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CASE REPORT

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Caudal regression syndrome—case report and review of literature

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Abstract Caudal regression syndrome is a rare disorder of distal spinal segments affecting the development of the spinal cord, with attendant sequelae. Intelligence is preserved. The exact etiology is elusive, though maternal diabetes, genetic factors, and hypoperfusion might play roles. Recently, the role of teratogens has been studied in animal models. Treatment is difficult, multidisciplinary, and largely supportive. Lower limb deformities with sensory and motor loss and neurogenic bladder call for intensive and long-term attention.

Keywords Caudal regression syndrome · Caudal dysplasia sequence · Sacral agenesis · Congenital malformations

Introduction

Caudal regression syndrome (CRS) is a rare and sporadic neural tube defect affecting terminal spinal segments. It manifests as total neurological deficit in the lower limbs and loss of bladder and bowel control. Several associated anomalies of other systems are frequently present and complicate the picture. A case report is presented, and the literature is reviewed.

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Case report

A 2.5-year-old boy, with a colostomy fashioned at birth for imperforate anus, was brought for further management and colostomy closure. He was the offspring of a nonconsanguineous marriage. His mother was not a diabetic. There was no other significant history, and an antenatal ultrasound had not been done. At birth he had lower limb deformities and imperforate anus, and a loop colostomy in the left upper quadrant was performed. There was a history of occasional dribbling of urine, though sometimes he passed in stream as well. On examination he was active and alert, in satisfactory general health, and had passed normal mental milestones. However, he had a significantly smaller and uniformly hypoplastic lower segment (Fig. 1). There was total sacral and partial lumbar spinal agenesis. He had small buttocks, a flat perineum, a short natal cleft, and dimples at the lateral aspects of his hips and knees. His hips were flexed and abducted, and popliteal webs were present. Equinovarus deformity was also present. He had severe anal stenosis (probably mistaken for imperforate anus at birth), left undescended (nonpalpable) testis, and short penis. Surprisingly, he was able to move his lower limbs, had sensations in the lower limbs and perineum, and had a weak anocutaneous reflex. The bladder was expressible. Other systems were clinically normal.

X-ray of the lower segment showed absence of all sacral and distal lumbar vertebrae, resulting in the fusion of iliac bones in the midline (Fig. 2). The bones of the limbs were hypoplastic with absent fibulae. Ultrasound revealed left renal agenesis with a normal right kidney. A distal cologram showed short but otherwise normal bowel. The urine was clear and renal biochemistry normal. A micturating cystourethrogram showed a fairly good capacity, smooth-walled bladder with no reflux. The bladder neck appeared open, and postvoiding residue was minimal. A urodynamic study could not be done due to financial constraints.

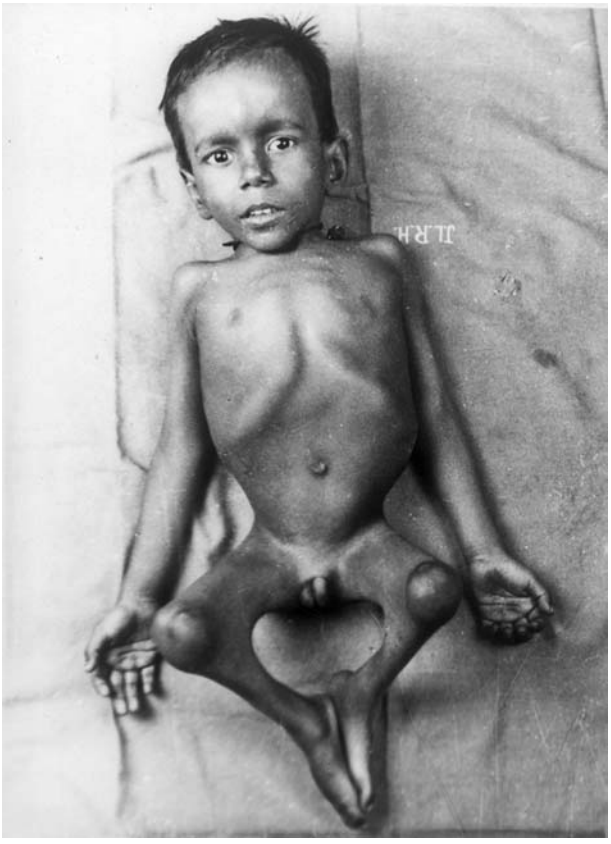

Fig. 1 A 2.5-year-old boy with caudal regression syndrom

The prognosis and natural history were explained to the parents, who agreed to the treatment. Anal cutback was done and a dilatation regime started. Perineal exercises were advised. The colostomy was closed after 8 weeks. Surprisingly, the boy showed satisfactory fecal continence in conjunction with dietary modifications and medications. In the same sitting, the first stage of the Fowler–Stephens orchiopexy was also carried out for left intraabdominal testis. The child is under regular follow-up, although the parents have refused any further work-up or interventions.

Discussion

CRS is a rare and usually sporadic disorder. It comprises developmental anomalies of the caudal vertebrae, neural tube, urogenital and digestive organs, and hind limbs, the precursors of all of which are derived from the caudal eminence [1]. This may result in various types of anorectal malformations, agenesis of spinal segments (usually sacral or lumbosacral), and multiple visceral anomalies [2]. In the most severe cases, the lower limbs are fused, also known as sirenomelia or mermaid syndrome. However, there is evidence suggesting that CRS and sirenomelia are different. The latter is supposedly the result of an early vascular aberration leading to a "vitelline artery steal" [3], whereas CRS is a heterogenous disorder inasmuch as the etiology and pathology are concerned [4]. Nevertheless, recent advances in the understanding of axial mesoderm patterning during early embryonic development suggest that sirenomelia represents the most severe end of CRS [5].

CRS is also referred to in the literature as caudal dysplasia sequence, sacral regression syndrome, and sacral agenesis. Duhamel coined the term CRS to describe this entity, which is a consequence of abnormal development of the structures derived from the caudal mesoderm of the embryo before the 4th week of gestation [6]. Some 300 cases have been reported so far [7]. The incidence is estimated to be approximately 1:60,000 births, with a male:female ratio of 2.7:1 [3]. This anomaly is not thought to be hereditary, and the recurrent risk is very small, although it is higher in diabetics [9].

The exact etiology [1, 4, 8, 10–16] and pathogenetic mechanisms are poorly understood, but maternal diabetes, genetic predisposition, and vascular hypoperfusion have been proposed. The syndrome occurs about 200–250 times more frequently in infants of diabetic mothers [17]. But because it has been found that 16–22% of the mothers of these patients have diabetes, it is clear that the syndrome is not specific to diabetes. Pregestational diabetes is undoubtedly a teratogen, and there is good evidence that gestational diabetes can be involved in the development of the most severe form of CRS [18].

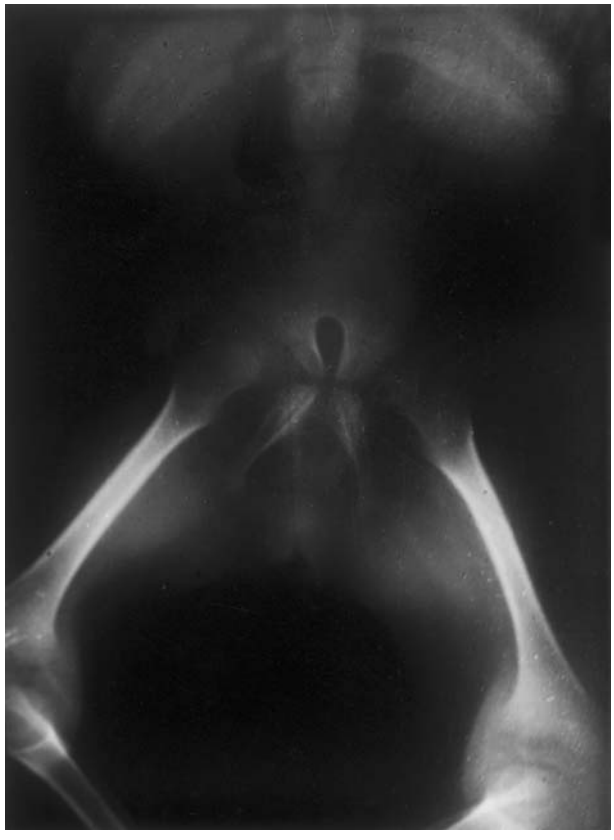

Fig. 2 X-ray of child's lower segment showing absence of all sacral and distal lumbar vertebrae, with fusion of iliac bones in the midline

Some of the parents have been found to have spina bifida occulta, suggesting a possible role of genetic factors. A recent experimental study looked at the role of retinoic acid in producing CRS in the mouse fetus [1]. Retinoic acid, when given in variable dosages to TO mouse fetuses, resulted in CRS in most of the survivors. They were found to have, in various combinations, agenesis of the tail, caudal vertebral defects, spina bifida occulta/aperta, imperforate anus, rectovesical or rectourethral fistula, renal malformations, cryptorchidism, gastroschisis, and limb malformations, including the classic mermaid syndrome. Histology revealed, in chronological order, pronounced cell death in the caudal median axis, hindgut, and neural tube, and consequently, failure of development of the tail bud in the high-dose group. In the low-dose group there were patches of hemorrhage, which subsequently coalesced into large hematomas, and the tail progressively regressed. Thus, this model showed a combination of cell death, vascular disruption, and tissue deficiency as the highlight of caudal regression. Low doses produced caudal regression, while high doses resulted in caudal agenesis. Also, high anorectal malformations have been induced in mice by all-trans retinoic acid [19].

In another case, a possible drug-related etiology for extreme caudal agenesis in a human fetus has been suggested [20]. The mother had used minoxidil solution for hair loss 4 years prior to and during gestation. She also received trimethoprim-sulfamethoxazole during the 1st trimester for an upper respiratory problem. There was no history of maternal diabetes or familial genetic diseases.

All of these studies and reports strongly suggest the teratogenic role of various chemicals in the genesis of CRS.

Pathology

The syndrome is the result of a neural tube defect that occurs before 28 days of gestation [21, 22]. Important defects are structural, with their secondary functional effects on the relevant systems seen in different combinations [10–14, 23, 24] (Table 1). The syndrome has a number of associated anomalies [2, 4, 25] (Table 2), again attesting to its heterogeneous nature. In a unique case report there was penile enlargement [26], while in another there was Alagille syndrome [27] along with the CRS.

Table 1 Pathology of caudal regression syndrome

Primary structural defect	Secondary effects
Agenesis/incomplete development of sacral /lumbar/thoracic vertebrae	Disruption of the appropriate length of distal spinal cord; flat buttocks, short natal cleft, and dimples in the buttocks
Spinal cord disruption	Neurological deficits affecting lower limbs (sensory and motor) and bladder and bowel continence; severely hypoplastic lower segment
Lack of movement in lower limbs	Lack of growth in affected parts; flexion and abduction at the hips; popliteal webs

Table 2 Associated anomalies in caudal regression syndrome

System involved	Anomalies/defects
Musculoskeletal system	Equinovarus and calcaneovarus, flexion contractures of hips and knees, hip dislocation, pelvic deformity, absent fibula, scoliosis, kyphoscoliosis, absence of ribs, bifid/fused ribs, syndactyly, polydactyly, hypoplastic/absent radii, Pierre-Robin syndrome
Gastrointestinal system	Anorectal malformation, tracheoesophageal fistula, abdominal wall defects, malrotation of gut, duodenal/ colonic atresia, inguinal hernia
Genitourinary system	Renal agenesis and dysplasia, nonspecific hydronephrosis, dilated ureters, ectopic ureters, vesicoureteral reflux, fused kidneys, absent bladder, vesical/cloacal exstrophy, rectovaginal and rectourethral fistulae, transposition of external genitalia, hypospadias, urethral atresia, mullerian duct agenesis
Miscellaneous	Myelomeningocele, hydrocephalus/ ventriculomegaly, congenital heart defects, facial clefts, strabismus, latex allergy

Diagnosis

Classic features are suggestive. Prenatal diagnosis by ultrasound is possible at 22 weeks of gestation, seen as sudden interruption of the spine due to absence of vertebrae and a frog-like position of the lower limbs [28]. However, sirenomelic fetuses have been diagnosed at 16 and 19 weeks' gestation [5] by the transvaginal route. First-trimester diagnosis is difficult because of incomplete ossification of the sacrum at that time. However, a short crown-rump length and abnormal appearance of the yolk sac have been proposed as early ultrasonographic signs of CRS [29]. In a recent case report, CRS was diagnosed antenatally after detection of a large nuchal translucency, although the diagnosis was not confirmed until 16 weeks [7]. Sonographic findings are variable, depending on the defect's extent and severity [30]. Because the syndrome is not associated with aneuploidy, a fetal karyotype is not warranted [30].

Treatment

The treatment is challenging for the treating physician as well as for the parents and calls for a multidisciplinary approach involving the pediatrician, pediatric surgeon,

orthopedic surgeon, physiotherapist, and social worker. Because the primary pathology is irreversible, the treatment is only supportive, with an aim to achieve as much normalcy as possible. Each system and its pathology are treated on their own merits. The pathologies that need special attention are orthopedic deformities and bladder and bowel continence, along with preservation of renal function. This helps the child to be independent and socially useful with a better quality of life. Scoliosis is the most common anomaly associated with lumbosacral agenesis, though no correlation has been found. Patients with types I and II sacral agenesis have an excellent chance of becoming community ambulators [31, 32]. Treatment of types III and IV sacral agenesis is controversial. The physiotherapist's role is crucial and cannot be overemphasized.

Prognosis

Survival is the rule if the vital systems are unaffected or minimally affected. These patients have normal intelligence and therefore lead otherwise normal lives except for neuromuscular deficits of the lower limbs and sphincters. However, secondary neurogenic bladder leading to progressive renal damage and deterioration of renal function remains an important comorbid factor; therefore, extensive and long-term urologic attention is needed.

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