Caudal regression syndrome: Case report

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Abstract

Introduction. Caudal regression syndrome is a congenital malformation ranging from agenesis of the lumbosacral spine to the most severe cases of sirenomelia. The etiology of this syndrome is not well known. Obstetric ultrasonography is the diagnostic tool of choice. Surviving infants usually have normal mental function and require extensive urologic and orthopedic assistance.

Clinical case. An obstetric ultrasound performed at 29 weeks gestation in a 38-year-old pregnant woman reports a single live fetus. Axial cuts of the spine show the absence of the sacral and coccyx portions, lower hypoplastic limbs are contracted and crossed in Buddha position. Therefore, it is considered a fetus suspected of having a caudal regression syndrome. At 38 weeks gestation, the baby was born, with hypoplasia of the lower hemibody, narrow hips, distal leg atrophy, lower limbs in flexo-abduction, bilateral equine foot, motor paresis of lower limbs, and permeable anus. A total column radiograph confirms the interruption of the distal column with the absence of a sacral column and no continuity with the hypoplastic pelvis.

Discussion and Conclusions. Antenatal screening probably gives the opportunity for a better management of this condition. Ultrasound and fetal MRI can be used to reach a prenatal diagnosis. Early detection and prompt treatment are very important to decrease the risk of complications and improve the prognosis. A multidisciplinary approach is required.

Key Words
Caudal regression syndrome, sacral agenesis, maternal diabetes, congenital malformation.

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INTRODUCTION[1]

Caudal regression syndrome is a congenital malformation ranging from agenesis of the lumbosacral spine to the most severe cases of sirenomelia. The etiology of this syndrome is not well known. Maternal diabetes, genetic predisposition, and vascular hypoperfusion have been suggested as possible causative factors. The degree of associated anomalies usually parallels the severity of the primary defect. Obstetric ultrasonography is the diagnostic tool of choice revealing the absent distal vertebrae of the fetal spine; magnetic resonance imaging is useful for a better evaluation of fetal anatomy. Perinatal management depends mainly on gestational age at diagnosis and severity of the lesion. It should include genetic counseling and serial ultrasonography to assess interval growth and amniotic fluid volume. Surviving infants usually have normal mental function and require extensive urologic and orthopedic assistance. Their long-term morbidity consists mostly of neurogenic bladder dysfunction, resulting in progressive renal damage and disabling neuromuscular deficits of the lower extremities. Neurosurgical and orthopedic intervention with physical rehabilitation is indicated to improve their quality of life.

CLINICAL CASE

The case was a 38-year-old woman with a gyneco-obstetric history of four pregnancies. The first ended in still birth at 36 weeks gestation; the second, in a miscarriage during the first trimester of pregnancy, and the third, in a cesarean section due to a macrosomic fetus. The newborn weighed 5100 grams. This recent pregnancy was a high obstetric-risk pregnancy. She attended her first prenatal checkup at 12 weeks of gestation (according to her last menstruation). Routine exams were indicated, which were within normal parameters. She had a pathological history of type 2 diabetes mellitus of more than 4 years of evolution, with...
insulin treatment, to which she showed poor adherence, resulting in poor metabolic control. Glycosylated hemoglobin (HbA1c) was reported as 8%. The obstetric ultrasound performed at 29 weeks gestation reports a single live fetus, with absence of the right kidney and the left kidney of dysplastic appearance. The urinary bladder had normal appearance, axial cuts of the spine show absence of the sacral and coccyx portions. Lower hypoplastic limbs were contracted and crossed in Buddha position. The estimated fetal weight was 1117 grams, corresponding to intrauterine growth restriction for the gestational age. It was not possible to observe the genitals. There were no other structural alterations evident at the time of the study. Therefore, the conclusion was a fetus with suspected caudal regression syndrome. The cesarean section was scheduled at 38 weeks gestation and a female baby was born, Apgar 6/7, weight 2587 grams, size 47 cm, head circumference 34 cm. The physical examination of the neonate shows hypoplasia of the lower hemibody, increase of soft tissue in the lumbosacral region, flattened buttocks with a short intergluteal cleft, external genitals of female appearance, narrow hips, distal leg atrophy, lower limbs in flexo-abduction, bilateral equine foot, motor paresis of lower limbs, permeable anus. No abnormalities of the genitourinary tract, posterior intestine, cardiac and respiratory systems were found. Neurological development is preserved. (Figures 1, 2). In the imaging studies of the newborn a total column radiograph confirmed the interruption of the distal column with the absence of a sacral column and no continuity with the hypoplastic pelvis. (Figure 3). An abdominal ultrasound reported both kidneys of normal size and shape, preserving their renal parenchyma-cortex relationship, both with significant calyceal ectasia. The right kidney measured 4.2 x 2.3 cm and the left one, 4 x 2.3 cm. The newborn with stable vital signs was examined with a multidisciplinary approach that included neurology, orthopedics, urology and rehabilitation.

■ REVIEW

**Definition**

Caudal regression syndrome (CRS) is a relatively uncommon congenital anomaly, a rare congenital disorder that affects the development of the lower segment. CRS occurs approximately in 0.1–0.4 of 10000 pregnancies. CRS, also known as caudal regression sequence, caudal dysplasia, caudal aplasia, femoral hypoplasia, phocomelic diabetic embryopathy, or sacral agenesis, consists of a spectrum of anomalies involving the caudal end of the trunk. CRS comprises various degrees of anomalous formation of the caudal trunk. The spectrum of disease can vary from isolated partial agenesis of the sacrococcygeal spine to the complete absence of sacral, lumbar, or lower thoracic vertebrae. Characteristic features include short intergluteal cleft, flattened buttocks, external genitals of female appearance, narrow hips, distal leg atrophy, lower limbs in flexo-abduction, bilateral equine foot, motor paresis of lower limbs, permeable anus. No abnormalities of the genitourinary tract, posterior intestine, cardiac and generally more affected than sensory function and is correlated with the level of spinal aplasia. In very mild cases, such as isolated coccygeal agenesis, patients may be asymptomatic. Associated anomalies are common, often involving abnormalities of the genitourinary tract, hindgut, cardiac, and respiratory systems. Intelligence and mental function are generally preserved.(1,2)
**Etiology**

The pathogenesis involves abnormal differentiation of the developing spine, spinal cord, and caudal mesoderm. Although CRS is rare in the general population, maternal hyperglycemia is thought to play an important role, and the malformation is seen much more commonly in infants of diabetic mothers.(1)

In 1961, Duhamel explained the spectrum of CRS, of which sirenomelia was thought to be the most severe form. Since then, numerous etiological theories have been proposed, but the underlying mechanisms are still not clearly understood. The first hypothesis, based on the overall malformation of the caudal body, postulates a primary defect in the generation of the mesoderm, an embryologic insult to the caudal mesoderm, occurring between 28 and 32 days of gestation. Interaction of genetic and environmental factors (teratogenic agents, such as cadmium or retinoic acid and vitamin A), maternal diabetes, insulin, embryonic trauma, severe fluctuations in temperature, vitamin deficiencies, lithium salts, radiation, stress, alcohol, amphetamines, and trypan blue during the third gestational week might interfere with the formation of the notochord, resulting in abnormal development of caudal structures. The second hypothesis, based on the aberrant abdominal and vascular pattern of affected individuals, postulates a primary vascular defect that leaves the caudal part of the embryo hypoperfused, an etiology based on the vascular theory associated with the presence of an abnormal, single umbilical artery.(2)

CRS is not specific to diabetes and only 1% of babies born to diabetic mothers may develop this type of malformation. Renshaw classified the spectrum of CRS into 5 types based on the type of defect and articulation between bones. Type I has total or partial unilateral sacral agenesis; Type II has variable lumbar and total sacral agenesis and the ilia

![Figure 3. Frontal radiograph of the neonatal pelvis demonstrates the absence of sacrum, coccyx and hypoplasia of pelvic bones.](image-url)
articulate with the sides of the lowest vertebra; Type III: has variable lumbar and total sacral agenesis and the caudal end plate of the lowest vertebra rests above fused iliac or an iliac amphiarthrosis; Type IV: has soft tissue fusion in both lower limbs and, Type V, also known as sirenomelia, has fused lower limb bones.(3)

**Diagnosis[2]**
Classic features are suggestive of CRS. Prenatal diagnosis by ultrasound is possible at 22 weeks of gestation, observed as a sudden interruption of the spine due to the absence of vertebrae and a frog-like position of the lower limbs. However, sirenomelic fetuses have been diagnosed at 16 and 19 gestational weeks by transvaginal route. A first-trimester diagnosis is difficult due to 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. In a recent case report, CRS was diagnosed before birth after detection of a large nuchal translucency, although the diagnosis was not confirmed until 16 weeks. Sonographic findings are variable, depending on the defect’s extent and severity. Because the syndrome is not associated with aneuploidy, a fetal karyotype is not warranted.(4)

The morphological ultrasound is oriented towards diagnosis and helps find other frequently associated malformations. Fetal magnetic resonance (MRI) makes it possible to confirm the diagnosis and to determine the level of the terminal medullary cone, which will be a major prognostic factor. The spinal cord is usually dysplastic and the terminal cone is too high.(3,5)

**Treatment**
Prenatal diagnosis is important so that appropriate patient counseling can be provided and postnatal interventions performed. Treatment depends upon clinical symptoms, including the degree of neurological deficits. The main goals of treatment include maintaining and improving renal, cardiac, pulmonary and gastrointestinal function, preventing renal infection and achieving continence. Urinary incontinence is treated with anticholinergic agents, which decrease the detrusor muscle tone, increase bladder capacity, and thus decrease intravesicular pressure and urinary frequency. Orthopedic intervention is necessary to correct the associated malformations. Physical therapy can help prevent secondary deformities, skin ulcers and contributes to improving the quality of life. Surviving infants usually have normal mental function, but do require extensive urologic and orthopedic assistance. Their long-term morbidity consists mostly of a neurogenic bladder dysfunction resulting in progressive renal damage and disabling neuromuscular deficits of the lower extremities. 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.(7)

**Discussion and Conclusions**
Caudal regression syndrome is a rare entity, characterized by sacrococcygeal dysgenesis with an abrupt termination of a blunt-ending spinal cord. The balance of glycemic figures in periconceptional women with diabetes, and the antenatal screening will probably offer the opportunity for better management of this condition. Ultrasound and fetal MRI can be used to reach a prenatal diagnosis. Early detection and prompt treatment are very important to decrease the risk of complications, thus improving the prognosis. A multidisciplinary approach is required. It should not be forgotten that the purpose of rehabilitation is not to correct all deformities, but to increase the functionality of everyday life.

**Síndrome de regresión caudal: reporte de un caso**

**Resumen**

**Introducción.** El síndrome de regresión caudal es una malformación congénita que va desde la agenesia de la columna lumbosacra hasta los casos más graves de sirenomelia. La etiología de este síndrome no es bien conocida. La ecografía obstétrica es la herramienta diagnóstica de elección. Los bebés que sobreviven suelen tener una función mental normal y requieren amplia asistencia urológica y ortopédica.

**Caso clínico.** Una ecografía obstétrica realizada a una mujer de 38 años a las 29 semanas de gestación reporta un feto único, vivo; los cortes axiales de la columna muestran la ausencia de la porción sacra y coxis; las extremidades inferiores se observan hipoplásicas, contraídas y cruzadas en posición de Buda. Por tanto, se concluye como un feto con sospecha de síndrome de regresión caudal. A las 38 semanas de gestación, nace el bebé, con hipoplasia del hemicuerpo inferior, caderas estrechas, atrofia distal de las piernas, miembros inferiores en flexoabducción, pie equino bilateral, paresia motora de miembros inferiores y ano permeable. Una radiografía de columna total confirma la interrupción de la columna distal con ausencia de columna sacra, sin continuidad con la pelvis hipoplásica.

**Discusión y conclusiones.** La vigilancia prenatal probablemente brinda la oportunidad de un mejor manejo de esta condición. La ecografía y la resonancia magnética fetal se pueden utilizar para llegar a un diagnóstico prenatal. La detección temprana y el tratamiento oportuno son muy importantes para disminuir el riesgo de complicaciones y mejorar el pronóstico. Se requiere un enfoque multidisciplinario.

**Palabras clave**

Síndrome de regresión caudal, agenesia sacra, diabetes materna, malformación congénita.
REFERENCES


Fecal microbiota transplants help patients with advanced melanoma respond to immunotherapy

- Date: February 4, 2021. Source: Science Daily

For patients with cancers that do not respond to immunotherapeutic drugs, adjusting the composition of the gut microbiome through the use of stool, or fecal, transplants may help some of them respond to immunotherapy treatment. Researchers at the National Cancer Institute (NCI) Center for Cancer Research conducted the study in collaboration with the UPMC Hillman Cancer Center at the University of Pittsburgh.

Some patients with advanced melanoma who did not respond to treatment with immune checkpoint inhibitors (ICI), did respond after receiving a transplant of fecal microbiota from a responder one. Results suggest that introducing certain fecal microorganisms into a patient's colon may help drug response by enhancing the immune system's ability to recognize and kill tumor cells.

In recent years, immunotherapy drugs called PD-1 and PD-L1 inhibitors have benefited patients with certain types of cancer, but new strategies are required to help unresponsive patients. This study is one of the first to demonstrate that altering the composition of the gut microbiome can improve response to immunotherapy. The data provide proof of concept that the gut microbiome can be a therapeutic target in cancer.

It is necessary to identify the specific microorganisms critical for overcoming a tumor's resistance to immunotherapy and investigate the biological mechanisms involved. Previous research suggests that communities of bacteria and viruses in the intestines can affect the immune system and its response to chemotherapy and immunotherapy. For example, tumor-bearing mice that do not respond to immunotherapy drugs can start to respond if they receive certain gut microorganisms from those that responded. Changing the gut microbiome may “reprogram” the microenvironments of tumors resistant to immunotherapy drugs, making them more favorable to treatment with these medicines.

To test whether fecal transplants are safe and may help patients with cancer better respond to immunotherapy, a small, single-arm clinical trial for patients with advanced melanoma was carried out. The tumors had not responded to one or more rounds of treatment with the ICI pembrolizumab (Keytruda) or nivolumab (Opdivo), administered alone or in combination with other drugs. ICI release a brake that keeps the immune system from attacking tumor cells.

Fecal transplants, obtained from patients with advanced melanoma who responded to pembrolizumab, were analyzed to ensure that no infectious agents would be transmitted. After treatment with saline and other solutions, the fecal transplants were delivered to the patients through colonoscopies, and each patient also received pembrolizumab.

Six out of fifteen patients who had not originally responded to pembrolizumab or nivolumab responded with either tumor reduction or long-term disease stabilization. One of these patients has exhibited an ongoing partial response after more than two years and is still being followed, while four other patients are still receiving treatment and have shown no disease progression for over a year.

The treatment was well tolerated, though some of the patients experienced minor side effects that were associated with pembrolizumab, including fatigue. The investigators analyzed the gut microbiota of all patients. The six patients whose cancers had stabilized or improved showed increased numbers of bacteria that have been associated with activation of immune T cells and responses to ICI.

In addition, by analyzing data on proteins and metabolites in the body, the researchers observed biological changes in patients who responded to the transplant. For example, levels of immune system molecules associated with resistance to immunotherapy declined, and levels of biomarkers associated with response increased.

Larger clinical trials are recommended to confirm the results and identify biological markers that could eventually be used to select patients most likely to benefit from treatments that alter gut microbiome. Future studies will identify which groups of bacteria in the gut are capable of converting non responders into responders. These could come from responder patients or healthy donors. If microorganisms critical for the immunotherapy response are identified, it may be possible to deliver these organisms directly, without a fecal transplant.

The clinical trial was conducted in collaboration with Merck, the maker of pembrolizumab.

Original Source: NIH/National Cancer Institute