Bladder and bowel dysfunction in children with anorectal malformations

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Voit pyytää minua etsimään totuutta, mutta eivät halua minua löytämään

Denis Diderot

Man kan begära att jag skall söka sanningen, men inte att jag ska finna den
Denis Diderot

Abstract

Background: Bowel dysfunction is seen in all children with anorectal malformations (ARMs) and is strongly related to associated anomalies commonly found in these patients. The presence of a megarectosigmoid (MRS) further contributes to chronic constipation and overflow incontinence. There is a great heterogeneity in reported functional results probably due to the fact that the criteria used to evaluate long-term outcome have been quite variable. In addition, results are often given for different ages together. By using more precise criteria as developed by the Krickenbeck conference 2005, and by following ARM patients longitudinally, the reporting of functional outcome should be more uniform and reliable.

Aims: To study the impact of spinal cord malformation on bladder and bowel function and to describe changes in bowel function during long term follow up in children with ARM.

To identify predictors influencing bowel functional outcome and evaluate outcome after surgical or conservative treatment of MRS. Finally, to longitudinally follow bladder function in these children and to identify the prevalence of neurogenic (NBD) and non-neurogenic bladder dysfunction.

Material and methods: 41 patients with ARM, excluding perineal fistulas, were consecutively included in this prospective longitudinal study. Investigations of bowel function were performed at ages 5, 10, 15 yrs. using a structured questionnaire and three weeks registrations of bowel movements, soiling, use of pads and enemas. 52 healthy children of similar ages and gender were used as control. The bowel was also investigated with a colostogram in the neonatal period, followed by a contrast enema 6 months after stoma closure and after that on an individual basis if MRS was diagnosed.

Investigations of bladder function were performed with urodynamics before and after the PSARP procedure and regularly during follow-up in patients with an obvious NBD. In addition, at the ages 5, 10 and 15 yrs. all children were aimed to be investigated with a structured urinary questionnaire, a three-day voiding/leakage diary and flow-residual measurements. Scoring systems were used for evaluation of bowel and bladder function.

Spinal cord malformations were diagnosed with spinal ultrasound followed by MRI in the neonatal period. Sacral anomalies were detected by plain radiographs.

Results: There was a successive improvement in bowel function during childhood and adolescence, but function did not achieve the level of healthy children. At the age of 10 years continence overall was achieved in 59%. Neurogenic bladder dysfunction was found in 22% of children with ARM and symptoms remained constant during follow up. Symptoms of non-neurogenic LUTD were present in 34%. However, the findings were transient and in most cases seen only at one of the follow up evaluations. Negative predictors for bowel function during follow up were spinal cord malformation in combination with NBD, complex type of fistula (high recto-urethral and bladder neck fistula) and sacral agenesis. Whether non-neurogenic

LUTD was associated with constipation and poor bowel function could not be confirmed even if these children had lower bowel scores than those with normal bladder function. MRS was not established as a predictor of bowel function, although girls with MRS at age 5 years had lower bowel scores compared to patients with normal rectal configuration. It was also shown that surgical treatment of MRS did not have better outcome regarding bowel function compared to bowel management only.
Conclusion: In this longitudinal study of ARM patients from childhood to adolescence, bowel function overall was shown to improve when estimated in relation to continence, soiling and constipation. Bladder function was also evaluated and NBD was diagnosed in 22%, and non-neurogenic bladder symptoms in 34% of the patients. Negative predictors for improvement in bowel function during growing up were spinal cord malformation, NBD and complex type of fistula malformation. MRS did not emerge as a predictor for functional outcome.

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Contents

List of publications

This thesis is based on the following articles:

I. **Borg H, Holmdahl G, Olsson I, Wiklund L-M, Sillén U.**
Impact of spinal cord malformations on bladder function in children with anorectal malformations.
J Pediatr Surg 2009;44(9):1778-85

II. **Borg H, Holmdahl G, Gustavsson K, Doroszkiewicz M, Sillén U.**
Longitudinal study of bowel function in children with anorectal malformations.
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III. **Borg H, Holmdahl G, Doroszkiewicz M, Sillén U.**
Longitudinal study of lower urinary tract function in children with anorectal malformation.
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IV. **Borg H, Bachelard M, Sillén U.**
Megarectosigmoid in children with anorectal malformations:
Long term outcome after surgical or conservative treatment.
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Abbreviations and Acronyms

ADHD	Attention-deficit-hyperactivity disorder
ARM	Anorectal malformation
BF	Bulbar fistula
BNF	Bladder neck fistula
CHARGE	Coloboma-Heart-Atresia-Retardation-Genital anomalies-Ear anomalies
CIC	Clean intermittent catheterization
DD	Delayed development
ELO	Elongation
LUT	Lower urinary tract
LUTD	Lower urinary tract dysfunction
LUTS	Lower urinary tract symptoms
MRS	Megarectosigmoid
NBD	Neurogenic bladder dysfunction
NF	Non fistula
PRF	Prostatic fistula
PSARP	Posterior sagittal anorectoplasty
PSARVUP	Posterior sagittal anorectovaginourethroplasty
PSS	Poor social support
TC	Tethered cord
UD	Urodynamics
UI	Urinary incontinence
VACTERL	Vertebrae-Anus-Cor-Trachea-Esophagus-Renal-Limb
VCUG	Voiding cystourethrography
VF	Rectovestibular fistula
VUR	Vesicoureteral reflux

Introduction

Anorectal malformations (ARMs) represent a spectrum of congenital abnormalities and involve the distal anus and rectum as well as the urinary and genital tracts.[1] They occur in approximately one in 4,000 to 5,000 live births. The pathogenesis of ARM is influenced by many factors and the condition is thought to be multigenic.[2] Children with anorectal malformations have a high incidence of associated anomalies and the defect may occur as part of a syndrome such as VACTERL (vertebral, anal, cardiac, tracheoesophageal, renal and limb anomalies) or caudal regression syndrome. The most frequent anomalies are genitourinary, cardiovascular, respiratory, gastrointestinal and vertebral with sacrum mostly affected.[3]. They also include anomalies of the central nervous system.

Anorectal malformation or imperforate anus has been a condition known since antiquity and throughout history different ways of creating an orifice in the perineum in children with ARM have been described. In early times, children who survived probably suffered from a perineal fistula, formerly described as a "low" defect. In 1835, Amussat, a French surgeon, performed what has been recognized as the first anoplasty.[4] During the early part of the 20th century, complex malformations were treated with a colostomy in the newborn period, followed by an abdomino-perineal pull-through without objective anatomic landmarks. Low defects (perineal fistulas) were surgically treated without a stoma.

Stephens made important studies of anorectal defects in the 1960s and suggested a dissection via a combined sacral and perineal approach.[5] This technique allowed surgeons direct exposure to the anatomy of the anorectal malformation and gave an excellent view of the fistula in most cases. In 1982, a new surgical approach, the posterior sagittal anorectoplasty (PSARP) pioneered by Peña and de Vries, led to improved functional outcomes in patients as it involved less risk of iatrogenic damage to pelvic structures.[6] According to current medical practice, in cases where there is a very high position of the rectum and/or vagina, an abdominal approach is also needed and laparoscopy can be used in combination with a posterior sagittal incision.

Bowel dysfunction should be expected in children with ARM and must be treated shortly after anorectoplasty and closure of a concomitant stoma.In addition, symptoms of bowel dysfunction are often aggravated by other congenital anomalies such as those affecting the vertebrae, spinal cord or urogenital tract, or by pelvic nerve damage acquired during reconstruction of the malformation. In these cases, urinary bladder function is also frequently affected. The prevalence of sacral and spinal cord abnormality increases in more severe ARMs and in those with urogenital abnormalities.[7]
Anomalies of the nervous control of the anorectum aggravate impaired bowel function, as does innate or acquired dilatation of the rectum, megarectosigmoid (MRS), an important contributing factor to the high levels of constipation found in these patients.[8,9]

Background

Anorectal malformation (ARM)

Embryology

Early in embryogenesis, the distal bowel and the bladder develop from a common structure, the cloaca, which normally exists until approximately 4 to 5 weeks of gestation (Fig 1).

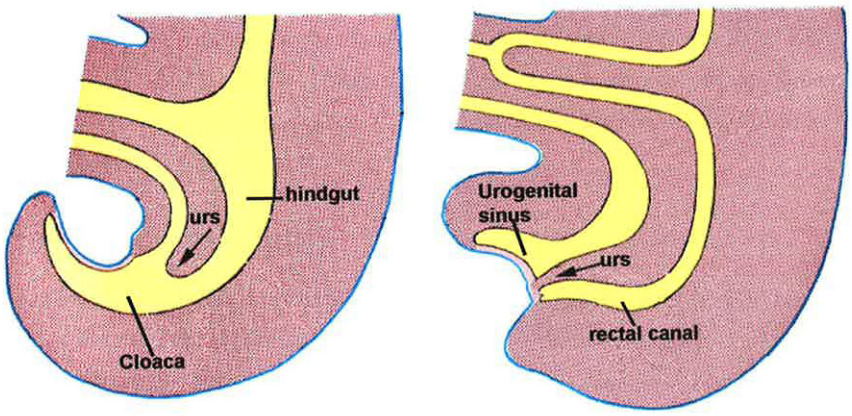


Figure 1. Drawings illustrate successive stages in the partitioning of the cloaca by the urorectal septum (urs) into rectum and urogenital sinus.

By the sixth week the cloaca has divided, resulting in a urogenital sinus, later giving rise to the bladder, and a separate hindgut forming the rectum.
The normal development of the hindgut critically depends on the cloacal membrane.[10] Recent studies indicate that the embryonic cloaca does not pass through any stages that are similar to anorectal malformations identified in neonates. Two major theories exist to explain the differentiation of the hindgut into a urogenital (ventral) and anorectal (dorsal) part: (1) septation of the cloaca; and (2) migration of the rectum. However, neither of these theories can be confirmed from electron microscopy studies and further studies are needed to explain the development of anorectal malformations.[10]

Classification

Anorectal malformation is a collective term for a broad spectrum of anomalies involving the termination of the hindgut. Pediatric surgeons and anatomists have proposed different classification systems. The terms “high”, “medium” and “low” have been the most widely accepted concepts and this classification for males and females was agreed by a convention of pediatric surgeons in 1986. This was designated the Wingspread classification of anorectal malformations.[11] In 1995, Peña

proposed a classification based on the type of fistula present.[12] He distinguished between perineal, vestibular, bulbar, prostatic, and bladder neck fistulas; imperforate anus without fistula; vaginal fistulas; cloacal fistulas; and rectal atresia or stenosis. Comparisions of outcome data have been hindered because of confusion relating to classification and assessment systems. In 2005, the Krickenbeck conference, a workshop of international authorities on congenital malformations of the pelvis and perineum, developed a classification based on surgical procedures, and anatomical and functional criteria, to better compare functional outcome.[13] These methods are intended to allow for a more common standardization of diagnosis and comparison of postoperative results.

Perineal fistulas in both male and female have traditionally been called "low" defects, where the rectum opens into a small orifice, usually stenotic, and located anterior to the center of the sphincter.

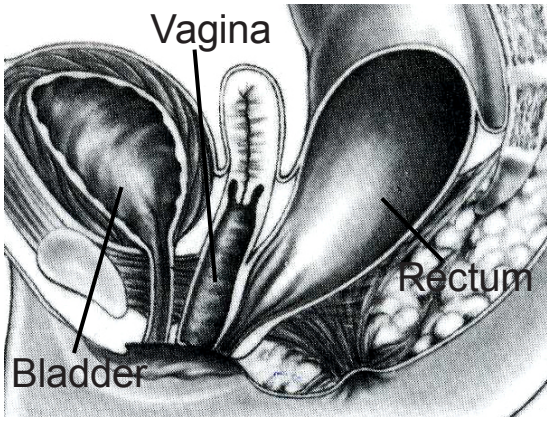
Rectovestibular fistula is the most common defect seen in girls. The rectum opens into the vestibule just behind the hymen. Most of these girls have a good sacrum and sphincteric mechanism (Fig 2).[14]

Rectourethral fistula is the most common defect in male patients. There are two types: (1) rectobulbar and (2) rectoprostatic. The fistulas open in the lower posterior (bulbar) and within the prostatic urethra, respectively. The latter is associated with a higher incidence of sacral dysplasia, spinal cord malformation and a flat bottom (Fig 3).[14]

Rectovesical or rectobladderneck fistula is the most severe defect in males. A typical appearance is characterised by a flat bottom, poor-quality muscles and abnormal sacrum, often combined with a spinal malformation.

Imperforate anus without fistula (non-fistula) is seen in less than 5% of the patients and is overrepresented in children with Down syndrome. In both males and females the rectum is located about 2 cm from the perineal skin. These patients usually have a normal sacrum and spinal cord and good functional prognosis.

Cloacal abnormalities are another spectrum of defects with a wide degree of variation and complexity. The urinary tract, vagina and rectum all drain into a common channel and single opening. A shorter channel, < 3 cm, can be repaired by a posterior sagittal approach. A longer common channel, > 3 cm, represents a more complex defect, which will require an abdominal approach. Urological malformations are overrepresented in this group and in comparison to other complex ARMs the degree of sacral and spinal cord abnormalities and muscle deficiencies correspond to the position of the defect (Fig 4).



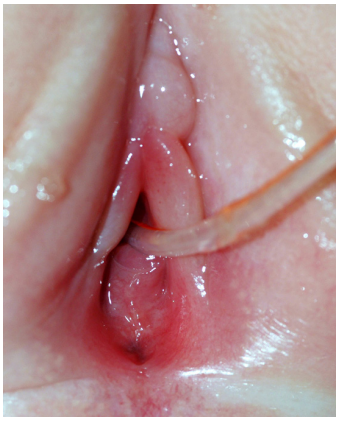
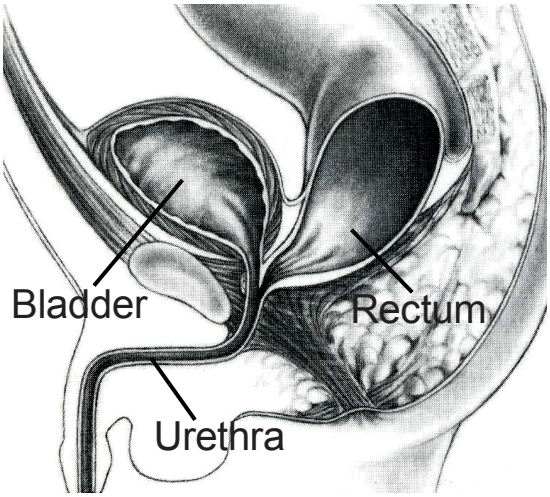


Figure 2. Rectovestibular fistula.



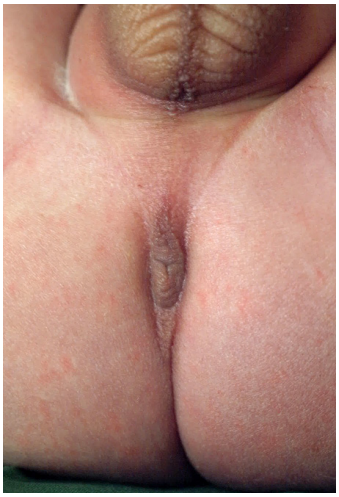
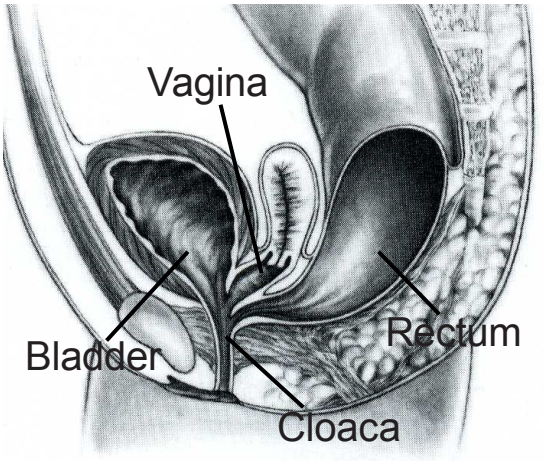


Figure 3. Rectoprostatic fistula



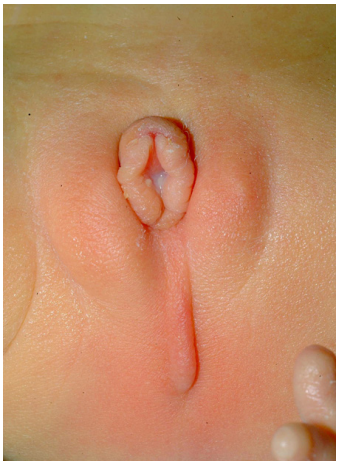


Figure 4. Cloaca

Associated malformations

Overall

The prevalence of associated congenital malformations is high in ARM children. In a recent paper 78% had at least one associated malformation, leaving only 22% with isolated ARM.[3] Genitourinary problems are the most frequent (50%), with vesicoureteric reflux as the most common. In addition, syndromes are quite common, including trisomy 21 and VACTERL

Spine and spinal cord malformations

Associated spine and/or spinal cord anomalies are reported in 30 to 50% of ARM patients.[1,15] The sacrum is the bony structure most affected, usually presenting as minor deformities (sacral dysplasia). Sacral agenesis is the most severe form, with one or several sacral vertebrae missing. The intraspinal malformations also found in children with ARM are often accompanied by severe sacral anomalies.[7,16]

The caudal regression syndrome, first described by Duhamel in 1961, is a spectrum of anomalies including lumbo-sacral agenesis and malformations of the anorectum, genitourinary tract, and spinal cord.[17] The organ systems are not affected equally in every case. A flat bottom, poor-quality muscles, an abnormal sacrum, poor midline groove and atrophy of leg musculature are common findings. Usually two types of abnormalities of the spinal cord are identified in MRI scans.[18] In the most severe form, the spinal cord has a characteristic high-lying, abrupt, club-shaped appearance with nerve roots in a double bundle (spinal cord regression) whereas in the other type, conus is elongated and stretched by a tight filum terminale and lipomatous tissue (tethered cord), sometimes associated with hydromyelia (Fig 5).

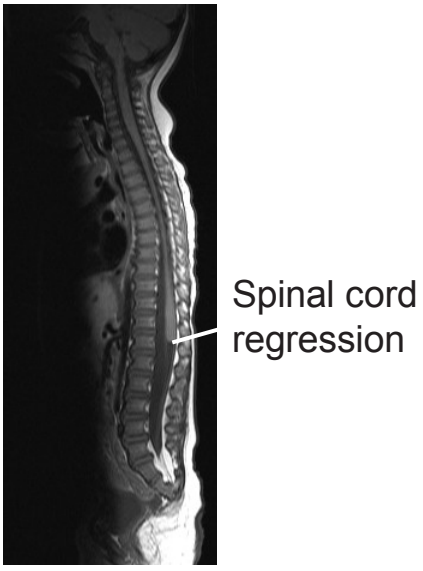


Figure 5A. Spinal cord regression

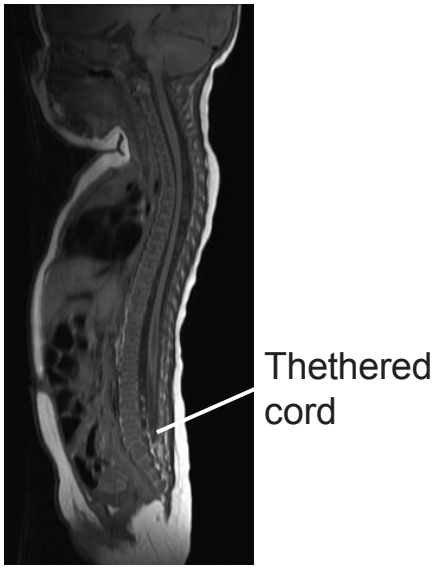


Figure 5B. Tethered cord with filum lipoma

Since the sacral nerves innervate the lower urinary tract and the anorectum, it is obvious that such neurospinal dysraphism will cause functional impairment of both these systems. Fecal incontinence and constipation as well as urinary leakage and obstruction have been reported in children with isolated sacral agenesis.[19,20]
In patients with short, club-shaped conus, the neurogenic bladder and bowel symptoms are relatively stable with an insignificant risk of deterioration during growth. However, in cases where the spinal cord is tethered, there is a risk of progressive neurological impairment and these patients need regular neurological evaluations, including bladder and bowel function assessments, until adolescence.

Summary of neonatal management
Once a child with ARM is born, a thorough perineal inspection gives the most important clues as to the patient´s type of malformation but must be supplemented with a series of investigations. See checklist below.

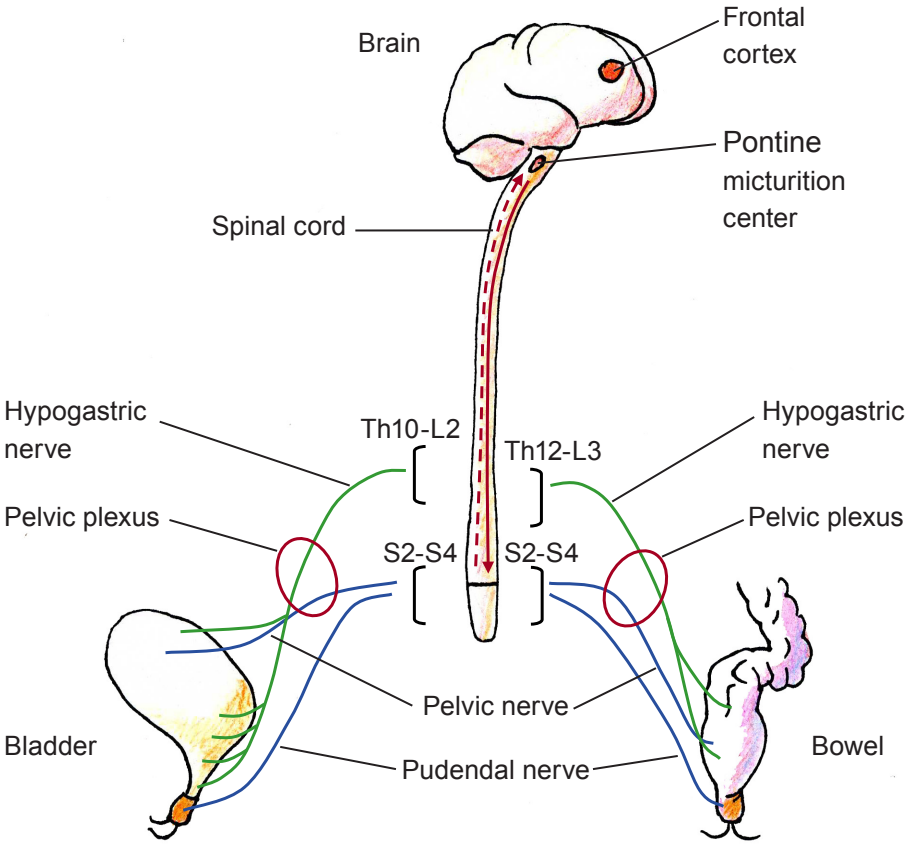
- Careful clinical assessment and inspection
- Nasogastric tube
- IV fluids
- Abdominal palpation
- Ultrasound abdomen, urinary tract and spinal cord
- Echocardiogram
- Plain film vertebrae /lateral including sacral ratio
- Urological evaluation of cloacae
- Antibiotic prophylaxis
- Definitive surgery for low lesions
- Descending colostomy for high-placed abnormality, or if in doubt
- VCUG (prophylactic antibiotics until VUR excluded)
- Distal colostogram to define fistula before definitive repair
- MRI and urodynamics in case of abnormal spinal ultrasound, or in case of a cloaca

Surgical treatment and follow up
The most commonly used surgical technique for ARMs worldwide is the posterior sagittal anorectoplasty (PSARP) under the protection of a colostomy. In recent years, these operations have been made as a primary one-stage repair in the newborn period, along with the use of laparoscopy with a minimized perineal incision.[21] The PSARP procedure involves a sagittal incision between the mid sacrum and the external sphincter with the patient in a prone position. The incision exposes the subcutaneous tissue, parasagittal fibers, muscle complex and levator muscles. The delicate part of the operation is the separation of the rectum from the urogenital structures. The rectum is then placed in the external sphincter, guided by an electrical stimulator, and the skin is closed. Anal dilatation of the neo-anus begins 2 weeks after the anoplasty and continues until the desired size is reached, usually between 2 and 3 months, after which the colostomy is closed.

Neuronal control of the bowel and bladder

Nervous control of the distal bowel and the lower urinary tract (LUT), have much in common (Fig 6).

Figure 6. Innervation of bladder and bowel



Both the defecation and the micturition reflexes are transmitted via the autonomic pelvic and the somatic pudendal nerves with connections to the brain. The type of autonomous innervation (pelvic nerve) is similar, with cholinergic transmission in the efferent contractile motor nerves (from spinal cord S2-S4) both to the rectal muscles and to the bladder detrusor. In addition, adrenergic transmission (from thoracolumbar spinal cord) is conducted by the pelvic nerves, with mainly inhibitory effects on the rectum and the bladder detrusor. In this way adrenergic transmission is of importance for both rectal and bladder reservoir functions. Adrenergic nerves also have excitatory effects on the bladder outlet and are active during the filling

phase of the bladder. They are also important for maintaining a high tonic activity in the internal anal sphincter, which is responsible for about 80-85 % of resting anal pressure.[22] The autonomic pelvic nerve also contains afferent nerve fibres from the distal bowel and the bladder, transmitting the urge for bowel or bladder emptying to the brain, thus making these processes conscious and voluntary. The somatic pudendal nerve mainly innervates the external anal sphincter, the external urethral sphincter and adjacent parts of the pelvic floor. Its main function is to induce a sphincter contraction to protect against leakage of feces or urine, when for example the individual feels the need to defecate or void but must postpone the actions due to an inappropriate time or localization. It is also activated in response to postural changes, coughing and running.

The enteric nervous system, responsible for peristaltic activity in the bowel, consists of two main structures: the myenteric plexus located between the longitudinal and circular muscle layers of the bowel wall and the submucous plexus. In the myenteric plexus there are pacemaker cells, the interstitial cells of Cajal, thought to have a major function in the propulsive function of the gut. In addition, autonomous innervation is not only seen in the anorectal region, but also in the remaining part of the gut with both excitatory cholinergic and inhibitory adrenergic systems. This complex nervous structure communicates with the central nervous system.

Bowel function in children

Bowel function in healthy children

Continence

Fecal continence is defined as the voluntary controlled passage of fecal material in an individual with a developmental age of at least 4 years. Loening-Baucke defines it as the ability to recognize when the rectum fills, to decide whether the contents are solid, liquid or gas, and then to empty the rectum in a socially convenient place at a socially convenient time.[23,24] The continence mechanism is of course related mainly to the anal sphincters. During the resting phase the internal sphincter tone corresponds to about 80-85% of the continence mechanism and the external sphincter provides the rest of the tone. There is also a 90 degree anorectal angle, which creates a valve mechanism and thus helps retain continence during sudden increases in intraabdominal pressure, such as coughing, etc.

Defecation

The physiological events of defecation can be summarized as rectal filling, relaxation of the internal anal sphincter and puborectalis, increased intraabdominal pressure, expulsion of feces and returning to the resting state. Rectal filling is controlled by colonic motility, mainly high amplitude propagating contractions (HAPC). The rectal distension thus induced, stimulates stretch receptors within the rectal wall, which triggers further rectal contractions and inhibition of the puborectalis, with straightening of the anorectum. In addition, rectal distension triggers the recto-anal reflex – an automatic reflex inhibition of the internal anal sphincter, mediated both

via enteric neurons and the external nerves. The stool then moves down into the anal canal stimulating sensory fibres, which is perceived at a cortical conscious level, producing a desire to defecate (Figure 7).

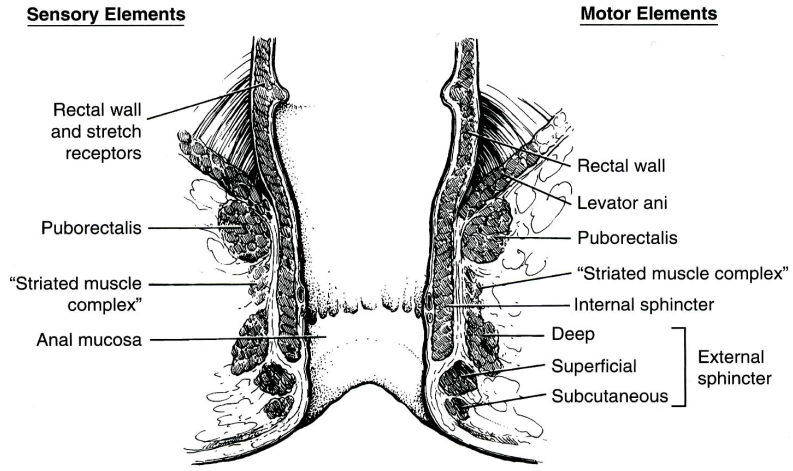


Figure 7. The main anatomic components of the rectum and anus

This reflex is also called the sampling reflex since it helps in discriminating between flatus, solid or liquid stool. The reflex can also be unconscious and be elicited several times an hour. However, if the sampling indicates feces and the child is in the proper position, there is further rectal contraction, both sphincters are inhibited, intraabdominal pressure is increased by straining, and defecation takes place. If the child is not in the proper position the puborectalis and external sphincter are contracted, pushing the stool back into the rectum.

Development of bowel habits

There is limited information concerning normal bowel habits and the prevalence of constipation and/or fecal incontinence in healthy children. Weaver et al studied the bowel habits of 350 preschool children (from 1 to 4 yrs.) and found that 96% opened their bowels from between three times a day to every other day.[25] There is a major decline in frequency of bowel movements from the neonatal period, with a frequency of 3 to 4 per day to less than 2 per day at the age of one year old.[26] The decline in frequency correlates with increasing whole gut transit time from less than 10 hours in infants younger than 3 months to 33 hours in children older than 3 years.[25] Most children achieve bowel control before or simultaneously with bladder control.[27,28] Since there has been a shift towards later toilet training, the age for bladder and bowel control is reported to be between 2 and 4 years old in the Western part of the world.[27]

Bowel dysfunction in healthy children

Definitions

It is not unusual for the pediatric population to suffer from functional constipation (FC), a definition of which can be found in the Rome III criteria.[29] According to the Rome III criteria for FC, children should have two or more of the following symptoms for at least 8 weeks: (i) two or fewer defecations per week, (ii) at least one episode of fecal incontinence per week, (iii) stool retentive posturing, (iv) painful or hard bowel movements, (v) large diameter stools that may obstruct the toilet or (vi) presence of large fecal mass in the rectum without objective evidence of a pathological condition.[30]

The terminology and the classification of leakage of feces are confusing. The terms available are soiling, encopresis and incontinence. The term **soiling** is defined as: the involuntary passage of fluid or semisolid feces into the clothing, usually as a result of overflow from an impacted rectum. The term is not recommended for functional bowel disturbances according to child psychiatric guidelines and the Rome III criteria.[30-33] Instead the terms encopresis and incontinence should be used. **Encopresis** is defined in the ICD-10 and the DSM-IV, both in respect to mental and behavioural disorders, as the passage of normal stools in socially inappropriate places, including clothing, in the absence of constipation.[31,33] It suggests **fecal incontinence** be used for all other conditions as an umbrella term for the depositon of feces in inappropriate places and can be divided into retentive and non- retentive forms.[30]

Etiology and Epidemiology

The onset of constipation is usually in the first 4 years of life, with symptoms occurring already during the first year in between 17 and 40% of constipated children.[30] A withholding behaviour plays an important role in the development and/or persistence of functional constipation. This behaviour may result from previous experience of painful defecation due to hard stools, anal fissures or lack of time for regular toileting. Some children refuse toileting outside their own home.[34] Long-term fecal impaction can eventually lead to a dilated rectum with decreased rectal tone and decreased rectal contractility, contributing to delayed evacuation of feces.[34] Normal rectal sensation, but higher compliance of the rectum, was found in constipated children compared with non-constipated children. This suggests that larger stool volumes are needed to trigger rectal sensation, such as the urge to defecate.[35]

Some epidemiological studies have been performed regarding bowel function in healthy children. In a study on Finnish individuals (n=594), aged 4 to 26 years, fecal incontinence and constipation occurred in 35 and 8% respectively. Constipation was overrepresented in females.[36] In a recent epidemiological study from Korea, including children between 5 and 13 years, abnormal bowel habits including constipation, painful defecation and fecal incontinence were reported in 31%.[37] This study also reported on urinary bladder dysfunction, the symptoms of which were identified in 46% of the group. There are other epidemiological studies showing similar prevalence of bowel and bladder dysfunction symptoms.[38-40]

Bowel function in ARM children

Definitions

Continence for ARM children has the same definition as for healthy children; voluntary bowel movements. This was decided during a conference 2005 and is named the Krickenbeck consensus document.[13,41] Peña postulated two concepts: total continence and voluntary bowel movements, where total continence excluded any form of soiling, even when minor soiling did not cause social problems.[12] According to the Krickenbeck document, leakage of stool should be referred to as soiling and graded from 1 to 3, according to its frequency. Constipation, also included in the definition of bowel function outcome in ARM patients, was also graded from 1 to 3, according to the amount of laxatives needed for its treatment. Retentive fecal incontinence as defined by the Rome III criteria can probably be used as a synonym for soiling induced by constipation.[30]

Etiology of fecal incontinence

Fecal continence problems dominate the significant morbidity following surgical correction of anorectal malformations. The three main factors involved in achieving continence; sphincter function, sensory function and motility, are all affected to a varying degree in patients with ARM.[42] Defective internal anal sphincters have recently been demonstrated in a histological study of specimens taken during PSARP procedures in girls with vestibular fistula.[43] In addition, when the anorectum has not been in the right position during fetal development, defective sensation in the anal canal can be anticipated as sensory connections to the CNS cannot be expected to be intact. Fecal continence will also be influenced by the fact that the voluntary striated muscles, represented by the levator muscle, muscle complex and external sphincter, are commonly under-developed and cannot function normally. All these congenital problems in ARM children contribute to their incontinence, especially early in life. A concomitant neurospinal dysraphism will exacerbate dysfunction of the pelvic floor.

Functional defects

An intact sensory mechanism is necessary for the communication between the anal canal and the voluntary muscles. Since the anal canal is affected in most patients with anorectal malformations, the sensation of rectal distension or the response to stimulated stretch receptors might be impaired. If the urge to defecate is reduced, then it is easier for the child to avoid defecation. Scarring as a result of surgery or perineal hemangiomas in the anorectal area might cause obstruction of the anal opening, thus aggravating the evacuation problem.

An additional defect often seen in ARM children is a dilated rectum, megarectosigmoid (MRS), which further aggravates bowel dysfunction, due to constipation and overflow fecal incontinence (soiling).[8,9,44-46] Characteristics of MRS include pronounced hypomotility, which in a few ARM children may also engage most of the large bowel. MRS has been reported in 10 to 50% of ARM patients.[8,9,46] Whether this is an innate phenomenon, secondary to a defective colostomy in the neonatal

period, due to outlet obstruction (anatomical or physiological), or a combination of two or more of these factors is under debate.
Another, smaller, group of patients suffers from fecal incontinence due to increased motility as a result of loss of rectal reservoir. This is often the consequence of defective surgical procedures. ARM patients with severe spinal cord malformations also fall into this group, not because of hypermotility, but because they do not have an adequate rectal reservoir due to poor sphincter function.

Bladder function in children

Normal bladder function
The bladder has two major functions, the storage and emptying of urine. The normal bladder fills to a volume adequate for the age of the child, and empties completely, periodically and voluntarily. During the filling phase the bladder should remain relaxed. During the voiding phase the detrusor-muscle of the bladder contracts, the bladder neck opens, the external sphincter relaxes and urine can be evacuated. Thus, perfect coordination between the bladder and the sphincter, including the pelvic floor, is the basis for normal voiding and continence.

The voiding pattern in a healthy newborn child has immature characteristics including undeveloped coordination between detrusor contraction and sphincter relaxation, resulting in interrupted voiding and incomplete emptying.[47-49] During the second year of life there is an increasing awareness of the desire to void and the functional bladder capacity increases at the same time as detrusor- sphincter coordination develops. Between 2 and 4 years the normal child develops conscious, voluntary control of the lower urinary tract.
In the western part of the world children achieve bladder control rather late. Recently there have been studies from developing countries showing that bladder control can be achieved much earlier, but the practicalities of toilet training have to be taken care of by the child's guardian.[50]

Micturation in older children (7 to 15 years of age) is characterized by between 4 and 7 voids per day with a complete and bell-shaped urinary flow. However, symptoms like urgency, voiding-postponement behaviour and the leakage of urine, signs frequently seen in functional bladder disturbances, are commonly recorded in the years children are attaining bladder control.[27] The number of children with such symptoms decreases with age, and at 15 years old only a few were identified.[51] Urinary incontinence (UI) in otherwise healthy children occurred on a weekly basis in 2.5% of 7 year olds and 1% of 11 to 12 year olds in a metaanalysis.[52] At the age of 16 years, girls had an UI prevalence of 0.7%. Overall, the prevalence of UI is higher in all age groups if UI incidents occurring less frequently than once a week are included in the figures.

Lower urinary tract dysfunction (LUTD) in healthy children
If the above symptoms occur regularly and frequently in a child after the age of 5

years old it is referred to as lower urinary tract dysfunction (LUTD), especially if one of the symptoms is urinary incontinence. Three main types of dysfunction have been identified: overactive bladder (OAB), dysfunctional voiding (DV) and voiding postponement (VP).[53] OAB is a bladder-filling disorder characterised by urgency, often in combination with incontinence and frequent voids, but with complete emptying at voiding. DV is induced by a lack of coordination between the sphincter and the detrusor at voiding, meaning irregular/fractionated flow curve, and often an increase in post-void residual urine. It is also often associated with complaints like starting problems, straining and intermittency at voiding. Also typical of this latter dysfunction is simultaneous symptoms of constipation and soiling, which suggests a dyscoordination also affecting defecation. When there is a combination of bladder and bowel problems the dysfunction is referred to as dysfunctional elimination syndrome (DES).[54] Urinary tract infection is common in children with DV and DES. VP is a behavioural dysfunction where the child postpones voiding voluntarily, and it may be associated with all the symptoms discussed earlier.

Neurogenic bladder dysfunction (NBD)

A classification of the neurogenic bladder induced by spinal cord or peripheral nerve abnormalities was suggested by van Gool (Table 1).[55]

Table 1. Pattern of neurogenic bladder dysfunction

	Detrusor		
	Underactive	Overactive	Clinical correlate
Sphincter			
Underactive	~ 40% Low risk	~10% Low risk	Incontinence
Overactive	~ 10% Intermediate risk	~40% High risk	Outflow obstruction

The dysfunction can cause either overactivity or underactivity of the sphincters and the detrusor. Usually there is a complex combination. The most common dysfunction is overactivity in the bladder outflow during detrusor contractions. This detrusor-sphincter dyssynergia induces incomplete emptying, often resulting in high intravesical pressure levels, which in the long run can damage the upper urinary tracts and the kidneys. Another pattern with more social implications, because of urinary leakage, but associated with little risk of renal damage is detrusor overactivity in combination with weak sphincteric function. A factor that has to be taken into consideration in neurogenic bladders is the change in elasticity of the bladder detrusor, due to an increase in collagen content, typically manifesting as an increase in basal bladder pressure during filling. When a bladder manifests such a pathological increase in basal pressure this is referred to as a poor compliance bladder, and this condition is also harmful to the upper urinary tracts and the kidneys.

Bowel management

The term bowel management for the treatment of fecal incontinence refers to a program designed to keep fecally incontinent patients artificially clean. The ideal regime is a combination of different treatment methods, which ensure that the patient has one bowel movement every day and stays clean between microclysmas or enemas.[56] Bowel management in spina bifida patients using salt water enemas via an inflatable balloon catheter was described by Shandling and Gilmour in 1987.[57] The problems these patients had with constipation and incompetent anal sphincters during enema instillation also apply to many ARM children. We have found that most of our patients tolerate the described method very well and the effectiveness of the enema is excellent. Many centres dealing with ARM patients advocate an antegrade colonic enema via an appendicostomy (ACE), but we have adopted that method in only a few cases.[58]

Aims of the study

The aims of this study are:

- to identify risk factors for neurogenic bladder dysfunction (NBD) in chil dren born with anorectal malformations

- to study changes in bowel function in children with ARM, with or without spinal cord pathology and NBD, as they grow up.

-to determine to what extent fecal continence can be achieved in relation to the age of the patient and the type of malformation, and evaluate risk factors in the delay of the maturation process.

-to study bladder function longitudinally in children and adolescents with ARM using non-invasive investigations in order to identify symptoms of lower urinary tract (LUT) dysfunction, paying special attention to urinary symptoms not related to NBD. The impact of poor bowel function on LUT symptoms was also investigated.

-to evaluate outcome of bowel function and configuration, after surgical or conservative treatment of megarectosigmoid (MRS) in children with ARM, excluding patients with perineal fistulas.

Patients

This study comprises a total number of 79 patients with ARM, excluding perineal fistulas, referred to The Queen Silvia Children´s Hospital between 1986 and 2007 for treatment of their anorectal malformations. For the number of patients in each study see table 2.

Table 2. Study population and characteristics

	Paper 1	Paper 2+3	Paper 4
Total	37	41	79
Time period	1995-2005	1995-2007	1986-2007
Non-fistula (NF)	3	4	8
Bulbar fistula (BF)	5	5	10
Prostatic fistula (PRF)	12	12	25
Bladderneck fistula (BNF)	1	1	2
Vestibular fistula (VF)	13	16	27
Cloaca	3	3	3
Rectourethral fistula (RU) unspecified			4
Sacral pathology			
Dysplasia	11	13	9*
Agenesis	8	8	2*
Spinal cord malformation			
Spinal cord regression	3	3	
Lipomyelomeningocele	1	1	
Tethered cord	2	2	3*
Thick filum/fibrolipoma	2	2	
Megarectosigmoid (MRS)	14	15	26
Urogenital malformations	21	21	
Neurodevelopmental delay	5	5	1*
Neuropsychiatric disorder	3	3	2*
Poor social support		3	6*
Chromosomal aberration	1	2	1*
*Only patients with MRS reported			

Investigations in the neonatal period included abdominal plain film, contrast enema via a transperineal punction, through the fistula or colostogram via the distal colostomy, spinal and sacral radiograph, ultrasound of the urinary tract and voiding cystourethrography. Since 1999 spinal ultrasounds have been routinely performed and,

in addition, magnetic resonance imaging (MRI) was carried out on 14 patients. This was owing to abnormal findings from their spinal ultrasound scans or urodynamic tests. A MRI scan was also made in patients with cloacal malformation. Chromosomal aberrations were ruled out if there was a high suspicion of abnormality or in cases of syndromes. For classification of type of fistula and associated malformations see table 2.

Methods

Urodynamic investigations

Urodynamic investigations were made before and after the PSARP procedure (paper 1) and also during follow up evaluations of ARM children with spinal cord malformation and/or NBD (paper 3).

A cystometric investigation was performed with computerized equipment. Intravesical, abdominal and subtracted detrusor pressures were recorded simultaneously and perineal electromyography (EMG) was performed using skin electrodes. Abdominal pressure before PSARP was measured via a catheter introduced in the colostomy or a vestibular fistula. Bladder filling and pressure recordings were obtained via a 6F double lumen transurethral catheter or two suprapubic 5F catheters introduced the day before the investigation. Bladder infusion (37°C saline solution) rate was 3 to 5 mL/min, depending on patient age and expected bladder capacity.

Expected bladder capacity was calculated using the following formula: capacity in millilitres = 30 + 2.5 x age (in months).[59] Detrusor overactivity was defined as detrusor contractions during filling exceeding 15 cm of water. Overactivity was also classified by cause according to the ICCS standardization document. The causes were neurogenic detrusor overactivity when there was a neurologic condition, or idiopathic when there was no defined cause.[29] A poorly compliant bladder was indicated by an increase in basal pressure during filling of more than 20 cm of water. Dysfunctional voiding was attributable to dyscoordination between the bladder detrusor and the sphincter/pelvic floor. Flow curve was irregular or fractionated and EMG activity increased during voiding contractions and there were often increased amounts of residual urine. The term used for dyscoordination in children with NBD is dyssynergia.[29]

Free voiding studies

Free voiding studies were performed for the investigation of bladder function at ages 5, 10 and 15 years (paper 3). The number of patients investigated in each age group was 25, 28 and 13 respectively. The reasons for the incomplete number of patients in the 5 year old group were: 7 patients were still using diapers, 2 were on CIC and 7 could not be followed up for social reasons. In the 10 and 15 year old groups, not all patients had reached the age for investigation.

A structured urinary questionnaire, a three-day voiding/leakage diary and flow-residual measurements were included in these evaluations. The urinary flow assessments were repeated 2 or 3 times with the amounts of post-void residual urine measured using ultrasonography. Bell and tower shape flow curves were defined as normal, whereas irregular, fractionated and plateau shapes were defined as abnormal. The flow curve was accepted, provided that voided volume exceeded 50% of expected bladder capacity. The bladder function questionnaire included data on voiding habits and age of complete day and/or night dryness. The questions were scored according to a system similar to what was described by the Toronto group (Table 3).[60]

Forty-five healthy children of similar ages and gender distribution were used as controls. The same questionnaire concerning bladder function at the ages of 5 and 10 was used in the healthy children, mainly the offspring of hospital staff. They did not perform urinary flow and residual urine measurements. When comparing bladder function in ARM children with the members of the control group, only scoring from the questionnaire was used in the statistical analyses. However, in the analyses

Table 3. Protocol for evaluation of bladder function

1

VOIDING HISTORY QUESTIONNAIRE

Dry during day	at.....months of age	
Dry during night	at.....months of age	
		Scoring
Does the child wet the bed during night?	☐ every night ☐ once or more/week ☐ once or more/month ☐ never	
Does the child get up to void during night?	☐ every night ☐ once or more/week ☐ once or more/month ☐ never	
Number of voiding during day	☐ > 7 times /day ☐ 3-7 times/day ☐ 1-2 times/day	2 0 3
When does the child void in the morning?	☐ within half an hour ☐ within 2 hours ☐ later	0 1 2
How often does the child postpone a voiding?	☐ always ☐ every day ☐ once or more/week ☐ once or more/month ☐ never	3 2 1 1 0
*Does the child have to hurry to the toilet (can not wait)?	☐ always ☐ every day ☐ once or more/week ☐ once or more/month ☐ never	3 2 1 1 0
*Does the child react with urgency defence like crossing legs or squatting?	☐ always ☐ every day ☐ once or more/week ☐ once or more/month ☐ never	3 2 1 1 0
Does the child wet underwear or clothes during the day?	☐ more than once/day ☐ every day ☐ 1-3 times/week ☐ 1-3 times/month ☐ never	4 3 2 1 0
Does the child have difficulties to start voiding?	☐ often ☐ sometimes ☐ never	2 1 0
Does the child void in more than one urine portion?	☐ often ☐ sometimes ☐ never	2 1 0
Does the child strain at voiding?	☐ often ☐ sometimes ☐ never	2 1 0

*Only one of these questions is included in the total scoring: The question with the highest scoring.

of differences between ARM patients, flow/residual measurements were also taken into consideration and included in the score of the patients. LUT dysfunction was considered to be indicated if the score was ≥4 for the 5 year old girls and for both girls and boys at the ages of 10 and 15, and a score of ≥5 in the 5 year old boys.

Evaluation of bowel function

Evaluations of bowel function were performed at ages 5, 10 and 15 years using a structured questionnaire and three weeks' registration of bowel movements and episodes of fecal leakage (soiling). The numbers and types of enemas and stool softeners used were also recorded. Times were indicated for voluntary bowel movements, soiling and enemas. The use and types of pads or diapers were also registered. Food allergies and/or dietary restrictions were documented. The bowel therapist gave instructions about recording bowel movements one month before the appointment and interviewed the parents and child about bowel habits. Questionnaires were completed at the hospital visit.

Bowel function outcome was evaluated with a scoring instrument described by Rintala and Lindahl, with slight modifications in which the factor "accident" in the scoring system was excluded.[61,62] The maximum bowel function score was 14 (Table 4).

Functional outcome was also evaluated according to the Krickenbeck consensus recommendation, which is a descriptive, non-scoring outcome classification of continence, soiling and constipation (Table 5).[13] Continence was defined as voluntary bowel movements and both soiling and constipation were classified in three grades. Social continence, i.e. continence achieved by individualized bowel management, was also evaluated.

Fifty-two healthy children, mainly offspring of hospital staff and with a similar age and sex distribution to the patient group, were used as controls. They answered the same questionnaires concerning bowel function, but did not carry out the three-week registration of bowel habits. Each control child performed only one registration on one occasion, and the controls were not followed longitudinally.

Radiological evaluation of MRS

All contrast enemas performed in ARM children included in the study were reviewed retrospectively by an experienced pediatric radiologist (MB) together with the pediatric surgeon (HB). In order to assess a change in configuration of the megarectum in relation to the different treatment strategies, conservative or surgical, measures of the rectum in relation to pelvic anatomical landmarks were performed according to a standardized protocol in each individual.

Radiological the normal rectum is characterized by an oval lemon shape, where the widest part is located within the pelvis. It is significantly wider than the sigmoid, which, unlike the rectum, is haustrated and the rectosigmoidal transition is located below the promontory/iliac crest (S2-3) and deviates from the midline. The mega-

Table 4. Protocol for evaluation of bowel function with scoring modified from Rintala [62]

Ability to hold back defecation	
Always	3
Problems less than 1/week	2
Weekly problems	1
No voluntary control	0
Feels/reports the urge to defecate	
Always	3
Most of the time	2
Uncertain	1
Absent	0
Soiling	
Never	3
Occasionally (once/twice per week)	2
Every day, no social problem	1
Constant, social problem	0
Constipation	
No constipation	3
Manageable with diet	2
Requires laxatives	1
Resistant to laxatives and diet/requires enemas	0
Frequency of defecation	
Every other day-twice a day	2
More often	1
Less often	1

Table 5. International classification (Krickenbeck) for postoperative results

1. Voluntary bowel movements Feeling of urge, Capacity to verbalize, hold the bowel movement	Yes/no
2. Soiling	Yes/no
Grade 1	Occasionally (once or twice per week)
Grade 2	Every day, no social problem
Grade 3	Constant, social problem
3. Constipation	Yes/no
Grade 1	Manageable by changes in diet
Grade 2	Requires laxative
Grade 3	Resistant to laxatives and diet

rectosigmoid is characterized by a cylindrical or saccular shape with widening and midline elongation above the promontory /iliac crest. The transition to normal calibre sigmoid colon is often sharp.

In the present study elongation (ELO) of the rectum above S2-S3 was registered in relation to level of vertebrae. For calculation of changes in elongation, each vertebra from S5 to Th11 was given a numerical value from 1 to 12. Since the radiological examinations have been performed in individuals of different ages and sizes, it was impossible to use a fixed width at the pelvic brim as a discriminator between normal and abnormal bowel.[63] Therefore, the width of the bowel in a frontal projection was measured at different levels: above the promontory at the level of S1 (SS^1) and at the widest part of the rectum (RR^1) within the pelvic ring (fig 8).

In MRS, SS^1 is often wider or equal to RR^1. To illustrate this relationship the sigmoid/rectal ratio (SR) was calculated (SS^1/RR^1).
Bowel emptying of contrast was estimated from 1-5, where 1 was poor and 5 complete.

Eleven children with ARM (5 girls, 6 boys) not considered radiologically to have MRS, were used as controls. The contrast enemas in the control patients were measured as described above and thus used for the evaluation of the diagnostic criteria used for the radiological diagnose of MRS.

Bladder management strategy

Children with ARM without NBD were instructed in potty training, i.e. regular voids in a relaxed position as soon as the child could sit steadily.
ARM patients with NBD were followed up with regular urodynamic investigations

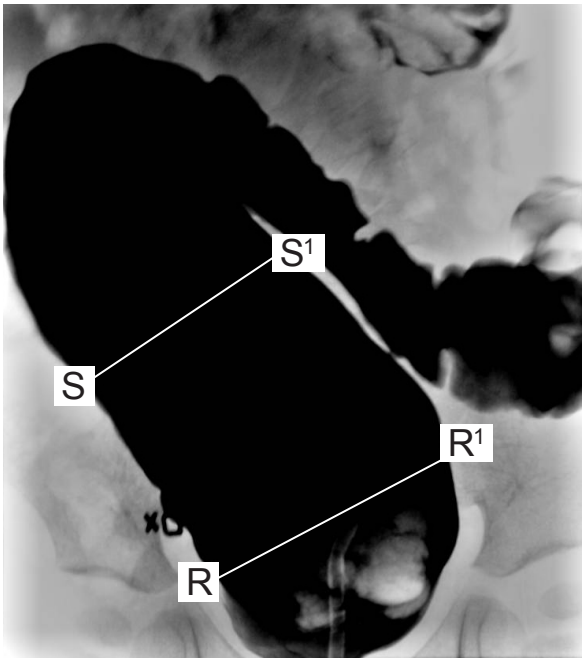


Figure 8. Radiological image of megarectosigmoid (MRS) in ARM patient. The SS¹ line illustrates bowel width above promontory and the RR¹ line rectal width within the pelvic ring, measures used for calculation of sigmoid-rectal (SR) ratio.

and appointments with a team including neurologist, urologist, pediatric surgeon and bowel and urotherapist. Bladder treatment in these children included: CIC (clean intermittent catheterization), anticholinergic drugs and, when necessary, surgical procedures to achieve continence (bladder augmentation, bladder-neck procedures and the Mitrofanoff procedure).

Bowel management strategy

As early as 4 to 8 weeks after stoma closure there was an evaluation of bowel habits including constipation, soiling or abnormal frequency of stool emptying. Bowel treatment was suggested according to the type of evacuation problem. Potty training was encouraged as early as the child could sit steadily and was always recommended if microclysmas or enemas were introduced.

Six months post-stoma closure, a contrast enema was performed, which provided information about the colonic configuration, including signs of megarectum and the degree of fecal impaction. The radiological information in combination with the reported bowel habits of the child helped in designing an individualized bowel management program for that particular child. If microclysmas were not sufficient, saline enemas (volumes 150 to 500 ml, 3 to 7 times per week) were introduced. Thorough information was given to the parents, underlining the importance of adherence to the instructions.

An important checkpoint was at preschool age (5 to 6 years) when children are expected to be independent when it comes to toileting. The bowel therapist evaluated the patient and together with the parents and school personnel identified special needs concerning bowel function and made sure that extra support was available during daily activities, if required. Adjustments to bowel treatment were made during childhood in response to the individual's bowel function.

When MRS was diagnosed the child was put on intensified bowel management therapy and close contact with the bowel therapist was recommended. These patients were followed up with contrast enemas at long intervals, which were repeated if bowel function deteriorated.

In the early period, surgical treatment of MRS was advocated in the patients with signs of constipation and pseudo-incontinence, who did not respond satisfactorily to symptomatic treatment.

Statistical methods

Descriptive statistics
Continuous variables were expressed as mean, median, standard deviation, min (minimum) and max (maximum) and range. Number and/or percentage described categorical variables.

Statistical analysis
For comparison between groups, a Mann-Whitney U- test was used for continuous variables (papers 1 to 4) and Fischer´s Exact test for dichotomous variables (papers 1 and 2). For tests between more than two non-ordered groups with respect to a continuous variable, a Kruskal-Wallis test was used (papers 2 and 3). Predictors for LUTD were investigated by using bivariate logistic regression and the association was described by odds-ratios (OR) and 95% confidence intervals (CI) (paper 3).
For analyses of changes over time within the group, Wilcoxon´s Signed Rank test for continuous variables was used (papers 1 and 4) and a sign test for ordered categorical variables (paper 4).
For comparison of the two groups, the Mantel-Haenszel Chi-square Exact test was used for ordered categorical variables (paper 4).
The analysis for selecting best predictors of bowel scores at 5 and 10 years old was performed using linear regression. The dependent variable bowel scores, at 5 and 10 years, were transformed by using Blom's transformation since they were not normally distributed. P-value and R^2 were presented from these models. For descriptive purposes, estimates of 95% CI from the model with the original values were presented. The set of statistically significant predictors with the largest R^2 was considered as the best one.
Since not all patients completed all visits at 5, 10 and 15 years, changes in scores from 5 to 10 years and from 5 to 15 years were investigated by using Mixed Models with Blom transformed bowel scores (see paper 2). Cronbach's alpha was calculated

in order to examine the internal reliability of the bowel scores.
All p-values were two-tailed and tests were conducted at 5% significance level (paper 1-4).

Ethical aspects

The Ethics Committee of the Medical Faculty, University of Gothenburg, approved all studies.

Results

Bladder function (paper 1 and 3)

The ARM children (excluding the boys with NBD) were day-dry later than the controls, mean 36.7 months (SD 10.6) and mean 28.6 (SD 8.2), respectively (p=0.0018). Age for night dryness was mean 41.8 (SD 11.7) and mean 35.9 (SD 15.1) months, respectively, p = 0.055. The number of ARM children not achieving night continence during follow- up was higher than in the group of control children (p=0.0175).

Neurogenic bladder dysfunction

Innate NBD (paper 1)

Cystometric investigation was performed in 37 cases before (mean, 0.5 year) and after anorectal surgery (mean, 1.7 years). Five boys (1 BNF, 4 PRF) and 3 girls (VF) were considered to have neurogenic bladder dysfunction (NBD) both before and after reconstructive surgery (Table 6).

Table 6. Type of LUTD (neurogenic and non-neurogenic) in ARM patients, shown according to cause and type of fistula. VF=vestibular fistula, BNF=bladder neck fistula, PRF=prostatic fistula, BF=bulbar fistula, NBD=neurogenic bladder dysfunction.

Type of LUTD	Number of patients (%) n=41 (total material)
NBD total	**9 (22%)**
-tethered cord, VF(3), BNF(1)	4
-caudal regression, PRF	3
-MMC (PRF)	1
-post-PSARVUP (Cloaca)	1
NonNBD total	**14 (34%)**
Urinary tract related	
-urethral stricture, hypospadia op (PRF)	3
-VUR with ectopic ureter (BF)	1
Non-urinary tract related	
-MRS, VF(4), BF(2), NF(1)	7
-perineal hemangioma, anal stricture,etc, VF(2), BF(1)	3

The urodynamic pattern in the 5 boys was characterized by neurogenic detrusor overactivity during filling and with urinary leakage. Compliance was normal during filling and bladder capacity was low with median 67%, (range 50-104%). The voiding pattern was fractionated without a proper detrusor contraction (Fig 9).

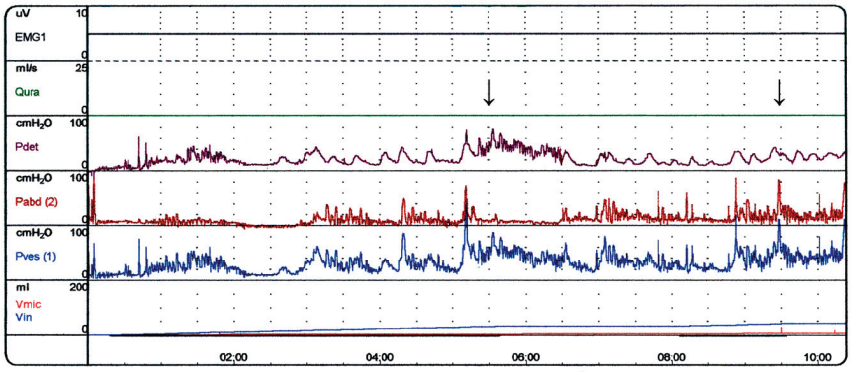


Figure 9. Cystometric registration in a boy with blunt high ending of the spinal cord and NBD, characterized by neurogenic overactice contractions during filling causing urinary leakage. Arrows indicate leakage.

On the other hand, the 3 girls (VF) considered having NBD both before and after reconstructive surgery, had a less severe urodynamic pattern, with overactivity during filling but without leakage. There was great variation in bladder capacity and in one girl it was 350% of expected normal capacity. The voiding was abnormal with a typical pattern of detrusor sphincter dyssynergia.

Postoperative NBD (paper 1)

One girl with cloaca had NBD only after reconstructive surgery, characterized by high bladder capacity and no spontaneous voiding, and hence requiring clean intermittent catheterization. Urodynamics was normal before surgery. Another girl with low cloaca had transitory bladder-emptying problems postoperatively, but recovered after a few months.

Follow-up NBD (paper 3)

The five boys with PRF/BNF and innate NBD had uncontrolled urinary leakage in response to neurogenic overactive contractions and incomplete emptying. They showed no improvement during follow-up, median 8 yrs. (age range 6 to 10). Indications of poor compliance were seen in three boys. Four of the five boys had been started on CIC at median age 2 yrs. (age range 0 to 7) and all five were treated with anticholinergic drugs. In two cases continence surgery was performed to treat the uncontrolled leakage. Poor compliance of the bladder with upper urinary tract deterioration was confirmed in one of the two boys.

In the three girls with VF and tethered cord, the urodynamic pattern was almost unchanged post-PSARP at age 5, and was characterized by dyssynergia at voiding. Emptying was normalized and the dyssynergia was less obvious at age 10.

The girl with high cloaca who developed NBD post PSARVUP remained unchanged. Urodynamics showed detrusor underactivity with limited ability to void spontaneously. CIC remained necessary and she was dry both day and night in between catheterizations at ages 5 and 10 years.

The girl with low cloaca, with a transitory high capacity and bladder-emptying problem postoperatively, remained free from bladder symptoms at later follow-ups (aged 5 and 10).

Correlation between NBD, perineal appearance and sacral and spinal cord malformation (paper 1 and 3)

Vertebral anomalies were found in 24 of 37 patients and the sacrum was affected in 19 cases (paper 1). Partial sacral agenesis was seen in 8 patients, of whom 7 were from the group of 8 patients with congenital NBD, and the remaining patient was a PRF boy without NBD. Minor sacral abnormalities were diagnosed in another 11 of the 37 children investigated in paper 1.

In the five boys with NBD, all with high fistulas (4 PRF, 1 BNF) and spinal cord malformation, spinal cord regression was found in three, an anterior lipomyelomeningocele with tethering in one, and tethering with a thick filum in the BNF patient. The 3 VF girls with NBD all had tethering of the spinal cord and in one case this condition was in combination with a thick filum and fibrolipoma (Table 6). The girl with cloaca, with NBD post PSARVUP, had a normal spinal cord. NBD without spinal cord malformation was not seen in any of the 37 patients included in paper 1, except for the girl with cloaca mentioned above. It could not be confirmed whether spinal cord malformation was present without NBD, since there were no MRI or ultrasound evaluations of the spinal cord for 10 patients. When including all patients from all four studies (n=79), 3 more patients with tethered spinal cords were identified, who all had normal bladder function.

The interpretation of the perineal appearance was critical when there was a suspicion of spinal cord pathology. All 5 boys with NBD had a typical flat perineum (except for one with a huge fibrolipoma), poorly developed muscles, poor midline and palpable defective sacrum (Fig 10).

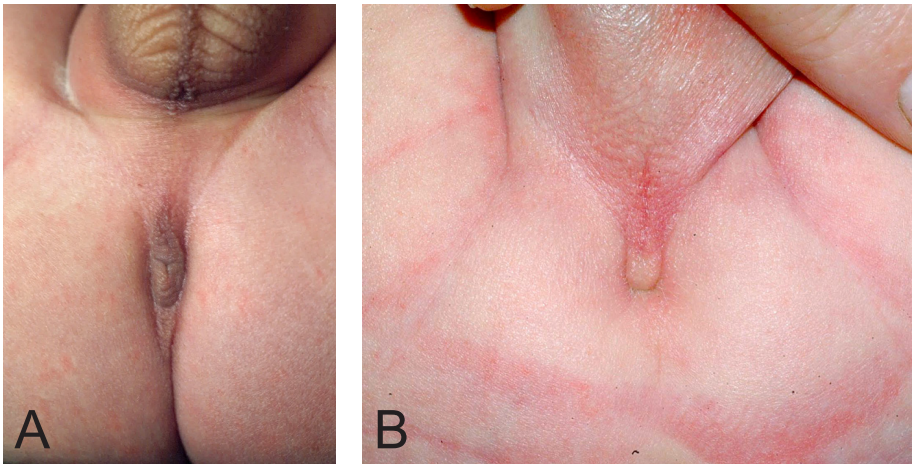


Figure 10. Perineal appearance in two boys with rectoprostatic fistula. A. Normal spinal cord. B. Spinal cord malformation

However, in the 3 girls with tethered cords and NBD and partial sacral agenesis in 2, the perineal appearance was no different from girls with VF without NBD and with normal spinal cords.
Spinal cord malformation at both the ages of 5 (p=0.011) and 10 years (p=0.055) was a predictor of NBD.

Non-neurogenic LUTD (paper 3)
No significant difference in bladder score was found between ARM children and controls at any age, when the 5 boys with NBD were excluded (Fig 11).

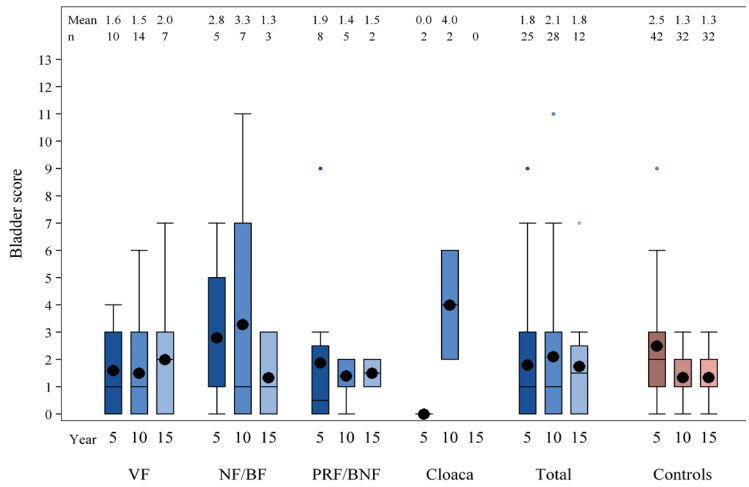


Figure 11. Bladder score in ARM patients (total and according to fistula group) and controls and age for follow up. Box edges are Q1 and Q3, horizontal line is median and large dot is mean. NBD boys not included.

According to scores, development in bladder function was not significantly different from 5 to 10 years in ARM children, when excluding boys with NBD (p=0.17). Non-neurogenic LUTD was estimated to be present in 14/41 (34%) in at least one of the follow-up investigations (Table 7).

*Table 7. ARM patients with non-neurogenic LUTD according to age, type of fistula and risk factors. *Patients with NBD or cloaca not included.*

		Bladder function D (LUT dysfunction), N (normal), - (not done)			
	Patient*	Age 5	Age 10	Age 15	Risk factors
VF (n=14)	1	-	N	D	DD
	2	D	(D)	N	Perineal hemangioma
	3	D	N	-	MRS
	4	D	D	-	MRS
	5	D	-	-	MRS
	6	N	D	-	MRS
Number LUTD of total		4/8	2/12	1/7	
NF + BF (n=9)	7	D	D	D	VUR, PSS
	8	D	-	-	Anal stricture
	9	D	-	-	MRS
	10	-	D	N	MRS, PSS
	11	N	D	-	MRS, autism
Number LUTD of total		3/6	3/7	1/4	
PRF (n=8)	12	D	N	D	MRS, urethral stricture
	13	D	D	N	Hypospadia op
	14	N	D	-	Hypospadia op
Number LUTD of total		2/8	2/5	1/2	
Total number LUTD (non-NBD)		9/22 (41%)	7/24 (29%)	3/13 (23%)	

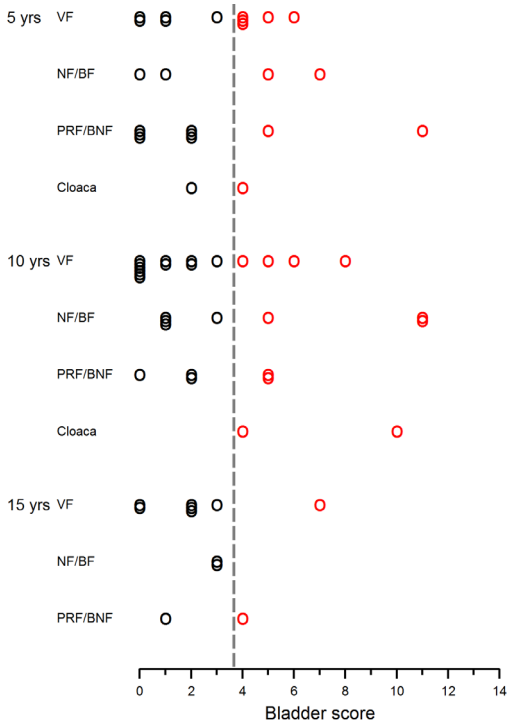


Figure 12. Bladder score in ARM patients according to fistula group and age at follow up. Patients with score to the right of vertical line considered to have LUTD (red circles). NBD boys not included.

Overall bladder scores are shown in fig 12. Characteristic for LUTD in the children without NBD and with normal spinal cords was that the finding was not constant but only seen at one of the follow up evaluations. Most of the children had a dysfunction classified as dysfunctional voiding, and only a few had overactive bladder syndrome. This dysfunction was more common in younger children, i.e. at the 5-year follow-up. The grade and frequency of LUTD was similar in the different fistula groups. All children had at least one risk factor beside the rectal malformation: MRS, urogenital malformations and neuropsychiatric diagnosis. However, none of the risk factors was shown to be significant predictors of LUTD. The same was true for sacral abnormalities and type of fistula.
No significant difference in bladder score was seen between the children with non-neurogenic LUTD and the 3 girls with tethered cords (at 5 yrs p=0.665, at 10 yrs p=0.101). The boys with NBD could not be scored (see methods).

Bowel function (paper 2 and 3)

Bowel score (paper 2)

Overall, there were significantly lower bowel scores in children with ARM, in all age groups, compared to the scores of control children, except for boys at 15 years (p = 0.095) (Fig 13).

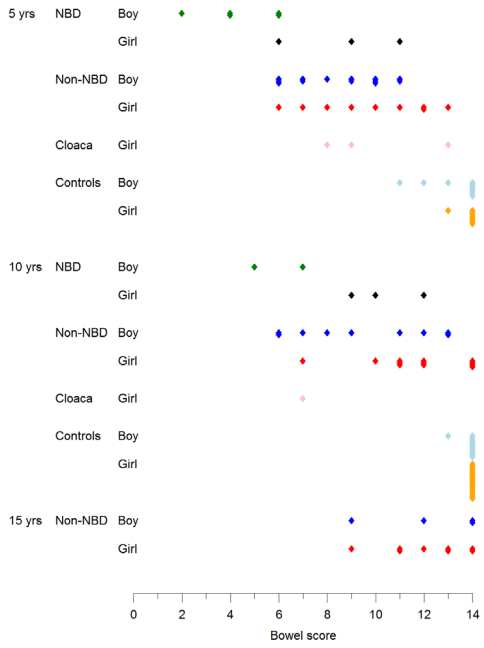


Figure 13. Bowel score in ARM patients (according to fistula group) and controls and age for follow up.

Bowel score increased with age in all fistula groups, except for boys with NF/ BF, where scoring was lower at age 10, probably due to additional problems with psychosocial pathology and anal stricture. Girls with VF improved their bowel score significantly between the ages of 5 and 10 (p=0.0208), but no further improvement was seen between the ages of 10 and 15. As expected, scoring was lower in the more complex malformations (PRF/BNF), and at age 5, bowel scores in PRF/BNF boys with a simultaneous spinal cord malformation and NBD were significantly lower than PRF boys with normal spinal cords. This was true also at the age of 10, where these boys still had low bowel scores. However, improvement was seen in PRF patients without spinal cord pathology between the ages of 5 and 10 (p = 0.0038) and between 5 and 15 (p= 0.029). See table 8.

Table 8. Bowel score according to type of of fistula

	Age 5		Age 10		Age 15	
Type of fistula	Scoring Median (range)	Number patients	Scoring Median (range)	Number patients	Scoring Median (range)	Number patients
NF/BF Normal spinal cord	10 (7-11)	5	7 (6-11)	7	14 (9-14)	7
PRF/BNF Normal spinal cord Abnormal spinal cord/NBD	9 (6-11) 4 (2-6)	8 5	12 (8-13) 6 (5-6)	5 2	13 (12-14)	2
VF Normal spinal cord Abnormal spinal cord/NBD	9 (6-13) 9 (6-11)	9 3	12 (7-14) 10 (9-12)	12 3	13 (9-14)	
Cloaca Normal spinal cord Normal spinal cord/NBD	11 (9-13) 8	2 1	7 9	1 1		

Girls with cloaca between the ages of 5 and 10 were also an exception to the general improvement trend, with no difference in bowel scores between the two investigations. Of the two girls with poor bowel function one had a permanent NBD post PSARVUP and the other had a transient bladder emptying problem. Bowel function was almost normal for age in the third patient.

Krickenbeck´s classification (paper 2)

When analyzing long-term functional outcome according to Krickenbeck´s criteria, VF girls with normal spinal cords without NBD achieved continence significantly earlier than boys with rectourethral fistulas (p=0.037 at 10 years). However, at the age of 15 the difference was not significant (Fig 14).

The same was true for achieving total continence, with a parallel continuous improvement until adolescence. Social continence could be established already at the age of five in both boys and girls, provided they were compliant with the individualized bowel management program.

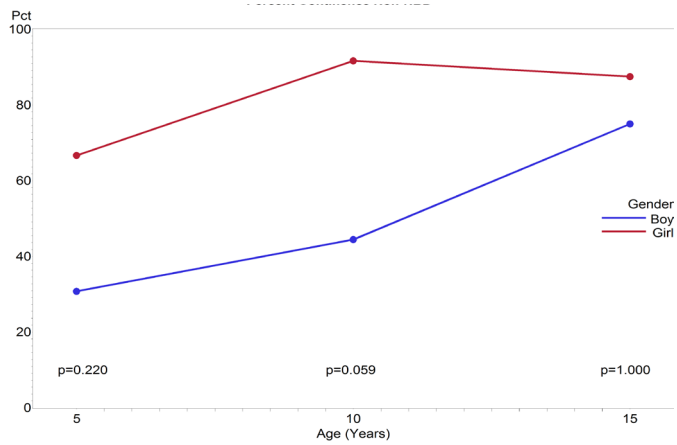


Figure 14. Continence (voluntary bowel movements according to Krickenbeck) in ARM patients with normal spinal cord at 5, 10 and 15 years. Pct=percent.

Soiling was more frequent in boys than in girls at all ages and clearly decreased between the ages of 5 and 15. Constipation was confirmed in all ARM children throughout childhood; with the highest degree found in patients with MRS. There was a reduction in proportion and grade of constipation with age. Grade 3 was only seen in 3 MRS patients at their 15 yrs. follow-ups as reported in paper 4 (1 conservatively, 2 surgically treated) (Fig 15).

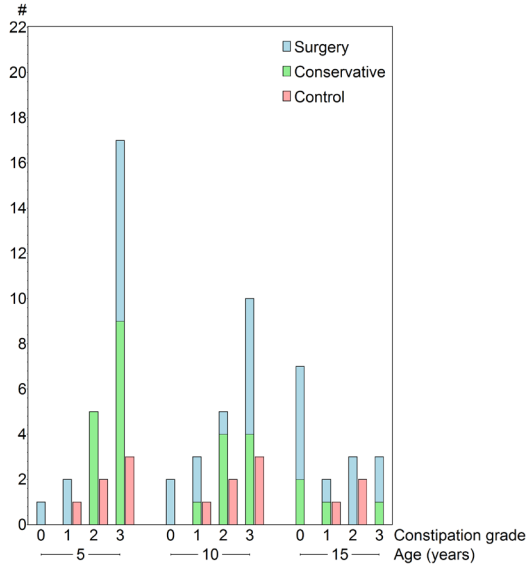


Figure 15. Number of MRS patients and controls with each constipation grade at 5, 10 and 15 years

VF girls with tethered cords and NBD achieved total continence at comparable ages to VF girls with normal spinal cords. The degree of soiling and constipation was also similar, with reduction over time. The PRF/BNF boys with spinal cord pathology and NBD did not achieve continence. These boys had the worst degrees of soiling and constipation. At the age of 5, 4/5 still needed diapers and all were on bowel management programmes, with daily water enemas. This regime had to continue but made social continence possible at age 10.

Predictive factors for bowel function (score) (paper 2)

According to a bivariate linear regression model, NBD, spinal cord malformation, partial sacral agenesis and PRF/BNF were all negative predictive factors for bowel scores at 5 years old. NBD and PRF/BNF, according to a multivariate model, were proven to be the strongest independent negative predictors at this age (Table 9).

Table 9. Predictive factors of bowel score at the age 5 in children with ARM

Variable	Bivariate linear regression		Multivariate linear regression *	
	Estimate (95%CI) for bowel score	p-value	Estimate (95%CI) for bowel score	p-value
NBD	-2.86 (-4.68--1.04)	0.0042	-2.34 (-3.99 - - 0.69)	0.0090
Spinal cord malformation	-3.04 (-4.92--1.16)	0.0036		
Sacral malformation	-1.96 (-3.68--0.24)	0.0286		
Sacral agenesis	-1.70 (-2.67--0.74)	0.0014		
Megarectosigmoid	0.57 (-1.35-2.49)	0.5457		
Psychosocial pathology	-1.88 (-3.94-0.17)	0.0855		
Fistula NF/BF	0.82 (-1.75-3.39)	0.5102		
Fistula PRF/BNF	-2.78 (-4.41--1.16)	0.0017	-2.35 (-3.86- -0.85)	0.0037
Vestibular fistula	1.75 (-0.08-3.58)	0.0736		
Cloaca	1.87 (-1.29-5.02)	0.2262		

*R^2= 0.39 for the multivariable model
NF=Non fistula, BF=Bulbar fistula, PRF=Prostatic fistula, BNF=Bladder neck fistula, NBD=Neurogenic bladder dysfunction

At the age of 10, spinal cord malformation was the strongest independent negative predictor, whereas VF was an independent positive predictor of bowel score. Although megarectosigmoid was not a predictor in bivariate linear regression at age 5, four VF girls with severe constipation due to MRS had significantly lower bowel scores than girls with normal rectums at that age (p=0.02).

Association between bowel function and LUTD (paper 3)

Children with LUTD, including the children with NBD, had lower bowel scores than children with normal bladder function, both according to age and type of fistula, but this was only significant at the age of ten when all fistula groups were analyzed together (p=0.045).

There was a clear association between NBD and low bowel scores in multivariate analyses (p=0.009). In cases when LUTD was caused by urethral anomalies (urethral stricture, hypospadia) no correlation to bowel score was found.
To investigate a connection between poor bowel function in ARM patients and the possibility of secondary bladder symptoms, patients with NBD or dysfunction due to urogenital anomalies were excluded. At follow-ups, these LUTD children had lower bowel scores compared to children with normal bladder function, but the difference was not significant. Megarectum, not surgically treated, was seen in almost all the non-neurogenic LUTD children.

Megarectosigmoid: Surgical and conservative treatments (paper 4)

Radiological findings in MRS and non-MRS patients

MRS was diagnosed radiologically in 26/79 (33%) patients, where in the group the majority had a dilated bowel already in the neonatal period. The elongation was above S1 in all MRS children with a variation between Th11 and S1, whereas in the non-MRS patients the elongation did not exceed S2 (p<0.0001) (Fig 16).

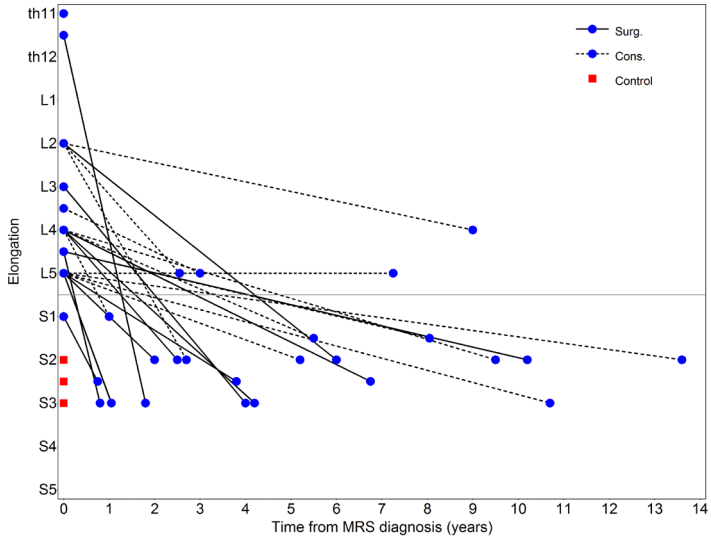


Figure 16. Individual values of rectal elongation from baseline to follow-up in ARM patients with MRS. Conservative and surgical treatments (blue dots, whole or dotted lines). Only baseline value for controls (red dots).

The width of the bowel at the promontory, in relation to rectal width within the pelvic ring, was calculated as the SR ratio. The ratio was median 0.60 (range 0.44-0.71) in non-MRS patients and median 0.93 (range 0.62-1.5) in the MRS group (p<0.0001). A cut-off level for SR ratio differentiating megarectosigmoid from non-MRS could be identified. According to ROC curve it was 0.64 (p=0.0411).

Radiological findings in surgically or conservatively treated MRS

The diagnostic contrast enema test was performed at an earlier age in the conservatively treated group than in the surgically treated group (median age 1.5 yrs and 2.9 yrs) (Table 10).

Table 10. Radiological findings in contrast enema in ARM patients with MRS, conservative andsurgical treatment. Variables presented as median (min; max).

Variable	Conservative (n=14)	p-value within group	Surgery (n=12)	p-value within group	P-value between groups
Age baseline (years)	1.5 (0.1; 8.3) n=14		2.9 (1.3; 6.0) n=12		0.0473
Age follow-up (years)	10.0 (2.8; 16.0) n=12		6.7 (4.0; 12.0) n=12		0.3120
Elongation baseline	7.0 (6.0; 12.0) n=14		6.8 (5.0; 11.5) n=12		0.6736
Elongation follow-up	4.5 (3.0; 7.0) n=12		3.5 (3.0; 4.0) n=12		0.0013
Diff Elongation (Follow-up to baseline)	-2.0 (-5.0; 0.0) n=12	0.0010	-3.3 (-8.5; -1.5) n=12	0.0005	0.0376
SR ratio baseline	0.92 (0.64; 1.05) n=14		0.97 (0.62; 1.50) n=12		0.2796
SR ratio follow-up	0.56 (0.30; 1.00) n=11		0.50 (0.40; 0.64) n=12		0.0485
Diff SR ratio (Follow-up to baseline)	-0.20 (-0.46; 0.09) n=11	0.0059	-0.48 (-1.0 0; 0.01) n=12	0.0010	0.0138

Elongation of the rectum in both groups was similar at baseline examination (p=0.6736) and reached above the promontory (S1) in all but one in the surgical group (Table 10, Fig 16).

Elongation at follow-up in the surgical group (after median 3.2 yrs.) had normalized in all children and did not exceed the level of S2 to S3. However, after median 6.4 yrs., in the conservative group a decrease to normal level was found in only two thirds of the patients and in 4 children the rectum still reached above the promontory. Difference in elongation between the baseline and the follow-up examination was significant in both groups (surgical p=0.0005 and conservative 0.0010) (Table 10).

Width of the bowel above the promontory was similar in both groups at baseline examination (p=0.2796). In the surgical group a decrease in width of the bowel above the promontory post resection was evident. This was illustrated by the change in sigmoid/rectal ratio between baseline and follow-up examinations, from median 0.97 to 0.5 (p=0.001). A significant but less pronounced decrease in this ratio was also seen in the conservative group, from 0.92 to 0.56 (p=0.0059).

Bowel emptying improved (conservative group 7/10, surgical group 9/12) from

baseline to follow-up tests, and there was no significant difference between the two groups (p=0.524).

Bowel function

There was no significant difference in bowel scores at ages 5, 10 and 15 years between the surgically and conservatively treated MRS patients (p=0.5535, p=0.5900, p=0.4562). This was also true when comparing bowel scores with a control group of ARM patients of the same ages without MRS (p=0.7613, p=0.1379, p=0.5687) (Fig 17).

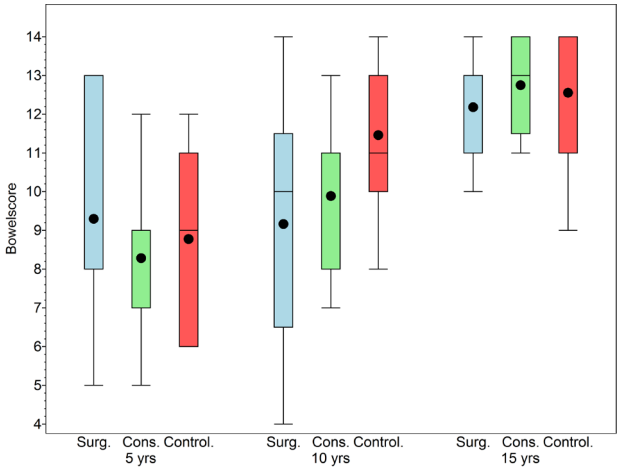


Figure 17. Change in bowel score by treatment and age group in MRS and non MRS ARM patients. Box edges are Q1 and Q3, horizontal line is median and large dot is mean.

A statistically significant improvement in bowel score over time could be confirmed in both groups.

At age 5, constipation grade 3 was over-represented in both the surgical and the conservative MRS groups. At age ten, the number of patients with constipation grade three fell in both groups, with a further reduction seen also at age 15 (Fig 15).

General discussion

In the middle of the nineties, 10 years after the introduction of the PSARP technique at our institution, we decided to introduce a structured care program for children with ARM. Due to all the different associated anomalies seen in these children, we tried to systematically investigate the organ systems in the newborn baby that might influence long-term functional outcome. Obviously bladder and bowel dysfunction were the dominant issues for these patients, since the malformation involves the anus, rectum, urinary and genital tract. In addition, it was already known at that time that sacral and neurological malformations negatively influenced bowel function outcome.
From this background, we identified several questions that needed to be answered, and these formed the embryo of this thesis.

In this prospective study of bladder and bowel function in children with ARM, subjects were followed from the newborn period until age 15 years. Although there were a limited number of patients in our series, it was a strength that patients were repeatedly evaluated for bladder and bowel function during childhood and adolescence, and that the number of care-givers was limited to only a few persons. The pediatric surgeon had overall responsibility, with regular appointments with the children, together with the specialist nurse.

The basic question in this study related to the development of bowel function in the ARM patients as they were growing up, compared with defecation patterns in healthy children.
In order to longitudinally follow bowel function, we used the Krickenbeck classification together with a multivariate scoring system described by Rintala.[62] The classification is based on fistula location instead of the traditional categories of low, intermediate and high anomalies. It also puts forward functional criteria (continence, soiling and constipation) to better compare functional outcome. This fistula-based, defined functional criteria approach, together with the scoring system, is superior to previous ways of reporting, which were often limited to good, fair or poor bowel function.[64-66] Hasset et al. were among the first to report on both types of fistula and of functional criteria according to Krickenbeck's classification, and more information has followed.[67,68] When reporting results according to Krickenbeck, most researchers choose to add a numeric value to the functional criteria. However, the problem is that in some papers a high score means good function whereas in others a high score means the opposite. A consensus document on scoring in line with the Krickenbeck criteria is necessary to make studies comparable.
Rintala published already in 1995 a scoring system based on variables for bowel function in ARM children, similar to what was later suggested in the Krickenbeck consensus in 2005. We modified the Rintala scoring protocol by omitting the variable "accidents" and by adding "social problems" to the soiling variable. The reason for excluding accidents was the difficulties in the interpretation of what constituted an accident and what constituted soiling. When asking the patients, nobody report-

ed complete uncontrolled emptying of the bowel at an inappropriate time or place, so therefore soiling became the main parameter for the determination of fecal leakage. The basic data for each follow-up was taken from a three-week report, which registered bowel habits (frequency, soiling) and the use of enemas and pads, together with information from a structured questionnaire.

In this study, functional outcome as regards continence, soiling and constipation was shown to improve with age, which was consistent with the increase in bowel score over time. Bowel function was poor in early childhood, but social continence at comparable ages to healthy children could be achieved if individualized bowel treatment and additional daily life support were given. However, overall ARM children did not reach the same level of bowel function as healthy children at any age, even if the difference diminished over time. This was probably related to the basic malformations including a pathologic anal canal and an abnormal pelvic floor with impaired sphincter function in the affected individuals, as earlier pointed out by the Peña group.[42] Normal bowel control requires a normal internal anal sphincter and normal sensation in the anal canal for the defecation reflex.[22] Obviously this fine interaction between nerves and muscles is not intact in these children, since the malformation implies that the anal canal is misplaced during fetal development. In addition, in a recent paper Lombardi et al. reported the histology findings for the anorectal canals of 52 ARM patients with perineal or vestibular fistulas. There were severe anomalies of the muscle coat and connective tissue, as well as the enteric nervous system of the part corresponding to the anal canal, which might also be true of children with more complex forms of ARM.[43]

An obvious limitation of the present study was that only one-third of the patients were reviewed at age 15, since the main improvements seem to take place during puberty. We have not found another longitudinal study of bowel function during childhood and adolescence in ARM patients from the PSARP era. Most studies report on patient cohorts of different ages. For example, our results regarding overall total continence, according to Peña´s definition, were at the same level at the follow-ups of 10 year old children (34%), as in groups consisting of mixed ages. However, in patients investigated at the age of 15, total continence was higher (62%).[12,62]

In the studies, we identified individuals with bowel function worse than could be expected for their type of malformation. In general, girls with VF had a good prognosis, but patients with more complex malformations (PRF/BNF) also improved over the years, provided there was normal nervous supply to the pelvic organs. A group of boys, with complex ARM malformations combined with a combination of spinal cord pathology and sacral agenesis, had no spontaneous functional improvement and therefore needed permanent bladder and bowel therapy. These boys, who had a poor prognosis regarding bowel and bladder function, could already be identified in the neonatal period because of an abnormal perineal appearance and obvious urinary incontinence. This called for further investigation of the spinal cord to identify NBD, preferably with the help of MRI and urodynamics. This means that

when the nervous supply to the bowel is further impaired by a spinal cord malformation, in combination with the already hypoplastic sphincters characteristic of ARM malformation, the functional outcome prognosis is poor and cannot be expected to improve with age.[12,62]
However, not all patients with spinal cord malformation have a poor bowel function outcome. In our study, children with less complex ARM, mainly vestibular fistula, in combination with tethered spinal cords, often had only minor impairment of bowel and bladder function, which is in accordance with reports in the literature. Opinion differs on the advantages of prophylactic detethering for patients with tethered cords (TC).[7,69,70] We have adopted a conservative approach to treatment of TC, as there is no evidence of benefits if neurological symptoms are absent.[69] Thus from our knowledge about the difference in prognosis for spinal cord malformations in complex and less complex forms of ARM, we can tell parents whether their children have neurological symptoms of importance for bowel and bladder function. In addition, if symptoms are stable or at risk of worsening we can also discuss with the parents the need for therapeutic interventions to achieve fecal and urinary continence.

Other risk factors periodically influencing bowel function were neuropsychiatric problems and poor social support. Fecal incontinence in children without ARM has been reported as being less easy to treat successfully when ADHD, developmental delay or other psychosocial co-morbidity is present.[71] In our study there were clear indications of lower bowel scores in patients with a type of ARM usually associated with a good prognosis if there was simultaneous psychosocial pathology. Periods of poor bowel function in these children were most pronounced between 5 and 10 years of age. Contributing factors were poor compliance with bowel management programmes and lack of parental support. The diagnosing of neuropsychiatric problems was often delayed, but when addressed and adequately treated, bowel function clearly improved in these individuals. For this reason early identification of these children is desirable in order to maximize their chances of becoming continent at comparable ages to ARM children without risk factors.

In addition to all the above-mentioned prognostic factors for bowel function, the presence of a megarectosigmoid influences the extent of possible improvement. Others have also recognized MRS as a risk factor for severe chronic constipation and overflow fecal incontinence.[8,9,44-46] Lately, intensified bowel management as treatment for MRS has been advocated and in selected cases resection of the dilated segment.[1,8,72] As far as we know there is no previous study reporting long-term change in radiological rectal configuration in relation to treatment modality of MRS, i.e. surgical or conservative. However, bowel management seems to be the treatment of choice, since bowel function in growing children was similar after surgical or conservative treatments in the present study, and outcomes did not differ from those of non-MRS ARM children. Finally, the recognition that rectal dilatation and elongation also disappeared over time in conservatively treated patients further confirms the importance of bowel management in ARM children.

The activity of the lower urinary tract and gastrointestinal tract is closely related when it comes to the physiological functions, i.e. the storage and evacuation of feces and urine. Clinically, LUT dysfunctions in otherwise healthy children often coincide with constipation, and treatment of the bowel problem has been shown to improve the bladder function.[73,74] We found LUTD in 41 % of ARM children without NBD and with normal spinal cords at the age of 5, compared to reports of prevalence as high as 9% in healthy children.[39] A connection between low bowel scores and symptoms of LUT in children without any other explanation for the LUTD than the bowel dysfunction related to the ARM was also suggested in our longitudinal study. However, significance was not obtained, which was probably explained by the small numbers of patients in the groups. In addition, the intensive bowel management program used in treating constipated ARM patients may have reduced LUT symptoms, which is in line with previous reports.[54,75]

Concluding remarks and clinical usefulness of the study

This longitudinal study has shown that bowel function in ARM children with normal spinal cord and good prognosis type of fistula improves over time, but do not achieve the functional levels of healthy children. The dysfunction is most pronounced in early years and regardless of type of ARM and associated malformations, these patients need individualized daily bowel therapy in order to become socially continent at comparable ages as their peers.

Our findings indicate that sacral agenesis is often combined with a spinal cord malformation (80%) and together represent important indicators of a more extensive neurological pathology with NBD found in 22% of these patients. We have also pointed out that bladder and bowel function in this selected group of ARM children will probably not improve as they grow up. Children with tethered spinal cords have a risk of neurological deterioration and therefore repeated urodynamics and control of lower limb neurology are mandatory at follow-up until adolescence. Early recognition, involving perineal inspection and an evaluation of the spine and spinal cord in the newborn period, will give important clues about the patient's type of malformation and the long-term functional outcome. Neurological symptoms, and a malformation of the spinal cord indicate the need for lifelong treatment of the bladder and bowel. Medical treatment and/or surgery for urinary incontinence should be offered already at young ages in these patients since bladder control is essential when striving for social fecal continence.

Finally, to our knowledge, this is the first study to show that conservative treatment of MRS with bowel management during childhood is as effective as surgical treatment when comes to long-term functional outcome and change in configuration of the rectum. A consistent and intensive bowel management program is therefore mandatory for the MRS children during growing-up and bowel resection should only be considered in therapy resistant severe cases.

Since problems related to bladder and bowel function in ARM children are changing over time, the care of these children must continue throughout adolescence and be managed by professional multidisciplinary teams at specialized referral centers.

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