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Understanding Caudal Dysplasia Sequence: Three Case Reports

Monica Kansal[1,2] Sanheeta Dasgupta[3] Tanveer Aujla[4] Manju Gupta[4] Gaurav Kumar[5]

[1] Department of Radiology, Kaashi Ultrasound Clinic, Noida, Uttar Pradesh, India
[2] Department of Radiology, Yatharth Superspeciality Hospitals, Noida, Uttar Pradesh, India
[3] Department of Obstetrics and Gynecology, Cloud Nine Hospital, Motherhood Hospital, Noida, Uttar Pradesh, India
[4] Department of Obstetrics and Gynecology, Motherhood Hospital, Noida, Uttar Pradesh, India
[5] Department of Physical Education, Hans Raj College, New Delhi, India

Address for correspondence Dr. Monica Kansal, MBBS, DMRD, DNB, Kaashi Ultrasound Clinic, D 196, Sector 108, Noida 201304, Uttar Pradesh, India (e-mail: rudrakshi0402@gmail.com).

J Fetal Med

Abstract

Caudal dysplasia or caudal regression sequence is a congenital malformation that is characterized by maldevelopment of the lower half of the body with variable involvement of the gastrointestinal, genitourinary, skeletal, and nervous system. Most cases are sporadic and associated with the presence of a single umbilical artery. We report three cases with varying morphological spectrum of caudal dysplasia diagnosed during the first trimester ultrasound.

Keywords

- caudal dysplasia
- caudal regression sequence
- single umbilical artery
- sirenomelia
- vascular steal

Introduction

Caudal dysplasia is a rare congenital malformation with an incidence of 0.01 to 0.05/1,000 in routine risk pregnancies and 200 times higher in diabetic pregnancies.[1–3] It is characterized by variable degrees of sacral agenesis, pelvic deformities, femoral hypoplasia, clubbed feet, and flexion contractures of lower extremities. Additionally, there can be associated severe malformations of a urogenital system like renal agenesis/dysgenesis, malformed genitalia, and gastrointestinal tract like imperforate anus. This malformation sequence is incompatible with life.

Sirenomelia is an extreme form of caudal regression characterized by a fusion of the lower limbs and a variable combination of associated anomalies.[4]

Case Reports

Case 1

A 30 year old primigravida spontaneous conception came for a routine first trimester scan at gestation of 12 weeks and 1 day. There was no history of consanguineous marriage, maternal diabetes, or drug intake. The scan findings revealed a dichorionic diamniotic (DCDA) twin live intrauterine gestation. A crown–rump length (CRL) discordance was observed. Twin A was normal in growth, morphology, and genetic markers. Twin B revealed growth lag with shortened length (corresponding to ~11 weeks) and nonvisualized distal spine and sacrum (►**Fig. 1**). Both lower limbs of the affected fetus revealed fixed flexion at the hip and knee joints giving a cross-legged tailor or the Buddha position

DOI https://doi.org/10.1055/s-0044-1786354.
ISSN 2348-1153.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

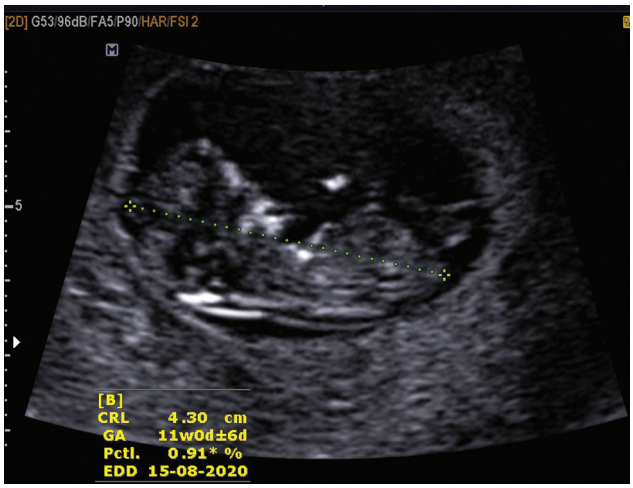

Fig. 1 Case 1. Twin B depicting shortening of the crown rump length (CRL).

(►**Fig. 2**). A single umbilical artery (SUA) was noted (►**Fig. 3**). An oval cystic structure was seen in the fetal abdomen on the left side. The fetal urinary bladder was visualized separately and appeared normal. The possibility of gastrointestinal or renal malformation or anal atresia was kept.

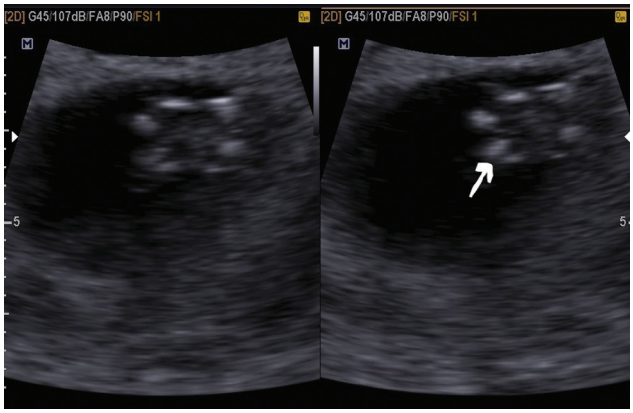

Fig. 2 Case 1. Flexion deformity at knee joint (*white arrow*) giving crossed-leg position.

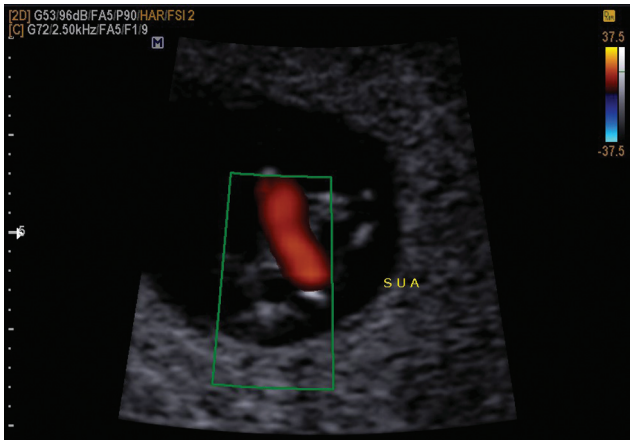

Fig. 3 Case 1. Single umbilical artery (type 1).

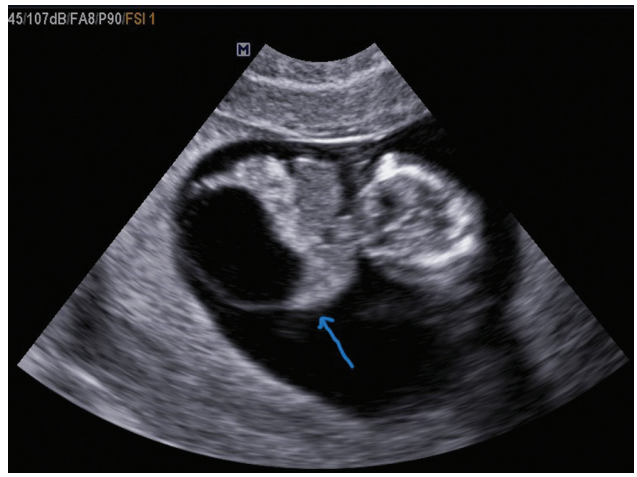

Fig. 4 Case 2. Anterior abdominal wall defect with herniating liver and intestines (*blue arrow*).

The patient underwent selective fetal reduction for the malformed fetus at a tertiary care center. She was followed up every 2 weeks till 20 weeks and every 4 weeks thereafter. She had an uneventful antenatal period. She had a normal glucose tolerance test at 29 weeks and no gestational diabetes.

Case 2

A 32 year old primigravida with spontaneous conception visited our clinic for a routine first trimester scan at 12 weeks and 4 days of gestation. She was a nondiabetic and a nonsmoker, and she was not taking any other drugs.

The scan revealed a single live intrauterine gestation with a fetal CRL corresponding to 11 weeks and 2 days suggestive of growth lag. A large anterior abdominal wall defect was noted with herniating liver, intestines, and stomach in a cystic sac covered by a thin membrane (►**Fig. 4**). The umbilical arteries were replaced by a tortuous single artery with an aberrant course (►**Fig. 5**). The umbilical cord consisted of two vessels and inserted left paramedian into the protruding abdominal viscera. The sacrum was poorly

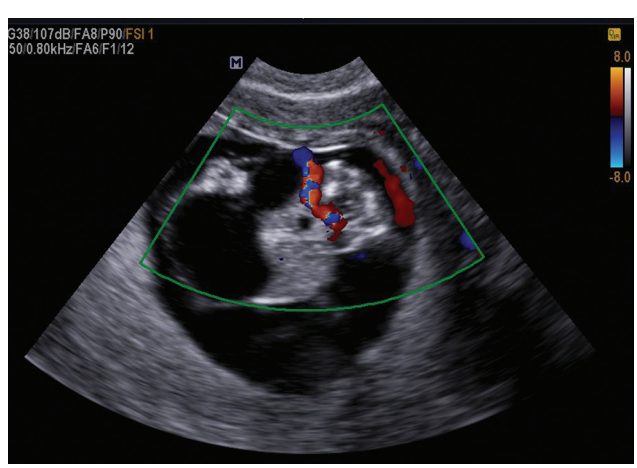

Fig. 5 Case 2. Single tortuous aberrant artery of vitelline origin—type 2 single umbilical artery.

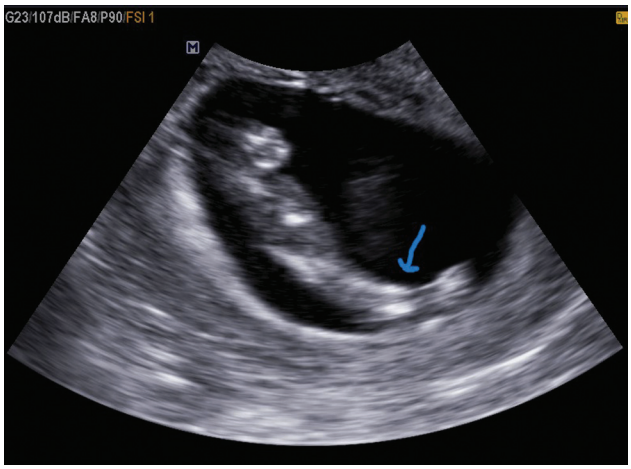

Fig. 6 Case 2. Two femurs and two tibias visualized with absent bilateral fibula—sirenomelia (*blue arrow*).

visualized. The fetal lower limbs were fused to from a single lower limb with restricted movements. Two femurs and two tibias were visualized with absent fibulas: sirenomelia (►**Fig. 6**).

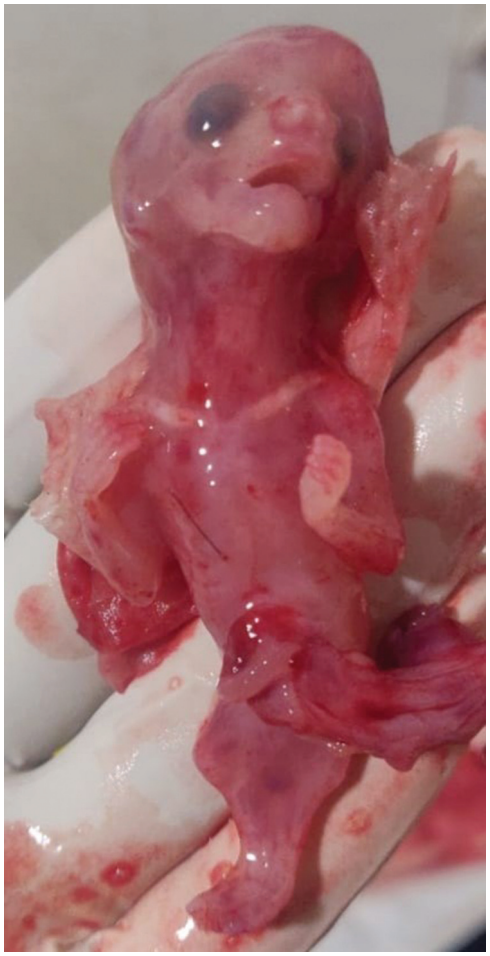

Fig. 7 Case 2. Abortus after termination depicting fused lower limbs and anterior abdominal wall defect.

Based on these findings, the patient was referred to the fetal medicine department for a chromosomal microarray but refused to undergo the procedure and opted for termination. Post-termination morphology of the abortus confirmed the findings (►**Fig. 7**). The sample was sent for chromosomal microarray which revealed normal study.

Case 3

Our third patient was a 35 year old primigravida who conceived after prolonged infertility treatment by in vitro fertilization (IVF) and frozen embryo transfer. The viability scan done at 6 weeks revealed a DCDA twin live intrauterine gestation. She was nondiabetic and normotensive with no significant medical history.

Routine first trimester screening was done at 12 weeks and 6 days of gestation. Twin A revealed normal morphology, growth, and genetic markers. Twin B was normal in growth. However, the morphology revealed absence of fetal right foot and distal segment of the right lower limb indicating a limb reduction defect (►**Fig. 8**). All segments of the left lower limb were present. The presence of an SUA was noted (►**Fig. 9**). A well-marginated intra-abdominal cyst was seen in the left side of the abdomen visualized separately inferior to the stomach. The fetal bladder was visualized separately. A possibility of anal atresia, enteric origin, or renal origin was considered (►**Fig. 10**).

The patient refused any invasive diagnostic procedure and underwent selective fetal reduction of the malformed fetus elsewhere. She was advised to rest with routine antenatal care and followed up every 2 weeks. She had episodes of spotting in the third trimester and was kept on conservative management. Her glucose tolerance test done in the third trimester revealed normal sugar levels.

Discussion

Caudal dysplasia sequence is also known as caudal regression syndrome (CRS). Sirenomelia is considered a severe form of CRS characterized by fusion of the legs and a variable

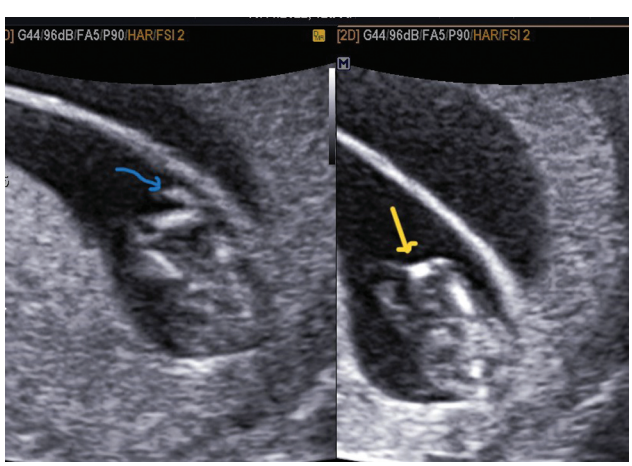

Fig. 8 Case 3. Absence of fetal right foot (*yellow arrow*). In contrast, the fetal left foot is well visualized and normal (*blue arrow*).

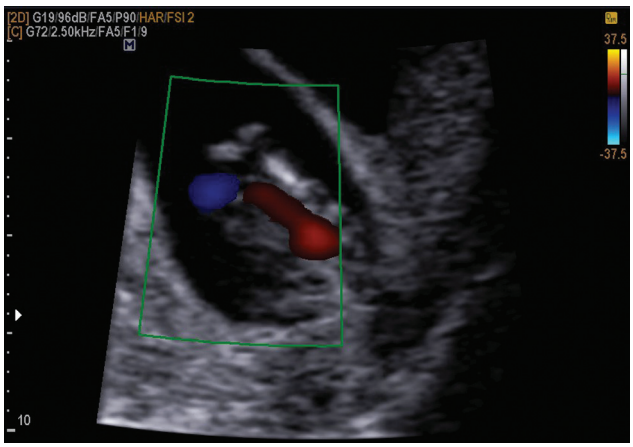

Fig. 9 Case 3. Single umbilical artery type 1.

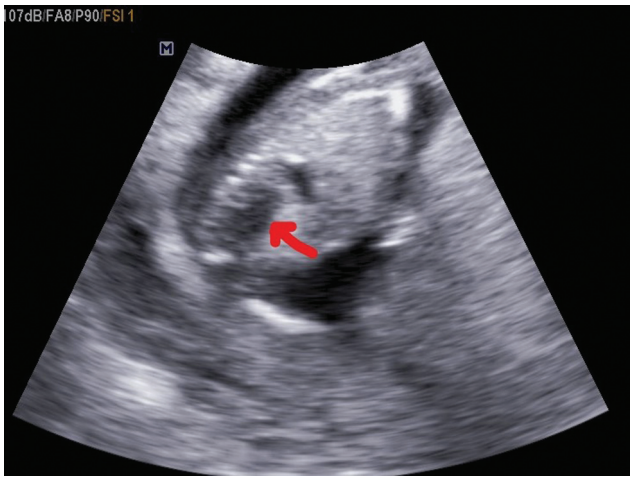

Fig. 10 Case 3. Intra-abdominal cyst on the left side of the abdomen visualized separate from and inferior to fetal stomach (*red arrow*).

combination of other abnormalities.[1] The prevalence of sirenomelia is approximately 1 in 100,000 live births.[1,2]

Caudal dysplasia sequence consists of a spectrum of varied combinations of anomalies involving musculoskeletal, gastrointestinal, genitourinary, and central nervous systems. The common factor in these abnormalities relates to defects in the development of caudal mesoderm and its derivatives.

There is underlying developmental disruption of structures derived from the caudal mesodermal axis of the embryo during the primitive streak stage.[5] Two important theories that have been proposed to explain the cause are the vascular steal hypothesis and the defective blastogenesis hypothesis.[6] Poor glycemic control in diabetic mothers before the eighth week of development exposes the embryo to hyperglycemic insult.[2]

The remarkable finding in our first case that led to suspicion was discordant CRL between twins.

In all our cases, no history of maternal diabetes was evident. Two of the conceptions were DCDA twins with the unaffected twin appearing normal in morphology, growth, and genetic markers. This reduces the possibility of maternal factors as the causative role.

One of the conceptions was IVF gestation with frozen embryo transfer after prolonged treatment for infertility.

A finding that was common to all three of our cases was the presence of an SUA.

SUA is a condition in which the cord has only one artery and one vein. It is seen in 0.5 to 6% of pregnancies.[7] It can be an isolated finding but shows an association with multiple congenital and chromosomal abnormalities. Umbilical cord formation starts between 3 and 5 weeks of gestation with a fusion of the yolk sac and body stalk. It consists of three vessels: two arteries and one vein. The umbilical arteries arise from allantois and carry deoxygenated blood from the fetus to the placenta. One of the umbilical arteries may undergo primary agenesis or secondary atresia with the persistence of a single allantoic artery of the body stalk resulting in an SUA (type I). Sometimes due to the failure of the development of the allantoic system, the embryonic circulation is supplied by the vitelline system where a single aberrant artery arising from the superior mesenteric artery (SMA) takes over the role of the umbilical artery (type II SUA). This results in vascular steal as minimal blood circulates through the distal aorta and caudal region of the embryo, and which becomes hypoplastic.[3,7]

It is a sporadic condition and fetal karyotyping is usually normal. However, despite the complexity of the phenotype, some studies have identified some common genetic features in CRS patients on whole exome sequencing. Involvement of genes such as HOXD13, CYP26A1, and HLXB9 has been suggested. CYP26A1 is a gene regulating retinoic acid catabolism and is upregulated by the CDX2 gene. Thus, variations in the CDX2 gene affect retinoic acid bioactivity.[8] Mutations and pathogenic variations in HLX B9 on chromosome 7 (causing Currarino's syndrome) and VANGL1 on chromosome 1 have also been associated.

An overlap in the phenotypic components of several distinct patterns of malformations predominantly affecting caudal structures has been observed. A common pathogenesis has been proposed for six such patterns of malformations such as sirenomelia, VACTERL (vertebral anomalies, anal atresia, cardiac anomalies, cleft lip, tracheoesophageal fistula, renal anomalies, radial ray anomalies, limb anomalies) complex, OEIS (omphalocele, exstrophy bladder/cloaca, imperforate anus and spinal defects) complex, limb–body wall defect (LBWD), urorectal septum malformation sequence, and MURCS (Mullerian duct aplasia–renal agenesis–cervicothoracic somite dysplasia) association. The presence of type 2 SUA has been observed in all cases of sirenomelia, and 30 to 50% cases of VACTERL association, OEIS complex, URSM (urorectal septum malformation) sequence, MURCS, and LBWD.[9]

Type 2 SUA was observed in case 2 and type 1 SUA in cases 1 and 3.

A cystic lesion was observed on the left side of the abdomen in cases 1 and 3. The stomach and urinary bladder were visualized separately in both of them. Transvaginal assessment was done and the possibility of anal atresia or renal pyelectasis was considered. A definitive diagnosis could not be made because of early gestation.

An abdominal wall defect was observed in one of the patients. The probable pathogenesis was the vitelline vascular steal causing maldevelopment of the abdominal wall musculature.

Based on the type of defect and articulation between bones, Renshaw and Pang classified CRS into the following five categories[1,10]:

- Type I: total or partial unilateral sacral agenesis.
- Type II: variable lumbar and total sacral agenesis with the ilia articulating with the sides of the lowest vertebrae.
- Type III: variable lumbar and total sacral agenesis with the caudal end plate of the lowest vertebrae resting above fused ilia or an iliac amphiarthrosis.
- Type IV: fusion of soft tissues in both lower limbs.
- Type V: fused bones of lower limbs (also known as sirenomelia).

A varied spectrum of musculoskeletal abnormalities was observed in our patients. Short CRL with nonvisualized distal spine and sacrum and fixed flexion deformity at bilateral hip and knee joints in case 1 (Renshaw and Pang type II), nonvisualized sacrum and fused bilateral lower limbs (sirenomelia) in case 2 (Renshaw and Pang type V), and unilateral absence of the fetal right foot was noted in case 3, suggesting a transverse limb reduction defect. Fetal CRL was normal in patient no. 3, but possible minor or partial defects in sacrum or coccyx could not be ruled out at this gestation. Based on the phenotypic spectrum, the fetus in case 3 was categorized as caudal regression sequence (Renshaw and Pang type I)

According to the defective blastogenesis hypothesis, maldevelopment of the caudal structures in embryos can be a result of toxic and teratogenic insults in the phase of gastrulation. However, no history of any external exposure was obtained in all three of our patients.

The variation in manifestations of caudal dysplasia depends on the intensity, time of initiation, and duration of the underlying event.[6,11]

It is possible that defective blastogenesis affects both organ formation and vascular development, and results in a variable spectrum of caudal dysplasia with sirenomelia as the most severe form.[11]

Implications for Clinical Practice

Caudal dysplasia sequence or CRS is a complex multisystemic disorder of variable spectrum affecting the caudal structures of the fetal body. Based on the spectrum of cases we have discussed, discordant CRL and SUA in the first trimester should raise a suspicion. Sacral ossification centers may not be visible before 12 weeks, so the fetal spine should be assessed after 12 weeks. The phenotypic abnormalities should be categorized into patterns of caudal malformation.

Antenatal management depends on the severity of malformations and the will of the patient to continue. Genetic testing in the form of amniocentesis and chromosomal microarray should be offered to all patients to assess the chances of recurrence.

Funding
None.

Conflict of Interest
None declared.

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