed at early school ages so as to prevent school problems. However, the optimal screening method is yet unknown. In the literature several questionnaires are used, such as the Child Behavior Checklist and Pediatric Symptom Checklist, and although sensitivity is described to be low in children with chronic illnesses, specificity is high.[87-89] Therefore when using such questionnaires as screening tool in clinical practice, behavioral problems can be excluded, but when the test indicates behavioral problems, further examination by a psychologist or psychiatrist is necessary to determine if the child indeed has behavioral problems. Multidisciplinary collaboration between neuropsychologists, developmental psychologists, and psychiatrists is necessary to develop a screening tool with higher sensitivity. Awaiting this, screening with the available tests and when indicated referral to a psychologist or psychiatrist for further examination is necessary in anorectal malformation patients, so that school problems might be prevented and psychosocial well-being might be improved.

Thus far, it has been shown that anorectal malformation patients are at risk for impaired growth, motor development, and psychosocial development. However, how does this influence the child's quality of life? Quality of life is hard to define and measure, as it is a multidimensional construct incorporating physical, mental, and social functioning. Compared to a healthy control group, quality of life of anorectal malformation patients has been described to be lower. Unfortunately no clear predictors could be identified[90,91], which was also the case in our study. However, in the large review study by Hartman et al., patients with a cloacal malformation, the most severe type of anorectal malformations, were excluded.[90] Therefore the following question was raised:

Do patients with the most severe type of anorectal malformation, cloacal malformation, experience more impaired quality of life than patients with other types of anorectal malformations?

Both groups, thus the cloacal malformation patients and the other female anorectal malformation patients, reported lower quality of life compared to the reference population (*Chapter 6*), but comparison between the groups showed no differences. This suggests that with regard to quality of life, the cloacal malformation patients do not form a separate group requiring more psychological guidance than other female anorectal malformation patients. Many quality of life questionnaires are available (such as SF-36, TAPQOL, etc.); the questionnaire used in this thesis is the PedsQL.[92] More recently, a questionnaire especially for patients with congenital colorectal malformations was designed, the Hirschsprung and Anorectal Malformation Quality of Life questionnaire (HAQL)[93], but, as it was designed for patients with colorectal anomalies, no reference values are available and therefore no comparison can be made with the normative population.

It is important to determine what needs to be measured: health status or health related quality of life (Table 1). Fayed et al. have analyzed the most frequently used questionnaires according to the WHO criteria, and found that the PedsQL almost exclusively measures more the health status rather than quality of life (96% of the questions, vs. 4%).[94] Until now, long-term follow up and research have mainly focused on continence and bowel management, complication rates, and health status. However, are we asking the right questions to the patients and ourselves? What are the things that matter most to the patient himself or herself? What factors determine health status and quality of life? For future research, it is necessary to obtain international consensus on the

Table 1: Organization of concepts based on World Health Organization definitions

Concept to measure	Definition used	Item example
Functioning, disability, and health	The interaction or the individual components of body functions, activities and participation that occur in the context of the environment or personal factors	In the past 4 weeks, how difficult has it been to walk short distances? (not at all to extremely difficult)
Health-related quality of life (a subcomponent of quality of life)[1]	A child's goals expectations, standards or concerns about their overall health and health-related domains	In the past 4 weeks, how satisfied have you been with your ability to walk short distance? (very dissatisfied to extremely satisfied)
Quality of life	A child'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	My life is as good as I ever expected (strongly agree to strongly disagree)

[1]Health-related quality of life is not a WHO definition but was subsumed as a component of WHO-defined quality of life in this analysis. Table from: Fayed et al. 2012 ©[94].

questionnaires to use both for measuring health status and quality of life. Only then different studies can be compared and data can be pooled, and more definite conclusions can be drawn.

Adolescence

Although adolescence is an exciting time period for everyone, this life stage was not further investigated in this thesis. The main reason for this was that the follow-up program in our hospital was still too young, and many of the children seen at this age were not included prospectively but retrospectively. The inclusion bias was therefore too strong and no conclusions could be drawn that concerned the general population of anorectal malformation patients. In general, adolescents with anorectal malformations tend to report better 'quality of life' or 'health status' than children, as measured with the PedsQL or the TACQoL (TNO-AZL Child Quality of Life Questionnaire).[95,96] Global feeling of self-worth –measured with the Self-Perception Profile for Adolescents- is

in adolescent anorectal malformation patients similar to the normative population; however they do have problems concentrating on school tasks because of worries of olfactory sense.[97] It therefore seems that rather than administering a questionnaire, interviewing is better suited to define the problems and needs of this patient group, while the bowel management should still be optimized individually.

Transition to adult care

Transition to adult care does not start at adolescence, but earlier at school age when the children become more independent. Children learn to understand the need for their medical treatment and the consequences when the treatment is not adhered to –e.g. not taking oral laxatives to prevent constipation-. It speaks for itself that it is important to guide the children and their parents in this process. When the children grow older into adolescence, they grow more independent and become 'ready for transfer'. The 'transfer readiness' has been measured in chronically ill adolescents, and it was found not only to be associated with older age, but also with a positive attitude towards transition and with the number of discussions related to future transfer.[98] It is therefore important that transfer to adult care is guided meticulously. All medical specialists treating the patient should do this, while the conversations can be prepared by the nurse practitioner.

Outcome in adulthood

Psychosexual function is important for all individuals. Although it can be hypothesized that it is at risk in anorectal malformation patients[99], not only because of the operations required in the genital area, but also because of the hypoplastic pelvic floor[100], psychosexual function has not yet been investigated with validated tests or questionnaires.

Are patients who underwent colorectal surgery in early childhood at risk for psychosexual problems?

Hirschsprung's disease is etiologically and operation-technically distinct from anorectal malformations, but these patients were also included in this study as they also generally undergo pelvic floor surgery in early childhood (*Chapter 7*). Both anorectal

malformation patients and Hirschsprung's disease patients reported problems with psychosexual function: moderate to severe erectile dysfunction was reported by 16% of the study sample, half of the female patients reported sexual dysfunction, and 38% of the female patients reported sexual distress. Presence of psychosexual problems was not clearly associated with quality of life as measured by the HAQL, type of malformation, or type of operation.

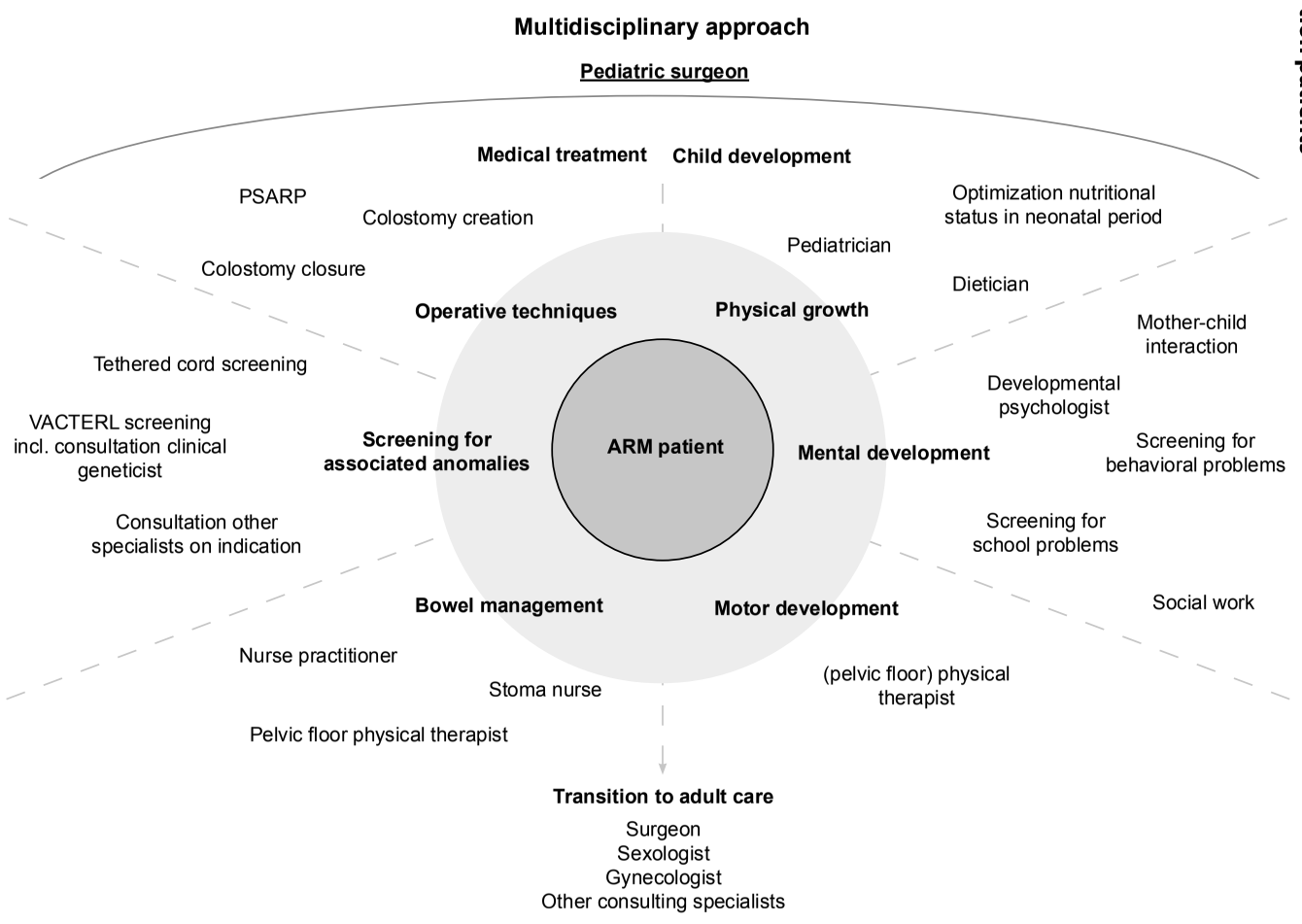
Several possible causes for psychosexual problems have been proposed in *Chapter 7*, such as abnormal anatomy of reproductive organs, abnormal innervation, and disturbances of sexual development. However, an even more important result of this study was that 60% of the patients felt that sexuality in the context of the congenital colorectal anomaly was insufficiently addressed during medical care. This did not only concern patients who experienced psychosexual problems, but also patients who did not report psychosexual problems. This indicates that an anorectal malformation is not only a birth defect requiring childhood surgery, but that it is also a chronic illness with sequelae into adulthood.

Further research is definitely needed to determine the optimal form and timing of addressing sexuality in anorectal malformation patients, as it is a delicate subject in a vulnerable period in life. This research should not only include the opinions of pediatric surgeons, sexologists, and gynecologists, but also the opinions of the patients, and collaboration between doctors and patients is essential. A plenary discussion, either online or in real life, can be used to obtain the opinions of patients and optimal education can be developed.

Recommendations for a multidisciplinary approach

A multidisciplinary approach (see also Fig. 1) is essential in anorectal malformation patients, not only because of the wide spectrum of anomalies, of the associated congenital anomalies, or of the problems with continence, but also because they are at risk for developmental problems, as has been shown in this thesis. Frequent hospital admissions and operations are not uncommon, and specialized treatment is necessary in a pediatric colorectal center. Herewith we propose a form of multidisciplinary approach in anorectal malformation patients (see also Table 2).

Fig. 1: General overview of multidisciplinary approach in anorectal malformation patients



Abbreviations: ARM, anorectal malformation; PSARP, posterior sagittal anorectoplasty; VACTERL, vertebral, anal, cardiac, trachea-esophageal, renal, and limb anomalies.

Table 2: Proposal of multidisciplinary approach in anorectal malformation patients

Age	Topic	Discipline	Relevance / intervention
Coordination of care	General coordinator of care	Pediatric surgeon/NP	General coordinator of care
Infancy	Surgical techniques	Pediatric surgeon	Prevent or treat complications
	Screen for associated anomalies	Pediatric surgeon/clinical geneticist	Detect genetic disorders
	Associated anomalies	Consulting specialists/pediatrician	Treat associated anomalies
	Bowel management	Bowel management team*	Treat constipation / incontinence
	Physical growth	NP/dietician/stoma nurse	Treat growth problems
	Mental development	Developmental psychologist	Observe mother / child interaction
Toddler/ preschool	Bowel management	Bowel management team*	Treat constipation / incontinence
	Associated anomalies	Consulting specialists/pediatrician	Treat associated anomalies
	Physical growth	NP/dietician/stoma nurse	Treat growth problems
	Motor development	(pelvic floor) pediatr physical therap	Treat constipation / incontinence
	Mental development	Developmental psychologist	Screen for behavioral problems
School age	Bowel management	Bowel management team*	Treat constipation / incontinence
	Associated anomalies	Consulting specialists/pediatrician	Treat associated anomalies
	Physical growth	NP/dietician/stoma nurse	Treat growth problems
	Motor development	(pelvic floor) pediatr physical therap	Treat constipation / incontinence
	Mental development	Developmental psychologist	Screen for behavioral problems
Adolescence into adult-hood	Bowel management	Bowel management team*	Treat constipation / incontinence
	Associated anomalies	Consulting specialists/pediatrician	Treat associated anomalies
	Mental development	Developmental psychologist	Screen for behavioral problems
	Transition to adult care	NP/Pediatric surgeon/sexologist	Educate for sexual problems

*Abbreviations: NP, nurse practitioner; pediatr physical therap, pediatric physical therapist. * including pediatric surgeon, nurse practitioner, stoma nurse, pelvic floor physical therapist, and psychologist and urologist when indicated.*

Fig. 3: Aspects of optimal care

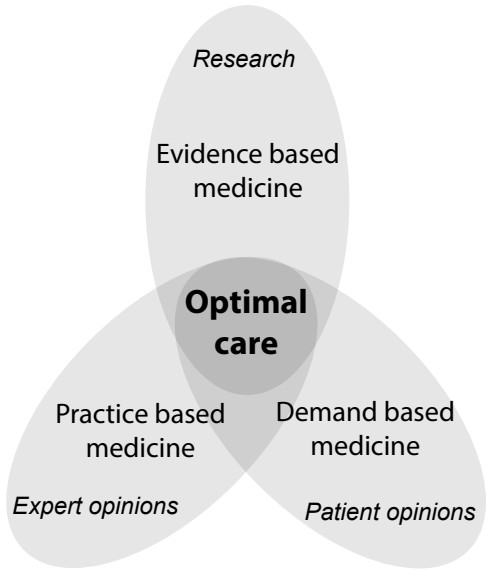


Figure based on article by Burgers ©[106].

A pediatric surgeon specialized in colorectal surgery is the principal specialist of anorectal malformation patients. To treat continence problems, a team of specialists is necessary to optimize treatment in individual patients. A nurse practitioner can coordinate bowel management and guide the children and parents through everyday problems. Furthermore, this team should include a stoma nurse and pelvic floor physical therapist, as well as a urologist when urogenital anomalies or comorbidity is present. The pediatric surgeon consults other specialists according to the nature of associated anomalies, such as the pediatric cardiologist or plastic surgeon.

Besides the bowel management program, also the general development of anorectal malformation patients should be optimized. We recommend consulting a clinical geneticist for all patients to detect possible syndromal disorders. Furthermore, when growth problems are detected early referral to the dietitian is in place. It is recommended to have a psychologist screen for motor developmental disorders and behavioral problems in childhood. In adolescence, the patients should be offered education concerning sexuality in the context of the congenital anomaly and referral to a sexologist or gynecologist should be offered.

During the complex medical care process described above, constant attention should be paid to the family's well-being and the parent-child interaction, as this has an influence on both the physical and psychosocial development of the child. Support from a social worker should be offered when necessary.

Future directions

In spite of all improvements, there is still room for more improvement. A window of opportunity remains in early childhood, namely the mother-child relation. Little is known on this subject in anorectal malformation patients, while it influences the entire development of the child. It does not only influence psychological development, but also growth, motor development, and perhaps even psychosocial well-being and participation in society. In addition, it could also influence the medical treatment, especially treatment of constipation and incontinence. Further research is definitively needed on this subject, but it is time-consuming to test the attachment relationship between mother and child. However it can be profitable, as intervention therapies have been described to improve mother-child interaction. This could not only have implications for anorectal malformation patients, but also for other congenital malformation patients requiring intensive medical treatment, such as those with esophageal atresia or congenital diaphragmatic hernia.

As has been shown in this thesis, anorectal malformations can have consequence into adulthood and perhaps throughout the entire life of the patient. Treatment of diseases in general, including anorectal malformations, can be further improved with three major cornerstones: evidence based medicine[101], clinical auditing registries such as the European Pediatric Surgical Audit[102], and development and measurement of patient related outcome measures[103,104]. An example of the latter is an initiative developed at Harvard Business School by Porter and Teisberg: the International Consortium for Health Outcomes Measurement (ICHOM).[105] However, treatment of anorectal malformation patients also requires an individual, patient-centered approach. Therefore a doctor-patient partnership is indispensable to combine evidence based medicine, practice based medicine, and demand based medicine (Fig. 3) into optimal care.

In order to find answers to the questions stated in the *General Discussion* section, longitudinal research is of essence. It naturally remains of utmost importance to treat the

disease and the symptoms, but with mortality already reduced to a minimum, the secondary goals of treatment have become of higher priority, necessitating a multidisciplinary approach. Longitudinal care can be balanced with longitudinal research, using standardized tests and questionnaires to screen for problems and measure outcome effects of interventions. Parent-child interaction and psychosocial well-being of children with ARM can be at risk. In long-term follow-up Validated tests are used to assess these issues and can guide care-givers for interventions and evaluations. Self-management may be stimulated by providing both standardized and individualized education on various aspects, including psychosexual wellbeing.[107] These are only examples of possible future longitudinal research, in which the physical and psychological effects of such interventions can excellently be evaluated.

Concluding, the treatment of anorectal malformation patients requires a multidisciplinary approach, combining patient centered individual care with population based screening and interventions. Longitudinal follow-up is of essence in this patient group, which provides an excellent opportunity to combine patient care and research, and to keep improving patient care in the future.

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Chapter 9

Summary

Nederlandse samenvatting

The research described in this thesis was performed with the aim to evaluate and improve multidisciplinary treatment of anorectal malformation patients. An overview of current literature on treatment of anorectal malformations is given in the Preface section, which also includes an overview of this thesis.

The results of the research are presented in two parts:

Part 1 focuses on postnatal care and contains retrospective studies, while **Part 2** focuses on long-term outcome from childhood into adulthood, and presents a cohort study and prospective studies.

Then, the General discussion, Recommendations, and Summaries form **Part 3**, and Appendices are provided in **Part 4**.

Part 1: Neonatal care

Chapter 1 Insight into the most ideal type and place of colostomy in anorectal malformations was gained from a retrospective cohort study and a systematic review of the literature. We included 180 patients born between 1990 and 2012. The mortality rate was 6%; the complication rate 22%. The most prevalent complication was prolapse (12%). Complication rates did not differ between loop and split colostomies or between transverse and descending or sigmoid colostomies. In the systematic review eight retrospective cohort studies were included (1982-2011; total 2,954 patients). The mortality rate ranged from 0.1 to 11%. The complication rate of loop colostomy was higher than that of split colostomy (63 vs. 45%); and more complications were seen in transverse than in descending or sigmoid colostomies (62% vs. 51%). The most important limitation of this study was that all studies considered were retrospective studies, with the preferred type of colostomy being surgeon-dependent. When a sigmoid colostomy is created, there is a risk that not enough bowel length can be gained in the posterior sagittal anorectoplasty (PSARP) operation. It was therefore concluded that the most ideal type of colostomy in anorectal malformation patients is split descending colostomy.

Chapter 2 The hypothesis that anorectal malformation patients with upper limb anomalies are more often diagnosed with a genetic disorder than are anorectal mal-

formation patients with other associated anomalies was tested. This was done in a two-center retrospective case study including 700 patients (born between 1990 and 2012). The prevalence of upper limb anomalies was 6% and radial dysplasia and thumb hypoplasia were most often reported (prevalence 2% each). These patients were indeed more often diagnosed with a genetic disorder, i.e. twice as much (23% vs. 11%) as anorectal malformation patients with other associated anomalies. Nine of ten patients with an upper limb anomaly who were diagnosed with a genetic disorder also met the criteria for the VACTERL (Vertebral, Anal, Cardiac, Tracheo Esophageal, Renal, Limb) association. It was therefore argued that the VACTERL-association should be treated as a diagnosis per exclusionem, and that a clinical geneticist specialized in dysmorphology should be consulted for all anorectal malformation patients. An algorithm was proposed for the genetic work-up of anorectal malformation patients, including the most relevant syndromes.

Chapter 3 Screening and treatment for tethered spinal cord was investigated in a retrospective case study including 110 neonates (born between 2004 and 2011). The prevalence of tethered spinal cord, as confirmed by MRI, was 9%. The sensitivity of spinal ultrasonography was 80%, specificity was 89%, the positive predictive value was 47%, and the negative predictive value was 97%. However, these figures were greatly influenced by the fact that not all children had undergone an MRI. A relationship between type of anorectal malformation and presence of tethered spinal cord could not be determined. Three patients underwent untethering surgery for respectively the following reasons: symptomatic tethered cord syndrome with pain in the legs, progressive syringomyelia on MRI, and a dermal sinus with tethering of the spinal cord. All operations were uncomplicated and the first patient's symptoms resolved. It was concluded that spinal ultrasound is a fairly effective screening method, the value of which is mainly determined by the clinical consequences, however. That is, performing an MRI when ultrasound is abnormal, and prophylactic vs. symptomatic tethered spinal cord surgery.

Part 2: Long-term outcome

Chapter 4 Growth and development until 5 years of age were investigated with a prospective cohort study, as part of a structural longitudinal follow-up program. In total 108 non-syndromal anorectal malformation patients born between 1999 and 2011

were included. Overall, weight was impaired until 2 years of age; height until 5 years of age. Patients with additional major comorbidity had significantly lower height and weight than patients without additional comorbidity. At 5 years of age, mean Z-score (95% CI) height was -1.8 (-2.7 to -1.1) and -0.7 (-1.3 to -0.1) in children with and without major comorbidity (p=0.019). The comorbidity in patients with impaired height was mainly of urogenital origin. Cognition was normal at all ages, irrespective of the type of malformation or comorbidities. Motor function development within the first 2 years of life was impaired in more than one third of patients. Testing with the Movement Assessment Battery for Children at 5 years of age (n=30) showed normal motor development in 70% of the patients, which was significantly below the norm. Mainly the gross motor skills were impaired. It was concluded that non-syndromal anorectal malformation patients are at risk for physical growth problems, especially when major comorbidity is involved, and for motor developmental problems. Nutritional status and bowel management should be optimized individually to prevent stunting, and screening for malnutrition as well as timely referral to the physical therapist is recommended.

Chapter 5 Neuropsychological functioning at 8 years of age was prospectively investigated in a cohort study with validated tests and questionnaires. Twelve of the 23 included anorectal malformation patients and 11 of the 20 Hirschsprung's disease patients (born between 1999 and 2006) had special education needs. In total 19% of the parents reported that a behavioral disorder had been previously diagnosed in their child (attention deficit hyperactivity disorder in five, anxiety disorder in one, and attachment disorder in two patients). Full-scale intelligence was normal in both groups, with mean (SD) IQ being 98 (17) and 96 (17), respectively. However, both groups had problems with sustained attention: mean (SD) Z-score working speed was -1.90 (1.94) and -1.43 (1.98), respectively, for anorectal malformation patients and Hirschsprung's disease patients (both $p<0.01$ compared to the normative population). Self-esteem was normal, as the mean (SD) Z-score of global feeling of self worth were 0.10 (1.29) and -0.20 (1.11), respectively. Self-reported quality of life was normal in anorectal malformation patients and slightly impaired in Hirschsprung's disease patients. No predictors for neuropsychological outcome could be identified with regression analysis, probably due to the relatively small patient samples. A hypothesis was presented, suggesting a link between problems with sustained attention and behavior on the one hand, and possible disturbance of the parent-child relationship in early childhood on the other hand (attachment theory of Bowlby). Although an inclusion bias was present, it was concluded that despite normal intelligence some half of anorectal malformation and

Hirschsprung's disease patients require special education or remedial teaching. Apart from surgical treatment, attention should be paid to early socio-emotional development so as to timely recognize behavioral problems.

Chapter 6 Cloacal malformation is the most severe type of anorectal malformation in females. Quality of life of patients with this malformation was compared to that of female patients with other types of anorectal malformation, namely anorectal malformation types perineal fistula and vestibular fistula. Quality of life was prospectively measured with the PedsQL in 58 patients in total, of whom 13 had a cloacal malformation, 31 an anorectal malformation type perineal fistula, and 14 an anorectal malformation type vestibular fistula. Self-reported (median age 12 years) and parent-reported (patient's median age 8 years) general quality of life did not differ between cloacal malformation patients and female patients with perineal or vestibular fistula. However, parents of cloacal malformation patients reported significantly lower scores on school functioning than parents of other patients (median score (IQR) 60.0 (56.3 to 75.6) and 80.0 (68.1 to 95.0), respectively; p=0.003). Compared to reference values, reported quality of life in both patient groups was impaired. For this reason it was recommended to monitor quality of life during follow-up.

Chapter 7 Psychosexual well-being was investigated in a two-center cross-sectional study in adult anorectal malformation and Hirschsprung's disease patients. Response to the invitation to participate was 32 and 37%, respectively, and thus in total 70 anorectal malformation and 36 Hirschsprung's disease patients were included (median age 26 years) and filled in the questionnaires. Moderate to severe erectile dysfunction was reported by 16% and 11%, respectively (vs. 5% in the normative population). Of the female patients, 50 and 53% reported sexual dysfunction and 38 and 20% sexual distress, respectively. Self-reported psychosexual problems were not clearly associated with different domains of the Hirschsprung and Anorectal Malformation Quality of Life Questionnaire (HAQL). The most striking result of this study was that 60% of the study population reported that sexuality in the context of the congenital colorectal malformation was insufficiently addressed during medical care. As this remains a delicate subject, especially for adolescents, education is definitely needed, and the optimal form and timing of this education should be established in close collaboration with the patients themselves.

Part 3: General discussion and recommendations

The **General Discussion** addresses the research described in this thesis, as well as the implications of the findings for the multidisciplinary approach. Both the strengths and the limitations of the presented studies are discussed. As many disciplines are involved in the treatment of anorectal malformation patients, an overview of the multidisciplinary approach is given. In addition, the importance of outcome registration is emphasized. Moreover, recommendations for further research are provided, such as the issue of mother-child interaction in early childhood. Lastly, an overview of important aspects of longitudinal follow up in anorectal malformation patients was provided.

Het onderzoek dat in dit proefschrift is beschreven had als doel de multidisciplinaire behandeling van patiënten met een anorectale malformatie te evalueren en te verbeteren. De Introductie geeft een overzicht van de huidige literatuur over de behandeling van anorectale malformaties. Vervolgens worden de resultaten van het onderzoek gepresenteerd in twee delen:

Deel 1 richt zich op neonatale behandeling en bevat retrospectieve studies, terwijl **Deel 2** zich richt op uitkomsten op de lange termijn, dat wil zeggen van de kinderleeftijd tot volwassenheid. Dit deel bevat een cohortstudie en prospectieve studies.

Deel 3 bestaat uit de Discussie, Aanbevelingen en Samenvattingen. **Deel 4** bevat de Appendices.

Deel 1: Neonatale behandeling

Hoofdstuk 1 Aanwijzingen voor meest ideale type colostoma en de beste locatie daarvan werden verkregen met een retrospectieve cohortstudie en een systematische review van de literatuur. De retrospectieve cohortstudie betrof 180 patiënten geboren tussen 1990 en 2012, van wie er 6% zijn overleden. Bij 22% van de patiënten kwamen complicaties voor, het meest een prolaps (uitstulping) van het stoma (12%). De complicaties waren niet gerelateerd aan het type stoma (dubbelloops of gescheiden) of de locatie (colon transversum of colon descendens/sigmoïd). De systematische review betrof acht retrospectieve cohortstudies (1982-2011; totaal 2.954 patiënten). De sterfte varieerde tussen 0,1 en 11% in de verschillende studies. Complicaties kwamen vaker voor bij een dubbelloops stoma dan bij een gescheiden stoma (63% vs. 45%) en vaker bij een stoma aangelegd op het colon transversum dan op het colon descendens of sigmoïd (62% vs. 51%). Een groot nadeel van dit literatuuronderzoek was dat het type stoma door de betreffende chirurg werd bepaald. Omdat er kans is dat bij de posterieure sagittale anorectoplastiek (PSARP) operatie niet genoeg darmlengte kan worden verkregen om de neo-anus in te hechten, werd geconcludeerd dat bij deze patiënten het meest ideale stoma type een gescheiden stoma is op het colon descendens.

Hoofdstuk 2 De onderzoeksvraag was of bij patiënten met een anorectale malformatie een genetisch syndroom vaker voorkomt bij patiënten met een bijkomende

congenitale afwijking aan de bovenste ledematen dan bij degenen met een andere bijkomende afwijking. Dit werd onderzocht in een retrospectieve cohortstudie met 700 patiënten geboren tussen 1990 en 2012 in twee kinderchirurgische centra (Nijmegen en Rotterdam). De prevalentie van congenitale afwijkingen aan de bovenste ledematen was 6%, met radiusdysplasie en duimhypoplasie als meest voorkomende (prevalentie 2% voor beide afwijkingen). Deze patiënten werden inderdaad vaker gediagnosticeerd met een genetisch syndroom, te weten tweemaal zo vaak (23% vs. 11%). Negen van de tien patiënten met een congenitale afwijking aan de bovenste ledematen en ook een genetisch syndroom voldeden ook aan de criteria voor een zogenaamde VACTERL-associatie (een combinatie van afwijkingen aan andere organen: Vertebraal, Anaal, Cardiaal, Tracheo-Oesofageaal, Renaal, Ledematen). De diagnose VACTERL-associatie is echter een diagnose per exclusionem en een klinisch geneticus gespecialiseerd in dysmorfologie dient bij alle anorectale malformatie patiënten geconsulteerd te worden om een genetisch syndroom uit te sluiten. Voor de genetische diagnostiek bij patiënten met een anorectale malformatie hebben we een algoritme opgesteld waarin de meest relevante syndromen beschreven zijn.

Hoofdstuk 3 De uitkomsten van screening en behandeling van *tethered cord* ('geklusterd ruggenmerg') werden onderzocht in een retrospectieve cohortstudie met 110 neonaten geboren tussen 2004 en 2011. De prevalentie van tethered cord, bevestigd middels MRI-scan, was 9%. De sensitiviteit van spinale echografie was 80%, de specificiteit 89%, de positief voorspellende waarde 47%, en de negatief voorspellende waarde 97%. Er werd gesteld dat deze percentages wellicht minder betrouwbaar zijn omdat niet alle kinderen een MRI-scan hadden ondergaan. Een relatie tussen het type anorectale malformatie en het optreden van tethered cord kon niet worden vastgesteld. Drie patiënten werden geopereerd vanwege tethered cord om de volgende redenen: vanwege symptomatisch tethered cord syndroom met pijn in de benen, progressieve syringomyelie op sequentiële MRI onderzoeken, of een dermale sinus met tethering van het spinale kanaal. Bij alle drie patiënten verliep de operatie ongecompliceerd en in geval van symptomen gingen deze in regressie. Er werd geconcludeerd dat spinale echografie een redelijk effectieve screeningsmethode is, waarvan echter de waarde voornamelijk bepaald wordt door de consequenties die aan een afwijkende echografie verbonden worden. Dat wil zeggen dat een MRI-scan verricht zou moeten worden wanneer de echografie afwijkingen laat zien, en de overweging wanneer tethered cord geopereerd wordt: preventief bij alle patiënten met tethered cord dan wel afwachten tot patiënten symptomatisch tethered cord syndroom ontwikkelen.

Deel 2: Langetermijn uitkomsten

Hoofdstuk 4 In het kader van een structureel longitudinaal follow-up programma werden groei en ontwikkeling tot de leeftijd van 5 jaar onderzocht in een prospectieve cohort studie. Er werden 108 patiënten met een anorectale malformatie geboren tussen 1999 en 2001 geïncludeerd, terwijl patiënten met een genetische aandoening die de groei en ontwikkeling kon beïnvloeden werden geëxcludeerd. Kinderen tot 2 jaar hadden een lager gewicht dan gezonde leeftijdgenoten en tot 5 jaar was de lengte kleiner. Kinderen met bijkomende ernstige aangeboren aandoeningen hadden meer groeiproblemen dan kinderen zonder bijkomende aandoeningen. Op de leeftijd van 5 jaar was de gemiddelde (95% CI) Z-score voor lengte -1.83 (-2.7 tot -1.1) en -0.70 (-1.3 tot -0.1) respectievelijk voor kinderen met en zonder bijkomende afwijkingen (p=0.019). Vooral kinderen met urogenitale afwijkingen hadden een kleine lengte. Op alle leeftijden was de gemiddelde cognitie normaal. Bij meer dan één derde van de kinderen liep de motorische ontwikkeling achter tot de leeftijd van 2 jaar. Op de leeftijd van 5 jaar werden 30 kinderen getest met de Movement Assessment Battery for Children. Het bleek dat bij 70% de motorische ontwikkeling normaal was, een lager percentage dan bij gezonde leeftijdsgenoten. Vooral de grove motorische vaardigheden waren onderontwikkeld. Groeiproblemen zouden mogelijk kunnen worden voorkomen door de voedingsstatus en de behandeling van constipatie te optimaliseren. Het volgen van de voedingstoestand en het tijdig verwijzen naar de fysiotherapeut bij motorische problemen wordt aanbevolen.

Hoofdstuk 5 In een prospectieve cohortstudie met 23 patiënten met een anorectale malformatie en 20 patiënten met de ziekte van Hirschsprung geboren tussen 1999 en 2006 werd het neuropsychologisch functioneren op acht jarige leeftijd onderzocht met gevalideerde tests en vragenlijsten. Respectievelijk 12 en 11 kinderen volgden speciaal onderwijs of *remedial teaching*. Bij acht kinderen (19%) was volgens de ouders in het verleden een gedragsstoornis gediagnosticeerd (aandachtstekort-hyperactiviteitstoornis bij vijf, angststoornis bij één, en hechtingsstoornis bij twee patiënten). De gemiddelde intelligentie was normaal in beide groepen met respectievelijk een gemiddelde (SD) IQ van 98 (17) en 96 (17). Beide groepen hadden echter problemen met vastgehouden aandacht: gemiddelde (SD) Z-score werksnelheid -1.90 (1.94) en -1.43 (1.98) voor respectievelijk patiënten met een anorectale malformatie en de ziekte van Hirschsprung (beide p<0.01 vergeleken met de normpopulatie). Het gevoel van eigenwaarde was normaal. De door de kinderen zelf gerapporteerde kwaliteit van leven

was normaal voor hen met een anorectale malformatie en licht verminderd voor hen met de ziekte van Hirschsprung. We konden geen voorspellende factoren voor het neuropsychologisch functioneren vaststellen, waarschijnlijk door de relatief kleine patiëntenpopulatie. Er werd een hypothese voorgesteld welke een verband suggereerde tussen de aandachtsproblemen en gedragsproblemen aan de ene kant en een mogelijke stoornis van de ouder-kind relatie in de vroege jeugd aan de andere kant (hechtingstheorie van Bowlby). Alhoewel er sprake was van een inclusie bias is het memorabel dat ondanks hun normale intelligentie ongeveer de helft van deze kinderen speciaal onderwijs of remedial teaching volgt. Naast de chirurgische behandeling moet daarom ook aandacht worden besteed aan de vroege socio-emotionele ontwikkeling zodat gedragsproblemen tijdig herkend worden.

Hoofdstuk 6 Cloacale malformatie is de ernstigste vorm van anorectale malformatie bij vrouwen. We hebben onderzocht of de kwaliteit van leven van deze patiënten vergelijkbaar is met die van vrouwelijke patiënten met een ander type anorectale malformatie, te weten perineale en vestibulaire fistel. De kwaliteit van leven werd prospectief gemeten met de PedsQL vragenlijst bij 58 patiënten, van wie er 13 een cloacale malformatie hadden. De zelf-gerapporteerde (mediane leeftijd 12 jaar) en door de ouders gerapporteerde (mediane leeftijd van patiënt 8 jaar) algemene kwaliteit van leven verschilden niet tussen zij met een cloacale malformatie en zij met een ander type malformatie. Wel rapporteerden ouders van patiënten met een cloacale malformatie lagere scores betreffende het schools functioneren, met een mediane score (IQR) 60.0 (56.3 tot 75.6) en 80.0 (68.1 tot 95.0), respectievelijk (p=0.003). De kwaliteit van leven van beide groepen was slechter dan de referentiewaarden. Het verdient de aanbeveling om kwaliteit van leven te monitoren tijdens de follow-up.

Hoofdstuk 7 Het psychoseksuele functioneren van patiënten met een anorectale malformatie en de ziekte van Hirschsprung is onderzocht in een cross-sectionele studie in twee centra (Nijmegen en Rotterdam). De respons op de uitnodiging om deel te nemen was respectievelijk 32 en 37%. Uiteindelijk vulden in totaal 70 patiënten met een anorectale malformatie en 36 patiënten met de ziekte van Hirschsprung de vragenlijsten in (mediane leeftijd 26 jaar). Matig tot ernstige erectiele dysfunctie werd door respectievelijk 16 en 11% gerapporteerd (vs. 5% in de normpopulatie). Van de vrouwelijke patiënten rapporteerden respectievelijk 50 en 53% seksuele dysfunctie, en 38 en 20% seksuele onvrede. De problemen waren niet duidelijk geassocieerd met diverse domeinen van de Hirschsprung and Anorectal Malformation Quality of Life Questionnaire (HAQL). De meest verrassende uitkomst was dat maar liefst 60% van de patiënten vond dat seksualiteit in de context van hun aangeboren afwijking onvoldoende aan bod was gekomen tijdens hun medische behandeling. Aangezien dit een delicaat onderwerp betreft, in het bijzonder voor adolescenten, is voorlichting wel degelijk nodig en moeten de optimale vorm en het optimale tijdsstip van deze voorlichting verder onderzocht worden.

Deel 3: Discussie en aanbevelingen

De **Discussie** bespreekt de onderzoeksresultaten in een breder kader, en gaat in op de implicaties van de onderzoeksresultaten voor de multidisciplinaire behandeling. Zowel de sterke als zwakke punten van de gepresenteerde studies worden besproken. Aangezien veel disciplines betrokken zijn bij de behandeling van patiënten met een anorectale malformatie wordt een overzicht van de multidisciplinaire behandeling gegeven. Daarnaast wordt ook het belang van goede registratie besproken. Verder worden aanbevelingen voor toekomstig onderzoek gegeven, bijvoorbeeld de moeder-kind interactie in de vroege jeugd. Tenslotte wordt een voorstel voor longitudinale follow-up beschreven.

PART 4: APPENDICES

List of publications

D van den Hondel, FK Aarsen, RMH Wijnen, CEJ Sloots, H IJsselstijn. Psychological well-being in school age children with anorectal malformation and Hirschsprung's disease. J Sex Med 2015;12(7):1616-25.

D van den Hondel, CEJ Sloots, CJM Meeussen, RMH Wijnen. To split or not to split: colostomy complications for anorectal malformations or Hirschsprung disease: a single center experience and a systematic review of the literature. Eur J Pediatr Surg 2014;24:61-9.

D van den Hondel, CEJ Sloots, SJ Gischler, CJM Meeussen, RMH Wijnen, H IJsselstijn. Prospective long-term follow up of children with anorectal malformation: growth and development until 5 years of age. J Pediatr Surg 2013;48:818-25.

D van den Hondel, CEJ Sloots, THR de Jong, M Lequin, H IJsselstijn, RMH Wijnen. Screening and treatment of tethered spinal cord in anorectal malformation patients. *Accepted Eur J Pediatr Surg*.

D van den Hondel, FK Aarsen, RMH Wijnen, CEJ Sloots, H IJsselstijn. Children with congenital coloretal malformations often require special education or remedial teaching, despite normal intelligence. *Accepted Acta Paediatr*.

HP Versteegh, **D van den Hondel**, H IJsselstijn, RMH Wijnen, CEJ Sloots, I de Blaauw. Cloacal malformation patients report similar quality of life as female patients with less complex anorectal malformations. *Accepted Eur J Pediatr Surg*.

D van den Hondel, CHW Wijers, Y van Bever, A de Klein, CLM Marcelis, I de Blaauw, CEJ Sloots, H IJsselstijn. Anorectal malformation patients with upper limb anomalies: genetic counseling is warranted. *Provisionally accepted Eur J Pediatr*.

D van den Hondel, MJ Madderom, A Goedegebure, SJ Gischler, P Mazer, D Tibboel, H IJsselstijn. Sensorineural hearing loss and language development following neonatal extra-corporal membrane oxygenation. Pediatr Crit Care Med 2013;14:62-9.

Curriculum Vitae

Desiree van den Hondel was born on November 25th 1987 in Dordrecht. In 2006, she graduated from secondary school at Johan de Witt-gymnasium in Dordrecht. In that same year, she enrolled for medical school at Erasmus Medical Center. During her third year of medical school, she got fascinated by research and started her research career at the Department of Pediatric Surgery and Pediatric Intensive Care Unit (supervisor Dr. IJsselstijn) at Erasmus MC-Sophia Children's Hospital Rotterdam. Desiree obtained her medical degree in 2012 and as of September 2012 she started her dissertation in the combined function of PhD-student (promotor Prof. Dr. R.M.H. Wijnen, co-promotors Dr. H. IJsselstijn and Dr. C.E.J. Sloots) and resident (ANIOS), both at the Department of Pediatric Surgery at Erasmus MC-Sophia Children's Hospital. Desiree currently works as resident (ANIOS) General Surgery (supervisor Dr. T.M.A.L. Klem) in the Sint Fanciscus Vlietland Hospital Rotterdam and she aspires a career in General Surgery.

PhD portfolio

Name PhD student	Desiree van den Hondel
Erasmus MC department	Dept. of Pediatric Surgery (Sophia Children's Hospital)
PhD period	September 2012 – October 2015
Promotor	Prof. Dr. R.M.H. Wijnen
Copromotors	Dr. H. IJsselstijn, Dr. C.E.J. Sloots

1. PhD training	**Workload**	
	Year	**ECTS**
General courses		
- Introductory Course on Statistics & Survival Analysis, Molmed, Erasmus MC	2012	0.5
- Biostatistical Methods I: Basic Principles, NIHES, Erasmus MC	2013	5.7
- BROK course, Erasmus MC	2013	1.0
- CPO mini course (patient orientated research and preparation for subsidy application), CPO, Erasmus MC	2013	0.3
- Literature search basic and advanced course and Endnote course, Medical Library, Erasmus MC	2013	1.0
- Research integrity, dept. medical ethics and philosophy, Erasmus MC	2013	2.0
- Workshop on Photoshop, Illustrator and Indesign CS, Molmed, Erasmus MC	2013	0.3
- Academical English, CEFR level C1.1, Erasmus University Rotterdam	2014	2.0
- Biomedical English Writing Course, Molmed, Erasmus MC	2014	2.0
- Research management, Molmed, Erasmus MC	2014	1.0
Specific courses		
- Capita selecta medical genetics, dept. clinical genetics, Erasmus MC	2013	0.4
- Course 'Treatment of Burns', Rode Kruis Hospital, Beverwijk	2013	0.3
- Symposium organ donation and transplantation in pediatrics, Groningen	2013	0.3
- Training 'Omgaan met groepen voor tutoren', Erasmus MC	2013	0.5
- Basic operative techniques (BOT) course, PAO Heyendaal, Radboudumc, Nijmegen	2014	0.3
- Fundamental Critical Care Support (FCCS) course, Nederlandse Vereniging voor Intensive Care (NVIC), Houten	2014	1.5
- Advanced Trauma Life Support (ATLS) , Stichting ATLS, Tilburg	2015	1.5
Seminars and workshops		
- Basic acute care (ABCDE method, BLS, AED, PBLS), Erasmus MC	2012	0.3
- 1st National training defaecation problems, Driebergen/Zeist	2013	0.3
- Advanced Pediatric Life Support Course, Erasmus MC	2013	0.3
- PhD day, PhD committee Erasmus MC	2013	0.2

- PhD day, Erasmus PhD Association Rotterdam, Camp Woudestein, Rotterdam	2013	0.2
2. Presentations and conferences		
Presentations		
- Oral presentation at 13th Congress of the European Paediatric Surgeons' Association, Rome, Italy	2012	2.0
- Poster presentation at 14th Congress of the European Paediatric Surgeons' Association, Leipzig, Germany	2013	1.0
- Podium poster presentation at 15th Congress of European Paediatric Surgeons' Association, Dublin, Ireland; 2nd prize	2014	1.0
- Two oral and one poster presentations at 16th Congress of European Pediatric Surgeon's Association, Ljubljana, Slovenia	2015	3.0
International conferences		
- 5th Annual Pediatric Colorectal Workshop, Erasmus MC, Rotterdam	2012	0.5
- International Congenital Diaphragmatic Hernia workshop, CDH Euro Consortium, Erasmus MC, Rotterdam	2013	0.5
- 6th Annual Pediatric Colorectal Workshop, Erasmus MC, Rotterdam	2013	0.9
- 3rd International Conference on Esophageal Atresia, Erasmus MC, Rotterdam	2014	0.5
Other		
- Attending research meetings of the surgical long term follow up team	2012-2014	0.5
- Symposia pediatric surgical group, Erasmus MC	2013	0.4
- Symposium Sophia 150 years: Children of the future	2013	0.4
3. Teaching		
Lecturing		
- Lectures on primary school, Calvijn College, Rotterdam	2013-2014	1.3
- Educational lectures for nurse practitioners and residents, dept. pediatric surgery, Erasmus MC	2012-2014	0.6
Supervising practicals and tutoring		
- Supervising nurse practitioner in training and medical interns, dept. of pediatric surgery, Erasmus MC	2012-2014	0.5
- Tutor first year medical students, Erasmus MC	2013	1.5
- Supervising 'acquaintance with the profession of medical doctor' ('Kennismaking Beroeps Praktijk'); first year medical students, Erasmus MC	2013-2014	0.5
Total		**37**

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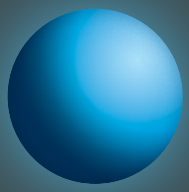
Desiree



One of the most alluring aspects of the pediatric surgery practice is the long-term follow up of patients with congenital anomalies. It is a good opportunity –and an obligation as well- to actually see the results of your work and to see how the children develop, not only physically but also psychosocially, and to see how they finally participate in society. Therewith presents the unique opportunity to combine research of short-term outcomes with that of long-term outcomes, even into adulthood. In this thesis, we aimed to optimize care of anorectal malformation patients with a multidisciplinary approach, and pioneered in the long-term follow up of this patient group.