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Review Article

Sacral Agenesis

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ABSTRACT

Sacral agenesis (SA) is a rare congenital neurological disorder characterized by the incomplete development of the sacral spine. This work summarizes the scientific literature on SA, including the following sections: pathogenesis, epidemiology, risk factors, genetics, clinical manifestations, radiological classification, diagnosis, and management. The aim of this work is to provide the most up-to-date and comprehensive medical narrative literature review for this rare congenital disease. This narrative review used PubMed, MEDLINE, Science Direct, and Embase databases. Between December 2022 and September 2023, the following terms were used for the inclusion of original articles: "rare disease," "caudal regression," "diabetic embryopathy," and "sacral agenesis.? The International Sacral Agenesis/Caudal Regression Association participated in reviewing this manuscript and drafting a paragraph on behalf of those living with this condition. The clinical manifestations of SA are heterogeneous. The most prevalent manifestations involve peripheral neurological, motor, urinary, and digestive issues. The prognosis depends on the severity and associated abnormalities. Patients usually exhibit normal mental function but require a multidisciplinary evaluation and largely supportive treatment that enables them to live successful lives. More awareness and research are needed.

Introduction

Congenital malformations of the spine and spinal cord constitute a broad and diverse group of diagnoses, commonly referred to as spinal dysraphisms. Dysraphism describes errors in forming a midline seam during the fusion of the neural folds in primary neurulation during the third and fourth weeks of embryogenesis.[1] From complete neurulation failure to occult spina bifida, the spectrum of spinal dysraphism comprehends diverse manifestations such as myelocele, meningocele, myelomeningocele, anencephaly, and sacral agenesis (SA). These conditions often share common risk factors and embryologic relationships, contributing to shared symptomatology. Although some of these defects are more common than others, studies of those that are more frequent or belong to this spectrum of disease can support the management of other less frequent and, therefore, less studied entities such as SA.[1]

SA, also known as caudal regression syndrome,[1] is a rare congenital neurological disorder characterized by incomplete development of the sacral spine. SA is often associated with neurogenic bladder, bowel incontinence, and orthopedic and neurological symptoms,[2] which may be a direct consequence of the agenesis or indirect due to other associated congenital

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malformations. The primary defect and any associated abnormalities determine the prognosis and treatment.

Pathogenesis

The specific mechanisms triggering the development of SA have not yet been identified; its growth has been associated with signaling defects of neural tube defects during the first four weeks of gestation.[3,4] There are different theories regarding its origin. One theory suggests that it may be due to a failure of induction, accompanied by a disturbance in the neural differentiation process during embryonic development, caused by signaling disruption. Another theory proposes that the abnormal neural tube configuration may result from a delay in the primary and secondary neurulation.[3,5] Primary neurulation begins in the third to fourth week and concludes with the closure of the posterior neuropore around postconceptual day 28 in humans. During this process, it involves the bending and fusion of the neural plate to form a hollow neural tube, driven by surrounding cells that guide the neural plate cells to proliferate, invaginate, and separate. In contrast, secondary neurulation occurs during the fifth week, following the completion of primary neurulation. Specifically, a hollow tube forms from the condensation and fusion of mesenchymal cells in the embryo's caudal region.[6]

The concept of caudal cell mass within secondary neurulation is equally crucial for understanding pathoembryogenesis. Secondary neurulation occurs between days 27 and 31 of embryonic development and involves significant neural growth originating from the caudal cell mass, a cluster of cells derived from the regressed primitive streak.[6] This mass forms the caudal segment of the spinal cord and spine. Disruptions in secondary neurulation are thought to lead to most cases of closed spinal dysraphism located caudally. In addition, some low sacral forms of SA may emerge due to secondary neurulation disruption, potentially resulting in dorsally limited myeloschisis or caudal skin defects.[7]

The association of SA with complex syndromes underscores the importance of the caudal cell mass and secondary neurulation in its pathogenesis.[7] Notably, the caudal cell mass is not only implicated in the formation of the spinal cord and the vertebral bodies in the lower sacral and below regions but also plays a crucial role in the development of surrounding structures, including the genitourinary tract, anorectal organs, hindgut, and elements involved in tube closure, indirectly contributing to the formation of other alterations, such as the anomalous anteroposterior septation of the cloaca and defective closure of abdominal wall, which may explain the diverse clinical phenotypes observed in SA.[2]

Epidemiology and risk factors

SA is a rare disease with an estimated prevalence of one in 25,000 to 100,000 live births and one in 350 live births to mothers with a diagnosis of diabetes mellitus.[8] Prevalence is variably reported and thought to be higher than estimated. Although prenatal diagnosis is feasible, its detection depends primarily on the clinician's experience. Mild cases may go unnoticed, whereas severe cases incompatible with life may go unreported.[9-11]

It is imperative to acknowledge that the infrequency of SA and the nature of clinical investigations pose inherent challenges in determining its risk factors. As a result, much of the evidence is extrapolated from animal studies. In this discourse, we have endeavored to integrate factors identified in animal and human research from various population samples.

Multiple risk factors are implicated in the development of SA and its associated anomalies. These risk factors include genetic predisposition; maternal diabetes or hyperglycemia; exposure to teratogenic agents; metabolic disorders; maternal age—below 19 or above 35 years; and hyperthermia during early gestation.[12,13]

Maternal diabetes

Maternal diabetes is widely recognized as the predominant risk factor in the development of SA,[3,14] and to date, there are two proposed pathophysiologic mechanisms. Given the high insulin levels in the maternal circulation, the first could promote the formation of free radicals, harming organogenesis. The second suggests that vascular hypoperfusion, hyperglycemia, and other biochemical factors can elevate glycolytic activity, possibly resulting in a lack of crucial metabolic substrates for embryogenesis.[15,16]

Evidence suggests that both type 1 and type 2 diabetes are important risk factors for SA. Newborns of diabetic mothers have between 200 and 400 times greater risk than the general population, with type 1 diabetes having a higher risk estimate.[12] However, most cases of SA are born to nondiabetic mothers.[17] The reason why the sacral region is specifically affected, whereas other areas of the nervous system are spared remains unknown. However, it may be related to elevated insulin or glucose levels during the formation of the sacral region.

Drugs and other teratogens

Factors such as insecticide exposure, contact with heavy metals, ochratoxin A, sulfonamides, and hyperthermia were identified as potential inducers of SA, but conclusive evidence is still lacking.[8] One of the most important studies investigating risk factors for SA is the National Birth Defects Prevention Study, with data from over 11,289 participants. This study evaluated various risk factors, including infant, maternal, and pregnancy-related characteristics. As in other studies, pre-existing type 1 diabetes and pre-existing type 2 diabetes were positively and significantly associated with SA. Among women without diabetes, smoking was identified as a risk factor.[12]

Preclinical studies have demonstrated the involvement of retinoic acid (RA) in the pathogenesis of SA. The evidence for this is supported by its interactions with decisive molecular pathways, including the cytochrome gene CYP26A1 and the expression of Wnt-3a. In the latter, RA has been implicated in modulating gene expression, notably affecting the expression of Wnt-3a, a crucial gene in tail bud maturation. Wnt-3a, a secreted signaling molecule, is critical to embryonic axial elongation and caudal region development. Disruption or downregulation of Wnt-3a expression, as seen in genetic mutants and RA-treated embryos, leads to phenotypic similarities indicative of caudal regression.[18] Furthermore, RA has been described as disrupting catabolism and contributing to the SA phenotype. Animal models, particularly murine studies, have provided insights demonstrating dose-dependent severity and elucidating critical periods of vulnerability during embryonic development.[1,19,20]

Genetics

Only 5% to 10% of all cases are considered hereditary, although more studies are needed to clearly understand the frequency of hereditary cases of SA.[21] The identified genetic variants are dependent on the clinical phenotype of SA.

Syndromic variants of SA, such as Currarino syndrome, are caused by autosomal dominant genetic variants in the homeobox gene *HLXB9*, also known as *MNX1* (motor neuron and pancreas homeobox 1). This gene encodes the nuclear protein HB9, which plays a significant role in embryonic morphogenesis.[22,23]

Isolated SA has been correlated with heterozygous nonsense variants in the *ID1* gene, which is usually implicated in cellular differentiation, cell growth, and negative regulation of insulin secretion.[21]

Variants in the *ISL1* and *PTF1A* genes can partially account for associated anomalies, affecting the development of external genitalia, rectum, and bladder. *ISL1* altered expression and genetic variants have been strongly linked to urinary malformations due to their role in developing pericloacal mesenchyme and the urorectal septum.[1,24,25] Conversely, *PTF1A* genetic variants are implicated in gastrointestinal malformations, likely due to their involvement in midgut, hindgut, and notochord histogenesis.[1] The *TBXT* gene has been identified as another disruptor of caudal notochord differentiation, leading to variable degrees of anorectal and axial skeletal malformations.[26]

Additionally, an exome sequencing study identified shared genetic variants in participants with syndromic SA. Inherited genetic variants were found in *PDZD2* and *CLTCL1*, whereas *de novo* genetic variants appeared in *SPTBN5*, *MORN1*, and *ZNF330*. Notably, *CLTCL1* and *PDZD2* are associated with glucose homeostasis and, by extension, diabetes. *MORN1* and *ZNF330*, expressed in the pancreas, may clarify the link to gestational diabetes. The study also identified heterozygous genetic variants in *PTEN*, previously associated with the condition, as well as in its direct regulator, *GLTSCR2* (compound), and *VANGL1*.[27]

More studies are needed to understand better the frequency of hereditable forms of SA and the role of other genes that could be risk factors that interact with environmental factors; all children with SA should have an evaluation with a geneticist to study if they are insulated or syndromic causes and to evaluate if molecular studies are indicated.

Other clinical risk factors

In the National Birth Defects Prevention Study case, mothers who had children with SA were more likely than controls to report hypertension during pregnancy and kidney, bladder, or urinary tract infections around conception. Other exposures associated with increased risk included overweight/obesity, Hispanic ethnicity, previous miscarriage, and periconceptional use of antihypertensive medication, although they were not statistically significant.[12]

Clinical manifestations

Clinical manifestations of SA are highly variable and depend on the disease phenotype. Symptoms can range from unnoticed to affecting multiple systems. A comprehensive head-to-toe examination is essential for timely treatment to identify subtle defects and enable symptom and deficit improvement where feasible.[3]

Although under-reported cases complicate the determination of the frequency of manifestations, data from reported cases consistently show a high prevalence of musculoskeletal system impacts. A comparative table of clinical manifestations in case series and cohort studies was included (Table 1). This table indicated that the musculoskeletal system is frequently affected, with conditions such as spinopelvic instability, foot and ankle deformities, and vertebral defects, including fused ribs and hypoplastic or absent vertebral bodies. These deformities often lead to physical, motor, and sensory deficits.[3] This finding aligns with embryologic theories suggesting that these musculoskeletal anomalies are secondary to primary defects in the neural tube and its product, the spinal cord. Magnetic resonance imaging (MRI) can help identify spinal anomalies like tethered spinal cord or myelomeningocele. Although some authors have conducted such imaging, they did not report these findings, creating an information gap concerning the incidence of these defects when imaging studies are not performed.[28,29]

Urinary and gastrointestinal manifestations are among the most common clinical symptoms of SA, with primary issues being urinary retention and constipation. Urinary and fecal incontinence can often occur as an overflow phenomenon.[9,38] Our findings also showed significant data for these symptoms (Table 1), with urinary incontinence and dribbling being the second most frequent clinical manifestations observed. Less frequent manifestations included arthrogryposis, paresthesias, spina bifida, and tracheoesophageal fistula.

Radiological classification

The term *caudal regression syndrome* was proposed in 1964[43]; this led to classifying clinical stage where sirenomelia was first considered the most severe stage type. Nowadays, some authors suggest that it should be considered as a different entity.[44]

Imaging appearances can vary considerably depending on the clinical stage. Often, the following can be seen[45]:

- Lumbosacral vertebral bodies with dysgenesis
- The level of atresia/dysgenesis is usually seen below L1 and is often limited to the sacral region.
- Severe narrowing of the rostral canal to the last intact vertebra
- Truncated spinal cord (blunt tip) terminating above the expected level (also referred to as wedged- or cigar-shaped conus medullaris)
- Associated abnormalities

The best-known classification of SA was proposed by Renshaw in 1978 and was based on the analysis of 23 children and their skeletal morphology, articulation pattern, and neurological deficits (Table 2).[46] Types I and II represent milder forms, characterized by an absent coccyx but without functional deficits. In contrast, types III and IV are severe clinical presentations that involve multiple systemic manifestations, including neurological impairment.[3,47]

According to the most up-to-date classification proposed by Guille et al., patients with lumbosacral agenesis can be grouped into two categories (I and II) and further divided into three types (A, B, and C) based on the relationship between vertebral deformity and the ability to walk.[2,48] Currently, there is no consensus on the best classification.[2]

Prenatal diagnosis

Although the aim is to diagnose patients during intrauterine life, some cases may go undetected for several years, particularly in minor cases of SA. Prenatal diagnosis is critical as it may provide valuable information for prognosis. Although SA itself cannot be treated *in utero*, fetal intervention for conditions like meningocele may be part of the prenatal care plan. Therefore, timely detection and appropriate imaging are essential to assess associated abnormalities and guide postnatal management. Transvaginal and abdominal ultrasound have been proved to be effective diagnostic methods during the prenatal period.[34,49,50] Imaging signs associated with SA include abrupt interruptions of the spine at the lumbosacral level and a “froglike,” “shield,” or “Buddha's pose” appearance.[49] Other signs include shortening of the crown-rump length and a prominent lower spine, which can be detected as early as nine weeks gestational age.[34]

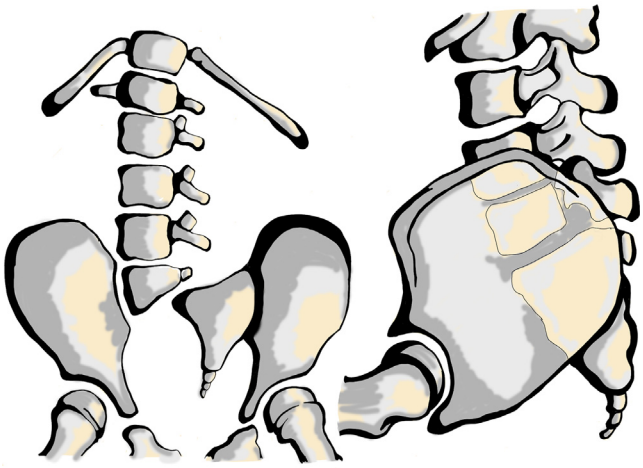
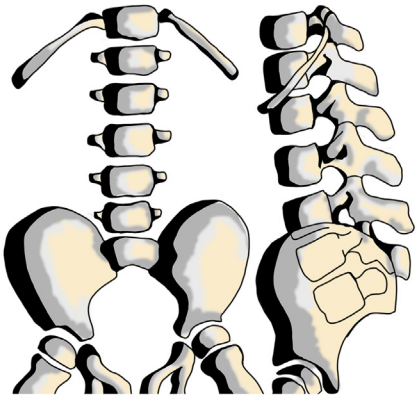
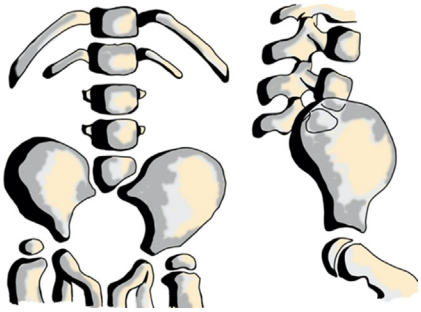
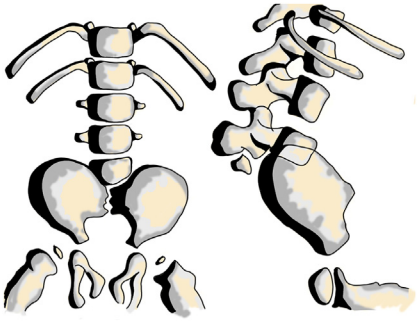
Prenatal and neonatal MRI and computed tomography help classify SA's clinical subtype. MRI sequences can identify abnormal patterns in the spinal cord such as the “drumstick” appearance, stretched conus medullaris termination, and tethered spinal cord.[1]

TABLE 1.
Clinical Manifestations of SA in Case Series Reports and Cohort Studies

Clinical Manifestation	Author (Year)															
	Purbasari et al.[30]	Vissarionov et al.[29]	Kumar et al.[28]	Bülent et al.[31]	Boruah et al.[32]	Emami et al.[33]	Subtil et al.[34]	Capitanucci et al.[35]	O Neill et al.[36]	Pang et al.[9]	Mariani et al.[37]	Guzman et al.[38]	Brooks et al.[39]	Andrish et al.[40]	White et al.[41]	Koontz et al.[42]
	% (n = 3)	% (n = 12)	% (n = 4)	% (n = 38)	% (n = 21)	% (n = 50)	% (n = 3)	% (n = 7)	% (n = 15)	% (n = 33)	% (n = 11)	% (n = 16)	% (n = 3)	% (n = 17)	% (n = 22)	% (n = 8)
Anomalies																
Spinopelvic instability*	66.66 (2)	100 (12)		86.8 (33)		28 (14)	66.66 (2)		26.66 (4)	24.24 (8)	90.9 (10)	50 (8)		82.35 (14)	27.27 (6)	62.5 (5)
Vertebral defects†	66.66 (2)	100 (12)	25 (1)	78.94 (30)	80.9 (17)				6.66 (1)	54.54 (18)					31.81 (7)	12.5 (1)
Arthrogryposis				2.63 (1)						9.09 (3)					9.09 (2)	
Foot and ankle deformity‡	66.66 (2)	100 (12)		73.68 (28)	33.3 (7)	50 (25)			40 (6)	60.60 (20)	90.9 (10)			88.23 (15)	54.54 (12)	37.5 (3)
Limb length discrepancies				39.47 (15)		48 (24)	100 (3)		46.66 (7)					11.76 (2)		37.5 (3)
Flexion contractures of the knees and hips§		25 (4)		7.89 (3)			100 (3)			27.27 (9)	9.09 (1)			58.82 (10)		
Urinary incontinence/ dribbling		41.66 (5)	75 (3)		28.6 (6)	60 (30)		100 (7)		48.48 (16)		87.5 (14)	75 (3)	100 (17)	40.90 (9)	100 (8)
Neurogenic bladder					81 (17)			100 (7)			100 (11)	43.75 (7)	75 (3)			
Vesicoureteral reflux								28.57 (2)		15.15 (5)	100 (11)	43.75 (7)	25 (1)			75 (6)
Kidney defects‖					23.8 (5)							50 (8)	25 (1)	41.17 (7)		62.5 (5)
Fecal incontinence		41.66 (5)			42.85 (9)	24 (12)							75 (3)			25 (2)
Anorectal malformations¶					52.38 (11)	22 (11)		100 (7)	13.33 (2)	78.78 (26)		31.25 (5)	25 (1)	11.76 (2)	27.27 (6)	37.5 (3)
Tracheoesophageal fistula										3 (9.09)		6.25 (1)			4.54 (1)	
Spina bifida	33.33 (1)				61.9 (13)						27.27 (3)					12.5 (1)
Spina bifida with myelomeningocele															40.90 (9)	
Myelomeningocele				52.63 (20)		18 (9)					18.18 (2)		25 (1)	17.64 (3)		
Tethered cord	100 (3)			36.84 (14)	33.3 (7)	58 (29)				30.30 (10)						
Lower extremity weakness		41.66 (5)				74 (37)				9.09 (3)						
Paresthesia		41.66 (5)	25 (1)													
Lipoma of the filum	33.33 (1)			18.42 (7)	28.6 (6)	22 (11)				24.24 (8)			50 (2)	11.76 (2)		
Flattening of gluteal cleft	33.33 (1)	100 (12)			33.3 (7)	38 (19)				6.06 (2)			25 (1)			
Gluteal skin dimpling	33.33 (1)				23.8 (5)	36.36 (4)							25 (1)			
Not specific anomalies#			25 (1)	15.78 (6)		4 (2)	33.33 (1)			24.24 (8)	9.09 (1)	6.25 (1)		35.29 (6)	9.09 (2)	

* Spinopelvic instability includes hip dislocation, fusion of iliac bones, scoliosis, and kyphosis.
† Vertebral defects include fused ribs, fusion, hypoplastic vertebrae, vertebral fusion, hemi- and butterfly vertebrae, and absent vertebrae.
‡ Foot and ankle deformity includes talipes equinovarus, calcaneovalgus, syndactyly, polydactyly, or absent phalanges and Buda's attitude in prenatal cases.
§ Includes Budas attitude in prenatal cases.
‖ Kidney defects include a small kidney, solitary kidney, ectopic kidney, rotated kidney, unilateral renal agenesis, double ureters, pelvic and horseshoe kidneys, and hydronephrosis.
¶ Anorectal malformations include the imperforate anus and rectal prolapse.
# Not specific anomalies include cardiac, respiratory, and craniofacial defects (congenital heart disease, Fallot tetralogy, pectus excavatum, pulmonary atresia, hemangioma, hydrocephaly, microcephaly, cleft palate).

TABLE 2.
SA Radiological Classification

Type 1	Unilateral total or partial SA	
Type 2	Partial SA with a partial but bilaterally symmetric defect and a stable articulation between the ilia and a normal or hypoplastic first sacral vertebra	
Type 3	Variable lumbar and total SA with the ilia articulating with the sides of the lowest vertebra present	
Type 4	Variable lumbar and total SA, the caudal end plate of the lowest vertebra nesting above either fused ilia or an iliac amphiarthrosis	

Abbreviation:
SA = Sacral agenesis
Images are based on the article Renshaw.[46]

Other associated imaging abnormalities include talipes equinovarus and calcaneovalgus deformity, joint flexion of both knees, and hip flexion-abduction abnormalities.[51] Computed tomography studies have allowed for identification of associated extraspinal abnormalities to provide diagnostic support.[52]

Management

Urinary incontinence

Owing to the diverse presentation of SA, every patient's treatment should be individualized and handled with a multidisciplinary approach.[10] Urinary incontinence is the most common symptom. Therefore, some patients may benefit from intermittent catheterization to reduce the risk of urinary tract infections. Special attention is needed for the latter, but periodic urine cultures and general urinalysis are not recommended. Antibiotic treatment for asymptomatic bacteriuria is also discouraged to prevent antibiotic resistance.[53,54] Catheterization, along with appropriately prescribed drug therapy, can help achieve continence.[55] Enterocystoplasty may be necessary if the latter is not enough.[56]

Kegel exercises and transcutaneous electrical nerve stimulation, which involve contracting, holding, and relaxing the pelvic floor muscles, can help manage urinary incontinence by strengthening the pelvic floor muscles and improving urine retention.[57]

Fecal incontinence management and bowel management program

SA disrupts neural control, resulting in muscle weakness and sphincter dysfunction, leading to fecal incontinence and constipation. Management often begins conservatively with dietary adjustments and lifestyle modifications. If needed, pharmacologic interventions and transanal irrigation techniques may follow. Surgical options are considered only after exhausting these prior strategies to address fecal incontinence effectively.[58]

Pharmacologic interventions like probiotics and laxatives can help manage fecal incontinence. High-quality data support the efficacy of laxatives in neurogenic bowel dysfunction management, with macrogol showing superiority over lactulose.[59] Stimulant laxatives can increase bowel movement frequency. Suppositories and enemas are adjunctive options.[58]

Approximately 40% of pediatric and adult patients with neurogenic bowel disease may require surgery if medical treatments fail. Surgical interventions aim to improve quality of life by facilitating controlled bowel movements and minimizing soiling incidents. Options involve procedures like Malone antegrade continence enema or tube cecostomy. Considering age, comorbidities, and family dynamics, these methods are tailored to individual needs to ensure optimal social integration. Other surgical techniques, like artificial anal sphincter implantation, are generally unsuitable for children due to their ongoing growth.[58]

Growth hormone effects on lower limb function

Growth hormone (GH) has shown positive effects on the growth and differentiation of neural stem cells. However, its application in treating lower limb deficiencies due to SA is not widely adopted and remains experimental. There is only one published report where GH was administered along with rehabilitation therapy for five years, showing improvements in a patient's condition.[60] Despite this, the potential for GH to influence the development and progression of scoliosis, a condition already associated with SA, raises concerns.[61,62] The relationship between GH administration and scoliosis progression is not clearly understood, with studies presenting diverse outcomes and no clear consensus.[63,64]

Surgical management

Surgery can address comorbid conditions associated with SA, such as urinary retention, erectile dysfunction, constipation, rectal abnormalities, tumors, and skin lesions. A multidisciplinary approach involving various surgical specialties is necessary to achieve optimal results. For instance, surgical treatment options for urinary incontinence include artificial bladder sphincter[65] or bladder augmentation,[66] such as the Mitrofanoff procedure that involves creating a conduit to a low-pressure reservoir that can be emptied through a stoma made of appendix or transverse ileal tissue.[67] This treatment requires an evaluation from surgical and pediatric subspecialties.

Patients with urinary incontinence have several treatment options, including bladder neck continence and augmentation cystoplasty. These procedures aim to maintain low bladder filling pressure and optimal storage volumes, which can be supported by intermittent catheterization.

Although, to date, there is no international consensus that clarifies indications for neurological surgery, it is mainly indicated for new onset or progressive neurological deficit, as well as bowel obstruction. Other indications may include patients with exposed spinal cords,[68-70] vertebral stabilization needs, or pain management. The orthopedic field plays a crucial role in surgically correcting anomalies and improving stability in the lower part of the pubic symphysis and upper part of the sacroiliac joint to reduce movement in the sacrum and alleviate pressure on abdominal organs. Different treatment approaches are proposed for managing more severe phenotypes. Some suggest subtrochanteric amputation or knee disarticulation followed by prosthetic adjustments for individuals classified as Renshaw type III or IV; spinopelvic fusion is recommended to address pelvic instability. Additional interventions may include correcting lower limb deformities through orthotic adjustments, performing open reduction or pelvic osteotomy for hip conditions, utilizing release osteotomy to enhance knee extension in cases of significant knee deformities, and considering surgical releases in the foot for older patients. Early intervention and orthotic support are crucial for achieving plantigrade footing.[71]

Prognosis

SA is a lifelong condition without a cure. The prognosis depends on the severity and associated abnormalities. Patients generally have normal mental function, although they require a comprehensive multidisciplinary evaluation and largely supportive treatment.[49] For patients with the more severe type III-IV SA, health complications are more common. Kidney involvement can increase the risk of stillbirth, and complications in the cardiac, musculoskeletal, respiratory, genitourinary, and central nervous systems may mainly contribute to neonatal mortality.[3]

However, several interventions can significantly improve the quality of life for individuals with SA. Clean intermittent bladder catheterization has been shown to enhance quality of life and reduce mortality rates. Similarly, an effective intestinal management program can help patients achieve fecal continence, thereby boosting their autonomy and self-esteem.

Individuals with orthopedic involvement may benefit from mobility aids such as wheelchairs. Proper wheelchair seating, tailored to the patient's specific needs, including small lower body size, fixed lower extremities, and shortened torso, can provide autonomy and comfort. This enables patients to participate in academic, work, and sports activities, thereby promoting independence, self-esteem, and physical health.

Reproductive health in women is not usually compromised; with appropriate and individualized care, it is possible to carry out

a pregnancy in some patients. However, it must be done from a multidisciplinary perspective and individualized to the clinical manifestations of the patient.[72] Regardless of all the manifestations each patient may experience, treatment options can enable patients to live a long and successful life.

Information for patients

iSACRA

To connect all patients with SA/caudal regression syndrome, the International Sacral Agenesis/Caudal Regression Association (iSACRA) provides support and information to patients and their families. iSACRA promotes awareness and collaborates in research and advocacy to enhance the quality of life of persons with this condition and to advance medical knowledge. The web site is www.isacra.org.

Patient voice

iSACRA commends the authors of this article for an extensive overview of the current medical issues and treatment options for those with this condition. Attention to this condition is sparse, making this information especially valuable to medical professionals who may never have encountered patients with it.

An opportunity to provide our voice to this article is to emphasize that the 1600+ individuals we are connected to with this condition worldwide are far more than patients. They are active and contributing members of the society. They are teachers, musicians, actors, artists, nurses, students, politicians, psychologists, athletes, writers, advocates, and chefs. They manage households. They are in committed relationships. They are adults leading busy and productive lives, with this rare condition as a part of that life. They are young children and teenagers who amaze their parents with their accomplishments. Some will consider themselves a contribution to earth's diversity. Some will note that navigating specific challenges has provided them with opportunities to develop valuable characteristics, including problem-solving skills, persistence, and empathy. All would agree that advancing knowledge of this condition will result in improved quality of medical care and, as a result, improved quality of life.

Conclusions

SA is a rare congenital disorder characterized by incomplete development of the sacral spine. Although the underlying pathophysiologic mechanism is not yet fully understood, maternal diabetes is the most frequently associated risk factor. The clinical manifestations are highly variable, reflecting the different degrees of involvement of the midposterior mesoderm. Most cases involve the musculoskeletal, peripheral neurological, digestive, and urinary systems.

Given its complexity, a team of multidisciplinary health care professionals should be involved in evaluating and managing patients. The treatment plan for individuals may include physical therapy, surgical correction of anomalies, and assistive devices to improve mobility and comfort levels. The prognosis directly depends on the severity of the primary and associated defects, the interventions' effectiveness, and the adherence to regular monitoring of the condition and potential complications, such as urinary tract infections. Nonetheless, with proper care, leading a long life and engaging in social, sporting, professional, and other activities is feasible.

Declaration of competing interest

The authors of this paper hereby declare that they possess no known competing financial interests or personal relationships that could be perceived as having influenced the work presented in this report. It is with utmost confidence and transparency that we affirm our commitment to upholding the highest standards of professional conduct.

We believe that this work has the potential to significantly contribute to the scientific community and advance our collective understanding in this field.

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References

1. Warner T, Scullen TA, Iwanaga J, et al. Caudal regression syndrome—a review focusing on genetic associations. World Neurosurg. 2020;138:461–467.
2. Jasiewicz B, Kacki W. Caudal regression syndrome—a narrative review: an orthopedic point of view. Children. 2023;10:589.
3. Boulas MM. Recognition of caudal regression syndrome. Adv Neonatal Care. 2009;9:61–69.
4. Singh SK, Singh RD, Sharma A. Caudal regression syndrome—case report and review of literature. Pediatr Surg Int. 2005;21:578–581.
5. Lee JY, Shim Y, Wang K-C. Caudal agenesis: understanding the base of the wide clinical spectrum. J Korean Neurosurg Soc. 2021;64:380–385.
6. Sergeenko OM, Savin DM, Diachkov KA. Association of spinal cord abnormalities with vertebral anomalies: an embryological perspective. Childs Nerv Syst. 2024;40:1415–1425.
7. Yang J, Lee JY, Kim KH, Yang HJ, Wang K-C. Disorders of secondary neurulation: suggestion of a new classification according to pathoembryogenesis. Adv Tech Stand Neurosurg. 2022;45:285–315.
8. Au KS, Ashley-Koch A, Northrup H. Epidemiologic and genetic aspects of spina bifida and other neural tube defects. Dev Disabil Res Rev. 2010;16:6–15.
9. Pang D. Sacral agenesis and caudal spinal cord malformations. Neurosurgery. 1993;32:755–779.
10. Esposito G, Totonelli G, Iacobelli BD, et al. Continence management in children with severe caudal regression syndrome: role of a multidisciplinary team and long-term follow-up. Pediatr Surg Int. 2022;38:1461–1472.
11. Qudsieh H, Aborajooh E, Daradkeh A. Caudal regression syndrome: postnatal radiological diagnosis with a literature review of 83 cases. Radiol Case Rep. 2022;17:4636–4641.
12. Nalbandyan M, Howley MM, Cunniff CM, Romitti PA, Browne ML, York N. Descriptive and risk factor analysis of nonsyndromic sacral agenesis: national birth defects prevention study, 1997-2011 HHS public access. Am J Med Genet. 2019;179:1799–1814.
13. Moore S. Genetics, pathogenesis and epidemiology of anorectal malformations and caudal regression syndrome. In: Anorectal Malformations in Children. Berlin, Heidelberg: Springer Berlin Heidelberg; 2006:31–48.
14. Marchincin SL, Howley MM, Van Zutphen AR, et al. Risk of birth defects by pregestational type 1 or type 2 diabetes: National Birth Defects Prevention Study, 1997–2011. Birth Defects Res. 2023;115:56–66.
15. Zepeda J, García M, Morales J, Pantoja MA, Espinoza A. Secuencia de regresión caudal: caso clínico-radiológico. Rev Chil Pediatr. 2015;86:430–435.
16. Mills JL. Malformations in infants of diabetic mothers. Teratology. 1982;25:385–394.
17. Aggarwal M, Sood V, Deswal S, Aggarwal KC. Caudal regression syndrome with bilateral popliteal webbing without maternal diabetes: a rare entity. Childs Nerv Syst. 2012;28:1819–1821.
18. Chan BWH, Chan KS, Koide T, et al. Maternal diabetes increases the risk of caudal regression caused by retinoic acid. Diabetes. 2002;51:2811–2816.
19. Abu-Abed S, Dollé P, Metzger D, Beckett B, Chambon P, Petkovich M. The retinoic acid-metabolizing enzyme, CYP26A1, is essential for normal hindbrain patterning, vertebral identity, and development of posterior structures. Genes Dev. 2001;15:226–240.
20. Roberts C. Regulating retinoic acid availability during development and regeneration: the role of the CYP26 enzymes. J Dev Biol. 2020;8:6.
21. Pitsava G, Feldkamp ML, Pankratz N, et al. Exome sequencing identifies variants in infants with sacral agenesis. Birth Defects Res. 2022;114:215–227.
22. Han L, Zhang Z, Wang H, et al. Novel MNX1 mutations and genotype-phenotype analysis of patients with Currarino syndrome. Orphanet J Rare Dis. 2020;15:155.
23. Hagan DM, Ross A, Strachan T, et al. Mutation analysis and embryonic expression of the HLXB9 Currarino syndrome gene. Am J Hum Genet. 2000;66:1504–1515.
24. Zhang R, Knapp M, Suzuki K, et al. ISL1 is a major susceptibility gene for classic bladder exstrophy and a regulator of urinary tract development. Sci Rep. 2017;7, 42170.

25. Ching ST, Infante CR, Du W, et al. Isl1 mediates mesenchymal expansion in the developing external genitalia via regulation of Bmp4, Fgf10, and Wnt5a. Hum Mol Genet. 2018;27:107–119.
26. Chen S, Lei Y, Yang Y, et al. A mutation in TBXT causes congenital vertebral malformations in humans and mice. J Genet Genomics. 2024;51:433–442.
27. Porsch RM, Merello E, De Marco P, et al. Sacral agenesis: a pilot whole exome sequencing and copy number study. BMC Med Genet. 2016;17:98.
28. Kumar Y, Gupta N, Hooda K, et al. Caudal regression syndrome: a case series of a rare congenital anomaly. Pol J Radiol. 2017;82:188–192.
29. Vissarionov S, Schroder JE, Kokushin D, Murashko V, Belianchikov S, Kaplan L. Surgical correction of spinopelvic instability in children with caudal regression syndrome. Global Spine J. 2019;9:260–265.
30. Purbasari U, Nazar H, Miraj F, et al. Caudal regression syndrome from radiology and clinical perspective: a case series and a proposed new integrated diagnostic algorithm. Radiol Case Rep. 2023;18:2478–2486.
31. Bülent MB, Akman YE, Ucpunar H, et al. Sacral agenesis: evaluation of accompanying pathologies in 38 cases, with analysis of long-term outcomes. Childs Nerv Syst. 2016;32:1693–1702.
32. Boruah DK, Dhingani DD, Achar S, et al. Magnetic resonance imaging analysis of caudal regression syndrome and concomitant anomalies in pediatric patients. J Clin Imaging Sci. 2016;6:36.
33. Emami P, Rahbar Z, Nejat F, Kajbafzadeh A, El Khashab M, et al. Neurological presentations, imaging, and associated anomalies in 50 patients with sacral agenesis. Neurosurgery. 2010;67:894–900.
34. Subtil D, Cosson M, Houfflin V, Vaast P, Valat A, Puech F. Early detection of caudal regression syndrome: specific interest and findings in three cases. Eur J Obstet Gynecol Reprod Biol. 1998;80:109–112.
35. Capitanucci ML, Silveri M, Nappo S, Mosiello G, Capozza N, De Gennaro M, et al. Agenesia totale del sacro e disfunzione vescicale neurogena [Total agenesis of the sacrum and neurogenic bladder dysfunction] [in Italian]. Pediatr Med Chir. 1997;19:113–116.
36. O'Neill OR, Jr Piatt JH, Mitchell P, Roman-Goldstein S, et al. Agenesis and dysgenesis of the sacrum: neurosurgical implications. Pediatr Neurosurg. 1995;22:20–28.
37. Mariani AJ, Stern J, Khan AU. Sacral agenesis: an analysis of 11 cases and review of the literature. J Urol. 1979;122:684–686.
38. Guzman L, Bauer SB, Hallett M, Khoshbin S, Colodny AH, Retik AB. Evaluation and management of children with sacral agenesis. Urology. 1983;22:506–510.
39. Brooks BS, El Gammal T, Hartlage P, Beveridge W, et al. Myelography of sacral agenesis. AJNR Am J Neuroradiol. 1981;2:319–323.
40. White R. Sacral agenesis: analysis of 22 cases. Urology. 1976;8:521–525.
41. Andrish J, Kalamchi A. Sacral agenesis: a clinical evaluation of its management, heredity, and associated anomalies. Clin Orthop Relat Res. 1979:52–57.
42. Koontz WW. Agenesis of the sacrum and the neurogenic bladder. JAMA. 1968;203:481–486.
43. Duhamel B. From the mermaid to anal imperforation: the syndrome of caudal regression. Arch Dis Child. 1961;36:152–155.
44. Isik Kaygusuz E, Kurek Eken M, Sivrikoz ON, Cetiner H. Sirenomelia: a review of embryogenic theories and discussion of the differences from caudal regression syndrome. J Matern Fetal Neonatal Med. 2016;29:949–953.
45. Weerakkody Y, Campos A, Yap J. Caudal regression syndrome. Reference article. Radiopaedia.org; 2023. Available at: https://doi.org/10.53347/rID-9580. Accessed July 13, 2023.
46. Renshaw TS. Sacral agenesis. J Bone Joint Surg Am. 1978;60:373–383.
47. Program Operations Manual System (POMS). "Caudal Regression Syndrome - Types III and IV,". Social Security Administration SSA; 2020. Available at: http://policy.ssa.gov/poms.nsf/lnx/0423022935. Accessed July 13, 2023.
48. Guille JT, Benevides R, DeAlba CC, Siriram V, Kumar SJ. Lumbosacral agenesis: a new classification correlating spinal deformity and ambulatory potential. J Bone Joint Surg Am. 2002;84:32–38.
49. Aslan H, Yanik H, Celikaslan N, Yildirim G, Ceylan Y. Prenatal diagnosis of caudal regression syndrome: a case report. BMC Pregnancy Childbirth. 2001;1:8.
50. Nagy GR, Csapó Z, Barakonyi E, Nagy B, Rigó J. Prenatal diagnosis and fetopathological investigation of dorsolumbosacral agenesis. Pathol Res Pract. 2009;205:490–493.
51. Kylat RI, Bader M. Caudal regression syndrome. Children (Basel). 2020;7:211.
52. Mottet N, Martinovic J, Baeza C, et al. Think of the Conus medullaris at the time of diagnosis of fetal sacral agenesis. Fetal Diagn Ther. 2017;42:137–143.
53. Romero Cullerés G, Sugrañes JC, Planells Romeo I, Giménez Pérez M. Características de las infecciones urinarias en pacientes con vejiga neurógena según el sistema de vaciado vesical utilizado en comparación con pacientes sin vejiga neurógena. Actas Urol Esp. 2010;34:251–257.
54. Kreydin E, Welk B, Chung D, et al. Surveillance and management of urologic complications after spinal cord injury. World J Urol. 2018;36:1545–1553.
55. Ye D, Chen Y, Jian Z, et al. Catheters for intermittent catheterization: a systematic review and network meta-analysis. Spinal Cord. 2021;59:587–595.
56. Moussali-Flah L, Cohen-Cohen S, Gómez-Peña F, Gómez-Peña G, Mosqueira-Mondragón C, Landa-García R. Manejo de la vejiga neurogénica en un hospital pediátrico de México. Rev Mex Uro. 2010;70:364–369.
57. Lúcio A, D'ancona CAL, Perissinotto MC, McLean L, Damasceno BP, de Moraes Lopes MHB. Pelvic floor muscle training with and without electrical stimulation in the treatment of lower urinary tract symptoms in women with multiple Sclerosis. J Wound Ostomy Continence Nurs. 2016;43:414–419.
58. Mosiello G, Safder S, Marshall D, Rolle U, Benninga MA. Neurogenic bowel dysfunction in children and adolescents. J Clin Med. 2021;10:1669.
59. Rendeli C, Ausili E, Tabacco F, et al. Polyethylene glycol 4000 vs. lactulose for the treatment of neurogenic constipation in myelomeningocele children: a randomized-controlled clinical trial. Aliment Pharmacol Ther. 2006;23:1259–1265.
60. Devesa J, Alonso A, López N, et al. Growth hormone (GH) and rehabilitation promoted distal innervation in a child affected by caudal regression syndrome. Int J Mol Sci. 2017;18:230.
61. Ziv-Baran T, Modan-Moses D, Zacay G, Ackshota N, Levy-Shraga Y. Growth hormone treatment and the risk of adolescent scoliosis: a large matched cohort study. Acta Paediatr. 2023;112:1240–1248.
62. Yun Y-H, Kwon S-S, Koh Y, Kim D-J, Ahn J, Lee SY. Influence of growth hormone treatment on radiographic indices of the spine: propensity-matched analysis. J Orthop Surg Res. 2017;12:130.
63. Vidil A, Journeau P, Soulie A, Padovani JP, Pouliquen JC. Evolution of scoliosis in six children treated with growth hormone. J Pediatr Orthop B. 2001;10:197–200.
64. Park M, Kim YJ, Oh KE, et al. The association between idiopathic scoliosis and growth hormone treatment in short children. Ann Pediatr Endocrinol Metab. 2022;27:207–213.
65. Gasmi A, Perrouin-Verbe MA, Hascoet J, et al. Long-term outcomes of artificial urinary sphincter in female patients with spina bifida. Neurourol Urodyn. 2021;40:412–420.
66. Szymanski KM, Misseri R, Whittam B, et al. Additional surgeries after bladder augmentation in patients with spina bifida in the 21st Century. J Urol. 2020;203:1207–1213.
67. Veeratterapillay R, Morton H, Thorpe A, Harding C. Reconstructing the lower urinary tract: the Mitrofanoff principle. Indian J Urol. 2013;29:316.
68. Schijman E. Split spinal cord malformations: report of 22 cases and review of the literature. Childs Nerv Syst. 2003;19:96–103.
69. Muthukumar N. The 'human tail': a rare cause of tethered cord: a case report. Spine. 2004;29:E476–E478.
70. Ilhan H, Tokar B, Atasoy MA, Kulali A. Diagnostic steps and staged operative approach in Currarino's triad: a case report and review of the literature. Childs Nerv Syst. 2000;16:522–524.
71. Phillips WA, Cooperman DR, Lindquist TC, Sullivan RC, Millar EA. Orthopaedic management of lumbosacral agenesis. Long-term follow-up. J Bone Joint Surg Am. 1982;64:1282–1294.
72. Shigenobu Y, Nagayama S, Manaka Y, et al. Pregnancy in a patient with caudal regression syndrome following continent bladder reconstruction. J Obstet Gynaecol Res. 2022;48:2615–2619.