Original Article

# Symptomatic lower urinary tract dysfunction in sacral agenesis: Potentially high risk?

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## ABSTRACT

**Introduction:** Sacral agenesis (SA) is a caudal regression anomaly that can cause neurogenic bladder but is not generally recognized as high risk. We studied the clinical presentation, upper urinary tract, bone and spine abnormalities, and urodynamic findings in patients with SA and compared them with related high-risk conditions, anorectal malformation (ARM), and cloacal malformation.

**Materials and Methods:** Patient records between May 2011 and December 2015 were identified and grouped into isolated SA without an overt anomaly (Group I), SA with overt caudal regression anomalies (Group II), and ARM or cloacal malformation without the SA (Group III). Distribution of clinical and urodynamic findings and factors associated with reduced eGFR were tested with rank sum test, *t*-test, and unadjusted odds ($P < 0.05$ significant) using R statistical program (version 3.1.3).

**Results:** Of 605 neurogenic bladder patients treated in the study period, 39 fulfilled the inclusion criteria. 12 were Group I, 5 Group II, and 22 Group III. Long-standing lower urinary symptoms were noted in all SA patients. Group I patients were older (14.5 years vs. 6 years and 5 years for II and III). Patients with SA (Group I and II) had poor compliance (6.7 ml/cm$H_2O$, interquartile range [IQR] 4–13.6 ml/cm$H_2O$), reduced age-adjusted bladder capacity (59%, IQR 22–85%), elevated end-fill pressure (22 cm$H_2O$, IQR 11–28 cm$H_2O$), hydronephrosis (88%), and reduction in eGFR (29%), all comparable to Group III. Most had Renshaw type II SA and tethered spinal cord rather than wedge-shaped termination. Limitations include small numbers and significant selection bias.

**Conclusions:** Symptomatic neurogenic bladder due to SA may cause renal damage similar to ARM but often eludes diagnosis.

## INTRODUCTION

Sacral agenesis (SA) is an unusual condition defined by the absence of part of all of at least two of the last sacral vertebrae affecting about 1 in 100,000 children.[1,2] The condition most often occurs as a part of a constellation of birth abnormalities affecting the lower limbs, bowel, genitourinary tract and caudal spine together termed "caudal regression syndrome."[3] Anomalies of the respiratory system, heart and neural tube as well as association with VATER or OIES syndrome have been noted.[4-7] The exact incidence of isolated SA is not known. In a study of 998 consecutive magnetic resonance imaging (MRI) scans for low backache from Portugal, SA was noted in 0.2% of patients.[8]

Abnormal development of the caudal cell mass is responsible for occurrence of SA.[7] Genetic abnormalities noted include terminal deletion 7q chromosome[9] and T gene (brachyury gene) at 6q27.[10] HLXB9 homeobox gene has been identified in some patients with sacral bony anomalies, anorectal malformation (ARM), and a presacral mass termed the Currarino Syndrome.[4,11] There is a strong association with maternal diabetes.[12] SA is potentially identifiable on an antenatal ultrasonogram. The S1 and S2 ossification nuclei can be seen at 15 and 17 weeks

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gestation and should be specifically recorded in diabetic mothers.[13]

SA is associated with lower urinary tract dysfunction (LUTD).[1] However, clinical guidelines on neurogenic bladder[14,15] and urodynamics (UDS)[16] do not identify this as a high-risk diagnosis. This article analyzes the clinical presentation, urodynamic findings, and upper urinary tract changes in patients with SA and compares them with a related but established high-risk birth abnormality, ARM, and cloacal malformation.

## MATERIALS AND METHODS

This is a retrospective analysis of all patients during the period May 2011 to December 2015 performed at a tertiary care hospital. Patients with symptomatic isolated SA (Group I), those having SA along with other obvious anomalies of caudal regression syndrome (Group II), and those with ARM or cloaca without SA (Group III) were analyzed and compared. Institutional ethics committee approval was taken (JBH-127/10-15).

Clinical data were retrieved from the outpatient file and UDS report. The Renshaw classification was used for classifying bony anomalies.[17] Briefly, Type I are those with unilateral partial or complete agenesis, Type II partial bilaterally symmetrical agenesis, Type III total SA with or without lumbar agenesis with the iliacs articulating with the last vertebra, and Type IV refers to total agenesis with the vertebral endplate resting on either fused iliacs or an iliac amphiarthrosis.

Urodynamic parameters were defined as per the International Continence Society terminology.[18] Bladder capacity was expressed as a percentage of expected bladder capacity (EBC) for age. For children under 12 years, EBC was estimated by the Koff formula.[19] All patients over 12 years were designated as having EBC of 390 ml (EBC at 12 years). A capacity estimate of <75% of expected capacity was classified "reduced". This would imply that an adult with 300 ml capacity would be classified as the lower limit of normal (76% of 390 ml).

Compliance was calculated using data points as the final pressure at capacity and the pressure at the start of filling. Compliance <12.5 ml/cm$H_2O$ was classified as "reduced."[20] All patients with a compliance of over 30 ml/cm$H_2O$ were assigned this same value for analysis.

Patients without detrusor overactivity during storage and having underactivity or acontractility during voiding were classified as lower motor neuron (LMN) type of LUTD. Those with detrusor overactivity during storage and detrusor sphincter dyssynergia during voiding were classified as upper motor neuron type (UMN) while those with a combination of these findings were classified as mixed LUTD.[1] Patients with UMN or mixed UMN-LMN lesions were clubbed together for analysis of impact on upper tracts.

Patients with unilateral or bilateral hydroureteronephrosis on ultrasonography were classified as having secondary upper tract damage. Micturating cystourethrogram and MRI imaging data were documented for those in whom these were available. Online calculators of the National Kidney Foundation were used to calculate eGFR.[21] An eGFR <75 ml/min/1.73 $m^2$ was classified as "reduced."

## RESULTS

A total of 4291 UDS were performed over the study period of which 1,180 were for neurogenic bladder representing 605 unique patients (those with a well-defined neurological lesion). Seventeen (2.8%) of these 605 patients had SA. Of these, 12 (2.0%) had isolated SA without obvious features of caudal regression. Of the remaining five, 3 had ARM, 1 had cloacal malformation, and 1 had associated severe hypoplasia of the lower extremities and pelvis. During the same period, 20 patients of ARM and 2 with cloacal malformation without SA underwent UDS testing, yielding a total of 23 (3.8% of 605 patients) with ARM and 3 (0.5%) with cloaca in the study period.

Lower urinary tract symptoms were noted in all 17 patients with SA. Symptoms noted were urinary frequency (17, 100%), urinary incontinence (14, 82%), constipation (14, 82%), voiding difficulty (11, 65%), fecal incontinence (8, 47%), orthopedic deformity (8, 47%), neurological symptoms (8, 47%), recurrent urinary infection (3, 18%), and uremic symptoms (1, 6%). Five of the 12 patients with isolated sacral anomaly and two with associated caudal anomalies had a shortened gluteal cleft with flattening. One had hypoplasia of the pelvis and lower limbs. One had an incidental horseshoe kidney.

On UDS, patients with SA (Group I and II combined) showed poor compliance (Median 6.7 ml/cm$H_2O$, IQR 4.0–13.6 ml/cm$H_2O$) with 71% of the 17 patients demonstrating reduced compliance of <12.5 ml/cm$H_2O$ [Table 1]. In these patients, the median end-fill pressure was comparable (22 cm$H_2O$ vs. 21 cm$H_2O$), age-adjusted bladder capacity was lesser (59%, IQR 22%–85% vs. 80%, IQR 56-100%), and hydronephrosis (on ultrasonography) was numerically but not statistically more common (88% vs. 55%, $P = 0.056$) as compared to Group III. Thirteen of these were bilateral and 5 of these patients had reduced kidney function with eGFR ranging from 25 to 68 ml/min/1.73 $m^2$. Micturating cystourethrogram was available for eleven of the 17 patients with SA. Secondary reflux was noted in 9 of these 11 patients (three bilateral). The type of LUTD was noted to be UMN, LMN, and mixed in 5, 3, and 1 in Group I; 2, 3, and 0 in Group II; and 8, 12, and 2 in Group III.

**Table 1: Comparison of isolated sacral agenesis (Group I), sacral agenesis with overt caudal regression anomalies (Group II) and anorectal or cloacal anomaly without sacral agenesis (Group III)**

| Parameter | Group I SA alone | Group II SA with overt anomalies | Group III ARM or Cloaca alone | Group I versus II versus III (*P*) | Group I + II (all forms of SA) | Group I + II versus III (*P*) | Group II + III (all with overt abnormalities) | Group I versus II + III (*P*) |
|---|---|---|---|---|---|---|---|---|
| Number | 12 | 5 | 22 | | 17 | | 27 | |
| Age (year), median (IQR) | 14.5 (7.8-21.0) | 6.0 (4.5-21.0) | 5.0 (3.0-12.8) | 0.063 | 10.0 (6.0-21.0) | 0.022 | 5.0 (3.5-13.0) | 0.038 |
| Compliance (ml/cm$H_2O$), median (IQR) | 9.0 (4.3-14.6) | 5.4 (1.9-11.5) | 4.7 (3.1-30.0) | 0.678 | 6.7 (4.0-13.6) | 0.977 | 5.0 (2.8-22.5) | 0.551 |
| Compliance reduced <12.5ml/cm$H_2O$ (%) | 8.12 (75) | 4.5 (80) | 14.22 (64) | 0.782 | 12.17 (71) | 0.909 | 12.27 (44) | 1.000 |
| DO (%) | 6.12 (50) | 2.5 (40) | 3.22 (14) | 0.580 | 8.17 (47) | 0.523 | 9.27 (33) | 0.528 |
| EFP (cm$H_2O$), median (IQR) | 19.0 (10.5-28.3) | 26.0 (21.0-26.0) | 19.0 (7.3-41.8) | 0.894 | 22.0 (11.0-28.0) | 0.712 | 21.0 (7.5-40.5) | 0.637 |
| Capacity reduced <75% of EBC for age (%) | 6.12 (50) | 3.5 (60) | 9.22 (41) | 0.704 | 9.17 (53) | 0.672 | 12.27 (44) | 1.000 |
| Capacity (fraction of expected), median (IQR) | 0.68 (0.30-0.85) | 0.40 (0.14-0.77) | 0.80 (0.56-1.00) | 0.102 | 0.59 (0.220.85) | 0.045 | 0.77 (0.43-1.00) | 0.229 |
| BOO (%) | 4.12 (33) | 2.5 (40) | 7.22 (32) | Distribution of voiding function | 6.17 (35) | Distribution of voiding function | 9.27 (33) | Distribution of voiding function |
| Acontractility or underactivity (%) | 7.12 (58) | 3.5 (60) | 14.22 (64) | | 10.17 (59) | | 17.27 (63) | |
| Normal voiding (%) | 1.12 (8) | 0.5 (0) | 1.22 (5) | (0.960) | 1.17 (6) | (0.949) | 1.27 (4) | (0.829) |
| UMN or mixed LUTD (%) | 8.12 (67) | 2.5 (40) | 10.22 (46) | 0.429 | 10.17 (59) | 0.613 | 12.27 (44) | 0.350 |
| HN (%) | 10.12 (83) | 5.5 (100) | 12.22 (55) | 0.062 | 15.17 (88) | 0.056 | 17.27 (63) | 0.370 |
| Reduced eGFR <75 ml/min per 1.73 $m^2$ (%) | 4.12 (33) | 1.5 (20) | 4.22 (18) | 0.596 | 5.17 (29) | 0.681 | 5.27 (19) | 0.311 |

SA=Sacral agenesis, ARM=Anorectal malformation, IQR=Interquartile range, DO=Detrusor overactivity, BOO=Bladder outlet obstruction, EFP=End-fill pressure, UMN=Upper motor neuron, LUTD=Lower urinary tract dysfunction, HN=Hydronephrosis, GFR=Glomerular filtration rate

Trends suggested that Group I patients (isolated SA) were older than Group II and III (14.5, 6, and 5 years, $P = 0.063$). However, there was no association between the age at presentation and the presence of poor compliance, reduced capacity, detrusor overactivity, presence of UMN-mixed LUTD, or reduced eGFR in patients with SA (Group I and II).

Of the 17 patients with SA, the bony abnormality noted was Renshaw Type I, II, III, and IV in 2, 13, 1, and 1 patient, respectively [Figures 1-3]. eGFR was reduced in five patients (one type I and four type II patients). MR imaging findings were available in 11 patients. Important findings noted were tethered cord (7), terminal intradural lipoma (5), syrinx (5), wedge-shaped termination of cord (3), skip bony vertebral lesions (3), and a normal MRI (1). In patients with a wedge-shaped termination, the cord was noted to end higher than usual at the T12 vertebral level. In all patients with a terminal midline lipoma, the cord was tethered and low lying. A thickened and split filum terminale was responsible for the tethering in one patient. eGFR was reduced in two patients each with a tethered cord and club-shaped termination. There was no difference in the distribution of hydronephrosis between the different types of spinal abnormality groups (tethered cord, wedge-shaped termination, or normal).

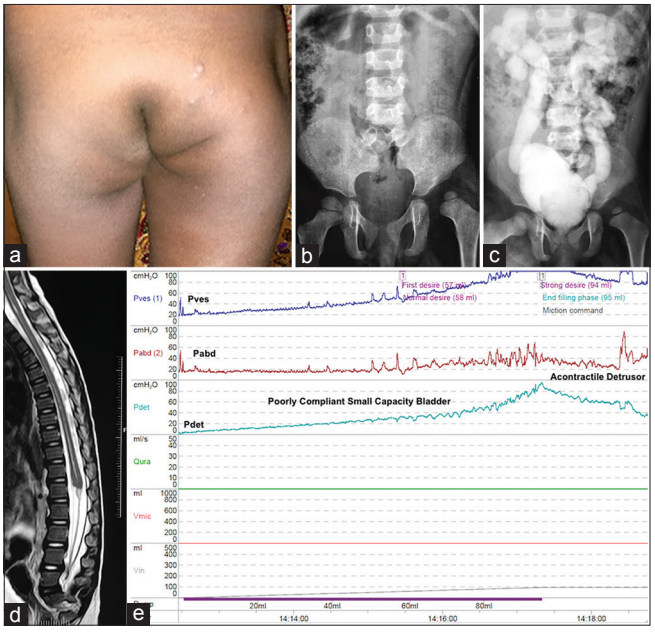


**Figure 1:** Isolated sacral agenesis (Renshaw type III) in a 4-year-girl. (a) Clinical photograph of the back showing short, flat gluteal cleft. (b) Plain X-ray showing absent sacrum with articulation of L5 with the iliac bones. (c) Micturating cystourethrogram showing grossly altered bladder morphology and bilateral secondary reflux. (d) magnetic resonance imaging spine T2 image showing wedge-shaped high termination at T12 level. (e) Urodynamics showing poorly compliant bladder with unsafe end-fill pressure

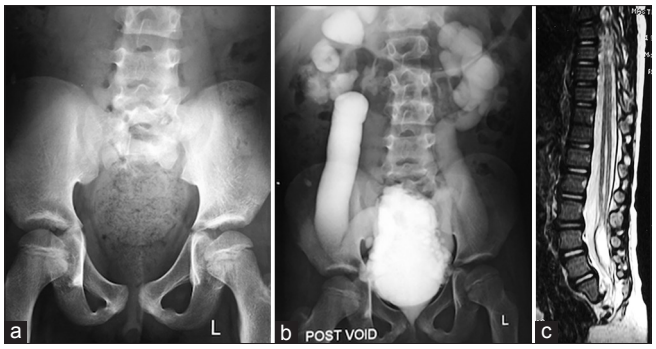


**Figure 2:** (a) Isolated sacral agenesis (Renshaw type II) in a 19-year-male with bilateral hydronephrosis, chronic kidney disease (serum creatinine 3.2 mg/dl). Urodynamics showing reduced compliance and dyssynergic sphincter. Plain X-ray showing absent S3-5 sacral segments and malformed S2. (b) Micturating cystourethrogram showing altered bladder morphology, multiple diverticuli and bilateral gross secondary vesicoureteral reflux. (c) Magnetic resonance imaging spine showing tethered spinal cord at L3, thickened filum, large terminal lipoma, syrinx from T12-L2 and the bony defect

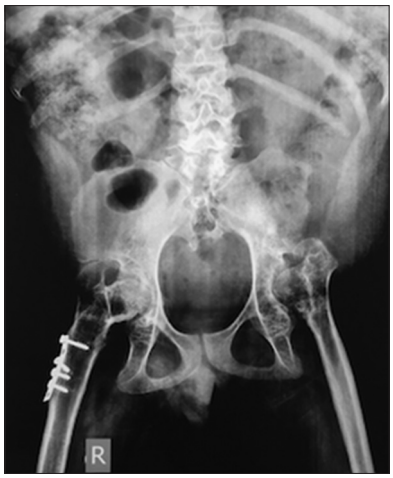


**Figure 3:** Sacral agenesis (Renshaw type IV) with hypoplastic lower limbs and pelvis in a 21-year-old male with bilateral hydronephrosis, normal renal function, and a poorly compliant bladder with acontractility on urodynamics. Plain X-ray showing lower limb and pelvic deformities and Iliac amphiarthrosis with complete absence of lower lumbar and sacral verterbrae

The unadjusted odds of reduced eGFR was calculated for age, sex, voiding symptoms, reduced compliance, end-fill pressure, detrusor overactivity, reduced capacity, Renshaw III-IV, and the presence of UMN-mixed LUTD. Only reduced capacity was associated with lower odds of reduced eGFR with a 5% reduction in the unadjusted odds for every percentage increase in age-adjusted bladder capacity ($P = 0.04$).

## DISCUSSION

SA is an uncommon cause of neurogenic bladder. The prevalence in our unit at 2.8% was more than the 1% described in literature.[22] Back stigmata are not always present (2/5$^{th}$ of our patients) and the findings of gluteal flattening or cleft shortening may be missed at a cursory examination. There is no recommendation regarding screening for isolated SA. However, all children with unexplained lower tract dysfunction should have an imaging of the spine along with a lateral film[23] and micturating cystourethrograms must always include an initial plain film. SA was missed in one patient referred with a micturating cystourethrogram without a plain film.

We chose to compare our patients of SA with those suffering from ARM and cloacal malformation with lower urinary tract symptoms, a related group of abnormalities of caudal fetal development that occur both in association with SA as well as in isolation. Recognized as a form of neurogenic bladder at high risk for renal functional deterioration, it offers a yardstick to assess the potential severity of unrecognized neurogenic bladder owing to SA.[14]

Four of the 27 (15%) patients with ARM or cloacal anomalies referred to the department had SA. An earlier series noted 35% prevalence of sacral abnormalities in children with imperforate anus.[24] A plain radiographic examination of the sacral spine is standard recommendation in children with ARM[24] and can help identify children for spinal MR imaging.

Most patients with SA had abnormality of bladder storage and combined with the late presentation resulted in a high prevalence of hydronephrosis. There was a high prevalence of secondary reflux in these patients (9 of 11 children out of the 17 with SA, for whom a micturating cystourethrogram was available). Secondary reflux might have caused underestimation of the pressures and the actual compliance might have been worse than observed. Voiding phase abnormality was noted in a majority of children with detrusor muscle weakness the commonest cause. Given these facts, antimuscarinics with clean intermittent catheterization is likely to be the mainstay of care. Similar to children with spinal dysraphism and ARM, follow-up UDS is likely to be crucial for the evaluation of response and identification of nonresponders for escalation of treatment. For those with refractory storage pressures, the high prevalence of poor compliance could be a potential marker for a less than optimal response to salvage intravesical onabotulinum toxin A injections.[25]

The authors recognize that there are no well-defined cutoff values for defining low compliance. The International Continence Society[18] and the International Children's Continence Society documents[22] do not provide specific cutoff values. Nevertheless, low compliance is a critical factor widely recognized as dangerous for the upper tracts and the term is freely used in literature and textbooks.[22] Contemporary studies have defined "low compliance" variously as <10 ml/cm$H_2O$,[26] <12.5 ml/cm$H_2O$,[20,27] or <20 ml/cm$H_2O$.[28] Others have stated the actual values noted without defining "low compliance."[29] We chose to provide both the actual data as well as a defined numerical value for "low compliance."

A bimodal age distribution has been described with most children identified in infancy and the remainder by age five.[23] There was considerable delay in diagnosis of all our patients especially those with isolated SA. This has also been documented earlier.[2,30] However, the impact of this delay on upper tract damage was unclear. Patients had similar UDS findings and upper tract changes regardless of age. Although 83% of our patients showed hydroureteronephrosis at presentation, the presence of SA seemed to be a more important factor rather than lack of a visible identifying marker. 15/17 (88%) of those with SA had hydroureteronephrosis as compared to 17/27 (55%) of those without the abnormality ($P = 0.056$). There was a high prevalence of upper tract changes in all the groups studied. Unsurprisingly, end-fill pressures showed a significant association with hydronephrosis in patients with SA.

Numbers were too small to comment upon any association between the severity of urinary tract dysfunction and that of the SA. However, the presence of significant upper tract changes in a majority of our patients with Renshaw types I and II and the reduction in eGFR in half of these patients lends credence to the view that severity of the bony abnormality cannot predict urodynamic severity or safety.[1,31]

Most patients with SA were noted to have abnormal spinal MRI. Wedge-shaped high termination of the conus at T12 has been described as a consistent finding.[23] However, this classical finding was noted in only about one-fourth of our patients. Tethered cord was the commonest anomaly noted in two-third of our patients often with an associated terminal lipoma. Others have noted similar findings.[32] Prophylactic surgical intervention for tethered cord has been reported in a setting of sacral spine anomalies and may be beneficial if an early diagnosis can be made.[32] A correlation has been described between the extent of anomalies in the vertebral column and those in the spinal cord.[33] The type of spinal cord abnormality on MRI did not seem to predict the possibility of upper tract damage in our patients.

There was a high overall prevalence of upper tract changes in our series of patients with caudal anomalies. The median age at first UDS evaluation was 5 years even in the children with ARM and cloacal anomalies, a group widely recognized as being at high risk of urinary tract damage.[14] Early institution of urinary tract management in children with neurogenic bladder has been shown to improve outcomes.[34] Hence, it is conceivable that had the children with obvious high-risk anomalies (Group II and III) been managed aggressively from infancy the impact of diagnostic delay in those with isolated SA would have become obvious. Late first UDS referral is the likely reason for significant and potentially preventable upper tract damage. The findings are a stark reminder of the need for early and aggressive evaluation and UDS-based management of all children with ARM, cloacal anomalies and various forms of the caudal regression syndrome.

Many of the children with hydronephrosis can be salvaged by an initial period of indwelling catheter drainage for rapid decompression followed by UDS-based management. This can retard and often reverse the changes even at a late stage. These children need multidisciplinary care preferably at a specialized tertiary care center.

One drawback of our study is selection bias. These were patients referred to the department with urinary tract symptoms. Hence, all patients with SA, ARM, and related disorders had LUTD. In fact, while the risk for LUTD is high in these patient groups, some patients may escape urinary tract damage.[35] The MRI findings and micturating cystourethrogram were not available for a significant minority. The overall number of patients is small and this limits the utility of statistical analysis. However, the number of patients in most other studies is small.

## CONCLUSIONS

Isolated SA is an uncommon cause for neurogenic bladder that often presents late and may result in renal damage. Careful examination and plain radiograph of the spine in children with unexplained lower urinary tract symptoms may enable early identification. Severity of the bony abnormality does not correlate with severity of lower tract abnormalities and once identified, all patients should undergo formal urological and neurological assessment. ARM and open spinal dysraphism are established high-risk factors for damage to the upper tracts. Our study suggests that upper urinary tracts might be at similar risk in some patients with symptomatic SA, but a delay in therapy is common as the diagnosis can be more elusive.

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