Neurogenic bladder and bowel dysfunction

Clinical aspects in children with spinal dysraphism

Peter Wide

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Abstract

Spinal dysraphism (SD) is a congenital malformation that to a varying extent, often severely, affects the life of the child and the family. Most individuals with SD suffer from neurogenic bladder and bowel dysfunction—with the risk of urinary tract infections, renal deterioration, urinary and fecal incontinence—that affects social participation and quality of life negatively. In newborns with SD, early detection of neurogenic bladder dysfunction and determination of post-void residual urine are required to determine the need of clean intermittent catheterization (CIC) and follow-up.

The non-invasive method of four-hour voiding observation with provocation test (VOP) was used to evaluate bladder function in 50 newborn children with SD. Voiding patterns for the children were described and compared with those of 50 healthy newborns evaluated with VOP in an earlier study. Comparison revealed significant differences among several variables. In particular, leakage at provocation test and not voiding with a stream were common in newborns with SD but did not occur in healthy newborns. VOP is a non-invasive standardized method to determine residual urine in newborns with SD. It also adds information on voiding pattern, frequency, voiding with a stream and leakage at provocation.

Findings in neonatal VOP of the same cohort of newborns with SD were then related to radiology, presence of urinary tract infections during the first year, and urodynamic findings and use of CIC at the age of one year. It was found that, in children with SD, not voiding with a stream may have a predictive value for the need of CIC at the age of one year, followed probably by lifelong CIC. Despite this, the presence of an open SD per se has stronger predictive value, and each child needs to be evaluated individually while considering a number of factors. The main value of VOP may be as a structured non-invasive screening method to uncover neurogenic bladder-sphincter dysfunction in the newborn. Studies with a larger number of subjects than the present are needed to evaluate the potential of VOP in newborns with closed spinal dysraphism in whom the neurological consequences vary.

A retrospective analysis detected renal damage on DMSA scintigraphy in 5 of 41 children with SD who were followed according to a proactive national program with minimal use of surgery. Median follow-up time was 10 years. High baseline pressure was confirmed as a risk factor for renal damage. Compliance with treatment and follow-up is likely to be an important factor for renal health. Therefore, efforts to support children and their families are crucial.

A questionnaire-based study of 107 children with SD (age 6–16y) in Sweden and Norway examined aspects of treatment for neurogenic bowel dysfunction focusing on incontinence, independence, general satisfaction and quality of life. It was found that transanal irrigation (TAI) and antegrade colonic enemas (ACE) are effective treatments, but are time-consuming and difficult to perform independently. The majority of children using TAI (72%) and ACE (63%) never went to the toilet alone to empty their bowels. As children achieving independence on the toilet reported higher quality of life, efforts to support independence are beneficial.

Continent, self-managing children with healthy kidneys enjoy high quality of life and contribute more fully to society. Therefore, further research is required to investigate and develop existing and new technologies and methods that mitigate the problems related to SD, and to make them accessible to all children with spinal dysraphism.

Populärvetenskaplig sammanfattning (In Swedish)

Från Överlevnad mot Oberoende

Under de senaste 50 åren har det skett en enastående utveckling av möjligheterna för barn som föds med ryggmärgsbråck. Tidigare har majoriteten av barn med ryggmärgsbråck avlidit redan som spädbarn men idag överlever de flesta till vuxen ålder. Utan aktiva insatser och uppföljning är dock risken för medicinska problem och allvarlig påverkan på livet mycket stor. Nu när nästan alla barn överlever ligger fokus på att också nå ökad livskvalitet och självständighet för personer med ryggmärgsbråck.

Nästan alla med ryggmärgsbråck måste hantera en allvarlig påverkan på blåsan och tarmen med risk för njurskador, inkontinens och förstoppning. I avhandlingens två första studier värderade vi en metod att, med minimalt obehag för barnet, bedöma blåsfunktionen. Detta för att kunna skilja ut de barn som behöver genomgå mer avancerade undersökningar och få hjälp med blåstömningen genom täta tappningar med kateter, så kallad ren intermittent kateterisering, RIK. När vi jämförde resultatet av testet för 50 nyfödda med ryggmärgsbråck med samma undersökning av 50 friska nyfödda fann vi stora skillnader. Mest tydligt var att de flesta nyfödda med ryggmärgsbråck (69%) men inga friska nyfödda läckte urin när man tryckte över blåsan. Av nyfödda med ryggmärgsbråck kissade de flesta (74%) inte med stråle vilket alla friska nyfödda gjorde. Att inte kissa med stråle talade också starkt för att barnet skulle komma att behöva hjälp med RIK för att tömma blåsan vid ett års ålder, och då sannolikt livet ut. Sammantaget visade avhandlingens två första arbeten att den metod för bedömning av blåsfunktion vi undersökt kan användas för att styra uppföljning och behandling av nyfödda med ryggmärgsbråck.

Avhandlingens tredje studie visade att aktiv uppföljning av barnen enligt ett nationellt vårdprogram lyckades förhindra njurskador hos de flesta, men att höga tryck i urinblåsan och återkommande urinvägsinfektioner ökade risken för skador. Även familjernas förmåga att i en pressad vardag klara av att genomföra de ofta krävande behandlingar och undersökningar som rekommenderas verkade vara viktig för att förhindra njurskador. Stöttning av familjerna är därför viktig.

Avhandlingens fjärde arbete berörde tarmen som nästan alltid är påverkad vid ryggmärgsbråck, med risk för svår förstoppning och avföringsläckage. Detta har påtaglig påverkan på barnen och deras familjer. En tredjedel av de 107 familjerna i vår enkätundersökning i Sverige och Norge (barn 6–16 år) beskrev att man fått avstå från aktiviteter såsom resor på grund av barnets tarmproblem och de barn som hade avföringsläckage rapporterade tydligt lägre livskvalitet än andra. Trots denna allvarliga påverkan finns det hittills inga studier som jämför de olika behandlingar som barnet kan använda. I vår enkät kartlade vi därför vilka metoder som användes och hur bra de fungerade. Vi ställde frågor till både barn och föräldrar, särskilt om avföringsläckage, hur nöjd man var med metoden, barnens livskvalitet och självständighet på toaletten. Det var utifrån svaren tydligt att båda de vanligaste typerna av tarmsköljning var effektiva men tidskrävande och svåra för barn och ungdomar att klara att utföra på egen hand. Ingen metod visade sig överlägsen den andra men de barn som klarade att sköta tarmtömningen själva skattade sin livskvalitet klart högre än övriga. Vi drar därför slutsatsen att det är viktigt att vårdpersonal diskuterar de olika behandlingsalternativen med barn och föräldrar, och tillsammans med dem väljer den metod som passar det enskilda barnet bäst. Då skapas bästa förutsättningar för att gemensamt arbeta vidare för att uppnå största möjliga självständighet.

Självständiga individer, med friska njurar och utan urin- och avföringsinkontinens upplever högre livskvalitet och behöver mindre sjukvård och andra samhällsinsatser. Det behövs mer forskning för att utveckla existerande och nya metoder att hantera de allvarliga komplikationer som riskerar att drabba barn och vuxna med ryggmärgsbråck.

List of papers

- I. **Wide P**, Duchén K, Mattsson S, Glad Mattsson G. Four-hour voiding observation with provocation test reveals significant abnormalities of bladder function in newborns with spinal dysraphism. J Pediatr Urol 2020. doi:<https://doi.org/10.1016/j.jpurol.2020.06.022>.
- II. **Wide P**, Duchén K, Mattsson S, Glad Mattsson G. Can a neonatal voiding observation with provocation test in children with spinal dysraphism predict bladder function at one year of age? In manuscript.
- III. **Wide P**, Glad Mattsson G, Mattsson S. Renal preservation in children with neurogenic bladder-sphincter dysfunction followed in a national program. J Pediatr Urol 2012;8:187–93. doi:[10.1016/j.jpurol.2011.02.003](https://doi.org/10.1016/j.jpurol.2011.02.003).
- IV. **Wide P**, Mattsson Glad G, Drott P, Mattsson S. Independence does not come with the method—treatment of neurogenic bowel dysfunction in children with myelomeningocele. Acta Paediatr 2014;103:1159–64. doi:[10.1111/apa.12756](https://doi.org/10.1111/apa.12756).

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Abbreviations

In this thesis I adhere to the terminology postulated by the International Children's Continence Society (Bauer *et al.*, 2015).

SD	spinal dysraphism
MMC	myelomeningocele
SCI	spinal cord injury
HN	healthy newborns
NBSD	neurogenic bladder-sphincter dysfunction
CIC	clean intermittent catheterization
VOP	voiding observation with provocation test
UDS	invasive urodynamic studies e.g. cystometry
RBUS	renal bladder ultrasound
VUCG	voiding ureterocystogram
DMSA	Dimercaptosuccinic acid renal scintigraphy
MAG3	Technetium-99m Mercaptoacetyl triglicine scintigraphy
GFR	glomerular filtration rate
UTI	urinary tract infection
NDOA	neurogenic detrusor overactivity
DSD	detrusor-sphincter dyssynergia
ENS	electro neurostimulation
TAI	transanal irrigation
ACE	antegrade colonic (or continent) enema
QoL	quality of life
RCT	randomized controlled trial

Figure 1. A child with open spinal dysraphism. (Illustration: Agnes Wide)

Background

Spinal dysraphism

Spina bifida, Latin for “split spine” (McComb, 2015; Brea and Munakomi, 2020), refers only to a lack of closure of the dorsal part of the bony spinal arch. It is common in humans, with a likely prevalence of over 10% (Eubanks and Cheruvu, 2009), and might be viewed as a normal variant when not accompanied by a malformation of the spinal cord. When both the bony spine and the tissue within the spinal canal are malformed, the term *spinal dysraphism* (SD) is used (McComb, 2015; Schwartz and Rossi, 2015; Kumar, Afsal and Garg, 2017; Reghunath, Ghasi and Aggarwal, 2019). It must be noted, however, that in the literature and clinical situations, the terms ‘spina bifida’ and ‘spinal dysraphism’ are often used synonymously (Schwartz and Rossi, 2015). As spinal dysraphism constitutes a heterogeneous group of conditions, the nomenclature is often difficult and is used in different ways (McComb, 2015). See Table 1 for one of many proposed classifications (Tortori-Donati, Rossi and Cama, 2000) and Figure 2 for an illustration of the most common forms. Anencephaly can also be considered as a form of SD but is not compatible with life.

Table 1. Simplified classification of spinal dysraphism. Adapted from Tortori 2000.

Spinal dysraphism = neural tube defects	
<i>Open spinal dysraphism = Spina bifida cystica</i>	
Myelomeningocele MMC	
Myelocele	
<i>Closed spinal dysraphism = Spina bifida occulta</i>	
With subcutaneous mass	
	Lipoma with dural defect (e.g. Lipo-MMC)
Without subcutaneous mass	
	Intradural lipoma
	Filum terminale lipoma
	Diastematomyelia
	Dermal sinus
	Caudal regression syndrome

In open spinal dysraphism, skin coverage is defective, neural tissue is exposed to the environment, and the malformation is obvious at clinical examination as illustrated in Figure 1 and 2 (Sahni and Ohri, 2019). In closed spinal dysraphism, however, skin coverage exists, but with visible findings related to the malformation in about half of the cases (Sanchez and John, 2014; Sewell, Chiu and Drolet, 2015; Tuite *et al.*, 2018; Ramos *et al.*, 2019; Sung and Lee, 2019). The most common and best-known form of open SD is myelomeningocele (MMC), a condition with usually profound effects on the life of those affected.

There are significant geographical variations in the prevalence of SD during pregnancy, with 50–100 incidents per 100,000 pregnancies reported in most of Europe and the US, but up to 400 in India (Gotha *et al.*, 2020) and even higher numbers in Ethiopia (Berihu *et al.*, 2018). Termination is common. Combined with preventive initiatives, this has contributed to a decline in birth prevalence to around 30–50 live births per 100,000 (Atta *et al.*, 2016). As survival to adulthood used to be low, SD has long been seen as a pediatric diagnosis. Today, however, in many countries there are more adults than children with spinal dysraphism (Mattsson and Gladh, 2005).

Spinal dysraphism includes various forms of defective closure of the spine and the spinal cord. The most common form is myelomeningocele/open spinal dysraphism, for which birth numbers are declining.

Figure 2. Forms of spinal dysraphism, from (Sacco *et al.*, 2019).

(a) normal situation, (b) closed spinal dysraphism (c) myelomeningocele.

Consequences of spinal dysraphism

The consequences of SD range from a mere risk situation with no significant neurological deficit to multiple severe problems that dominate the life of the affected person. Most forms of SD share the risk of so-called tethered cord syndrome, in which the spinal cord is fixed during spinal growth, either congenitally or after surgery, giving rise to increased malfunction of the cord with deterioration of the bladder, bowel or limb function (Safavi-Abbasi *et al.*, 2016; Stein *et al.*, 2020). Tethered cord may also give rise to symptoms such as herniation in the upper spine, development of scoliosis or pain. Most open SDs are located from the lower thoracic to sacral levels, affecting signaling beyond those levels. In particular, signaling from the brain via the spine to the target organs such as muscles and internal organs is often severely affected. Thus, partial or total paresis of the lower limbs as well as neurogenic bladder and bowel dysfunction are common.

Most individuals with open SD also have a problem with the turnover of fluid in and around the brain, resulting in excess fluid in the ventricles—hydrocephalus. Standard treatment is to insert a ventriculoperitoneal shunt that transports excess fluid from the brain ventricles to the peritoneal cavity. Even if well treated, hydrocephalus is often linked to cognitive issues that limit the ability to manage the consequences of spinal dysraphism (Iddon *et al.*, 2004). Widely varying secondary complications such as scoliosis, osteoporosis, joint contractures and pressure ulcers are common in people with spinal dysraphism (Phillips, Burton and Evans, 2017; Marreiros, 2018) and impact daily life (Wagner *et al.*, 2015).

Spinal dysraphism often has a severe impact on affected individuals and their families.

Major advances in recent decades

Whereas life expectancy, in relation to years and quality of life, has changed dramatically for newborns with spinal dysraphism during the past 50 years, much still depends on where in the world the child is born and under which conditions (Rosano *et al.*, 2000). In the middle of the last century, the prognosis was so poor that surgery was recommended only for the small minority of children surviving the first year of life (Norman, 1949). Before the development of shunts to treat hydrocephalus, survival was 10–12%. Yet up to the 1980s, and despite progress in care, the medical profession debated whether at all to offer surgical treatment to children with spinal dysraphism (Pruitt, 2012). A recent study on the prevalence and survival of newborns with spinal dysraphism in a region of Ethiopia reported an SD prevalence of 1310 (still or live) births per 100,000. Half of those pregnancies were diagnosed with the severest form, anencephaly, but even among the 644 per 100,000 that were diagnosed with spina bifida, neonatal survival was less than 50% (Berihu *et al.*, 2018). Moreover, although the availability of care is improving (personal communication), it is unlikely that a newborn with SD in this region will benefit much from the recent advances in care described here.

As folic acid deficiency is a risk factor for SD, fortification of food has been shown to decrease the incidence of spina bifida and has been declared mandatory in many countries (Atta *et al.*, 2016). Folic acid supplementation with tablets is also recommended widely for fertile women. Furthermore, the development of ventriculoperitoneal shunts to treat hydrocephalus has extended and improved the life of affected individuals. Children with SD are generally born with healthy kidneys and normal renal function (Tanaka *et al.*, 2019). Renal damage is mainly related to high pressure in the bladder and urinary tract infections (UTIs), risk factors that have been successfully reduced, due mainly to the introduction of clean intermittent catheterization (CIC) (Bauer, 2003; Lamin and Newman, 2016; Diamond *et al.*, 2017). Although already described in ancient Egypt, catheterization of dysfunctional bladders was introduced more broadly in the early 1970s by Lapides (Lapides *et al.*, 1972; Bloom, 2017). Active follow-up with radiology and urodynamics, and the development of several renal protective surgical procedures, have further reduced the risk for renal damage. Urological surgery is effective in reducing bladder pressures and incontinence, but carries significant short-term and long-term complications. Whether or not it affects quality of life remains unknown (Snow-Lisy, Yerkes and Cheng, 2015). Despite major advances, however, NBSD remains a prevalent cause of end-stage renal disease, demanding dialysis and renal transplant (Ouyang *et al.*, 2015).

Increasing detection of children with closed spinal dysraphism

With improved techniques for prenatal ultrasound and magnetic resonance imaging, more cases of “minor” closed spinal dysraphism are being found (Bauer, 2008; Tuite *et al.*, 2018). In contrast to open SD, a significant proportion of children with closed SD are diagnosed after the perinatal period and sometimes during evaluation of other findings such as anorectal malformations. Tethering of the spinal cord is often present and constitutes a threat to the

cord, especially in the growing child (Tu and Steinbok, 2013; Safavi-Abbasi *et al.*, 2016; Stein *et al.*, 2020). Detethering surgery is indicated in the presence of clinical symptoms or deterioration (Tuite *et al.*, 2018). Such symptoms may be a change in function of the limbs, changes in bladder function, pain in the back or neck or progression of scoliosis. Most neurosurgeons nowadays recommend conservative follow-up in the absence of clear symptoms, but are eager to act promptly with surgery in the presence of progressive neurological symptoms. Therefore, evaluation is very important. As changes in bladder function do not always cause symptoms that are noticeable for the individual, tools for objective evaluation of bladder function are central to the management of patients with tethered cord (Tuite *et al.*, 2018).

Neurogenic bladder dysfunction affects most individuals with open spinal dysraphism, but only a smaller proportion of individuals with closed spinal dysraphism. If, however, bladder dysfunction is present in closed spinal dysraphism, active management is often as important as in open spinal dysraphism (Peyronnet *et al.*, 2018).

Figure 3. A happy couple. (Illustration: Agnes Wide)

Introduction of prenatal surgery

Prenatal closure of open spinal dysraphism has been developed in recent decades and is now considered standard treatment in parts of the world (Heuer, Moldenhauer and Scott Adzick, 2017; Mazzola *et al.*, 2019). Positive short-term and medium-term consequences of prenatal surgery have been reported regarding ambulation and the risk of developing hydrocephalus. However, the risks for the mother and fetus are still considerable, and only a limited number of fetuses can be offered this treatment (Blumenfeld and Belfort, 2018; Mazzola *et al.*, 2019; Sacco *et al.*, 2019). The long-term effects on bladder function are still unknown (Horst *et al.*, 2017; Brock *et al.*, 2019).

Instead of dying as young children, most individuals with spinal dysraphism can live a long life if the circumstances are good. Serious medical complications are still common, but prenatal surgery is as an option that seems to reduce some of them.

Future challenges

Despite the advances achieved, newborns with open spina bifida face extensive challenges even in a society with good health care resources (Alriksson-Schmidt *et al.*, 2018; Bendt *et al.*, 2020). Many individuals remain largely dependent on others for their everyday life and need help even in intimate situations such as managing their bladder and bowel. This has a negative effect on quality of life. Urinary and fecal incontinence is an important issue with

respect to quality of life (Szymanski *et al.*, 2017, 2018). The use of CIC and bladder-relaxing medication reduces problems with incontinence, but a significant number of individuals will not be continent despite optimal conservative measures (Lapides *et al.*, 1972; Wiener *et al.*, 2017; Johnston, Wiener and Todd Purves, 2020). Sometimes urological surgery can revolutionize the situation, but this still carries a significant risk of complications or failure in the longer perspective (Faure *et al.*, 2017; Hoen *et al.*, 2017). Cognitive difficulties specific to those affected by hydrocephalus impose challenges in achieving and upholding good health. State of the art practice for children with open spina bifida demands extensive health care resources, which are not available worldwide (Maison and Lazarus, 2017). As the absolute majority of children with open SD are born in other circumstances, attempts are being made to find solutions to provide medical care at lower cost (Maison and Lazarus, 2017; *The International Federation for Spina Bifida and Hydrocephalus*, 2020). If prenatal surgery is shown to be superior to postnatal intervention, it will take a long time to make this treatment available to all fetuses with spinal dysraphism.

Following the positive development of increased survival into adulthood of individuals with spinal dysraphism, the need to develop transition strategies. It has become evident that there is a lack of a prepared and well-developed adult health care with good knowledge about the specific problems related to the diagnosis (Mattsson and Gladh, 2005; Cardona-Grau and Chiang, 2017; Fremion and Dosa, 2019). Knowledge and education related to sexual and reproductive health is often lacking among health care personnel despite the presence of relevant literature (Mourtzinou and Stoffel, 2010; Visconti *et al.*, 2012; Snow-Lisy, Yerkes and Cheng, 2015; Wiener, Frimberger and Wood, 2018; Streur *et al.*, 2020).

The literature on many aspects of neurogenic bladder and bowel dysfunction as well as other complications of SD is based mainly on case series and cohorts from single institutions, whereas randomized controlled trials are rare. For several reasons, it is difficult to obtain this kind of studies about children with SD, as recognized already in a review by Norman during the late 1940s (Norman, 1949). Despite the shortage of scientific proof, substantial clinical experience is available, often in regional multidisciplinary teams dedicated to improving health for individuals with SD. Lack of experience and know-how related to this uncommon condition may become a considerable issue because incidence is decreasing. However, the presence of recommendations and structured follow-up programs may counteract this (Bauer *et al.*, 2012, 2015; Rawashdeh *et al.*, 2012; Groen *et al.*, 2016; Przydacz, Chłosta and Corcos, 2018; Gammie *et al.*, 2019; Mazzola *et al.*, 2019; Stein *et al.*, 2020). The formation of national patient quality registers such as the Swedish MMCUP and the National Spina Bifida Patient Registry in the US will contribute significantly to increasing our knowledge (Routh *et al.*, 2016; Alriksson-Schmidt *et al.*, 2017).

More research and worldwide access to prevention, effective treatments and multidisciplinary health care services are warranted. With better diagnostic tools, more children with closed spinal dysraphism are being diagnosed. For these patients, a non-invasive screening method is desirable to guide further evaluation and follow-up.

Bladder problems in spinal dysraphism

Function of the urinary tract

The urinary tract consists of the kidneys producing urine, the ureters transporting urine from the kidneys to the bladder, the bladder enabling storage and controlled emptying of the same fluid, and the urethra transporting urine out of the urinary tract and the body. The urine is formed primarily by filtration of the blood in the glomerulus. This system is vulnerable to high pressure propagated backwards from the bladder via the ureters. The main task of the urinary tract is excretion of substances from the body, to repel bacteria and keep the individual free from urinary tract infections. Thus, the body prioritizes expulsion (Lindström *et al.*, 1984; Zeng *et al.*, 2012). Moreover, as social beings, our ability to control the emptying of the bladder, i.e. be continent, is an important factor.

Storage phase

Micturition phase

Figure 4. Bladder control during storage/filling phase (A) and micturition phase (B)

From (Seth, Panicker and Fowler, 2013)

Bladder function is divided into two phases: storage and micturition. Regulation of bladder function is complex, with innervation from several systems balancing each other (Seth, Panicker and Fowler, 2013). During the storage phase and when the bladder is partially filled, low-grade signaling from nerves in the bladder wall through the pelvic nerve to the spinal cord and from there to sympathetic nerves through the hypogastric nerve inhibits the bladder muscle and stimulates the internal urethral sphincter to retain continence, see Figure 4. Additionally, an increase in somatic nerve signaling through the pudendal nerve increases the

tone of the external urethral sphincter. As the bladder fills up, increasing tension in the bladder wall causes afferents in the pelvic nerve to signal with increasing intensity (Lindström *et al.*, 1984). Signals are passed through the spinal cord and activate the pontine micturition center and cortical structures, resulting in a sensation of the need to void. When we want to urinate, micturition is initiated from cortical centers. Signals are then sent down from the pontine micturition center through the spinal cord to sacral levels, and the increased parasympathetic signaling in the pelvic nerve causes bladder muscle contraction. Simultaneously, somatic signals in the pudendal nerve cause the external urethral sphincter to relax (Seth, Panicker and Fowler, 2013). Interestingly, this micturition reflex is arranged as a positive feedback loop as the bladder muscle contraction results in increased afferent signaling propagated into the micturition reflex (Zeng *et al.*, 2012). This may partly explain the common phenomena of bladder overactivity (Lindström *et al.*, 1984). For most people, the micturition reflex is automatic but initiated and moderated by our will. Keeping this complicated nervous control in mind it is understandable that altered function of nerves involved in bladder control, whether congenital or acquired, can affect bladder function differently depending on the site of the affection and whether it is total or partial (Bauer, 2008).

Bladder function is under complicated nervous control and is easily disturbed.

Normal bladder function in children

The bladder starts functioning during the fetal period and is initially not consciously controlled. However, research has falsified the theory that the neonatal bladder is completely controlled by spinal reflexes. It has been shown that most infants wake up before voiding if asleep, indicating central communication although the child cannot void at will (Gladh *et al.*, 2000). Neonatally, the bladder is often emptied incompletely, whereas most infants still empty their bladder completely at least once during a four-hour observation time (Holmdahl *et al.*, 1996; Gladh *et al.*, 2000). As the child grows, so does the bladder, and the frequency of interrupted voids and of incomplete bladder emptying declines (Van der Cruyssen *et al.*, 2015; Wen *et al.*, 2015). Usually during the second or third year of life, the child becomes gradually more aware of the bladder filling and starts to be able to control micturition. The environment, and mainly the caregivers, can affect this process profoundly, for example, through early potty training (Duong *et al.*, 2010).

Bladder capacity increases with age and can be estimated in milliliters using a formula of $(\text{age (years)} + 1) \times 30$ (Austin *et al.*, 2016). In the normal bladder, it is the urine production during the night when the bladder activity is low, that stimulates bladder growth (Mattsson *et al.*, 2019).

Bladder function changes dramatically during the first year of life.

Neurogenic bladder-sphincter dysfunction (NBSD)

Figure 5. Consequences of neurogenic bladder-sphincter dysfunction

Most children with open SD have a normal renal function at birth (Tanaka *et al.*, 2019). This is probably true also for children with other forms of SD. Bladder function, however, is rarely normal in children with open SD as the neurological control of the bladder mediated through nerves in the spinal cord is disturbed (Bauer *et al.*, 2012; Rawashdeh *et al.*, 2012). There is a variable combination of disturbance of urine storage (leading to incontinence) and voiding (leading to residual urine). A classical model for risk estimation related to the parts of function that are affected was proposed by Madersbacher, who described four combinations of bladder muscle and sphincter function and the resulting clinical problems, see Figure 6. (Madersbacher, 1990). This model can be useful,

but because bladder and sphincter function can change during childhood, a specific child cannot safely be labeled as being without risk of renal damage. Therefore, individual, repeated follow-up is required (Bauer *et al.*, 2012; Edwards and Jacobs, 2019; Stein *et al.*, 2020).

Despite advances in care, a recent French study reported urological problems as the leading cause of death in hospital for people with spinal dysraphism and that the median age at death was only 41 years (Peyronnet *et al.*, 2020).

Figure 6. Madersbacher classification system of neurogenic bladder dysfunction. The large circle is the bladder and the small circle is the urethral sphincter. Adapted from Madersbacher, 1990b, Stohrer *et al.*, 2009.

Children with spinal dysraphism are born with normal kidney function but the bladder dysfunction entails a risk of renal damage resulting in morbidity and mortality, as well as incontinence with serious effects on quality of life.

Disturbance of storage function

A normal storage function requires a compliant bladder wall that lets the bladder volume increase dramatically during filling without increasing pressure in the bladder. In NBSD, bladder compliance is often reduced, leading to high bladder pressures or leakages. During evolution the functions related to survival (good emptying of the bladder) have been “prioritized” over those “only” related to quality of life (continence). This might explain why the bladder itself is an unstable organ in need of constant inhibition from higher levels of the nervous system (Lindström *et al.*, 1984; Seth, Panicker and Fowler, 2013). Inhibition is usually affected in children with MMC, leading to involuntary contractions of the bladder muscle and neurogenic detrusor overactivity (NDOA). Detrusor overactivity can lead to urgency, leakages and, if combined with high or uncoordinated sphincter activity, high intermittent bladder pressures. It has also been postulated that NDOA can contribute over time to the development of bladder fibrosis and decreased bladder compliance (Compérat *et al.*, 2006; Kroll, 2017). Apart from affecting bladder muscle function, spinal dysraphism often impacts sphincter function, either through an abnormal tone or lack of coordination with the bladder muscle. A high sphincter tone is related to problems with emptying, risk of renal damage and difficulties with catheterization. Children with decreased sphincter tone often have severe incontinence.

Defective sphincter function, often in combination with overactive bladder muscle contractions, frequently results in severe urinary incontinence.

Disturbance of voiding function

Due to neurological dysfunction, most children with open SD lack a normal micturition reflex. Normally functioning bladders remain calm until a person decides to void and then contracts combined with a relaxation of the bladder sphincter. In most children with SD, however, there are uncoordinated involuntary contractions during the filling or no contractions at all. Lack of relaxation or even contraction of the sphincter during bladder muscle contraction is common. This phenomenon is called bladder-sphincter dyssynergia (DSD) and constitutes a risk of bladder-emptying problems, infections and renal damage (Stoffel, 2016).

Defective emptying is common in neurogenic bladder-sphincter dysfunction, entailing a risk of urinary tract infections and renal damage.

Tools for evaluating the urinary tract

Table 2 shows several tools for evaluating bladder and renal function in children with SD. Further description of the methods is beyond the scope of this thesis. For further details see, *inter alia*, papers by the International Children’s Continence Society (Bauer *et al.*, 2012, 2015; Austin *et al.*, 2016).

Table 2. Tools for evaluating bladder and renal function.

<i>Investigative Tools</i>	<i>Non-invasive</i>	<i>Invasive</i>
History	x	
Clinical examination	x	x
Micturition/CIC charts	x	
4-h voiding observation with provocation test	x	
Uroflowmetry with residual measurement	x	
Invasive urodynamics		
<i>Filling cystometry</i>		x
<i>Natural filling cystometry</i>		x
<i>Video cystometry</i>		x
Renal bladder ultrasound (RBUS)	x	
Voiding cystourethrogram (VCUG)		x
Renal scintigraphy		x
Renal function laboratory tests eGFR/GFR [#]		x

[#] S-Creatinine is an insensitive marker for early renal insufficiency in children with SD, whereas S-cystatin C seems more useful (Fox *et al.*, 2014; Dangle *et al.*, 2017).

A wide range of non-invasive and invasive methods are available for evaluating renal and bladder function.

Treatment of neurogenic bladder/sphincter dysfunction

The main goals for treatment of NBSD are found in Figure 7 and should be part of repeated discussion with children and families during follow-up.

Figure 7. Goals for treatment of neurogenic bladder-sphincter dysfunction.

A number of treatments are available for children with NBSD to achieve the goals above, see Table 3 and text below.

Table 3. Treatment methods used in neurogenic bladder-sphincter dysfunction.

Conservative measures	
	Clean intermittent catheterization (CIC)
	Bladder-inhibiting drugs;
	Anticholinergic drugs
	β-3 stimulants
Surgical procedures	
	Intramural botulinum toxin A
	Bladder augmentation
	Catheterizable stoma (Mitrofanoff)
	Bladder neck surgery and injections
	Vesicostomy/SP catheter
	Other surgical techniques

Clean intermittent catheterization

As clearing urine from the urinary tract is important, the use of a catheter to empty the bladder repeatedly during the day (CIC) is the mainstay of treatment of NBSD. In a child with open spinal dysraphism, CIC is usually initiated at birth and for most individuals will be a lifelong treatment. Parents are taught the technique in the neonatal ward. The technique and the material used are adapted to the child’s age and status. Goals are set for positioning the child during CIC; initially prone, but as soon as possible sitting and finally on the toilet. Moreover, goals are set for the child’s participation, the ultimate aim being that the child performs the practical procedure by him/herself at least by the time he/she starts school. Many children, however, will still need some support to manage CIC even at higher ages. Although most countries permit only single use catheters at CIC, two high-quality randomized controlled trails show that single use catheters are not superior to multiple use catheters concerning frequency of urinary tract infections (Kiddoo *et al.*, 2015; Madero-Morales *et al.*, 2019). The two variants of catheters most commonly used for CIC are plastic untreated catheters and catheters covered with a hydrophilic surface. Today, there is no proof that any kind of catheter is superior to others or that a sterile technique would better reduce the frequency of UTI (Prieto *et al.*, 2014, 2015).

Clean intermittent catheterization is the cornerstone in treatment of neurogenic bladder-sphincter dysfunction.

Urotherapy

Urotherapy is the first-line treatment for daytime urinary incontinence and is commonly used for any form of idiopathic bladder and bowel dysfunction in children (Glad Mattsson *et al.*, 2010; Maternik, Krzeminska and Zurowska, 2015; Chang *et al.*, 2017; Niemczyk and Pospeschill, 2017; Yang *et al.*, 2017; Tekgul *et al.*, 2020). Standard urotherapy should be individualized but include key elements such as:

- demystifying the disorder
- instructions to establish optimal micturition behavior
- guidelines for drinking and eating
- exact documentation of the symptoms
- continuous and supportive contact with the treatment team (Chang *et al.*, 2017)

Specific urotherapy may include bio-feedback, neuromodulation, cognitive therapy and psychotherapy (Chang *et al.*, 2017). Although other measures such as clean intermittent catheterization and anticholinergic drugs are usually needed for children with neurogenic bladder-sphincter dysfunction, the components of standard urotherapy are often useful and should be offered during childhood, with a special focus on self-management.

Individualized urotherapy with a focus on self-management is important throughout childhood.

Drugs to inhibit bladder and sphincter muscle tone and contractions

To inhibit parasympathetic stimulation of the smooth muscle of the bladder wall, antimuscarinic/anticholinergic drugs are often used (Rawashdeh *et al.*, 2012; Wiener *et al.*, 2018). The first and most commonly used drug, oxybutynin, was introduced in the early 1970s at about the same time as the introduction of CIC (Diokno and Lapides, 1972). These drugs target the receptors for acetylcholine and are in varying degrees selective for the M3 subpopulation, the most common muscarine receptor in the bladder wall (Kroll, 2017). Effects on receptors (e.g. M1, M4-M5) in other parts of the body cause common side effects such as dry mouth and constipation. Anticholinergic drugs are administered orally, transdermally or intravesically (Kroll, 2017). Other bladder-inhibiting drugs, mirabegron and vibegron, work with the sympathetic nervous system during bladder filling to ensure that the bladder does not contract prematurely. They target β -3 receptors located mainly in the bladder neck region (Park *et al.*, 2018; Kopp Kallner, Elmer and Altman, 2019; Jian *et al.*, 2020; Shi *et al.*, 2020). These drugs add new means of counteracting neurogenic detrusor overactivity and may become important as part of conservative measures to prevent renal damage and decrease incontinence (Kroll, 2017; Park *et al.*, 2018; Gotoh *et al.*, 2020). Some studies have also found gabapentin effective in reducing neurogenic detrusor overactivity (Carbone *et al.*, 2006; Dash *et al.*, 2016). To relax the urethral sphincter in high-risk patients α -receptor antagonists have been trialed, with some studies reporting significant effects (Schulte-Baukloh *et al.*, 2002; Kakizaki *et al.*, 2003), but their clinical value in children with NBSD is doubtful (Kroll *et al.*, 2016; Kroll, 2017).

Anticholinergic drugs are the main adjuvant to CIC in the treatment of NBSD with incontinence and risk of renal damage. β -3 stimulants, which target the sympathetic nervous system, are promising new additions to the treatment arsenal.

Urinary tract infection in NBSD

There is an old medical saying that “urine is sterile”, which we know is inaccurate (Aragon *et al.*, 2018). Standard cultures show that most people with NBSD have bacteria in their urine even when they are healthy. In fact, a stable bacterial colonization of the bladder is considered to lower the risk of urinary tract infection, which is defined as bacteria in the bladder that give rise to significant clinical symptoms. Experts generally agree that antibiotics should be prescribed only for bacteriuria in the presence of clear clinical symptoms but more liberally in the presence of vesicoureteral reflex (VUR). In children with SD, bladder sensation is usually abnormal, and symptoms of UTI may not be straightforward. Urine dipstick analyses are useful, and other methods of supporting treatment decisions are being tested (Gupta *et al.*, 2019). A plausible definition of UTI needing treatment is proposed in the ongoing UMPIRE study, see Table 4 (Routh *et al.*, 2016). Problems with technique or adherence to CIC increase the risk of UTI, as may insufficiently treated constipation. The presence of stone-forming bacteria can also be a problem. To eradicate such bacteria from the bladder, high fluid intake combined with more frequent CIC, antibiotics or bladder irrigation with water or saline can be recommended.

Table 4. Suggested definition of UTI in NBSD. Adapted from (Routh *et al.*, 2016)

Urinary Tract Infection Definition used in UMPIRE protocol

Regardless of use of catheterization or spontaneous void,

all three of the following are required:

1. >100,000 CFU/ml of 1 or 2 speciated organisms
 2. 10 WBC/HPF on urine microscopy and/or leucocyte esterase > 2+ on dipstick
 3. At least 2 of the following symptoms
 - Fever > 40 degrees Celsius
 - Gross hematuria
 - Abdominal, suprapubic, or flank pain or tenderness
 - New or worsening incontinence
 - New or worsening urinary urgency, frequency, or hesitancy
 - Pain with catheterization or urination
 - Malodorous/cloudy urine
 - In infants less than 1 year old:
 - Failure to thrive, dehydration, hypothermia, increasing spasticity, febrile seizures or fussiness/irritability
-

Bacteriuria in patients with NBSD should only be treated in the presence of significant symptoms.

Antibiotic prophylaxis

To reduce the risk of urinary tract infections, antibiotic prophylaxis can appear to be an attractive alternative. Asymptomatic bacteriuria in NBSD is present in 42–76% of children (Rawashdeh *et al.*, 2012). Yet randomized studies have not found that prophylactic antibiotics prevent recurrent UTI (Rawashdeh *et al.*, 2012). They may even increase antibiotic resistance in bacteriuria in children with spinal dysraphism (Zegers *et al.*, 2017). Although there is no consensus concerning their role in treating NBSD, antibiotic prophylaxis can be useful in children with repeated UTIs or in high-risk situations such as dilated vesicoureteral reflux (Rawashdeh *et al.*, 2012). A plausible rationale, especially with the increase in multi-resistant bacteria, is that avoidable risk factors should be addressed and that prophylactic antibiotics be used selectively.

Randomized studies have not found that prophylactic antibiotics prevent recurrent UTI in patients with neurogenic bladder sphincter dysfunction but may contribute to the development of bacterial resistance. Antibiotic prophylaxis should thus be used selectively.

Neuromodulation

Electroneurostimulation (ENS) is well documented in treating bladder and bowel dysfunction in adults, with several ENS methods available to alter neurological functioning. In transcutaneous nerve stimulation (TENS), transmission using pads is non-invasive; in percutaneous tibial nerve stimulation, needles are used; and in the best-documented method, sacral neuromodulation, electrodes and a stimulator are implanted by neurosurgery (Wright and Haddad, 2017). The latter method is approved by the US Food and Drug Administration and is an accepted standard treatment for several bowel and bladder disorders in adults (Mirbagheri *et al.*, 2016; Lo *et al.*, 2020). In children, neuromodulation is promising, and the non-invasive modalities are considered attractive due to the almost complete lack of side effects (Maternik, Krzeminska and Zurowska, 2015). However, more studies are required to confirm its effect and help find its role in the treatment arsenal (Gladh, Mattsson and Lindstrom, 2001, 2003; Maternik, Krzeminska and Zurowska, 2015; Wright and Haddad, 2017; Barroso *et al.*, 2019; Buckley *et al.*, 2019). A few studies have reported positive results of electrical stimulation on neurogenic bladder-sphincter dysfunction (Gladh, Mattsson and Lindstrom, 2003; Hagerty, Richards and Kaplan, 2007)—one from our research group—but more research is required to elucidate the potential of this modality. The protocol for a new multicenter RCT of transcutaneous tibial nerve stimulation in adults with NBSD has just been published (Birkhäuser *et al.*, 2020).

Techniques for neuromodulation are promising and attractive alternatives for treatment of bladder dysfunction, but more research is needed.

Surgical treatments

Several surgical techniques have been developed to increase bladder capacity, lower bladder pressures, increase continence and enable a convenient route for bladder emptying. Commonly used methods are variants of bladder augmentation, creation of a catheterizable stoma canal, and increasing bladder outlet resistance to improve continence (Rawashdeh *et al.*, 2012). Although surgical techniques are often effective for renal protection and increased continence, complications are common (Snow-Lisy, Yerkes and Cheng, 2015). To ensure bladder drainage and thus prevent kidney damage, surgical methods such as a suprapubic catheter or vesicostomy can be used, especially in infancy and early childhood (Mandell *et al.*, 1981). Botulinum toxin A strongly inhibits acetylcholine release in the nerves that normally stimulate bladder muscle contraction and, if successful, prevents overactive detrusor contractions (Cooley and Kielb, 2019). It can be administered to the bladder wall through multiple injections using a cystoscope. The effect of one treatment often lasts for 3–9 months, but a drawback in children is that cystoscopy and often general anesthesia are needed (Naqvi *et al.*, 2020). Moreover, the effect is often reduced after repeated injections, and this may be due to local changes in the mucosa (Traini and Vannucchi, 2019).

Many surgical methods can be effective in reducing incontinence and bladder pressure, but complications are common. Bladder injections with botulinum toxin require less invasive procedures but have mainly temporary effects.

The interplay of bladder and bowel dysfunction

Understanding is growing concerning the close interplay between bowel and bladder function. Problems in one system will often contribute to problems in the other. The literature supports this common experience among patients, families and clinicians (Austin *et al.*, 2016; Yang *et al.*, 2017).

The closeness of the two organ systems can be explained in a variety of ways:

- anatomical—they share a compartment in the small pelvis
- neurological—innervation is partly by shared routes
- embryological—they have a common ancestor in the cloaca
- barrier—contents of both systems have to pass the same pelvic floor
- behavior—bladder and bowel habits have a substantial effect on the function and dysfunction of both systems

Other mechanisms have also been suggested. Recently, bowel dysfunction has been shown to result in bladder dysfunction via the spread of hypersensitization from one system to the other. This might be an important mechanism in chronic visceral pain and other forms of visceral dysfunction (Fowler, 2004; Grundy *et al.*, 2018). The reciprocal influence of the bowel and the bladder is evident in children with neurogenic as well as idiopathic bladder and bowel dysfunction.

The bladder and bowel go together in all children, with or without spinal dysraphism. Malfunction and insufficient treatment of one system affects the other.

Figure 8. The interplay of bladder and bowel dysfunction. Illustration by Tryggve Nevéus, with permission.

Bowel problems in spinal dysraphism

Normal large bowel function

The large bowel in humans have three major tasks: hosting bacteria involved in producing, for example, vitamins; reabsorption of water, electrolytes and vitamins; and the formation, temporary storage and transportation of stools (Preziosi and Emmanuel, 2009). Whereas the role of the microbiota of the gut is mainly unknown, researchers have become increasingly interested in its function in recent decades. Relations to several diseases have been proved, but causality and therapeutic potential remain to be explored (Daliri *et al.*, 2020). The large bowel has two layers of smooth muscle: the inner circular and the outer longitudinal. These are responsible for the two forms of contractions that dominate the motility of the large bowel, i.e. rhythmic phasic contractions and mass movement contractions. Colonic motility is mainly regulated internally by smooth muscle and the intrinsic nervous system of the bowel. Nevertheless, extrinsic factors also have major effects on motility, including signaling from the central nervous system, the autonomic nervous system, hormones and inflammatory mediators. The physiology of continence and evacuation of the bowel requires complex cooperation between the rectum, the anal sphincters and the pelvic floor (Bajwa and Emmanuel, 2009).

Large bowel motility is mainly regulated internally but is also influenced by extrinsic factors.

Neurogenic bowel dysfunction

The most common problems related to neurogenic bowel dysfunction are constipation and fecal incontinence. Disturbed neuronal transmission in spinal dysraphism may affect bowel function through a number of mechanisms. The parasympathetic nervous system exerts a stimulating effect on the motility of the large bowel whereas the sympathetic system has an opposing, motility-inhibiting effect. Parasympathetic signaling is provided to the more proximal part of the bowel via the vagal nerve (cranial nerve X) and to the distal part through sacral nerves (S2-S4), which explains why the distal part of the colon is the most severely effected in SD and spinal cord injury (SCI). Sympathetic (inhibiting) signaling originates from Th9-L2 and is therefore less often affected (Preziosi and Emmanuel, 2009). Through the gastrocolic reflex, food intake stimulates colonic motility. This reflex can also be affected in neurogenic bowel dysfunction, adding to the already slow transit of colonic contents (Preziosi and Emmanuel, 2009).

The site and completeness of spinal affection influence the type of problem experienced by the individual. The most common problem with motility is slow transit, but hypertonicity and reflex emptying are also common in high-level SCI (Preziosi and Emmanuel, 2009). Voluntary control of the external rectal sphincter is mediated through the pudendal nerve (S2-S4). Issues related to the perception of rectal filling and the efficacy of defecation are also important. Individuals with spinal dysraphism usually experience a combination of slow transit, lack of perception of rectal filling, ineffective defecation, and lack of sphincter

control. If untreated, these dysfunctions result in severe constipation often accompanied by fecal incontinence (Ambartsumyan and Rodriguez, 2018).

Neurogenic bowel dysfunction in spinal dysraphism is usually characterized by slow colon transit, defective rectal sensation, ineffective defecation and anal sphincter insufficiency.

Treatment of neurogenic bowel dysfunction

Randomized studies on treating neurogenic bowel dysfunction in children are sparse (Velde *et al.*, 2013). Case series, experience and one randomized controlled trial indicate that treatment with oral constipation drugs have a positive effect on constipation and incontinence, and that macrogol is superior to lactulose (Rendeli *et al.*, 2006). However, overwhelming experience suggests that enemas are needed to help many individuals achieve effective emptying and reduce incontinence. Stepwise treatment strategies starting with conservative treatments and progressing to more active measures have been recommended (Velde *et al.*, 2013; Ambartsumyan and Rodriguez, 2018; Emmanuel, 2019). The main methods for enema are transanal irrigation (TAI) and antegrade continent/colonic enemas (ACE) (Kelly, 2019). The goals of treatment are continence and to relieve constipation using a method that allows self-management and has a minor effect on the person's daily life (Ambartsumyan and Rodriguez, 2018).

The goals of treatment are continence and to relieve constipation using a method that enables self-management and has a minor effect on the person's daily life.

Oral drugs

Many oral drugs for treating constipation can be, and often are, used in neurogenic bowel dysfunction (Ambartsumyan and Rodriguez, 2018). However, oral medication is often not sufficient to relieve constipation and fecal incontinence. The study by Rendeli reported a decrease in incontinence episodes using macrogol (PEG4000), but continuing fecal incontinence of five episodes a week (Rendeli *et al.*, 2006), which is much higher than in patients using enemas (Mattsson and Gladh, 2006; Kelly, 2019; Johnston, Wiener and Todd Purves, 2020). Most people would consider this unacceptable. Experience indicates that doses of stool softeners must be kept low in patients with anal sphincter dysfunction as many of them are dependent on slightly harder stools to prevent fecal incontinence.

Monotherapy with oral constipation medication rarely achieves the goals of treatment. Low doses can be a valuable adjuvant to other methods.

Digital evacuation and stimulation

Manual evacuation of stools can be effective in reducing the amount of stool in the rectum, but the patient will remain constipated and the method has disadvantages related to personal

integrity if the assistance of another person is required. The method is common among adults with spina bifida (Wiener *et al.*, 2017). Digital stimulation to activate a reflex defecation is commonly used by adults with neurogenic bowel dysfunction caused by traumatic spinal cord injury but does usually not work well in patients with spinal dysraphism. It is not commonly used in children (Wiener *et al.*, 2017; Emmanuel, 2019; Nelson and Orr, 2019).

Digital evacuation is commonly used by adults with spinal dysraphism.

Electroneurostimulation and anal plug

Electroneurostimulation to enhance bowel function has become a well-established treatment for various forms of bowel dysfunction in adults, mainly through the FDA-approved sacral neuromodulation technique (Mirbagheri *et al.*, 2016). In children, there is growing evidence that neuromodulation could become an effective and well-tolerated treatment alternative, but supporting data is still sparse (Wright and Haddad, 2017). Use of an anal plug can be an adjuvant treatment to prevent fecal incontinence in selective patients with neurogenic bowel dysfunction in SD (Van Winckel *et al.*, 2006).

Electroneurostimulation is an effective treatment of fecal incontinence in adults but there is insufficient knowledge about its effects in children with bowel dysfunction.

Transanal irrigation (TAI)

Transanal irrigation was described as early as 1500 B.C. in the Papyrus of Ebers. The method is widely used but has been heavily criticized because of the widespread theories that the it could solve a wide range of health and existential problems. TAI has been shown to be an effective and safe method of reducing constipation and incontinence (Christensen *et al.*, 2006; Mattsson and Gladh, 2006; Ausili *et al.*, 2010; Choi *et al.*, 2015). Fluid is infused or injected into the colon through the anus, often using a dedicated irrigation system see Figure 9 (Mattsson and Gladh, 2006; Lopez Pereira *et al.*, 2010; Mosiello *et al.*, 2017). As in children with SD the anal sphincter tone is usually low and voluntary control over the sphincter is lacking a cone or a balloon can be needed on the catheter to keep the fluid from leaking out of the anus during infusion. Several products have been developed to facilitate use and enable self-management. TAI has been shown to be cost-effective in patients with neurogenic bowel dysfunction for whom standard bowel care is unsuccessful (Emmanuel *et al.*, 2016). Studies have shown that whereas normal defecation in healthy subjects empties the sigmoid, washout fluid during TAI reaches through the sigmoid and left colon and induces emptying of both segments (Christensen *et al.*, 2003). Tap-water is the most widely recommended irrigant and while pain and discomfort are common, serious complications such as bowel perforation are rare (Mosiello *et al.*, 2017).

TAI is effective in reducing constipation and fecal incontinence but is time-consuming, relatively invasive and often difficult to perform independently.

Transanal irrigation (TAI)

Antegrade colonic enema (ACE)

Figure 9. Principle of transanal irrigation (TAI) and antegrade colonic enema (ACE).

(Illustration by Agnes Wide)

Antegrade colonic enemas (ACE)

Antegrade colonic enema for the treatment of constipation was introduced by urologist Pat Malone in the early 1990s (Malone, Ransley and Kiely, 1990) using the appendix to create a catheterizable stoma to the cecum as a route for administering bowel washouts see Figure 9. The principle had been used as early as in 1902 for the treatment of ulcerative colitis (Corbett, 1945). In recent decades, ACE has gained popularity as a treatment option, first in children with spinal dysraphism, then in children with anorectal malformations (Stenström *et al.*, 2013), and intractable idiopathic constipation (Halleran *et al.*, 2019). It is also used in adults (Patel *et al.*, 2015; Chan and Delicata, 2016).

New techniques have been developed: laparoscopic (Kim, Beasley and Maoate, 2006), robot-assisted laparoscopic (Zee, Kern and Herndon, 2017), left colon location (Anselmo *et al.*, 2017), use of a tube in the stoma (Bevill *et al.*, 2017), and cecostomy (Halleran *et al.*, 2019). Although this is a broad selection of methods, none seems clearly superior to the others (DeFreest, Smith and Whyte, 2014; Kuizenga-Wessel *et al.*, 2016; Grabski *et al.*, 2018; Ayub *et al.*, 2019; Halleran *et al.*, 2019; Kelly, 2019; Soyer, 2020). According to scintigraphy studies, a washout through a channel to the cecum induces highly effective emptying of all parts of the colon (Christensen *et al.*, 2002). A recent literature review, however, shows that the complication rate is high (Soyer, 2020). Short-term complications, mainly stomal complications such as stomal stenosis, prolapse or granulation, were reported for 18–57% of patients. Reoperation for stomal complications was also common. Adding long-term issues, mainly leakage from the stoma, most studies reported complications in 30–70% of the patients, with some reporting up to 95% with complications (Soyer, 2020).

ACE is effective in reducing constipation and fecal incontinence but time-consuming, requires surgery, and minor complications are common.

Contrasting treatment choices

In a personal communication with parents of children with SD and colleagues in Norway, we detected a positive attitude to offering ACE surgery at a relatively low age to children with neurogenic bowel dysfunction due to SD. This may have been influenced by an article by Aksnes et al (Aksnes *et al.*, 2002), positive experiences, and the need for better methods. The attitude in Norway contrasted with the relatively conservative management common in Sweden at the time. We found the purported differences in recommendations of treatment method dissatisfying as the needs of the children should be the same. Literature on ACE and TAI consisted mainly of single-center reports without any comparison and often without information on the views and experiences of the children.

When discussing methods in neurogenic bowel dysfunction, increased self-management is often an argument for choosing ACE, but comparative evidence and experiences from patients are lacking.

Summary

- *Non-invasive screening methods are desirable for evaluating bladder function in newborns and infants.*
- *More widely spread knowledge and structured health care are needed for children with spinal dysraphism.*
- *Controversies remain concerning the best way to follow up children with neurogenic bladder sphincter dysfunction.*
- *Knowledge is lacking about how children with spinal dysraphism, and their parents, perceive treatment of neurogenic bowel dysfunction in relation to effect, satisfaction and independence.*

Aims

The overall aim of the studies was to answer clinically relevant research questions about follow-up and treatment of neurogenic bladder and bowel dysfunction in children with spinal dysraphism.

Aims of specific studies:

- I. to acquire data from voiding observation with a provocation test in a consecutive geographical cohort of newborns with spinal dysraphism evaluated for possible neurogenic bladder-sphincter dysfunction and to compare this with corresponding data for healthy newborns.
- II. to determine whether neonatal voiding observation with provocation test in children with spinal dysraphism has a predictive value for bladder function at one year of age.
- III. to determine prevalence of, and risk factors for renal damage in children with neurogenic bladder-sphincter dysfunction followed in accordance with the Swedish national guidelines.
- IV. to investigate how children with open spinal dysraphism and their parents assessed their chosen method for bowel emptying in terms of satisfaction, fecal incontinence, time spent on the toilet, independence, and impact on quality of life.

Ethical considerations

All studies were approved by the regional ethical committee, Linköping, Sweden. Paper IV was also approved by the regional ethical committees in Lund, Sweden and Oslo, Norway. Written informed consent was obtained by children and/or guardians in Paper IV. Research questions have evolved during clinical work with children with spinal dysraphism, and knowledge acquired during the studies can be helpful in the treatment and follow-up of this group of patients, including the participants. For Papers I–III, data from standard clinical care has been collected, analyzed and presented anonymously. In Paper IV data was collected via a questionnaire and then anonymized and presented at group level. In developing the questionnaire used in Paper IV, other patients were asked to provide feedback on the construction and wording of the questions. Questionnaires may cause harm or discomfort, but risks were considered low and were outweighed by the possible benefits of the study.

Material and methods

Papers I and II

Participants in Papers I and II were all children ($n=50$) with spinal dysraphism evaluated neonatally for suspected neurogenic bladder-sphincter dysfunction at the pediatric neuro-urology and bowel unit (PNUT in Swedish) in H.R.H. Princess Victoria's Children's Hospital, University Hospital, Linköping, Sweden. At this clinic, children with spinal dysraphism have been evaluated and followed in a structured way since the early 1990s and form the basis for the first Swedish national follow-up program for NBSD, which was published in 1998 (Gladh and Mattsson, 1998). The structured method of evaluating bladder function in neonates using 4-hour voiding observation was published first by Holmdahl and colleagues in Gothenburg (Holmdahl *et al.*, 1996) and was found useful by clinicians. It has been studied in healthy newborns and newborns with different diagnoses (Holmdahl *et al.*, 1998; Bachelard *et al.*, 1999; Sillén *et al.*, 1999; Gladh *et al.*, 2000; Sillen *et al.*, 2000; Sillen and Hjalmas, 2004; Wen *et al.*, 2014) and has been included in several follow-up programs. From clinical observations and discussions with preclinical colleagues, visual observation of the quality of voiding—whether it is by dribbling or with a stream—as well as maneuvers to provoke leakage from the child's bladder were added to the protocol in our institution to create the voiding observation with provocation test (VOP).

As PNUT is the only unit in the southeastern health care region of Sweden (1 million inhabitants) that evaluates possible neurogenic bladder-sphincter dysfunction in neonates, it is reasonable to assume that the two papers include all live-born children with open spinal dysraphism and most children with closed dysraphism diagnosed in the perinatal period from this geographical area. In Paper II, one child was excluded due to lack of data from after the neonatal period. In the same paper, children with closed spinal dysraphism undergoing primary neurosurgery after the first VOP, but before urodynamic studies at one year of age, were excluded from some of the analyses.

Initial care of newborns with open spinal dysraphism

If diagnosed prenatally, children were most often referred to the tertiary hospital prenatally and was born in the same hospital. When not diagnosed prenatally, children were transported to the university hospital within 24 hours of birth. Evacuation of urine from the urinary bladder was usually started from birth either by sterile intermittent catheterization or via an indwelling catheter. Primary neurosurgical back closure was performed no later than 48 hours after birth, but most often within 24 hours after, using standard postnatal neurosurgical technique. During the first two weeks, renal bladder ultrasound and voiding observation with provocation (VOP) were performed. Timing was determined by the child's health status, other clinical procedures for the child, and availability of skilled staff. A choice was then made whether to continue bladder evacuation or not. In most cases, this meant teaching the parents how to perform clean intermittent catheterization (CIC) or to rely on the child voiding or leaking spontaneously. VCUG was performed within the first month and invasive urodynamics within the first three months. Due to hydrocephalus, most children had a ventriculoperitoneal shunt implanted during their first weeks of life.

Methods in Papers I and II

In Paper I a descriptive method was used to present data from VOP for newborns with SD. Protocols from VOP were anonymized and data was registered, analyzed and presented. As most data was not normally distributed, the material was described using medians and range. In the second part of the study, the results from VOP of newborns with SD were compared with results from the same test of healthy newborns published earlier by our research group (Gladh *et al.*, 2000). In this study VOP with the same protocol was performed on 50 healthy newborns recruited at the maternity ward. There were no significant differences between the groups related to gender, age, gestational age or diuresis. For background data see Table 5. Nonparametric methods were used to test for differences.

Table 5. Background data. (Paper I)

	Newborns with SD		Healthy newborns
	n=50		n=50
Girls n (%)	22 (44%)		25 (50%)
Age, median (range), days	10 (3-37)		9 (3-14)
Type of spinal dysraphism	Open SD	Closed SD	
Number	37	13	
Neurosurgery* prior to VOP	37	4	
CIC prior to VOP	36/37 (97%)	2/13 (15%)	0

*Neurosurgery was carried out on children with open SD postnatal neural tube closure and on children with closed SD individualized surgery including detethering.

Paper II investigates whether VOP has a predictive potential for later bladder function and need of CIC. Bladder function was assessed by reevaluation of the UDS performed around the age of one year. Data was collected about the use of CIC, anticholinergic drugs, results of

RBUS, laboratory tests of renal function and VCUG. Data from neonatal VOP (from Paper I) about children using CIC at the age of one year was compared with that of children who did not. For this analysis, children who had gone through detethering neurosurgery between the neonatal VOP and the one-year evaluation were excluded because such surgery entailed a considerable risk of influencing the outcome. Positive and negative predictive values for the use of CIC at one-year evaluation were calculated for leakage at provocation and not voiding with a stream. UDS data for children with open and closed spinal dysraphism were also compared. The study design in this paper is a retrospective cohort study.

Paper III

Included in this study were all children with NBSD due to SD born 1993–2003 who were followed at our institution. Like the children in Papers I and II they represent a complete geographical cohort from the southeastern health care region of Sweden. The study was done in 2009 when the children were aged 6–16 years. The median follow-up time was 11 years. As in Papers I and II, there was a mix of children with open and closed spinal dysraphism, with the vast majority (35/41) having open spinal dysraphism. The children had been followed according to national guidelines, and the timing of the different measures is shown in Table 6 (Gladh and Mattsson, 1998).

Table 6. Standard urological follow-up according to the Swedish national program 1998, with permission. (Gladh and Mattsson, 1998)

Age	UDS	VCUG	RBUS	Pyelo- graphy	Renal function	Renal scintigraphy	GFR
0–1 month	x	x	x		S-creatinine U-analysis		
3–6 months	x				S-creatinine U-analysis	DMSA, MAG3 or DTPA	
12–18 months	x		x	x ¹	DDAVP ² , Cystatin-C S-creatinine U-analysis		
>18 months yearly	x		x ³		DDAVP ² , Cystatin-C S-creatinine U-analysis Blood pressure	RBUS yearly, Scintigraphy every 3 rd year	x ⁴

1. Pyelography omitted from program after a few years
2. DDAVP = 1-desamino-8-D-arginine vasopressin test (Abyholm and Monn, 1979)
3. Every 3rd year scintigraphy/renography
4. Every 3rd year with scintigraphy/renography

Medical records and urodynamic studies were analyzed. Renal damage was defined as the presence of scarring on renal scintigraphy (DMSA). Several analyses were done of risk factors for developing renal damage. Children were divided into a high-pressure and a low-pressure group depending on the bladder pressure in UDS at their maximum CIC volume at the same age. The frequency of urinary tract infections and renal damage between the groups was compared.

Paper IV

To explore the experience of treatments used, a questionnaire was sent out to all children with open SD who were followed at three tertiary centers: Lund in the southern health care region; Linköping in the southeastern health care region; and Oslo University Hospital (Rikshospitalet), Norway. Together, these three centers serve a population of around four million people, about a third of Sweden's and Norway's aggregated population. The questionnaire was a combination of an instrument for measuring quality of life, PedsQL 4.0 (Varni *et al.*, 2003; Petersen *et al.*, 2009) and a questionnaire, constructed for the study, regarding the treatment of bladder and bowel dysfunction with a focus on independence, satisfaction, fecal incontinence and time spent on toilet. Of the 172 questionnaires sent out, 106 were returned, a response rate of 62%. Descriptive data was presented. Satisfaction, fecal incontinence, independence on the toilet, and quality of life were compared among children using different methods of bowel evacuation. A comparison was also made of reported quality of life in those who were independent on the toilet and those who were not.

Statistical analyses

Studies were descriptive, with analytical elements. In Papers I and II, data was most often not normally distributed. Therefore, medians and range were used. For comparison and hypothesis testing, Kruskal-Wallis test was used for three groups. To compare two groups, Mann-Whitney U-test was used for scale variables and Chi-square or Fisher's Exact test on nominal variables depending on the number of children. In Paper III, the material was described using medians and proportions. To test hypotheses, Chi-square test or Fisher's Exact test was used depending on the number of children. To explore the contribution to renal damage of the dichotomous variables related to bladder pressure and UTIs, binary regression analysis was used. In Paper IV, comparisons were made using T-test, Mann-Whitney U test or Chi-square test/Fisher's exact test depending on the number of respondents. Correlations between the level of fecal incontinence and satisfaction were also calculated. SPSS 16-26® software, IBM Corp. in Armonk, NY, US, was used for the analyses.

Results and discussion

Bladder function in newborns with spinal dysraphism (Paper I)

Abnormal voiding patterns

Bladder function evaluated with four-hour voiding observation with provocation test revealed significant abnormalities compared with a group of 50 healthy newborns, see Table 7.

However, the variation in voiding pattern is more apparent than the differences in median values for specific variables. The variation likely reflects differences in neurological deficit in regulation of the bladder and sphincter, whose cooperation is discussed in the introduction.

Thus, two children with the same or similar diagnoses may differ in voiding patterns.

Whereas one might display small frequent leakages resulting in a functionally very small bladder, the other could have a large bladder that neither voided nor leaked if not severely overfilled. Both voiding patterns are clearly pathological and offer two extremes that frame the pattern of a healthy child. In a larger material, cluster analysis might have been useful to identify and characterize phenotypes of NBSD in the newborn.

Absence of a stream

As seen in Table 6 all 50 healthy newborns in the comparison group voided with a stream whereas only 26% of children with spinal dysraphism and only 14% of those with open spinal dysraphism did so. Thus, not voiding with a stream should raise suspicion of bladder-sphincter dysfunction or other urological problems, such as posterior urethral valves, and lead to further investigation.

Leakage at provocation test

Paper I revealed that 69% of children with SD and 84% of those with open SD leaked at bladder provocation, whereas none of the healthy newborns did, see Table 6. Thus, leakage at provocation in a newborn should motivate further evaluation.

Implications

The VOP could be particularly useful in two situations. One is with an infant in whom closed spinal dysraphism has been diagnosed but where the clinical consequences of the malformation are unknown. Incomplete bladder emptying and a voiding pattern indicating neurogenic bladder-sphincter dysfunction will lead us to introduce CIC, and perform invasive urodynamics and radiology (RBUS and VCUG). Combined with MRI findings and neurological examination, these will provide a sound basis for determining the need for detethering neurosurgery. If a completely normal voiding pattern is found in a newborn with closed SD in the absence of other pathological findings, it is even plausible to plan for follow-up and postpone invasive UDS. The availability of a non-invasive screening test for bladder function is particularly valuable because detection rates of less severe forms of closed spinal dysraphism are increasing. For these children, the complications from SD may be severe, whereas the prognosis for most children is excellent (Macejko *et al.*, 2007; Veenboer *et al.*, 2013; White *et al.*, 2015; Peyronnet *et al.*, 2018). There is a need for prognostic factors, which

have been hard to find (Yerkes *et al.*, 2017) and we argue that VOP provides improved opportunities to detect NBSD in the asymptomatic child with closed spinal dysraphism. The other situation is when parents of a child with SD report wet diapers and only small volumes when performing CIC. It can be pedagogically challenging to explain that leakage is not active voiding and that the bladder function may be severely disturbed even if the diaper is wet all the time. In this situation the four-hour VOP offers a standardized non-invasive means of determining residual volumes and voiding patterns. This is useful both for clinical decisions and discussions with the family.

Table 7. Results of VOP for newborns with spinal dysraphism and healthy newborns, volume group median and range (ml). (Paper I)

	Newborns with SD				Healthy Newborns	P value ^{&}
	All SD	P value SD vs HN	Open SD	Closed SD	HN	
Number of children	50		37	13	50	
	<i>median</i>		<i>median</i>	<i>median</i>	<i>median</i>	
	<i>(range)</i>		<i>(range)</i>	<i>(range)</i>	<i>(range)</i>	
Voiding frequency	5.6 (0–14)	<0.001 [¤]	6.1 (0–14) #	4.6 (2–8) \$	4.0 (2–7)	<0.001
Maximum voided volume	18 (0–67)	<0.001 [¤]	15 (0–42) #	31 (11–67) \$	35 (15–77)	<0.001
Median voided volume	8.3 (0–36)	<0.001 [¤]	6.5 (0–22) #	19 (5–36) \$	23 (10–49)	<0.001
Median residual volume	13 (0–80)	<0.01 [¤]	17 (0–80) #	6.0 (0–28) \$	7.5 (0–34)	<0.005
Minimum residual volume	1.0 (0–80)	<0.01 [¤]	5.0 (0–80) #	1.0 (0–7) \$	0.0 (0–26)	<0.01
	<i>fraction (%)</i>		<i>fraction (%)</i>	<i>fraction (%)</i>	<i>fraction (%)</i>	
Voiding with stream	12/46 (26%)	<0.01 [€]	5/37 (14%) °\$	7/13 (54%) °	50/50 (100%)	
Leakage at provocation	33/48 (69%)	<0.01 [€]	30/37 (81%) °\$	2/11 (18%) °	0/50 (0%)	

& = Kruskal-Wallis between open SD, closed SD and HN; [¤] = Mann Whitney; [€] = Fisher's Exact Test

\$ Significant difference compared with open SD, $p < 0.05$, Mann Whitney

Significant difference compared with HN, $p < 0.01$, Mann Whitney

° Significant difference compared with HN, $p < 0.05$, Fisher's Exact Test

\$ Significant difference compared with closed SD, $p < 0.05$, Fisher's Exact Test

Data for visual observation of voiding and for provocation test missing for four and two children, respectively.

Neonatal VOP related to UDS at one year of age (Paper II)

Most children (34/49, 69%) had bladder drainage, generally CIC, at the age of one month see Table 8. During the first year of life, seven children were put on CIC, three of them after primary detethering neurosurgery due to closed spinal dysraphism. Two children stopped using CIC due to acceptable bladder emptying. At one year of age, 39/49 children (80%) used CIC for bladder emptying. Use of CIC was related to lower maximum voided volume ($p<0.005$) and lower median voided volume ($p=0.01$) in the neonatal VOP. For children with open spinal dysraphism, use of CIC at one year was related to higher residuals in neonatal VOP. These findings are not surprising because children who lack a normal micturition reflex will have lower voided volumes and a greater likelihood to need CIC to ensure bladder evacuation. Having residuals, “the bladder already half full”, may also make voided volumes smaller. Residual volume is one of the main factors that determine whether or not to maintain CIC after the neonatal period. Since information from neonatal VOP had been used in decisions regarding CIC for these children, a relation between neonatal residuals and use of CIC is plausible. No relation was found between the use of CIC and other variables from VOP, but the pattern is often more pathological than single variables.

Table 8. Data from one year of age on use of CIC, results of radiology and UDS. (Paper II)

	Open SD n=37	Closed SD n=12	Total n=49
Bladder drainage at 1 month (CIC or SP cath), n (%)	32 (86%)	2 (17%) *	34 (69%)
Normal RBUS neonatally, n (%)	34 (92%) &	11/11 (100%), 1 no RBUS	44 (94%)
VUR at neonatal VCUG, n (%)	8 (22%)	2/8 (25%)	10 (22%), 4 no VCUG
VUR III-V at neonatal VCUG, n (%)	6 (16%)	2/8 (25%)	8 (16%), 4 no VCUG
Bladder drainage (CIC) at 1 year, n (%)	31 (84%)	8 (67%)	39 (80%)
Anticholinergic treatment, n (%)	7 (19%)	1 (8%)	8 (16%)
Febrile UTI first year, n (%)	10 (27%)	5 (42%)	15 (31%)
Cystometric bladder capacity, md (range), ml	68 (9-217)	73 (30-323)	73 (9-323)
Leak-point pressure ^e , md (range), cmH ₂ O	27 (8-66)	30 (19-100)	27 (8-100)
NDOA at 1 year of age, n (%)	32 (87%)	11 (92%)	43 (88%)
DSD at 1 year of age, n (%)	13 (35%)	3 (25%)	16 (33%)
Maximal Detrusor pressure > 40cmH ₂ O at 1 year of age, n (%)	5 (14%)	0 (0%)	5 (10%)
Compliance at 1 year of age ml/cmH ₂ O	5.4 (0.4-39)	13 (2.9-50)	5.7 (0.4-50)

&Two children AP measurement 4 and 7 mm, respectively, 1 child renal agenesis/single kidney

*Significant $p<0.001$ Fisher's Exact Test compared with open SD

^eDetrusor leak-point pressure or detrusor overactivity leak-point pressure: see Methods.

Children who did not void with a stream during neonatal VOP significantly more often used CIC at one year of age ($p<0.005$, Fisher’s Exact Test). As a predictor of CIC at one year in this specific cohort, a positive value of 91% was calculated for not voiding with a stream at neonatal VOP; the negative predictive value was 60%. However, the usefulness of this in the clinic is uncertain.

Voiding patterns detected by the VOP were heterogenous, as were the findings in urodynamic studies at one year of age. Cystometric capacity varied greatly as did leak point pressure and compliance, see Table 8. Most of the children had healthy kidneys neonatally, but vesicoureteral reflux was common (22%). A high-risk detrusor pressure of over 40 cm H₂O was found in 10% of children, all with open SD, and DSD was present in 33%.

Anticholinergic drugs were used by 16% of the children. The quartile of children with the highest voiding frequency during neonatal VOP had lower compliance ($p=0.025$), higher detrusor pressure at the end of the cystometric filling phase ($p=0.015$), and higher detrusor pressure at maximum volume in the CIC chart or at VOP at the time of UDS ($p=0.007$). This might be explained by children having small bladders or neurogenic detrusor overactivity leading to lower compliance, as postulated by some authors (Comprat *et al.*, 2006), but the findings must be interpreted carefully due to the limitations of the study. If correct, these findings would support the prophylactic use of anticholinergic drugs promoted by some authors (Ab *et al.*, 2004; Dik *et al.*, 2006).

Renal preservation (Paper III)

In Paper III, we evaluated a cohort of children with NBSD due to SD that had been followed at our unit according to what subsequently became a national follow-up program. As in other studies, most children had normal kidneys at birth; only two (5%) had hydronephrosis. Some degree of vesicoureteral reflux was present in 11/39, whereas five children had the more clinically relevant dilated VUR (all grade III-IV). The vast majority (93%) were using CIC and most (56%) were treated with anticholinergic drugs to prevent either renal damage or incontinence.

Table 9. Children with renal damage. (Paper III)

Child	Age (years)	Sex	GFR ml/min/1.73m ²	UTIs per year	Bladder capacity (ml)	Resting Pressures (cmH ₂ O)	Anti-cholinergic treatment	Botulinum injection	Bladder augmentation
1	15	F	87	2	400	40	Yes	No	Yes*
2	15	M	65	0.33	475	45	Yes	Yes	Yes*
3	13	F	>90	0.23	260	5	No	No	No
4	13	F	84	1	290	30	Yes	Yes	No
5	9	M	>90	0.11	160	30	Yes	Yes	No

* Bladder augmentation performed after end of study

At follow-up after a median of 11 years (6–16 years), 5/41 (12%) were found to have renal damage, defined as scarring on DMSA scintigraphy. Data for these children is presented in Table 9. One boy aged 15 had a GFR just below normal level (10th percentile) whereas all the children had normal creatinine levels. Two of the five children with renal damage were not followed from birth and had renal damage when entering the program. Thus, 3/39 (8%) had acquired renal damage during follow-up as assessed by the national program. Levels of renal damage shown in Paper III are lower than those in historical data, and low or on par with other recent publications (Snow-Lisy, Yerkes and Cheng, 2015). Most published studies are retrospective single-center cohorts, and the lack of conformity of definitions makes comparison difficult. Moreover, many studies use RBUS or laboratory findings as an indicator of renal damage, but even modern eGFR calculations are unreliable in children with spinal dysraphism (Abrahamsson *et al.*, 2008; Szymanski *et al.*, 2020). In Paper III, scarring on DMSA scintigraphy was used to detect renal damage. This method is much more sensitive, particularly for unilateral damage (Abrahamsson *et al.*, 2008; Ayazi *et al.*, 2015; Bush *et al.*, 2015). The Swedish national program is proactive, based on repeated UDS combined with an evaluation of the upper urinary tract with ultrasound and scintigraphy. It has many similarities with the protocol used in the UMPIRE study (see Table 6 and Table 10).

Table 10. Treatment and follow-up program in the UMPIRE study.

Diagnostic procedure or intervention	Age	Birth	3 mos	6 mos	9 mos	1 yr	2 yr	3 yr	4 yr	5 yr
Foley catheter placement-intermittent catheterization		X								
Teach family CIC technique†		X								
Medical history		X	X	X	X	X	X	X	X	X
Physical exam		X	X	X	X	X	X	X	X	X
Blood pressure			X			X	X	X	X	X
Serum creatinine			X			X	X	X	X	X
RBUS		X	X	X	X	X	X	X	X	X
Urodynamics			X			X	X	X		
DMSA Nuclear Scan			X							X
GFR Nuclear Scan										X

Adapted from (Routh *et al.*, 2016). Anticholinergics and more frequent UDS if hostile bladder (see Table 12) are diagnosed.

There has long been some controversy as to whether this is necessary to keep renal damage low or whether a more conservative follow-up using renal bladder ultrasound as the main tool is sufficient. The proactive approach is recommended by most authorities and organizations

(Dik *et al.*, 2006; Bauer, 2008; Rawashdeh *et al.*, 2012; Routh *et al.*, 2016; Tuite *et al.*, 2018; Stein *et al.*, 2020) whereas the British Association of Pediatric Urologists recommends a more conservative approach (Lee *et al.*, 2016). A review by Snow-Lisy *et al.* indicates that it is unclear which is the superior and most cost-effective approach (Snow-Lisy, Yerkes and Cheng, 2015).

When judging the number of children with renal damage in Paper III, we must consider that the follow-up time from a lifetime perspective is short and that there is a continuing risk of progressive renal deterioration. In a cross-sectional study of patients with spina bifida, Imamura *et al* found that young adults with renal scarring significantly more often had hypertension and decreased glomerular filtration rate (GFR), see Table 11 (Imamura *et al.*, 2018). This highlights the importance of preventive measures in childhood. In Imamura’s study no significant relation was found between UDS findings and the presence of renal scarring. However, a significant portion of the patients with renal scars had been through bladder augmentation and only UDS data after surgery was used, which may explain this otherwise surprising finding.

Table 11. Analysis of factors associated with renal function during the transition to adulthood.

	DMSA renal scan		Odds ratio	p (Chi-2 test)
	<i>no scarring</i>	<i>scarring</i>		
	Hypertension		4.82	0.0032
Present	9 (15%)	13 (46%)		
Absent	50 (85%)	15 (54%)		
	Decrease in eGFR		6.20	0.033
Present	2 (3%)	5 (18%)		
Absent	57 (97%)	23 (82%)		
	Proteinuria		1.30	0.71
Present	5 (8%)	3 (11%)		
Absent	54 (92%)	25 (89%)		

Adapted from (Imamura *et al.*, 2018).

During the study period, none of the children had been through renal protective urological surgery, but two later underwent bladder augmentation. This reflects a relatively conservative surgery strategy compared with many other centers (Snow-Lisy, Yerkes and Cheng, 2015; Wiener *et al.*, 2018). The fact that only 20% of patients in Paper III were completely bladder continent may also be the result of such surgical conservatism. A recent study using the US National Spina Bifida Patient Registry reporting 36% bladder continence in children with MMC in relevant ages also revealed a higher prevalence of urological surgery (Wiener *et al.*, 2018). Another study using the same registry reported that 22% of patients over the age of five years had a history of bladder continence surgery, but only 55% of those who had had surgery reported continence (Liu *et al.*, 2018).

Table 12. Urodynamic risk classification used in UMPIRE study. Adapted from (Routh *et al.*, 2016; Joseph, 2019)

Normal
Capacity as predicted by age
End-filling pressure <15 cm H ₂ O
Normal voiding contraction
Minimal post-void residual
Safe
End-filling pressure <25 cm H ₂ O
Bladder (detrusor) leak-point pressure <25 cm H ₂ O
Intermediate
Neurogenic bladder overactivity
Reduced compliance
End-filling pressure 25–39 cm H ₂ O
Bladder (detrusor) leak-point pressure 25–39 cm H ₂ O
Hostile
Neurogenic bladder overactivity
Bladder (detrusor) sphincter dyssynergia
End-filling pressure >40 cm H ₂ O
Bladder (detrusor) leak-point pressure >40 cm H ₂ O

As high bladder pressure is the best-known risk factor for renal damage, children were divided into a high-pressure group and a low-pressure group, see Table 13. Children in the high-pressure group had more renal damage ($p<0.05$). The healthy urinary bladder is normally highly compliant, with a mean pressure of 9.6 cm H₂O at full bladder (Houle *et al.*, 1993). High bladder pressure has long been known to be a significant risk factor for renal damage. The scientific basis for this is often attributed to the study by McGuire and colleagues from 1981, who presented results suggesting that a leak-point pressure higher than 40 cm water was related to increased risk of renal failure (McGuire *et al.*, 1981). It has been suggested that a pressure under 30 or 25 cm should be considered safe (Joseph, 2019). This is also in accordance with the strategy used in the ongoing UMPIRE study in which hostile bladders, see Table 12 require CIC and anticholinergic treatment. Despite its small cohort, Paper III supports the hypothesis that pressure over 30 cm H₂O constitutes risk of renal damage.

Table 13. Renal damage in high-pressure and low-pressure group. (Paper III)

Resting pressure*	Renal damage		
	No	Yes	Total
>30 cmH ₂ O	3	4	7
<30 cmH ₂ O	34	1	35
Total	37	5	42

*highest detrusor pressure (without NDOA) registered at maximum CIC volume in at least two fillings of UDS

Only three children in Paper III were on prophylactic antibiotics during the study. This is a low frequency compared with what is often reported, but in line with recent recommendations to use antibiotic prophylaxis neonatally and otherwise only in the presence of dilated VUR, recurring UTI or hostile bladder (Stein *et al.*, 2020). The largest register-based study from the US National Spina Bifida Patient Registry reported the use of daily antibiotics by 12% of children of the same age as those in Paper III and 17% in adults (Wiener *et al.*, 2018). Evidence from randomized controlled trials indicates that the use of antibiotic prophylaxis does not improve outcome (Zegers *et al.*, 2011, 2017).

While analyzing the results of Paper III, we noted that 4/5 children with renal damage had experienced a challenging social situation as well as difficulties in following the recommended treatment and follow-up. This is in line with the experience that the social situation of children with chronic health issues strongly affects the development of the disease and complications. Trying to meet the often extensive needs of a child with spina bifida is challenging for any family. Thus, it is not surprising that families with social challenges may not manage to fulfill recommended treatment and follow-up. Timely performance of CIC probably has a central role in this matter. This finding indicates that society, including health care, should support families of children with special needs and pay special attention to social risk factors.

Treatment of neurogenic bowel dysfunction (Paper IV)

Talking to young people with spinal dysraphism and their parents, we frequently get the impression that they have learnt, and accepted, to handle their bladder, but that the bowel problems make them struggle. As suspected, the use of treatment methods varied among the three tertiary centers taking part in Paper IV particularly regarding the use of ACE and TAI, see Table 14. This might be due to differences in treatment tradition and experiences. It might also relate to single-center studies on TAI and ACE reporting a high degree of success and satisfaction with the methods (Aksnes *et al.*, 2002; Mattsson and Gladh, 2006). Although every child’s needs are unique, these substantial differences in use could not be explained by variation in needs. Rather, tradition and the strategy of clinicians play a major roll, which is unsatisfactory from a patient point of view. Thus, the study was performed to evaluate children’s and parent’s views and experiences of the treatment.

Table 14. Use of methods for bowel evacuation. (Paper IV)

<i>Method for evacuation of the bowel</i>	Total n (%)	Sweden n (%)	Norway n (%)
Ordinary/spontaneous	20 (19%)	10 (16%)	10 (24%)
Rectal micro-enema	4 (4%)	4 (6%)	0 (0%)
Transanal irrigation (TAI)*	50 (47%)	44 (67%)	6 (14%)
Antegrade continence enemas (ACE)	32 (30%)	6 (9%)	26 (62%)

* Peri-Steentm users included (n=4)

It is important to acknowledge that(Rendeli *et al.*, 2006) few randomized controlled trials have been conducted on treatment of bowel dysfunction in this patient group. Indeed, such a study would likely be difficult to conduct (Kelly, 2019). Data comes most often from single-center cohorts, which makes comparison difficult. Lately, data from national patient registries has complemented literature with a broader description of the use of different methods and the presence of symptoms. Wiener *et al* published a study from the US National Spina Bifida Patient Registry with more than 5,000 patients, of whom around 4,000 were children over the age of five (Wiener *et al.*, 2017). Table 15 shows the methods used. Age groups differed, as evidenced by reports that adolescents used ACE significantly more and TAI significantly less than the younger patients. Compared with our study and other European data, the reported use of enemas was less common, but absolute levels are difficult to interpret.

Table 15. Distribution of NBD management techniques among patients with spina bifida aged 5–19 according to age in the National Spina Bifida Patient Registry, 2009–15. Adapted from (Wiener *et al.*, 2017).

Method	Percentage of patients 5–19 years	Commentary
Oral medication	6.4	
Time evacuation	4.2	
Suppositories	5.4	
Digital stimulation	2.6	
Disimpaction (manual)	1.7	
Mini enema	3.9	
Standard enema	3.1	
Cone enema	6.9	2.9 in adolescents
Antegrade enema	19.7	27.2 in adolescents
Colo- and/or ileostomy	2.5	

What do children and parents report

There was a spectrum of experiences in all the treatment groups in Paper IV, but the majority in all groups was either satisfied or very satisfied with the method used. Comparing the respective ACE and TAI groups, children’s satisfaction did not differ, though parents of children using ACE were slightly but significantly more satisfied ($p=0.01$). Satisfaction was not related to age or gender. Both children and parents in the ACE group reported a perception that the child emptied its bowel more completely than was reported in the TAI group. This finding is logical because using ACE (if not left colon location) the entire length of the colon is flushed in the direction of the anus. Scintigraphy studies by Krogh *et al* illustrated the potential of almost total colon cleansing with ACE compared with the left colon cleansing achieved with TAI (Christensen *et al.*, 2002, 2003). This is also in line with the clinical experience and tendency shown in Paper IV that children using ACE enemas performed the evacuation less often than did those using TAI. The frequency of bowel

emptying required to prevent fecal incontinence and constipation is relevant because children with neurogenic bowel dysfunction have to spend a lot of time on the toilet.

In our study, as in others, the most common length of time spent on the toilet for bowel emptying was 45–60 minutes on each occasion in the TAI and ACE groups. This, combined with the need of facilities in the toilet and the risk of fecal incontinence, may explain the finding that almost a third of the families had refrained from activities such as traveling due to the child’s bowel dysfunction.

In a survey of all Danish children with open spinal dysraphism, 46% of children aged 6–18 years reported some or major influence of the bowel function on QoL or social activities. For children aged 2–18 years, 37% of parents reported moderate or severe impact on parent QoL or social activities, see Table 16 (Krogh *et al.*, 2003). An interview study with parents of children using TAI confirms that the treatment can be tolerated by children but places considerable strain on them, their parents, and their daily life and relations (Sanders *et al.*, 2014). All these findings underline the need for substantial support for children with neurogenic bowel dysfunction and their families.

Table 16. Self-reported or parent-reported bowel function, and influence on quality of life and social activities in Danish children with open spinal dysraphism. Adapted from (Krogh *et al.*, 2003).

	Age 6–10 years (n=46)	Age 11–18 years (n=37)
Normal defecation	26%	32%
Digital stimulation or evacuation	17%	24%
Enemas	41%	32%
Need help for defecation	54%	59%
Fecal incontinence at least once a month	59%	38%
Use of diapers due to fecal incontinence	48%	38%
Bowel function has some or major impact on QoL or social activities	46%	46%

Fecal incontinence

In Paper IV, one-third of the parents (n = 35, 34%) reported that their child had no fecal incontinence at all. Leakage about once a month was reported for 47% of the children, and more than once a week for 6%. These levels are almost the same as those reported in a study of Danish children, see Table 15, and probably similar to those in the study from the US National Spina Bifida Patient Registry discussed above, in which 46% of individuals reported fecal incontinence not more than once a month. In our study there was no significant difference in fecal incontinence between the ACE and TAI groups (children p = 0.30, parents p = 0.36).

The high level of satisfaction found in Paper IV concurs with findings in several other studies that have reported a marked reduction in symptoms using invasive treatment, either transanal irrigation (TAI) (Mattsson and Gladh, 2006; Faaborg *et al.*, 2009; Emmanuel, 2010; Velde *et al.*, 2013; Choi *et al.*, 2015; Emmanuel *et al.*, 2016; Ausili *et al.*, 2018; Caramico-Favero, Guedes and Morais, 2018) or antegrade colonic enema (ACE) (Velde *et al.*, 2013; Gor, Katorski and Elliott, 2016; Ambartsumyan and Rodriguez, 2018; Halleran *et al.*, 2019). However, as shown in Paper IV, both methods were found demanding and time-consuming. In one study, a child when asked what was worst in her situation responded “the TAI treatment” (Mattsson and Gladh, 2006) (personal communication), a very dissatisfying response regarding a recommended treatment.

Independence does not come with the method

While effective, TAI is difficult to perform alone. Paper IV shows that only 12% of children using TAI reported that they always went to the toilet on their own to empty their bowel. The proportion was higher (31%) among ACE users, but the difference was not statistically significant ($p=0.06$), and the majority of the children in both groups never went alone (TAI 72%, ACE 63%). The most common answer to “What is good with your method?”, given by ACE users, relates to independence (41%) and increased likelihood of independence on the toilet is probably the most common motive for performing surgery to create a stoma for ACE. The findings in this study, however, indicates that independence does not come with the method. Rather, follow-up, adjustment and support are vital components of any treatment of bowel dysfunction. This is also supported by follow-up studies of ACE users and TAI users, suggesting that a lack of ongoing outpatient follow-up might explain the high cessation rates found (Yardley *et al.*, 2009; King *et al.*, 2017). To support clinicians in follow-up and adjustments, a number of papers have been published, including the paper by Svetanoff with a troubleshooting algorithm for ACE (Svetanoff *et al.*, 2020) and the corresponding guidance for TAI given in the consensus article by Mosiello et al (Mosiello *et al.*, 2017).

In the present study, the vast majority of ACE users had used TAI before. The questionnaire, however, does not ask how long TAI had been used and with what level of support. To the question about difficulties related to the ACE method, children’s replies included “dressing/undressing”, “cleaning my bottom” and “hanging up the water bag”. Asked what was good about the ACE method, one child responded, “more pleasant, I do not have to have my mum touch my bottom”. This child refers to the matter of personal integrity, which likely becomes more important as the child gets older, but which should be considered when dealing with bladder and bowel problems as early as in infancy. Unfortunately, we did not include any questions on this aspect in the questionnaire in Paper IV.

Independence and quality of life

Many studies on self-reported quality of life have shown the impact of fecal incontinence. Szymanski et al showed that the extent of urinary incontinence affects QoL, whereas for fecal incontinence its mere existence significantly lowered QoL (Szymanski *et al.*, 2017). For the children in Paper IV, frequency of fecal incontinence was negatively correlated to satisfaction, as reported by both the children ($p=0.01$) and the parents ($p<0.01$). Interviews with young people with spinal dysraphism indicate that the neurogenic bladder and bowel dysfunction may contribute to making them “outsiders in society” (Fagerskiöld and Glad Mattsson, 2010). A large recent study on the US National Spina Bifida Patient Registry found a significant positive relation between fecal continence and employment rate (Wiener *et al.*, 2017). Urinary continence also enhances social participation and intimate relations (Vu Minh Arnell and Abrahamsson, 2019).

Comparing children using ACE and TAI, no difference in QoL was found, but those children who went to the toilet independently rated QoL higher regardless of bowel emptying method ($p<0.001$). This was true for the whole group of children using ACE or TAI, but also within each group of users. In a recent, comprehensive systematic review of self-management in spina bifida, Sawin et al describes a number of interesting issues (Sawin *et al.*, 2020). They report that the literature clearly shows that individuals with spina bifida have delayed development of self-management and that managing the bladder and bowel is particularly demanding in this respect. Studies found that good self-management related to better health status and more independent living, whereas poorer self-management was related to higher numbers of urinary tract infections and visits to emergency departments (Sawin *et al.*, 2020).

Based on the findings in the review, the authors recommend that health personal facilitate the development of self-management by starting at an early age to assess and address hindering and facilitation factors. They also highlight the importance of neuropsychological testing to assess and describe the strengths and challenges of the specific child. Moreover, the authors describe several promising interventions that enhance self-management. Many of these take place outside a traditional health care setting, in a summer camp, at home or via an app. However, more studies are needed to determine the efficacy of such interventions. Achieving independence on the toilet demands that the child can perform a number of tasks and maintain momentum in the process. It has been shown that cognitive problems, likely related to the presence of hydrocephalus, have a negative impact on these abilities (Steinhart *et al.*, 2018). Specifically, time-processing skills and the ability to focus on what the child is doing on the toilet seem to be critical to achieving independence (Donlau and Falkmer, 2009).

Critical remarks

Apparently, although most children in our study were satisfied or very satisfied with their method, none of the methods enjoyed universal approval. One child using ACE answered the question “What is bad with your method?” with a simple “Everything”. Another child using TAI answered the question “What is good with your method?” with a similar straightforward assessment: “Nothing!”. These critical remarks by the children should remind us of the importance of involving them and their parents in decisions about treatment, discussing pros and cons, and setting expectations right. It is important to remember that information and discussions need to be offered repeatedly during the child’s upbringing as the ability to take part, and the needs and priorities of the child will change with increasing age (Sawin *et al.*, 2020).

Methodological considerations

Research on neurogenic bladder and bowel dysfunction in children with spinal dysraphism mainly consists of single-center reports of series of children receiving a specific treatment. The wide variation in cohorts is likely due to bias related to availability of care. Comparative studies are few, as are randomized controlled trials (RCT). However, RCTs have contributed relevant knowledge about catheter variants (single-use or multi-use) and the use of prophylactic antibiotics. There are obvious difficulties in conducting randomized trials of treatments involving surgery and of neurogenic bowel dysfunction as individual physical and social factors play a central role in treatment and affect the choice of treatment strategy. Papers I and II report on a cohort from our tertiary center in Linköping, Sweden. Considering the organization of the Swedish health care system, it is plausible that the cohort matches the geographical cohort of all children in the southeastern health care region born with open SD. On contrary there are probably children with closed SD not diagnosed perinatally and thus not included in the study.

A reasonable criticism of these studies is that the cohort represents mixed diagnoses, which limits the conclusions we can draw. In Paper II, we use data from the national patient register on Spina Bifida (*MMCUP – The Swedish National MMC Follow-Up Program and Quality of Care Registry*, 2020). Together with the US National Spina Bifida Patient Registry and others, the MMCUP is becoming an increasingly important source of knowledge (Castillo *et al.*, 2019). Though limited by lack of complete coverage, drop-outs and quality of the data in the registers, registries will likely provide the basis for reports like that in Paper III but with much bigger patient cohorts. Paper III is a retrospective study and has limitations related to the size of cohort and the varying follow-up time, which from a lifetime perspective is short. In the future, a larger cohort would be needed to find cut-off pressures for increased risk, and elucidate the contribution of other risk factors, as suggested by Joseph, see Table C (Joseph, 2019), and the creators of the UMPIRE protocol (Routh *et al.*, 2016).

Randomized controlled trials have major advantages in determining the causality and superiority of a treatment or follow-up strategy. Unfortunately, they are difficult to conduct in a rare and complex diagnosis such as spinal dysraphism, in which inter-individual variation is large. To achieve enough power, multicenter, national or even international projects are needed. Another weakness of RCTs is their difficulties in answering multiple research questions. An interesting initiative to handle this problem is the ongoing UMPIRE study using an iterative quality improvement protocol to improve follow-up for children with spinal dysraphism. In the UMPIRE study, a steering committee with representatives from study sites, centers for disease control and prevention (CDC) and study protocol developers are planning to make repeated adjustments to the follow-up protocol using data from interim analyses (Routh *et al.*, 2016).

Using a cross-sectional study like that in Papers I, III and IV has the advantages of allowing large amounts of data to be collected in a short time and without extensive resources. Multiple variables can be analyzed, and the descriptive data achieved can make it possible to reach a

comprehensive understanding of areas such as treatments and symptoms at a specific point in time. However, there is a risk of bias, and conclusions about causality cannot be drawn. As examples from this thesis show, there is a lack of a control group in Paper III, and Paper IV may contain bias concerning the reasons for using a specific method for bowel emptying.

The underlying hypothesis of Paper IV was that regional experience and single-center studies affected the treatment policies at tertiary centers. As this is at least partly dissatisfying from a patient perspective, a questionnaire-based cross-sectional study design was chosen. We wanted to examine the distribution of methods used for bowel evacuation in different regions and ask children and their parents about their experiences. The study design does not allow comparison of the effects of treatment methods as the choice of method was not randomized and could have been affected by several factors that cause bias. Furthermore, the drop-outs and their uneven regional distribution with possible bias problems are significant weaknesses. None the less, the study gives a voice to the young people affected, answers relevant questions and poses new ones about the basis for treatment recommendations made by health professionals. A drop-out analysis might have added valuable information, but we assumed that a lack of response to the questionnaire and a reminder reflected unwillingness or inability to take part. Thus, in line with the Helsinki Declaration ('World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects.', 2013) we did not pursue these individuals or analyze their medical records. This is based on the researcher's responsibility to protect privacy, integrity and the right to self-determination of research persons, and the principle not to do harm. Thus, no drop-out analysis was performed.

Conclusions and clinical implications

Neurogenic bladder-sphincter and bowel dysfunction are the most unpredictable and life-changing consequences of being born with spinal dysraphism. There is a need for non-invasive and low-cost methods to provide information on bladder function in newborns with SD, especially for children with closed SD where the clinical consequences vary greatly and in whom signs, and symptoms may not be obvious. Early determination of post-void residual urine is mandatory in children with spinal dysraphism. Four-hour voiding observation with provocation test (VOP) is a non-invasive standardized method for acquiring this information. It also adds information on voiding pattern, frequency of voids, voiding with a stream, and leakage at provocation. Neonatal VOP may have a predictive value for the need of CIC at one year of age, and later in life, and may prove useful in planning treatment and follow-up of infants with closed spinal dysraphism.

Rates of renal damage in children with SD followed in accordance with the Swedish national follow-up program were found to be low, and high bladder pressures were confirmed as an important risk factor. Renal deterioration remains a threat for individuals with SD, with controversies remaining concerning the optimal and most cost-effective treatment and follow-up strategy. The impact of the child's social situation and specific cognitive problems related to hydrocephalus pose critical challenges for society in relation to individuals with spinal dysraphism and their families. Not acknowledging this may have severe effects on the health and life of affected individuals and may be costly for society. Achieving self-management has many positive consequences. Children with spinal dysraphism have a delayed development of self-management, with specific challenges related to the bladder and bowel. Regarding treatment of bowel dysfunction, it is clear that independence on the toilet does not come with the choice of method, and that there is no single method that suits all. The invasive methods TAI and ACE are effective but time consuming and demanding. Children and parents should be informed in detail about treatment options and be involved in choosing how to proceed. This discussion must be repeated during the child's upbringing and adapted to age and abilities. The study indicates that health care professionals need to provide individualized support and trouble-shooting as well as continuous assessment and cooperation to facilitate independence regardless of the treatment method used.

Future research

- The utility of four-hour voiding observation with provocation test in evaluating newborns with closed spinal dysraphism should be assessed in a study with a greater patient base. Possibly cluster analysis could prove useful in such work. In a longer perspective this may save children from going through unpleasant invasive urodynamic studies, save resources and facilitate qualified evaluation of these children even in a low-resource setting.
- The role of drugs or other minimal invasive methods of increasing sphincter resistance to achieve continence without major urological surgery should be investigated. Hyaluronic acid has been used as a bulking agent in sphincter insufficiency, but results have been disappointing and new alternatives are needed (De Vocht *et al.*, 2010; Pakkasjärvi and Taskinen, 2018). Duloxetine, a drug that is intended to increase the tone of the sphincter, has been tried in adults (Thor, 2003), but has not proved to be clinically useful in children.
- New treatments of neurogenic bowel dysfunction should be developed that combine the efficacy of TAI and ACE with being less demanding, quicker and easier for children to perform independently. Such treatments may involve measures to enhance propulsion and reduce transit time. Using electrical stimulation, it might theoretically be possible to do this with an on/off mode to allow good evacuation and reduce the risk of incontinence. A single pilot study using transcutaneous interferential electrical stimulation on children with spinal dysraphism presented promising results (Kajbafzadeh *et al.*, 2016) as did a study with transrectal electrical stimulation (Palmer, Richards and Kaplan, 1997). However, much more research is needed (Lu and Di Lorenzo, 2016; Southwell, 2020).
- The potential for electrical stimulation as treatment for neurogenic bladder dysfunction should be examined further. Studies with case series on intravesical electrical stimulation to enhance bladder contraction and bladder emptying show promising results (Gladh, Mattsson and Lindstrom, 2003; Hagerty, Richards and Kaplan, 2007). Since there is no alternative active treatment option, a randomized trial should be conducted. In particular, children with relatively good bladder function (presence of micturition reflex) and incomplete spinal injuries could benefit from this treatment.
- New studies using patient registers could be used to relate radiological and urodynamic findings to long-term outcome.
- Interventional studies are needed to support children and adults with spinal dysraphism and hydrocephalus to achieve self-management and social participation despite existing cognitive challenges.
- Long-term evaluation of the effects of prenatal surgery for open spinal dysraphism should be done and are ongoing.
- Studies are needed to find treatment and follow-up programs that can be cost effective and feasible in low-income countries.

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Papers I-IV and appendix

Papers

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*“Men glöm nu inte bort:
Nästan alla har vi ett ben kort
kanske bara någon millimeter eller så,
men det går ju bra ändå...”*

*för vi bor ju faktiskt
alla i en backe,
ja alla i en backe...”*

(Hagelbäck and Hagelbäck, 1997)

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