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Case report

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First case report of caudal regression syndrome in a Syrian patient with unusual clinical presentation

Abstract

Agenesis of the sacrum, lumbar and thoracic vertebrae, is a congenital malformation, associated with other complex genetic syndromes.

Sacral agenesis is the partial, or total absence of lower vertebral bodies, can occur isolated or in association with other syndromes including spinal cord anomaly such as (VACTREL syndrome, and Currarino triad).[1]

The incidence of sacral agenesis is 1/50 000 in general population but is 200 times more frequent in infants of diabetic mothers.[2]

Usually, children with sacral agenesis have dysmorphic features; to note that around 20% of the cases are undetected until the age of 3- 4 years old and many are diagnosed after unsuccessful toilet training.

One of the rarest congenital disorders is "**Caudal regression syndrome"** that affects the distal spinal segments and result in sequelae on the development of the spinal cord.

This syndrome has a low incidence in general population, it is characterized by lower limbs deformities with sensory and motor loss, along with neurogenic bladder however, intelligence is conserved.

The exact etiology is vague, yet there is an obvious relation with maternal diabetes. Also, the true cause is still unknown, some theories, state the role of *genetic factors*, *hypoperfusion*, and *teratogens* in the pathogenesis of this syndrome.

Treatment is mostly supportive, and multidisciplinary. Prenatal imaging studies allow for consistent detection and diagnosis. The physical exam and the diagnostic test required in the newborn period help in the detection of probable complications and establishing a prognosis.

We present a clinical case of a girl with a diagnosis of Caudal regression syndrome, describing the workup and management of this patient.

Keywords: caudal regression syndrome, caudal vertebral dysgenesis, caudal vertebral agenesis, sacral agenesis, neural tube defects

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Introduction

The first description of Caudal regression syndrome (CRS) was done in 1852 by Geoffroy Saint-Hilaire and Hohl, but the creation of "caudal regression syndrome" term was done in 1964 by Duhamel.[3]

CRS correspond to a spectrum of clinical phenotypes with different degrees of malformation of the lower body with involvement of structures arising from all 3 layers of the trilaminar embryo.[4]

Caudal vertebral agenesis or dysgenesis are characteristics of CRS. This rare congenital anomaly is very frequently associated with spinal cord malformations, and it has an estimated incidence of approximately 0.1 to 0.25 per 10,000 births[5], with male- female ratio of 2.7:1.3.[3]

Anomaly of the distal spinal segments is a cause of this syndrome, and it spreads to an extensive variety of malformations, such as partial agenesis of the spinal cord, related pelvic deformities, imperforate anus, developmental sexual disorders, bilateral renal dysplasia or aplasia, cardiac problems, pulmonary hypoplasia, and sirenomelia (mermaid syndrome); a congenital anomaly of the lower limbs and the lower spine, characterized by total or partial fusion of legs; one foot, no feet or both feet rotated externally, may be present in affected infants.[6–8]

Moreover, the CRS is associated with high morbidity due to bowel and bladder dysfunction and neurologic deficit.[1]

CRS, is not known to cause mental delay in infants, usually intelligence is conserved, but specific lower limbs deformities are seen, such as hypoplasia of the femur and frog- leg position; a lower extremity flexion contracture.[6–8]

At the embryonic level, CRS is due to the defect in the posterior medial mesodermic axis that occurred prior to the 28th day of gestation in the initiation of caudal elements in the embryo. This defect is responsible of the absence of development of the caudal mesoblastic yolk.[9]

The possible risk factors for CRS are diabetes in mother; either diabetes mellitus, or gestational diabetes, in addition to vascular hypoperfusion, and genetic predisposition, but till now the precise etiology is still unidentified.[10]

The most severe form of the disease may be linked to gestational diabetes, also pre- gestational diabetes, is suspected to be a teratogen.[11]

In early pregnancy, severe hyperglycemia disturbs the closure of the embryonic neural tube resulting in high risk for neural tube defects (NTDs), this will lead to premature maturation, due to decline of

mitosis, cellular disorders, and changes. In fact, maternal diabetes can cause an increase in the production of oxygen- free radicals, due to the alteration of the oxidative metabolism, and this can be teratogenic to the developing embryo.[11]

Around 1% of infants from diabetic mother can have CRS. The association of CRS with diabetes mellitus in the mother; either type I or II, can reach 22% of cases. The risk for development of CRS in a child is 200 to 400 times higher in insulin-dependent diabetic females than in females without diabetes.[12]

In some cases, mutation in the VANGL1 gene can be correlated to CRS, the mode of inheritance of this pathologic variant is autosomal dominant, but the implication of this gene in the pathophysiology of CRS is unspecified.[10]

Some theories, suggests other multiple genetic transmissions with different modes: X-linked dominant, multi-factorial polygenic, with lowered penetrance and different expressivity.[10]

Kampmeier was the first to suggest the "vascular theft" theory in 1927, and this theory was then, re-announced in 1986 by Stevenson. Adra et al., thought Stevenson's "vascular theft" theory as a probable etiology of the CRS pathology.[10]

Through the embryonic development phase, the least caudal structures are isolated from the cephalic elements such as the brain, the spine, and the spinal cord, consequently the absence of cognitive variations in this syndrome.[8]

The CRS includes 2 groups:

The first group is mainly characterized by the end of the spinal cord above L1. The sacrum finishes at S1 and is absent in some cases.

Dysgenesis in the second group is less severe, with a low implantation of the spinal cord and bound by a thickened filum terminale or intraspinal lipoma.[8]

Case presentation

We present the case of a 4-year-old girl, known to have failure to thrive, dysmorphic features, sacral agenesis, popliteal webbing, chronic abdominal distension with bilateral hydronephrosis, with a current weight of 7 kg (below the 5th percentile) from a Syrian first-degree consanguineous parent, and a mother with a medical history of unfollowed diabetes mellitus type II diagnosed 6 years ago, started on insulin injections then switched to oral anti- diabetics.

Diabetes was not controlled during pregnancy, first five months no treatment taken, last HbA1c done was one or two years ago with unknown value, she had also a background of irregular gynecological follow-up, 4 pregnancies with 4 deliveries and one death (at day 4 of life, not investigated).

Mother mentioned that no adequate prenatal follow- up was done, but morphologic echography was performed and was normal. No prenatal complications were present during pregnancy, as per mother, but she took sometimes oral anti-diabetics for peaks of hyperglycemia, HbA1c was not repeated, oral glucose tolerance test not performed.

At a peripheral hospital, C/section was done term for repeat, obtaining a syndromic baby, unknown Apgar score and exact gestational age. At the physical exam birth weight was 3.5 kg (no official documentation available). Post-natal, spine MRI was made for newborn because she has dysmorphic features, showed cysts on the left kidney with hydroureteronephrosis, and thinning of the left renal cortex, right kidney hydronephrosis, complete agenesis of the vertebrae with similar agenesis of the spinal cord, and the spinal cord was ending at T9 with syringomelia from T10 to T12. No past surgical history known.

Currently, patient was presenting for signs of respiratory distress and grunting, two days prior to presentation she started having mild productive cough, along with one episode of post- prandial vomiting and one episode of watery diarrhea. At this time, no fever was documented.

One day prior to presentation, she developed sudden onset of tonic-clonic seizures, for few seconds followed by dyspnea and grunting, without fever or any other associated symptoms.

As by parents, for financial issue, patient was not followed- up regularly by pediatrician, no vaccination done for financial issue, no additional work- up completed to reach a diagnosis.

In ER, patient was looking ill, hypotonic, febrile, tachycardic, tachypneic, she was also in severe respiratory distress, her oxygen saturation was in the late 80 s, oxygen by nasal cannula was given 1L/min but she was still tachypneic she has also one tonic- clonic seizure and she received once Diazepam intrarectally.

Patient has also hyperglycemia, HGT was above 600 mg/dL. Her condition got worse rapidly, she was put on non- rebreather face mask, but her oxygen saturation did not improve so she was intubated immediately, and ABGs was taken showed severe metabolic acidosis (pH 7.03/ pCO_2 16/ pO_2 90/ HCO_3- 4), then she was admitted to PICU for management and investigation.

During inspection we noted, dysmorphic features; patient has circular face, noticeable cheekbones, horizontal palpebral fissures, short nasal bridge, round tip, thin lips, complete palate, short neck, and normal thorax (Figure 1).

Figure 1 Dysmorphic features.

On chest auscultation, regular S1, S2, no murmurs during auscultation, good bilateral air entry, presence of referred rhonchi. Soft abdomen was on palpation, but distended, no visceromegaly or palpable masses noted, her spine was linear without a pit on the lumbosacral area, and sacral bone was non- palpable, but no imperforate anus with normal position.

In addition to dysmorphic features, we were able to observe an evidence of developmental sexual disorder, with clitoromegaly and pubic hair (Figure 2).

She has obvious reducing of the lower extremities with popliteal webbing and bilateral varus club foot (Figure 3).

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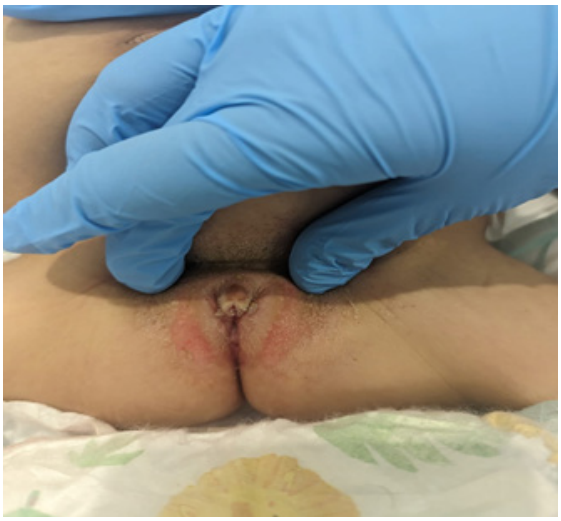

Figure 2 Clitoromegaly with pubic hair.

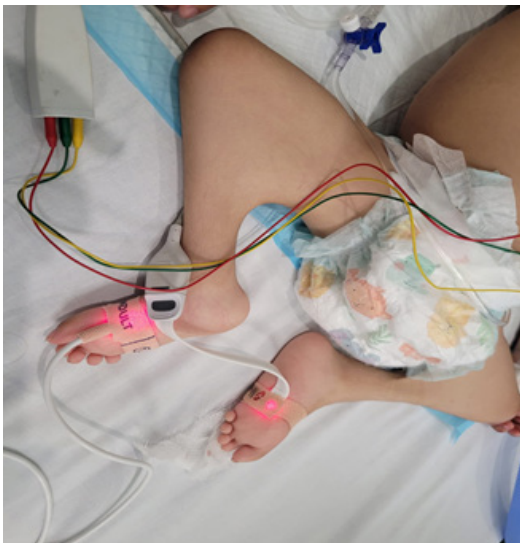

Figure 3 Popliteal webbing and bilateral varus clubfoot.

Extensive blood work- up was done showed severe leucocytosis (WBC 51 000), severe anemia (Hemoglobin 5.2 mg/dL), with prolonged INR (INR 2.9), and mildly low albumin level (Albumin 2.7), however she has normal liver enzymes (SGOT 30, Alkaline phosphatase 138, GGT 36). Concerning renal function, our patient had elevated creatinine level (Creatinine 3, 5), with severe hypocalcemia (Ca 2.8), hypokalemia (K 2.6), hyperphosphatemia (Ph 9.1), and severe acidosis (CO_2 8).

Thus, for this patient's condition, urgent management was to start dialysis and to give her blood transfusion with fresh frozen plasma.

Chest x-ray was taken post- intubation, cardio- thoracic index was 0.54, no evidence of consolidation or pneumothorax seen, but moderate diffuse bilateral infiltrates. This x-ray helped us also, to understand the bone abnormalities, and we were capable to detect complete agenesis of the sacrum with a lumbar-iliac fusion (Figure 4). Echocardiography done showed ejection fraction of 42%, with mild mitral regurgitation and dilatation of the left ventricle. Renal/ bladder ultrasound was ordered to assess if there is renal agenesis, or hypoplastic kidneys, and pronounced urinary bladder compatible with a neurogenic bladder.

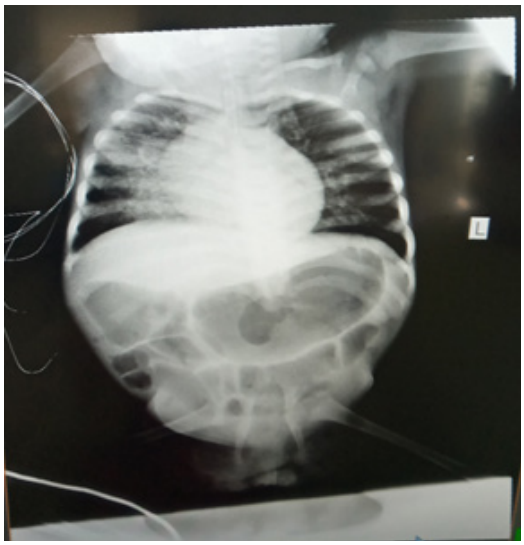

Figure 4 Chest x-ray.

Ultrasound of the brain and abdomen/pelvis ultrasound were requested to evaluate brain structures and to rule out visceral anomalies. Endocrine panel was too part of the work- up to rule out congenital adrenal hyperplasia or other endocrinopathies.

During her stay at PICU, multidisciplinary consultations (neurology, cardiology, endocrinology, and orthopedics), were needed to preserve a close monitoring of all possible risk factors and complications, but unfortunately all the required management was not accomplished because the patient was deteriorating rapidly, she had cardiorespiratory arrest few hours after PICU admission and passed away.

Discussion

The CRS is an infrequent inborn abnormality. Although the precise etiologic factor is unidentified, it is associated with genetic predisposition, vascular hypoperfusion and presence of diabetes in mother.[3]

Like the presented case, this variation is marked by sacral agenesis at the level of iliac and lumbar vertebrae with their analogous spinal segments and multiple abnormalities in the lower limbs and in other organs. Early intra- uterine diagnosis allows early syndrome recognition.

Prenatal ultrasound is used often and is the main tool in the complete assessment of the spine and lower limbs; furthermore, it is helpful in the diagnosis of CRS by the identification of a sudden termination of the lumbar spine and hypoplastic lower limbs.

After elaborating a prenatal diagnosis, we must concentrate on specifying the grade of dysgenesis as well as the related congenital anomalies with the determination of founding a prognosis and an appropriate plan of the therapeutic management postnatally.[3,4]

Renshaw's categorization, which was created in 1978, classifies the syndrome in 4 degrees based on the severity of the sacral agenesis, and involvement of iliac and lumbar vertebrae.[13]

Not well-developed buttocks and abnormalities of feet are seen in mild cases, where usually no clinical signs are observed, or only external stature anomalies are evident. In addition to external body disturbances, in more severe cases (type III or IV defects),

abnormalities of genito-urinary system, respiratory and nervous system functions can be detected.[14] So, based on this organization, our patient fit in grade IV (whole sacral agenesis with iliac-bones union). This cluster is associated with a bad prognosis with a higher neurological effect and multisystemic sequels, mostly at a renal level. Torre et al noted that in patients with caudal agenesis more frequent congenital kidneys anomalies are present - the most common is kidney agenesis, and often in about 37% is VUR.[14]

In caudal regression syndrome the most common presenting symptoms are usually, recurrent urinary tract infections, and neurogenic bladder with dribbling. Loss of sphincter control, history of constipation and perianal anesthesia are also frequently seen.[15]

This case is an unusual clinical presentation of caudal regression syndrome, undiagnosed previously, and not followed-up, and it is also an obvious example of the large range of alterations that can affect the developing fetus because of untreated and unfollowed diabetes in pregnant females. Since the elevated correlation between this defect and the diabetic mother, and its development during the early stages of pregnancy, it is mandatory to have an anticipatory approach based on firm glycemic control prior to the embryonic organogenesis period, or even before in high-risk patients. Also, appropriate direction and pregestational genetic tests are essential. Treatment is a challenge for the physician as well as for the parents, and it requires a multidisciplinary approach involving a pediatrician, a pediatric surgeon, an orthopedic surgeon, an endocrinologist, a nephrologist, a physical therapist, and an urologist depending on the degree of severity. Knowing that the initial pathology is not curable and unalterable, treatment is only supportive, with the unique objective of achieving a life as normal as possible, and to delay to most probable serious complications.

Conclusion

In conclusion, this case report highlights the complex clinical manifestations and challenges associated with Caudal Regression Syndrome (CRS), a rare congenital anomaly illustrated by caudal vertebral agenesis or dysgenesis. The presented case involved a 4-year-old girl with CRS, significant dysmorphic features, sacral agenesis, and multiple systemic complications, emphasizing the multisystemic nature of this syndrome. While treatment for CRS remains predominantly supportive and aimed at improving the quality of life, the prognosis varies based on the severity of malformations. Moreover, this case underscores the critical need for preventive measures, such as strict glycemic control in diabetic mothers during the embryonic organogenesis period, and pregestational genetic tests for high-risk patients.

Finally, Caudal Regression Syndrome poses intricate challenges for both healthcare providers and parents. A comprehensive and proactive approach, including early detection, genetic counseling, and supportive care, is essential for optimizing outcomes in affected individuals.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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