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Sacral agenesis and neurogenic bladder: long-term outcomes of bladder and kidney function

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Summary

Background—Sacral agenesis (SA) is a rare congenital condition that refers to the absence of part or all of two or more lower sacral vertebral bodies. It can be associated with neurogenic bladder dysfunction that does not necessarily correlate with the level of spinal or skeletal defect. Patients with SA should undergo urodynamic studies (UDS) to guide lower urinary tract (LUT) management.

Objective—This review aimed to update the present institutional experience since 1981 of this rare patient population with detailed, long-term follow-up of bladder and kidney function.

Study Design—A single institution, retrospective, IRB-approved review was performed on patients born after January 1, 1981 with an isolated diagnosis of sacral agenesis without spina bifida, and followed with urologic involvement at Boston Children's Hospital. Records were reviewed for demographics, radiologic imaging, UDS including cystometrogram (CMG) and electromyography (EMG), surgery, and blood chemistries. Comparisons were made between groups of patients based on age at diagnosis, with specific focus on renal function and stability of neurogenic bladder lesion.

Results—Forty-three patients were identified: 23 female and 20 male. Thirty-seven children (86%) had a known age of diagnosis. Nineteen were diagnosed before 2 months old, including five who were diagnosed prenatally, 11 were diagnosed between 2–18 months, and seven were diagnosed after 18 months. All 43 had UDS, with 24 (55.8%) studied at the time of diagnosis. Twenty had serial full UDS, with 30% demonstrating neurourologic instability. None developed end-stage renal disease (ESRD) or required spinal cord detethering.

Discussion—Many children with SA appeared to be diagnosed prenatally or early in life; SA was mostly identified during evaluation of associated anomalies. Though UDS aid in urologic management, testing was not routinely utilized at the time of diagnosis.

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Conclusions—This review of long-term follow-up in SA patients showed stable LUT and renal function, with minimal risk of progression to ESRD.

Summary Table

	Group 1	Group 2	Group 3	Group 4	Adjusted <i>P</i> -value
<i>Age at diagnosis</i>	<2 months	2–18 months	>18 months	unknown	
<i>n</i>	19	11	7	6	
7					
<i>Most recent method of bladder emptying</i>					
Voiding	7 (36.8%)	3 (27.3%)	2 (28.6%)		1.00
CIC	13 (68.4%)*	8 (72.7%)	5 (71.4%)		1.00
<i>No hydronephrosis on recent ultrasound</i>	13 (68.4%)	5 (45.5%)	3 (42.8%)		0.90
<i>Recent serum creatinine (ng/dl)</i>					
Median	0.4	0.4	0.55		0.91
IQR	0.3–0.5	0.4–0.7	0.4–0.8		0.91

* One patient utilized both CIC and voiding to empty

Keywords

Sacral agenesis; Neurogenic bladder; Urodynamics

Introduction

Sacral agenesis (SA) is a rare congenital condition that refers to the absence of part or all of two or more lower sacral vertebral bodies [1,2]. This defect has been attributed to failure of neuralization at day 28 of fetal development. First described by Hohl in 1852, this condition was reported again in 1910 by Joshi and Yadhav when they described total absence of the lumbosacral spine. Since the 1940s, there have been additional cases published [3–9]. Sacral agenesis occurs in approximately 0.1–0.25 per 10,000 pregnancies, with an overall incidence of 0.09–0.43% – there is a strong association with maternal diabetes mellitus (DM) [7]. As SA can present with varying developmental anomalies with associated neurologic, orthopedic and gastrointestinal malformations [3,10,11], it was described by Duhamel, in 1964, as part of the spectrum of sacrococcygeal malformations known as caudal regression syndrome (CRS) [2]. Sacral agenesis may be associated with Currarino triad and homeobox gene abnormalities [12–17].

From a urologic perspective, SA has an association with neurogenic bladder dysfunction (80%) [9–11,18–21]. However, the level of skeletal and spinal bony defect does not necessarily predict the severity or type of lower urinary tract dysfunction [8,18–20,22]. Thus, patients merit formal evaluation, including a neurologic and urodynamic assessment at diagnosis, as such studies guide initial and long-term management [18,23]. Although more recent reports have provided insight with long-term follow-up in SA patients [24–27], little

has been reported regarding the stability, or lack thereof, of the neurogenic component of the lower urinary tract and long-term renal function.

The present review aimed to update the institutional experience of SA since 1981 [18], with emphasis on the long-term outcomes of the neurogenic bladder lesion, renal function and surgical intervention. Unlike previous reports, it was focused on children with SA and without spina bifida or Currarino syndrome.

Materials and Methods

Patients

A single institution, retrospective, IRB-approved chart review was performed on children born after January 1, 1981 who had an isolated diagnosis of SA in the absence of spina bifida, and were followed with urologic involvement at Boston Children's Hospital through October 10, 2014. Current Procedural Terminology (CPT) coding, urodynamic testing, and/or radiologic evaluation at outpatient clinic visits identified the patients included in this analysis. Records were reviewed to obtain information regarding demographics, radiologic imaging, UDS, surgical procedures, serum creatinine and bladder outcome. Patients with SA that were neither referred to the urology clinic nor seen in consultation were excluded; additionally, SA patients without UDS were excluded.

Urodynamic evaluations

Urodynamic evaluations were performed as previously described [28]. Cystometrogram (CMG) was performed via either urethral catheterization or a catheterizable conduit, and electromyography (EMG) was assessed with the use of a concentric needle electrode positioned in the external urethral sphincter muscle. A full urodynamic study (full UDS) refers to the simultaneous performance of both CMG and EMG. An upper motor neuron (UMN) lesion was defined as the presence of detrusor overactivity and detrusor sphincter dyssynergia (DSD), whereas a lower motor neuron (LMN) lesion was defined as detrusor underactivity or areflexia with a denervated external urethral sphincter. Mixed lesions were noted when components of both UMN and LMN lesions were present.

Data collection

Patients were grouped based on age at diagnosis, with the following designations: <2 months of age including prenatal diagnosis (Group 1); 2–18 months of age (Group 2); 18 months of age (Group 3); and unknown (Group 4). Information was collected via retrospective review of records that included demographics, history of DM, presenting symptoms or findings, and associated congenital anomalies. Neurogenic bladder dysfunction was compared longitudinally, based on available UDS. Lower urinary tract management and urological surgeries performed from January 1981 through October 2014 were recorded along with data on renal function (from serum creatinine levels), presence of hydronephrosis on renal ultrasound (RUS), and presence of VUR on VCUG or RNC.

Data analysis

Data were compiled using SPSS Data Collector (IBM, Armonk, NY) and analyzed using packages base and q-value of R statistical software v.3.0.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria, <http://www.R-project.org>) [29]. Descriptive statistics were used to characterize patient cohorts, with comparisons based on age-specific groups at diagnosis, as outlined above. Rates of categorical variables were compared using the Fisher's exact test. Creatinine levels were compared using the Kruskal-Wallis test. Due to the large number of tests performed, adjustment for multiple testing was performed using q-values. Adjusted *P*-values <0.05 were considered statistically significant.

Results

Patient demographics

Based on CPT codes, 119 patients referred to Boston Children's Hospital for SA, and who were born after January 1, 1981 and followed through October 10, 2014, were initially identified. From this group, 14 with cloacal exstrophy, nine with Currarino syndrome, seven with multiple combined cranial-caudal anomalies, and 24 with myelomeningocele were excluded, as these represented different disease entities that had been included for analysis in other databases. Another 22 were excluded as they had no recorded urologic involvement or evaluation. Ultimately, the cohort consisted of 43 patients (Table 1); of these, 23 were female and 20 male. The age at diagnosis was known in 37 of the 43 (86%), and of these, the median age at diagnosis was 1.5 months, with an interquartile range (IQR) of 0.0–14.9. The majority was diagnosed before 18 months of age, with 19 diagnosed prenatally or before 2 months of age (Group 1); 11 in infancy between 2–18 months of age (Group 2); and seven near or after the age of toilet training at >18 months of age (Group 3). These groups were compared. Follow-up ranged from 6 weeks to 26.2 years, with a mean of 9.1 years (median 8.4 years and IQR 1.8–15.2 years). Three individuals had one visit to Boston Children's Hospital for a second opinion, four had two visits, and all remaining patients had more than three visits.

Diabetes mellitus history

The rates of maternal DM, pre-existing or gestational, requiring insulin and the rates of family history of diabetes were compared across groups (Table 2). Although the incidences appeared highest in Group 1, this was not statistically significant.

Symptoms and findings at presentation

At diagnosis, the presenting findings, complaints and symptoms varied between the groups (Table 2). Patients that were diagnosed early (Group 1) appeared to have no specific symptoms, while the children in Group 2 and Group 3 appeared more likely to have UTIs, urinary incontinence or constipation. These differences were not statistically significant.

Associated congenital anomalies

There was a higher incidence of reproductive, cardiovascular and musculoskeletal anomalies in patients in Group 1 (Table 2). If any surgery was required, patients diagnosed in the

neonatal period had a greater likelihood of needing urologic and gastrointestinal, and/or orthopedic surgical procedures, whereas those diagnosed later in life appeared to undergo primarily isolated urologic procedures (Table 2). These differences were not statistically significant.

Neurogenic bladder lesions

All 43 had UDS, with 38 (88%) having a full study to determine the type, if any, of the neurogenic bladder lesion. One boy had an inconclusive EMG, which prevented full characterization of his lesion. The distribution is shown in Fig. 1. The remaining five had a partial study (CMG only) and, thus, the external urethral sphincter function could not be assessed. Twenty of these 38 had serial full UDS, with the mean interval between studies of 50.2 months (range 6.2–166.4 months). Twelve of these 20 (60%) had a stable lesion type; of the remaining eight, two had incomplete EMG assessments, which prevented comparison. Six had changes in their lesion, as noted: no deficit to UMN (two), UMN to no deficit (two), and mixed to LMN (two). Thus, 30% demonstrated a changing neurourologic lesion.

Management of lower urinary tract function and outcome

The initial management of bladder emptying was compared across all groups (Table 3). The majority of the patients diagnosed before 2 months of age (Group 1) were managed initially without specific intervention; this observational strategy was observed to be higher than in other groups, but not statistically significant. Children in Groups 2 and 3 were more likely to be managed with a variety of modalities, including: CIC, anti-cholinergic medications and surgery. At the time of the most recent follow-up, the method of bladder emptying was assessed (Table 3). In every group, the majority of the patients required CIC, which was performed mostly via the urethra. There was a similar incidence of volitional voiding across all three groups. No statistically significant between-group differences were found.

Urological procedures for maintenance of bladder function

The incidence of urologic procedures for preservation of bladder function was also compared among the groups (Table 3). In each group, one patient underwent vesicostomy creation prior to establishing care at the present institution; information regarding indication(s) for these procedures was not available. The incidence of ureteral reimplantation was greatest in Group 2 (72.7%), while Group 3 had the highest percentage undergoing bladder augmentation (57.1%) and continent catheterizable stoma creation (42.9%). Bladder neck procedures appeared to be more prevalent in Group 3 (42.9%). However, none of these between-group differences were statistically significant.

Upper urinary tract outcome and renal function

Surrogates for renal function included: a lack of hydronephrosis on RUS, absence of VUR, serum creatinine levels, and need for renal replacement therapy (Table 3). Based on the most recently available RUS, the majority of patients in all groups had normal upper urinary tracts. The majority of patients in all groups also had no VUR, but when VUR was present, it was highest in Group 2 (27.3%) and tended to be bilateral. The incidence appeared lower

in Groups 1 and 3, and was more often unilateral. None of these differences were statistically significant.

The average serum creatinine at the most recent assessment was 0.48 mg/dl in Group 1 (range 0.2–1.2), 0.51 mg/dl in Group 2 (range 0.3–0.9), and 0.7 mg/dl in Group 3 (range 0.3–1.6) during the period of follow-up. No finding differed significantly between the three groups. No patient developed end stage renal disease (ESRD) or required renal replacement therapy, and no patient underwent spinal cord detethering.

Discussion

This updated institutional review demonstrated that the majority of individuals are diagnosed early in life, which is facilitated in part by comprehensive prenatal care and imaging – either prenatally or in the immediate postnatal period. Previously, a correlation with a maternal history of DM (gestational or otherwise) has been confirmed, and others have reported [18,30]; however, the majority of patients in the present study were born to mothers who had no diabetic history. Nevertheless, it appears that prenatal care and planning can be helpful for initiating early evaluation.

Despite earlier diagnosis of many patients with SA, a significant proportion is detected later in childhood – near or after the time of expected toilet training. This may be related to subtle physical signs noted only on a careful history and/or physical examination, including, in some, delays in toilet training. In the present study, the majority of patients in Groups 1 and 2 tended to have other associated anomalies facilitating early diagnosis. Regardless of age or symptoms at diagnosis, all individuals with SA warrant thorough evaluation and diligent surveillance.

Urodynamic testing is a key component to the evaluation and identification of the neurogenic bladder lesion associated with SA. These studies can comprehensively assess lower urinary tract function or dysfunction, and in these instances provide insight and help guide management toward maintaining low-pressure safe storage bladders with adequate compliance to preserve the upper urinary tract. For example, this data may help determine if a patient's current bladder management is appropriate. This information can guide treatment – whether to adjust medical management or prompt consideration for surgical intervention. The present institutional experience has been limited by the amount of available serial UDS, due to deferred or missing documentation, and varied practice patterns among healthcare teams. For patients diagnosed with SA at the present institution, UDS is performed to establish a baseline and then at intervals based on changes in clinical picture.

Based on the timeframe of documented follow-up for each patient, the present data suggest that, in contrast to children with myelomeningocele, the majority of SA patients have stable lower urinary tract innervation. A small percentage does demonstrate a neurologic change in lower urinary tract function, with no clear explanation of why this occurred. The pathophysiology of these changes can only be speculated, given the relative rarity of this condition and availability of studies for patients evaluated.

A limitation of the present study revolved around the availability of urodynamic studies, as many patients were referred or transferred their care to the present institution. Urodynamic studies may not have been similarly performed, or these records were unavailable for review. Nonetheless, when combined with imaging modalities and careful surveillance of clinical symptoms, subsequent urodynamic studies provided information to characterize the extent of genitourinary involvement of SA and the severity of dysfunction. These studies guide management towards optimal outcomes to achieve efficient bladder emptying and to determine the need for further intervention(s).

When followed and managed closely after the age of toilet training, the majority of patients demonstrated a need for assistance in bladder emptying with CIC. When the urinary tract is closely monitored, such patients are less likely to develop hydronephrosis or VUR, suggesting that surveillance is important – not just to document stability but also to prevent deterioration with maturity and to initiate appropriate surgical intervention, when necessary. Careful surveillance of the upper urinary tract may trigger the need for ureteral reimplantation for VUR, as a consequence of high bladder pressures, particularly in patients with an UMN lesion. To maintain low bladder filling pressure and adequate storage volumes over a lifetime, these individuals may need to undergo lower urinary tract surgery such as augmentation cystoplasty and/or a bladder neck continence procedure. As the need for vesicostomy appeared to increase with advancing age at diagnosis, these patients may have demonstrated more concerning presentations of abnormal lower urinary tract function, such as urinary retention, severe hydronephrosis, or high-grade VUR, which necessitated urinary diversion. The need for such procedures would support the goal of preserving overall renal function, as no one in the present study developed ESRD or a need for renal replacement therapy.

Although the present study identified a significant number of patients with SA and neurogenic bladder dysfunction, it was limited by its retrospective nature, reliance on available medical records and referral to urology. As a tertiary referral center, some patients were concurrently managed at other centers, which complicated data retrieval. Regarding long-term renal function, these patients were studied over a relatively short interval, and further follow-up as these patients enter adulthood would be necessary to assess for long-term ESRD incidence.

Conclusions

Patients with SA and neurogenic bladder dysfunction merit long-term follow-up to recognize their initial needs and anticipate specific changes as they transition from infancy into childhood and adulthood. It is recommended that annual or biennial UDS be performed in longitudinal surveillance, with emphasis on the need to pursue additional testing if there is a change in clinical symptoms or radiological findings. Specific protocols, including urodynamic evaluation, imaging and laboratory work-up, should be included during serial follow-up. Consequently, when managed appropriately, patients demonstrate stable neurourologic function. As they mature, renal function appears preserved, although surgery is often needed to maintain continence, appropriate lower urinary tract function, and upper urinary tract health.

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Fig. 1. Neurogenic bladder lesion by urodynamic evaluation

All 43 had at least one urodynamic study, either full or partial. Of the 38 patients with full UDS studies, the type of lower urinary tract function could be characterized (UMN = upper motor neuron; LMN = lower motor neuron; Mixed = a combination of UMN + LMN lesions).

- 20 of 43 patients had available subsequent full UDS evaluations
 - 12/20 (60%) demonstrated stable neurourologic status
 - 6/20 (30%) revealed a significant change in neurourologic status
 - 2/20 (10%) had indeterminate findings on serial studies

Table 1

Patient demographics

	Group 1	Group 2	Group 3	Group 4	Adjusted <i>P</i> -value
<i>Age at diagnosis</i>	<2 months	2–18 months	>18 months	unknown	
<i>n</i>	19	11	7	6	
<i>Gender</i>					
male	10 (52.6%)	3 (27.3%)	3 (42.9%)	4 (66.7%)	0.91*
female	9 (47.4%)	8 (72.7%)	4 (57.1%)	2 (33.3%)	

* Compared only groups with known age

Table 2

Associated conditions and procedures by age at diagnosis

	Group 1	Group 2	Group 3	Adjusted <i>P</i> -value
<i>n</i>	19	11	7	
Diabetes history				
Maternal diabetes	8 (42.1%)	4 (36.4%)	2 (28.6%)	0.98
Family history of diabetes	4 (21.1%)	2 (18.2%)	0	1.00
Symptoms and findings at presentation and diagnosis[*]				
Recurrent UTI	2 (10.5%)	4 (36.4%)	3 (42.9%)	0.63
Febrile UTI	3 (15.8%)	5 (45.5%)	3 (42.9%)	0.67
Reflux	0	2 (18.2%)	1 (14.3%)	0.63
Retention	0	0	0	N/A
Urinary incontinence	2 (10.5%)	3 (27.3%)	3 (42.9%)	0.65
Frequency/urgency	0	1 (9.1%)	1 (14.3%)	0.75
Constipation	2 (10.5%)	5 (45.5%)	2 (28.6%)	0.63
Fecal incontinence	0	1 (9.1%)	0	0.91
No symptoms	12 (63.2%)	2 (18.2%)	0	0.10
Unknown	2 (10.5%)	2 (18.2%)	1 (14.3%)	1.00
Associated congenital anomalies^{**}				
ENT	3 (15.8%)	1 (9.1%)	1 (14.3%)	1.00
Eye	1 (5.3%)	0	1 (14.3%)	0.91
Pulmonary	2 (10.5%)	1 (9.1%)	0	1.00
Hematologic	0	0	0	N/A
Cardiovascular	5 (26.3%)	1 (9.1%)	0	0.77
Gastrointestinal	13 (68.4%)	9 (81.8%)	3 (42.9%)	0.75
Hepatobiliary	1 (5.3%)	0	0	1.00
Musculoskeletal	13 (68.4%)	4 (36.4%)	2 (28.6%)	0.63
Metabolic/endocrine	1 (5.3%)	0	0	1.00
CNS	6 (31.6%)	1 (9.1%)	3 (42.9%)	0.75
Skin	1 (5.3%)	0	0	1.00
Neoplasia	0	1 (9.1%)	0	0.91
Surgical procedures for congenital gastrointestinal, orthopedic, and urology anomalies				
Urologic	0	4 (36.4%)	4 (57.1%)	0.06
Gastrointestinal	1 (5.3%)	0	0	1.00
Orthopedic	0	1 (9.1%)	0	0.91
Urologic and gastrointestinal	4 (21.1%)	4 (36.4%)	2 (28.6%)	0.98
Urologic and orthopedic	4 (21.1%)	1 (9.1%)	1 (14.3%)	1.00
Gastrointestinal and orthopedic	0	0	0	N/A

	Group 1	Group 2	Group 3	Adjusted <i>P</i> -value
Urologic, Gastrointestinal, and Orthopedic	8 (42.1%)	1 (9.1%)	0	0.59
No surgical procedures recorded	2 (10.5%)	0	0	0.98

* Presenting symptoms of patients, with many patients having more than one symptom.

** Incidence of concurrent congenital anomalies by organ system. Patients may have more than 1 system involved.

Table 3

Bladder emptying and maintenance of bladder outcome initial management of bladder emptying

	Group 1	Group 2	Group 3	Adjusted <i>P</i> -value
<i>n</i>	19	11	7	
Initial management of bladder emptying *				
CIC	4 (21.1%)	4 (36.4%)	2 (28.6%)	0.98
Anti-cholinergic	3 (15.8%)	5 (45.5%)	2 (28.6%)	0.75
Alpha-blocker	0	0	0	N/A
Surgery	2 (10.5%)	0	1 (14.3%)	0.98
Other	0	1 (9.1%)	0	0.91
None	12 (63.2%)	4 (36.4%)	1 (14.3%)	0.63
Most recent method of bladder emptying **				
Voiding	7 (36.8%)	3 (27.3%)	2 (28.6%)	1.00
CIC	13 (68.4%) **	8 (72.7%)	5 (71.4%)	1.00
<i>via urethra</i>	9 (47.4%)	7 (63.6%)	3 (42.9%)	0.98
<i>via continent cutaneous stoma</i>	3 (15.8%)	1 (9.1%)	2 (28.6%)	0.98
<i>route unknown</i>	1 (5.3%)	0	0	1.00
Incidence of urologic procedures for maintenance of bladder outcome ***				
Number of patients with procedures	13	9	7	
Vesicostomy	1 (5.3%)	1 (9.1%)	1 (14.3%)	1.00
Ureteral reimplant	7 (36.8%)	8 (72.7%)	2 (28.6%)	0.63
Bladder augmentation	5 (26.3%)	1 (9.1%)	4 (57.1%)	0.63
Continent catheterizable stoma	3 (15.8%)	1 (9.1%)	3 (42.9%)	0.75
Bladder outlet (sling, reconstruction, AUS)	6 (31.6%)	2 (18.2%)	3 (42.9%)	0.91
Recent assessment of upper urinary tract and level of renal function				
Last reported renal ultrasound				
No hydronephrosis	13 (68.4%)	5 (45.5%)	3 (42.8%)	0.90
Unilateral hydronephrosis	4 (21.1%)	4 (36.4%)	1 (14.3%)	0.98
Bilateral hydronephrosis	2 (10.5%)	1 (9.1%)	2 (28.6%)	0.91
Unknown	0	1 (9.1%)	1 (14.3%)	0.75
Last VCUG or RNC				
No reflux	15 (78.9%)	8 (72.7%)	6 (85.7%)	1.00
Unilateral reflux	3 (15.8%)	0	1 (14.3%)	0.91
Bilateral reflux	0	3 (27.3%)	0	0.58
Unknown	1 (5.3%)	0	0	1.00
Reflux Grade (range)	1–2	1–5	2	

	Group 1	Group 2	Group 3	Adjusted <i>P</i> -value
Recent Serum creatinine (ng/dl)				
Median	0.4	0.4	0.55	0.91
IQR	0.3–0.5	0.4–0.7	0.4–0.8	0.91

* Patients may be managed by more than one treatment approach

** One patient utilized voiding and CIC

*** Patients may have undergone more than one surgical procedure