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CAUDAL REGRESSION SYNDROME (SACRAL AGENESIS) WITH ASSOCIATED ANOMALIES

KAUDAL REGRESYON SENDRONU (SAKRAL AGENEZİ) İLE İLGİLİ ANOMALİLER

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SUMMARY

Background data: CRS, also referred to as caudal dysplasia and sacral agenesis syndrome, is a rare congenital abnormality in which a segment of the spine and spinal cord fails to develop. The etiology is thought to be related to maternal diabetes, a genetic predisposition, teratogens, and vascular hypoperfusion, but no true causative factor has been determined. Since there is also no true cure, treatment is difficult, multidisciplinary, and largely supportive. Intensive and long-term attention is required for lower limb deformities with sensory or motor loss, or neurogenic bladder.

Objective: To evaluate the radiological and clinical data of pediatric patients with spinal problems related to congenital or neuromuscular conditions using magnetic resonance imaging (MRI).

Study design: We present ten cases of caudal regression syndrome (CRS) among 65 consecutive pediatric cases that were diagnosed with congenital spinal column deformities at the Department of Orthopedics and Traumatology, Baltalimani Bone Disease Hospital, İstanbul, Turkey, between 2006 and 2009.

Materials and Methods: The clinical and radiological findings were reviewed to classify each patient by Renshaw's and Guille's classifications. The mean age was 81 (30–180) months. The clinical and radiological findings of these cases, along with the lifetime management, are outlined and the literature is reviewed.

Results: In this study, 11.3% of patients were diagnosed with CRS in combination with congenital and spina bifida (SB) related spinal deformities. This indicates that the condition may not be as rare as most studies suggest. Our retrospective study reveals the various concomitant conditions which often occur with CRS.

Conclusion: The goal of this study was to show the variations of CRS, and to provide insight into the management of this disorder. Caudal regression syndrome is still associated with structural and systematic problems including genitourinary, gastrointestinal, orthopedic, neurological, respiratory and cardiac anomalies. The first step in the early management of CRS should be an accurate prenatal diagnosis. We need larger studies to determine the utilities of the classifications, and to improve them. It is possible that there are under- or misdiagnosed patients in many centers who are receiving treatment for accompanying disorders.

Key words: Caudal regression syndrome, congenital scoliosis, magnetic resonance imaging, sacral agenesis, sacral displasia, spina bifida.

Level of evidence: Retrospective clinical study, Level III

ÖZET

Çalışma planı: 2006-2009 yılları arası konjenital omurga deformiteli 65 pediatrik hasta arasında kaudal regresyon sendromu (KRS) olan 10 olgu incelendi.

Amaç: Konjenital omurga problemleri olan pediatrik hastalar klinik ve radyolojik olarak incelendi, manyetik rezonans görüntüleme sonuçları değerlendirildi.

Veriler: KRS (kaudal displazi, sakral agenezi sendromu) omurganın kaudal segmentinin ve spinal kordun gelişme kusuru olarak tanımlanan nadir konjenital anomalisidir. Etiyolojisinin maternal diabet, genetik predispozisyon, teratojenler ve vasküler hipoperfüzyon ile ilişkili olduğu düşünülür. Ancak gerçek bir olumsuz etmen tam olarak tanımlanmamıştır. Kesin bir tedavisi olmamasından dolayı tedavisi güç, multidisipliner ve daha çok destekleyicidir. Sensoriyal veya motor kayıp ile birlikte alt ekstremite deformiteleri ve nörojenik mesane problemleri yoğun ve uzun dönem dikkat gerektirir.

Metod: Klinik ve radyolojik bulgular her bir hasta için Renshaw ve Guille sınıflaması ile değerlendirildi. Ortalama yaş 81 (30-180) ay idi. Klinik ve radyolojik bulguları ile birlikte literatür bilgisi değerlendirildi.

Sonuçlar: Hastaların %11.3 de konjenital ve spina bifida ile ilişkili KRS bulundu. Çalışmamızda KRS unun bu hasta gurubunda nadir olmadığı, farklı eşlik eden anomalilerin sıklıkla birlikte bulunduğu gösterildi.

Tartışma: KRS genitoüriner, gastrointestinal, ortopedik, nörolojik, solunum ve kardiyak anomaliler içeren strüktürel ve sistematik problemler ile ilişkilidir. Tedavi ve önlem için ilk adım doğru prenatal teşhistir. Daha geniş seriler ile yapılmış sınıflama ve tanımlamaya ihtiyaç vardır.

Anahtar kelimeler: Kaudal regresyon sendromu, konjenital skolyoz, manyetik rezonans görüntüleme, sakral agenezi, sakral displazi, spina bifida.

Kanıt düzeyi: Retrospektif klinik çalışma, Düzey III

INTRODUCTION

Caudal regression syndrome (CRS), also known as caudal dysplasia and sacral agenesis syndrome, is an uncommon malformation seen in 0.1–0.25 of 10,000 normal pregnancies[19]. The syndrome occurs more frequently in the offspring of diabetic mothers[21]. The incidence is about 1 in 350 infants of diabetic mothers, which is an approximately 200-fold increase in incidence for diabetic patients than for the general population[16].

CRS may range from an absent coccyx as an isolated finding without neurological sequelae, to sacral or lumbosacral agenesis[16]. It can affect the lower extremities, the lumbar and coccygeal vertebrae, and corresponding segments of the spinal cord. Neurological, orthopedic, gastrointestinal, genitourinary and cardiac anomalies, imperforate anus, malformed genitalia, renal dysplasia or aplasia, and congenital heart defects are commonly seen[3].

Sirenomelia, a syndrome characterized by fused lower extremities, causes the fetus to resemble a mermaid. It was previously thought to be the most severe form of CRS. Sirenomelia develops as a result of a vascular steal phenomenon that causes severe ischemia of the caudal portion of the fetus. In sirenomelia, an aberrant vessel derived from the vitelline artery shunts blood from the high abdominal aorta directly through the umbilical cord to the placenta. This vessel acts as the second umbilical artery. Due to severe hypoperfusion below the umbilical artery in sirenomelia, only one umbilical artery is found, the lower limbs develop as a single extremity or fused, renal agenesis (a lethal condition) takes place, and the anus is absent.

Renshaw classified patients into four types, according to the amount of sacrum remaining and the characteristics of the articulation between the spine and pelvis (Table-1)[12].

Type I refers to either partial or total unilateral sacral agenesis. Type II refers to partial sacral agenesis with a bilaterally symmetrical defect, a normal or hypoplastic sacral vertebra, and a stable articulation between the ilia and first sacral vertebra.

Table-1. Renshaw's Classification (Renshaw, 1978).

Type I	Either partial or total unilateral sacral agenesis.
Type II	Partial sacral agenesis with bilaterally symmetrical defect, a normal or hypoplastic sacral vertebra, and a stable articulation between the ilia and first sacral vertebra.
Type III	Variable lumbar and total sacral agenesis, with the ilia articulating with the sides of the lowest vertebra present.
Type IV	Variable lumbar and total sacral agenesis, with the caudal endplate of the lowest vertebra resting above either fused ilia or an iliac amphiarthrosis.

Type III refers to variable lumbar and total sacral agenesis, with the ilia articulating with the sides of the lowest vertebra present. Finally, Type IV is variable lumbar and total sacral agenesis, with the caudal endplate of the lowest vertebra resting above either a fused ilia or an iliac amphiarthrosis. Although the Renshaw classification system does not separate sacral agenesis patients with myelomeningocele from those without, he did point out that the function of sacral agenesis patients with myelomeningocele was worse, and more closely approached that of patients with myelomeningocele alone. The classification of CRS by Guille et al.[7] considers the presence (Group I) or absence (Group II) of myelomeningocele (Table-2). Three types of spinal deformities are described. In Type A, there is either a slight gap between the ilia or the ilia are fused in the midline. One or more lumbar vertebrae are absent, and the caudad aspect of the spine articulates with the pelvis in the midline, maintaining its vertical alignment. In Type B, the ilia are fused together, some of the lumbar vertebrae are absent, and the most caudad lumbar vertebra articulates with one of the ilia, with the most caudad aspect of the spine shifted away from the midline. In Type C, there is total agenesis of the lumbar spine, the ilia are fused together, and there is a visible gap between the most caudad intact thoracic vertebra and the pelvis. This classification is more reliable for predicting the ambulation potential and in guiding surgical treatment. According to Guille et al., Group I and Type A patients should have correction of the spinal column and lower extremity deformities, as they have a high potential of being able to walk.

Table-2. Guille's Classification (Guille et al, 2002).

GROUP I	Absence of myelomeningocele	
GROUP II	Presence of myelomeningocele.	
	Type A	There is either a slight gap between the ilia or the ilia are fused in the midline. One or more lumbar vertebrae are absent. The caudad aspect of the spine articulates with the pelvis in the midline, maintaining its vertical alignment.
	Type B	The ilia are fused together, some of the lumbar vertebrae are absent, and the most caudad lumbar vertebra articulates with one of the ilia, with the most caudad aspect of the spine shifted away from the midline.
	Type C	Total agenesis of the lumbar spine, the ilia are fused together, and there is a visible gap between the most caudad intact thoracic vertebra and the pelvis.

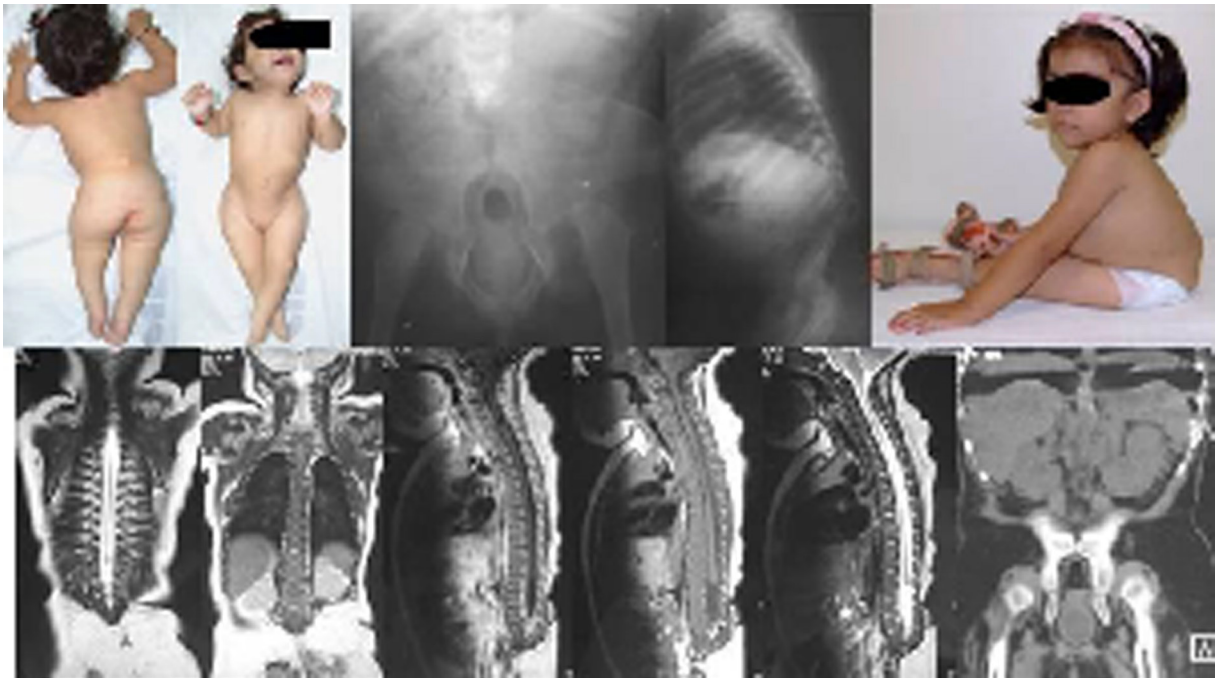

Figure-1. 2-year-old female, Renshaw IV, Guille I/C (the patient received surgery for foot deformity).

Our study aims to review the clinical and magnetic resonance imaging (MRI) results of patients with CRS to better understand the condition and its concomitant anomalies.

MATERIALS AND METHODS

Between the years of 2006 and 2009, 65 consecutive pediatric patients with spinal column deformities (scoliosis, kyphosis, etc.) were seen at the Department of Orthopedics and Traumatology. Ten (11.3%) of these 65 patients with congenital spinal column deformities had caudal regression syndrome (CRS). Aretrospective study was conducted for these ten cases (seven female, three male). The MRI results and radiological and clinical data were reviewed to classify each patient by Renshaw's and Guille's classifications. The mean age was 81 (30–180) months, and the mean follow-up time was 50 (36–72) months.

RESULTS

All participants were children with an age range from 15 to 180 months. The mean age was 6.5 years at diagnosis. Among 65 pediatric cases that were diagnosed with congenital spinal column deformities, ten (11.3%) patients were diagnosed with SA related to CRS.

Table-3. Spinal column abnormalities by MRI.

MRI Findings	Number
Partial or total sacral agenesis/lumbar agenesis	10 (100%)
Multi-level hemivertebra anomalies	3 (42.8%)
Syringohydromyelia	3 (42.8%)
Spina bifida	3 (42.8%)
Tethered cord	2 (28.5%)
Diastomatomyelia	1 (14.2%)
Diaphragm hernia	1 (14.2%)
Chiari malformation	1 (14.2%)
Sacral dermal sinus	1 (14.2%)

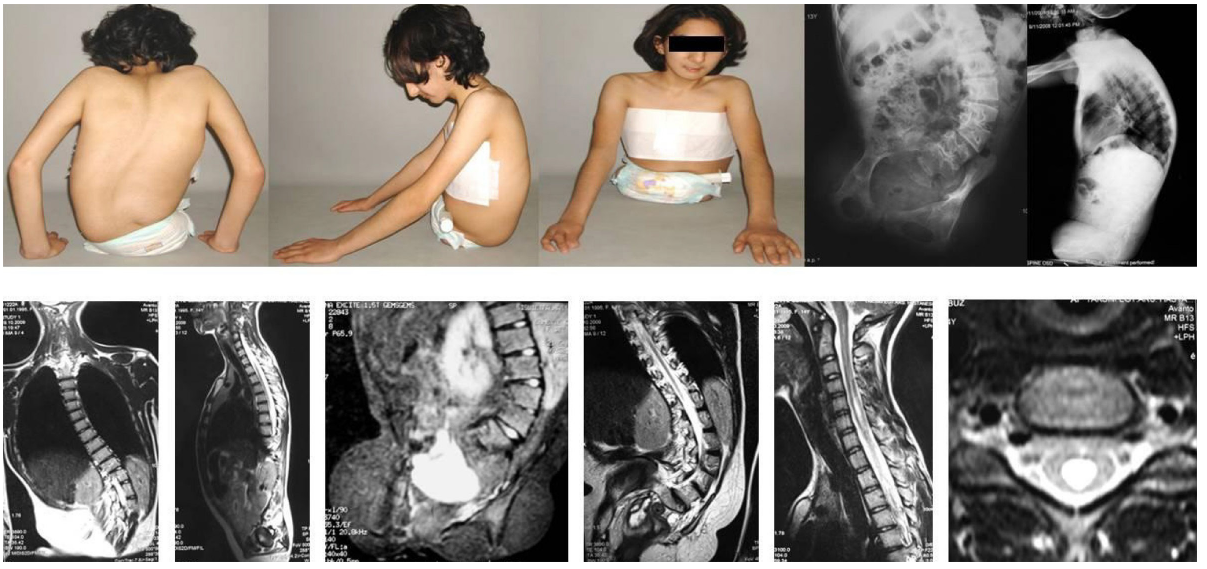

Figure-2. 14-year-old female, Renshaw I, Guille I/C (the amelia patient received surgery for cleft mouth, syndactyly and ectopic anus).

According to Renshaw's classification (Table-1), three patients were defined as type IV, two patients were type III, two patients were type II, and three children were defined as type I. Our study also revealed that, according to Guille's classification (Table-1), four patients were type II/B, three patients were I/B, two patients were II/A, and one patient was I/C.

The following conditions were diagnosed: one ectopic anus, one cleft mouth, four urinary system anomalies, one cardiovascular anomaly, two cases of thoracic insufficiency syndrome, four hip dislocations, one syndactyly, three inguinal hernia, one diaphragm hernia, four cases of scoliosis, and one amelia. All cases, regardless of the classification type, including the case with amelia, had tethered cord. Spinal column abnormalities are outlined in Table-3. The most common pathology was hip dislocation (42.8%), followed by scoliosis (28.5%), urinary system anomalies (28.5%), and TIS (28.5%).

MRI findings revealed partial or total sacral agenesis in all patients and multi-level hemivertebra anomalies in three of them. Syringohydromyelia and spina bifida were both seen in three of the patients.

Two of the patients were also diagnosed with tethered cord. Diastomatomyelia, diaphragm hernia, Chiari malformation and sacral dermal sinus were observed, each in a single patient.

One patient had a mother with gestational diabetes. Three patients confirmed a history of marriage between relatives. There was a family history of sacral agenesis in two patients. None of the mothers reported any radiation exposure or drug history.

Six patients received neurosurgical intervention. Meningomyelocele resection alone was performed in two patients, and another two underwent ventriculoperitoneal shunting in addition to meningomyelocele resection. One patient received surgery for foot deformity (Figure-1). The single patient with amelia received surgery for cleft mouth, syndactylia and ectopic anus (Figure-2), and another patient received surgery for diaphragm herniation (Figure-3).

According to the criteria of Hoffer et al., three of our patients were non-ambulatory, including one patient who was using an orthopedic device for deformity. Two patients were community ambulators. Our patients reported problems functioning in physically-demanding situations, although most were able to participate in low-demand physical activities.

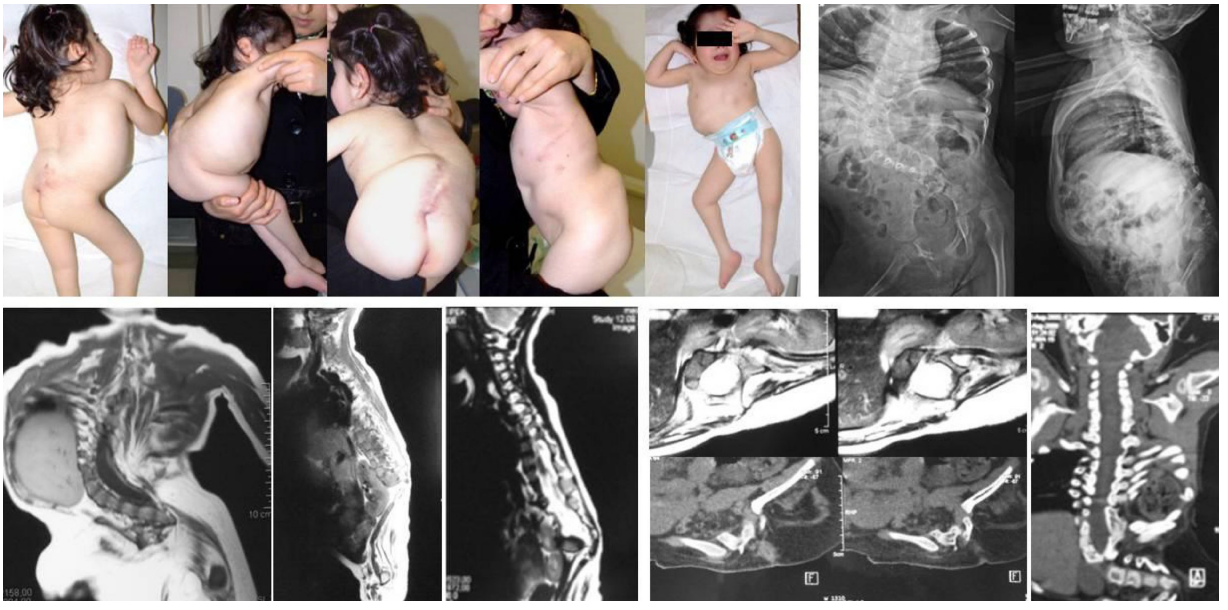

Figure-3. 5-year-old female, Renshaw IV, Guille II/A (patient received surgery for a diaphragm hernia).

DISCUSSION

With its speculative etiology, CRS remains associated with structural and systematic problems including genitourinary, gastrointestinal, orthopedic, neurological, respiratory and cardiac anomalies. Although there are no clearly determined causative factors, evidence suggests factors including maternal diabetes, genetic predisposition, and vascular hypoperfusion[1].

Some authors have suggested that CRS is a component of diabetic embryopathy. There have been many reports showing that maternal diabetes is associated with CRS[2,20]. Several studies have reported a partial genetic contribution to disease development[18,21]. A homeobox gene, *HLXB9*, was suggested to be the major locus for dominantly inherited sacral agenesis[15]; however, another subsequent study confirmed that the *HLXB9* gene is not involved in the pathogenesis of CRS[10]. Since normal spinal development requires a close interaction between genes and the environment, it has been suggested that both genetic factors and teratogens may take part in the pathogenesis of CRS.

Some authors have suggested that there are critical stages of embryological development, and several disorders may originate from environmental factors affecting the genetic structure during these periods[6].

Rojansky et al. reported that pharmaceuticals, such as minoxidil, trimethoprim sulfamethoxazole, chemicals, fat solvents and appetite suppressants may play roles in the etiology of CRS[14]. Hyperglycemia, hypoxia, and ketone or amino acid abnormalities have also been suggested to be teratogens for infants of diabetic mothers[11].

In the light of continuing developments, caudal regression syndrome is thought to be a spectrum of malformations resulting from a defect of the caudal axial mesoderm during embryogenesis. Although the exact process leading to the development of CRS has not been established, it has been proposed that it occurs before 28 days of gestation[17]. Tortori-Donati et al. have suggested a theory of multisegmental early embryonic chorda-mesodermal derangement[19]. In their opinion, if such derangement involves the most caudal segment, it will result in CRS. The severity of the malformation and its segmental level would affect the residual spinal function and clinical deficits[19]. An interesting case report of sirenomelia accompanying anencephaly seemed to confirm this idea[13]. Another study has reported the combination of CRS, agenesis of the corpus callosum and partial lobar holoprosencephaly as a result of diabetic embryopathy[8]. Even these rare cases can be supposed to reveal important evidence for the complexity and heterogeneity of the process of development of CRS. Clarification of the etiology is vitally important, but it is also important to make the best possible attempt to manage the symptoms of CRS.

The first step in the early management of CRS should be an accurate prenatal diagnosis. Discussions regarding the potential sequelae should be considered with the parents. If the parents agree to continue with the pregnancy in spite of the CRS diagnosis, the neonatal team should inform and prepare the mother and family what to expect in the immediate newborn phase. If possible, consultations from other disciplines such as cardiology, pulmonology, nephrology, pediatric surgery, and gastroenterology, along with orthopedics and neurosurgery, should be arranged for shortly after delivery.

Medical management should be aimed at the systemic problems that develop as sequelae from CRS.

Respiratory problems arise from abnormal chest shape and size. As maternal diabetes causes surfactant insufficiency in newborns, respiratory distress syndrome should also be considered. Some severely affected infants require long-term ventilator support, and optimum functioning and outcome correlate to the degree of severity of the respiratory compromise.

Congenital heart defects can be seen in CRS. Hemodynamic problems can arise depending on the level of cardiac lesion. An echocardiogram should be performed, and heart sound, pulse, oxygen saturation and blood pressure should be monitored for the immediate management of hemodynamic problems

Common nephrological problems, such as neurogenic bladder, renal malformations such as unilateral renal agenesis, and hydronephrosis could cause frequent urinary tract infections and progressive renal damage. Preservation of renal function is essential for long-term management.

Immediate management of serious gastrointestinal problems, such as imperforate anus, tracheoesophageal fistulae, duodenal/colonic atresia, and abdominal wall defects should be considered.

Although patients are more likely to present initially to a pediatric surgeon, urologist or orthopedic surgeon than a neurosurgeon, progressive neurological deficits may develop later in life for patients with unrecognized pathologies. Early neurosurgical intervention is preferred in all cases of recognized occult spinal dysraphism.

Because the primary pathology is irreversible, the aim of treatment is only to support and protect. Each system should be treated as issues develop. It is important that the physicians responsible for care are aware of the pathogenesis of this disorder, and are able to work as a team to best support the patient and family emotionally, physically and medically. Care conferences can be scheduled to continue communication between all the specialty physicians, family doctors and parents. This should be the goal of any caregiver in the treatment of CRS. In severe cases of CRS, hospice care may be an

appropriate choice for the infant and family.

Since there is no true cure, caring for a child with CRS could be difficult. However, the prognosis depends on the severity of spinal involvement and associated malformations. According to Renshaw's classification[12], the best prognosis is associated with type l and type II CRS. In both type l and II, the patient has a stable midline spinal column. This allows spinal stability between the ilia and normal or hypoplastic first sacral vertebra. If the patient does not suffer with myelomeningocele, with the use of orthopedic intervention such as spinal fusions and L-rod implantations, these patients may become ambulatory. Most patients are of normal intelligence, and none of our patients were mentally retarded.

However, for infants that present with type III or IV CRS, the prognosis is grimmer. Perinatal death is frequently related to the structural defects of other organ systems, mostly the kidneys. Early neonatal death results from complications of the central nervous, gastrointestinal, cardiovascular, musculoskeletal, genitourinary and respiratory system malformation-related sequelae. The majority of survivors require ongoing neurological, orthopedic, nephrological and genitourinary intervention, at a minimum.

Especially for patients like those in our study, genetic and pre-pregnancy counseling and screening, along with counseling of diabetic mothers, provide the most hope for prevention of this debilitating disease.

In this study, 11.3% of the patients were diagnosed with CRS in combination with congenital and SB-related spinal deformities. This indicates that the condition may not be as rare as most studies suggest. Our retrospective study allowed us to see the various concomitant conditions which often occur with CRS.

An interesting observation was that only one patient had the risk factor of gestational diabetes. Furthermore, a history of marriage between relatives in three of the cases suggests that consanguineous marriage may play an important role in the development of CRS. The history of drug administration was also unremarkable in our study.

The ratio of spinal cord abnormalities was similar to previous studies, as well as accompanying system anomalies like respiratory, genitourinary, cardiac and gastrointestinal anomalies. It has been reported that urinary tract involvement is common in CRS. Our results, showing four affected patients, are similar to previous findings[20].

The ambulatory status of the patient did not have a statistically significant association with the classifications of Renshaw and Guille. There is no doubt that it is hard to classify a complicated disorder and find relationships between the types and findings. The amount of sacrum remaining and the type of articulation between the spine and the pelvis constitute the basis of the Renshaw classification[12]. However, Guille et al. have proposed another method to predict the ambulatory potential and to identify candidates for corrective surgery of the lower extremities, by considering the presence or absence of myelomeningocele and the midline alignment of the articulation between the spine and the pelvis.

According to their classification, patients for whom the vertebral column articulates with the pelvis in the midline and who do not have a myelomeningocele have the best potential for walking.

In an outcome study, it was suggested that the Renshaw classification did not correlate with the findings, as a classification system should[4]. Emami-Naeini et al. reported very similar findings to ours, in a recent study of 50 patients with sacral agenesis. Their results also revealed similar contradictions with previous studies and classification systems[5]. We need larger studies to determine the utilities of the classifications and to improve them. Furthermore, it is possible that there are under- or misdiagnosed patients in many centers who are being treated for accompanying disorders.

CONCLUSION:

The goal of this study was to show in which variations CRS patients may be discovered, and to provide insight into CRS and the management of this disorder. Doubtless, new advances will establish the link between genomic instability, maternal conditions and environmental factors, and reveal better methods of dealing with CRS.

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