Caudal regression syndrome: 2 Case reports and literature review

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Keywords

Caudal regression syndrome ; caudal dysplasia syndrome ; caudal agenesis ; sacral agenesis ; sacral dysgenesis ; sacral regression ; nervous system malformations ; spine ; sacrum ; congenital ; anorectal malformation ; imperforated anus ; musculoskeletal ; VACTERL ; vertebral defects ; renal agenesis ; vesico-ureteral reflux ; neurogenic bladder ; neurogenic bowel

Abstract

Caudal regression syndrome (CRS) is a rare congenital disorder in which there is abnormal fetal development of the caudal partition of the spine. CRS has a broad clinical spectrum with variable anomalies of the lumbosacral spine, lower limbs, anorectal complex and genitourinary tract. Patients present with a variety of symptoms or features. We report two clinical cases, describing the clinical manifestations and diagnosis of these patients. We discuss the importance of screening for additional anomalies, early intervention and multidisciplinary follow-up.

Introduction

Caudal regression syndrome (CRS) is a rare congenital disorder in which there is an abnormal fetal development of the caudal partition of the spine. CRS encompasses a broad clinical spectrum with variable anomalies of the lumbosacral spine, lower limbs, anorectal complex, and genitourinary tract (1).

We present two clinical cases describing the clinical manifestations and diagnosis of these patients. We discuss the importance of screening for additional anomalies, early intervention, and multidisciplinary follow-up.

Case report 1

A 6-month-old girl was referred to the pediatric neurological department for evaluation of constipation associated with a sacral dimple. Since the introduction of solid foods, she had difficulty passing stools with a frequency of 2 to 3 bowel movements per week. Frequent enemas and laxatives were necessary. Sometimes even manual evacuation was required.

She was born at term but small for gestational age. Her birth length was 45 cm (-2.1 SD) and birth weight was 2660g (-1.6 SD). However, her head circumference was within the normal range. The pregnancy was complicated by gestational hypertension, which was treated with labetalol. There were no other chronic maternal conditions, infections, or drug use reported during pregnancy. In particular, the mother did not suffer from diabetes. Prenatal ultrasound showed no anomalies.

On clinical examination she presented with a sacral dimple and an abnormal intergluteal cleft, with the anus positioned more ventrally. The lower limbs appeared shorter compared to the rest of the body. She had no motor or sensory deficits and normal lower limb reflexes. She achieved expected motor and cognitive milestones. Additional imaging revealed sacral and coccygeal dysgenesis, a dysplastic lumbar vertebra with a neural cleft and a hemivertebra at Th9. These anomalies contributed to the development of a secondary S-shaped thoracolumbar scoliosis. In addition, partial fusion was observed between the right 6th and 7th ribs and the left 2nd and 3rd ribs (Fig. 1a). Magnetic resonance imaging also showed a tethered cord, tight filum terminale and a dilated ventriculus terminalis (Fig. 1b). Ultrasound and voiding cystourethrogram examinations revealed a crossed fused renal ectopia with hydronephrosis, a small overactive bladder, and a Mullerian duct anomaly, with agenesis of the right adnex and suspicion of a unicornuate uterus (Fig. 1c).

She is currently 18 months old and requires frequent enemas, laxatives and manual evacuation of stools. She receives a low dose of anticholinergic drugs and prophylactic antibiotics for her neurogenic bladder dysfunction and vesicoureteral reflux. She had one urinary tract infection (UTI) before being diagnosed and treated.

Case report 2

A newborn with CRS was referred to our institution at 14 days of age for further diagnosis and management. He was born with an imperforate anus and immediately underwent colostomy. X-ray examination showed sacral agenesis. On day 12 he had hydronephrosis and experienced suboptimal bladder emptying, which necessitated a bladder catheterization. Other clinical features included a sacral Mongolian spot, bilateral rocker bottom feet, moderately limited hip extension, and hypotrophy of the lower legs, particularly on the left side. Lower limb and anocutaneous reflexes were weak, while plantar reflexes were absent. Sensation appeared normal, although objective testing is not feasible in a newborn at two weeks of age. He was born at term to a non-diabetic mother.

Further magnetic resonance imaging revealed a sacral agenesis without no other vertebral anomalies. The conus medullaris ended bluntly with a normal position at the L1 vertebral level. Abdominal ultrasound showed a left renal agenesis with hypertrophy of the right kidney. A micturating cystourethrogram showed a small bladder and urinary dribbling. The bladder neck was open, and the urethra was dilated due to a hypercontractile external sphincter. This sphincter dyssynergia required early catheterization. He had a febrile UTI at the age of 10 days after cystography, which was treated with therapeutic antibiotics. Prophylactic antibiotics were started after this UTI. Intermittent catheterization and oxybutynin were instituted to treat the overactive neurogenic bladder with hydronephrosis.

Figure 1: **(A)** RX full spine; **(B)** MRI showing tethered cord, tight filum terminale, dilated ventriculus terminalis; **(C)** Voiding cystourethrogram showing a small oval shaped bladder, dilated ureter, and overflow of contrast in Mullerian duct.

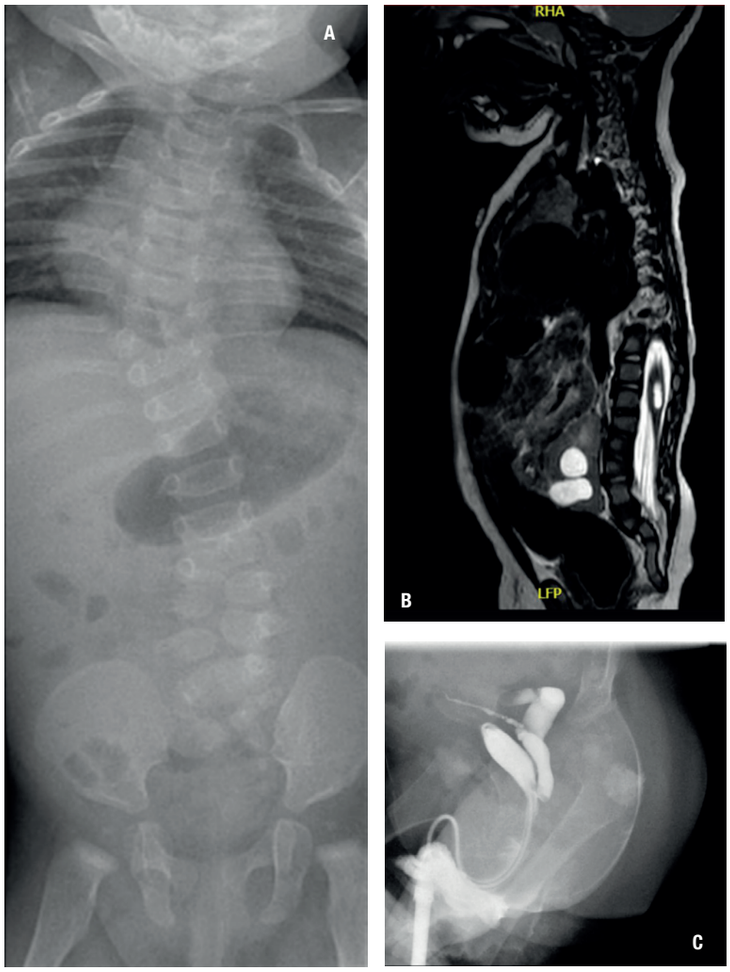
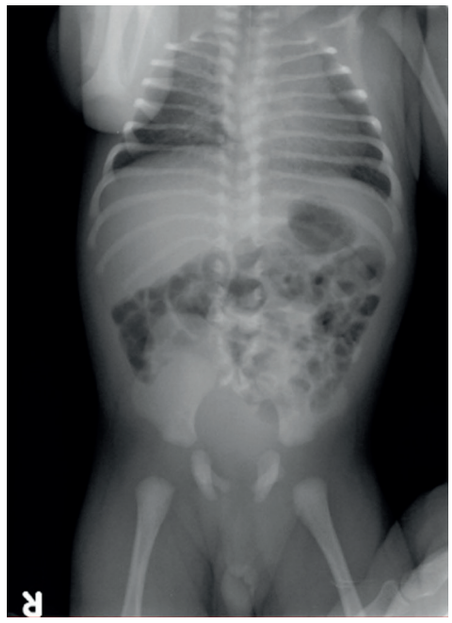


Figure 2: Sacral agenesi.



A laparoscopic pull through procedure was performed at 4 months of age with colostomy removal 6 months later. He is currently 10 years old and has regular follow-up visits in the departments of pediatric neurology, gastroenterology, nephrology, urology and orthopedics. He walks with orthoses. He performs regular enemas to establish fecal continence. He has continued intermittent catheterization, had multiple intravesical Botox injections, a detrusorectomy and a bladder augmentation without achieving full urinary continence. He has a normal renal function.

Discussion

CRS is also known as caudal dysplasia syndrome, caudal agenesis, sacral agenesis, sacral dysgenesis or regression. Duhamel was the first to use the term CRS to describe this entity in 1961(1). The incidence is estimated to be 1-5/100.000 live births (2).

Pathoembryogenesis and Etiology

CRS is caused by a developmental failure in the secondary neurulation during the early stages of gestation. Secondary neurulation comprises further neural development of the caudal cell mass occurring distal to the caudal neuropore after completion of primary neurulation. The caudal cell mass gives rise to the caudal spinal cord distal to S2 (conus medullaris), the filum terminale and the distal nerve roots by canalization and retrogressive differentiation in the fifth week of gestation. Besides the formation of the caudal spinal cord, the caudal cell mass is also involved in the formation of the sacrum and the development of the primitive cloaca into the genitourinary tract and anorectal organs (3,4).

If also part of the true notochord fails to develop, both the primary and secondary neurulation processes are affected (5). Depending on the severity of the original damage, the final degree of vertebral aplasia will range from absence of the coccyx to aplasia of all coccygeal, sacral, lumbar, and lower thoracic vertebrae (2,5,6).

The exact cause of the insult is unclear but maternal diabetes is the most associated environmental factor (3). The prevalence of CRS is reported to be 200 times higher in diabetic pregnancies (7,8). Most cases are sporadic but Currarino syndrome, a dominantly inherited sacral agenesis, is often associated with mutations within the HLXB9 gene (9,10). Other associated factors include teratogens, such as retinoic acid, and vascular anomalies that alter blood flow (3,11).

Clinical manifestations

Patients with CRS present with a broad range of symptoms or features. This is illustrated in Tables 1 and 2 by the presenting features of CRS patients found in the literature. Classic external features consist of shortened intergluteal cleft, small gluteal masses, flattened buttocks, bilateral buttock dimples, narrow hips, distal leg atrophy, and talipes deformities, with or without proximal joint deformities and contractures (3). Other orthopedic anomalies include caudal vertebral agenesis (usually sacrococcygeal), vertebral dysplasia or agenesis, hip dysplasia, popliteal webbing, frog leg position and in extreme cases, sirenomelia (3).

Although the neurological manifestations include both motor and sensory deficits, motor impairment is usually predominant with relative sparing of the sensory function (2). Patients with CRS present with a a broad spectrum of disability, ranging from individuals who can walk to complete limb hypotrophy. Several reports show that the motor level corresponds well with the level of the vertebral defect (3,6). High sacral defects correlate with more severe motor deficits and short conuses that are blunted, club or wedge shaped and have lost their usual taper, as if the caudal portion is missing (3,12). Low sacral malformations are associated with conuses that are extremely elongated to well below L1 and are variously tethered by thick filums or distended by large terminal hydromyelia (3). Neurological symptoms may be progressive in case of an associated tethered cord (6).

The incidence of genitourinary anomalies is reported to be approximately 72% (13). The most common anomalies include neurogenic bladder, renal dysplasia or agenesis and impaired renal function. Hydronephrosis, dysplasia or agenesis of other parts of the genitourinary system and renal ectopia have also been described (13,14). Urinary incontinence

Table 1: Presenting features of patients with caudal regression syndrome published in the last five years. (NR: Not reported, M: male, F: Female).

Cases	Age at diagnosis	Sex	Main presenting feature(s)	Spinal anomalies	Other anomalies present?
Ferreira et al., 2021	Newborn	F	Prenatal suspicion of spina bifida occulta: meningocele with lowered medullary cone. Neonatal diagnosis Currarino syndrome with recto-sacral mass	Partial sacral agenesis, anterior myelomeningocele, spinal cord tethering, cone in L4	Gastro-intestinal
Soltani et al., 2018	Newborn	M	Paraplegia, atrophic legs, and flexion contracture both knees	Vertebral column ending to dysplastic L2 vertebra. Club shape conus T12 level.	Limb, genitourinary
Mehdi et al., 2021	Newborn	M	Widely spaced nipples, slanting eyes, low set ears, underdeveloped genitals and lower limbs. Curved spine with thoracolumbar dimple and hair growth.	Total sacral and partial lumbar agenesis. Not further reported.	Limb, genitourinary, cardiac
Bevanda et al., 2020	Newborn	M	Anus atresia and rectovesical fistula	Sacral agenesis below S2, Cone ending T11-12 level.	Limb, genitourinary, gastro-intestinal, cardiac
Ponde et al., 2021	3 days	M	Anorectal malformation	Sacral agenesis below S3. Not further reported.	NR
	14 months	M	Congenital talipes equinovarus deformity	Total sacral agenesis. Not further reported.	Limb, other not reported
Mwamanenge et al., 2023	2 months (born 30 weeks gestation)	M	Respiratory distress syndrome due to transposition of great arteries with large VSD, bilateral hip and knee flexion contracture, dimples femoral trochanter area, short neck, low-set ears, undescended testes and microphallus	Complete agenesis lumbar, sacral and coccygeal spine. Not further reported.	Limb, genitourinary, gastro-intestinal, cardiac
Khandelwal et al., 2020	2 months	NR	Bilateral talipes equinovarus	Complete sacral agenesis. Wedge-shaped cone ending T12 level.	Limb, genitourinary
Dayasiri et al., 2020	2 months	M	Narrow pelvis, dimpled buttocks, bilateral knee flexion contractures, leg muscle atrophy, congenital talipes equinovarus, microphallus, displaced patulous anus, and constant leakage of urine and stools	Agenesis L5 and below. Thickened cone ending L1 level.	Limb, genitourinary, gastro-intestinal
Diallo et al., 2022	5 months	M	Chronic constipation	Agenesis L3 and below. Squared cone ending T11 level, with tapering ending L2 level. Syrinx T11-L1 (17 x 1 mm)	Limb, gastro-intestinal
Khanna et al., 2019	8 months	M	Anal imperforation and superior vesical fissure	Sacral agenesis, not further specified.	Genitourinary, gastro-intestinal
Karthiga et al., 2021	8 months	M	Reduced movement of lower limbs	Dysplastic L5 and S2 vertebra, Sacral agenesis S3-S5. Low lying conus with thickened filum terminale and tethered cord, dorsolumbar syringohydromelia.	Limb
Hage et al., 2020	13 months	F	Chronic urinary bladder infections	Sacral agenesis S3-5. Drumstick-shaped cone ending L1 level.	Limb, genitourinary
Ali Akhaddar, 2020	2 years	M	Walking disability and sphincter incontinence (hypoplastic and akinetic lower extremities)	Agenesis below T9. Abrupt termination cone at T6 level.	Limb
Kang et al., 2021	31 months	M	Chronic constipation	Agenesis distal sacrum. Club-shaped cone ending at T12/L1 level, thickened filum terminale.	Gastro-intestinal, genitourinary, hearing impairment
Graul et al., 2019	18 years	F	Scoliosis and back pain	Partial sacral agenesis below S2, only 4 lumbar vertebrae, cone ending at S1/S2 level	No
Shin et al., 2019	29 years	F	Pelvic mass identified during a routine gynecological examination, chronic constipation	Asymmetrical sacral agenesis below S2 level right, below S4 level left. Anterior sacral meningocele.	Genitourinary, gastro-intestinal
Rebelo et al., 2020	48 years	M	Chronic constipation after anal imperforation correction surgery	Right partial sacral agenesis. Not further reported.	Gastro-intestinal

Table 2: Radiographic features in prenatal diagnosis of caudal regression syndrome published in the last five years. (NR: Not reported, M: Male, F: Female).

Cases	Age at diagnosis	Sex	Radiographic features
Taylor et al., 2019	21 weeks gestation	NR	Complete sacrococcygeal agenesis, abnormalities lumbar vertebrae at L4-L5, atrophic lower limbs, mild bilateral talipes.
Mahmoud et al., 2023	24 weeks gestation	NR	Sacral agenesis and abrupt termination of lumbar spine at T12/L1 level. Spinal cord stops at the mid-thoracic level.
	29 weeks gestation	NR	Malaligned spine with mild thoracic kyphosis, absent lumbar lordosis and absent sacral spine. The spinal canal appears wide and ends abruptly. Termination spinal cord just below level of fetal kidneys. Ventricular septal defect, and two vessels umbilical cord.
Zhang et al., 2019	26 weeks gestation	NR	Shorter spine, partial agenesis lumbar and sacrococcygeal vertebrae. Flexed lower limbs without movement, left-sided talipes varus, situs ambiguous with levocardia, complex congenital heart defect (heterotaxy syndrome).
Kylat & Bader, 2020	30 weeks gestation	F	Hypoplastic lower limbs with bilateral clubfoot, low vertebral and sacral anomalies, polyhydramnios.
Charach et Yagel, 2021	30 week gestation	NR	Polyhydramnios, horseshoe kidney, a missing lumbar and sacral vertebral column.

and/or constant dribbling are the most frequent urological symptoms among children aged four and older (85%) (6). Recurrent urinary tract infections are also common (74%), sometimes leading to end-stage renal disease (6).

Gastrointestinal anomalies include imperforate anus, anorectal atresia, fistulas, esophageal or duodenal atresia, bowel incontinence, or obstipation, with a reported overall incidence of approximately 42% (13). CRS occurs in approximately 13 to 54% of patients with imperforate anus, necessitating a thorough assessment of neonates with imperforate anus (6).

In 24% of patients, CRS may be associated with pulmonary hypoplasia or dysplasia and congenital cardiovascular anomalies, such as patent ductus arteriosus, ventricular septal defect, atrial septal defect, vascular anomalies of the pulmonary artery and aorta and its branches (13).

Because multiple systems are often involved, CRS may be a component of complex syndromes, including VACTERL (vertebral anomaly, anal atresia, cardiac anomaly, tracheoesophageal fistula, renal anomaly, limb anomaly), OEIS (omphalocele, cloacal exstrophy, imperforate anus, spinal defects), and Currarino triad (caudal agenesis, presacral mass, anorectal anomalies) (2).

Diagnostic workup

Prenatal ultrasound is a sensitive tool for the diagnosis of major defects. Diagnostic features are most commonly a sudden interruption of the spine due to the absence of vertebrae, disproportionately smaller lower extremities, and a froglike position of the lower limbs. Transvaginal ultrasound has proven to be an effective tool for earlier prenatal detection of CRS (15). In the first trimester CRS can be suspected by observing of a short crown-rump length or an increased nuchal translucency measurement (15,16). Prenatal magnetic resonance imaging is valuable to assess the degree of vertebral body dysgenesis and genitourinary, gastrointestinal, and musculoskeletal anomalies.

As in our patients CRS is often diagnosed postnatally in cases with more subtle clinical signs at presentation. Postnatal investigations were performed in the first case because of obstipation with a sacral dimple and, in the second case because of an imperforate anus with a neurogenic bladder.

Postnatal evaluation for CRS should include plain abdominal radiographs and ultrasound of the spine and kidneys. MRI of the spinal cord is indicated in all cases with signs of spinal dysraphism or CRS, such as vertebral or midline cutaneous abnormalities, imperforate anus, neurogenic bladder or other urogenital anomalies (6). In the presence of urinary tract abnormalities, a thorough urological evaluation is recommended to prevent irreversible renal damage secondary to urinary incontinence and urinary tract infections. A voiding cystourethrogram is needed to rule out vesicoureteral reflux.

A classification system described by Pang et al. depends on the amount of remaining sacrum and the articulation between the pelvis and the spine (3). Notably, the motor level closely aligns with the level of the vertebral defect (3,6). This structured framework serves as a valuable tool for consistent documentation, outcome prediction and effective treatment planning. Pang's classification divides CRS into five types (3). It identifies the complete absence of the sacrum with or without lumbar vertebrae agenesis as type I and II respectively. Type I and II are further divided into type Wide (W) and Narrow (N) based on the position of the ilia. In type W the ilia articulate with the lateral sides of the lowest vertebrae, whereas in type N the caudal endplate of the lowest vertebrae is resting above the articulate or fused ilia. In type III, S1 is present but the lower sacral segments are missing to varying degrees. Type IV consists of various forms of hemisacrum. Type V includes total to subtotal coccygeal agenesis (2,3).

Treatment and Prognosis

Prognosis depends on the severity of spinal involvement and associated malformations. If vital systems are unaffected, infants with CRS are expected to survive and they usually have a normal mental function (6,17). Although patients with CRS patients face many challenges, most have a good quality of life (14). Most children are ambulatory (18). Early diagnosis and supportive management of the associated anomalies are very important to prevent further consequences. For example, neurogenic bladder was present in both our cases. Early intervention with catheterization or anticholinergic drugs to prevent renal damage is warranted. These cases corroborate the importance of a multidisciplinary approach and long-term follow-up.

Conclusion

Caudal regression syndrome is a rare congenital disorder with a variable presentation. Various anomalies of the lumbosacral spine, nervous system, lower limbs, anorectal complex and genitourinary tract can be present. This entity should be considered when a child presents with anomalies of the sacrum, lower limbs or suffers from chronic constipation or neurogenic bladder. Early diagnosis and multidisciplinary follow-up may prevent further complications.

Conflicts of interest

The authors declare no conflict of interest.

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