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Case Series

Caudal Regression Syndrome Child and Family Concern about the Lifestyle and Outcome Expectancy: Case Series

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Submitted: 13 April 2022

Accepted: 05 May 2022

Published: 07 May 2022

ISSN: 2373-9312

Keywords

- Caudal regression syndrome
- Family concern
- Outcome

Abstract

Background: Caudal regression syndrome (CRS), or sacral agenesis (or hypoplasia of the sacrum), is a rare congenital abnormality with an estimated incidence of approximately 0.1-0.25:10,000 of normal pregnancies, resulting from a developmental failure of a segment of the vertebral column and spinal cord. In genetic counseling, most cases of caudal regression are sporadic or associated with maternal diabetes. It is associated with urinary malformations, anorectal malformation with the other associated spectrum of cardiovascular, pulmonary, gastrointestinal, and musculoskeletal abnormalities.

Aim: We reported our review of the clinical, radiological, management outcome and the family challenges of a series of cases with CRS to obtain a clue and understanding of this co-morbid pathology with its concomitant anomalies.

Conclusion: The target of this series is to highlight that the complex spectrum of CRS needs to be addressed and shaped for each case because of the variety of anomalies. Parents' counseling regarding the expected outcome should be considered. A multidisciplinary approach is a cornerstone, the purpose is not to correct all deformities but decrease the patients' long-term morbidity, increase the functionality of everyday life, and thus, survival is the role.

ABBREVIATIONS

CRS: Caudal Regression Syndrome; MRI: Magnetic Resonance Imaging

INTRODUCTION

Caudal regression syndrome (CRS), or sacral agenesis (or hypoplasia of the sacrum), is a rare congenital abnormality with an estimated incidence of approximately 0.1-0.25:10,000 of normal pregnancies, resulting from a developmental failure of a segment of the vertebral column and spinal cord [1]. In genetic counseling, most cases of caudal regression are sporadic or associated with maternal diabetes (the incidence is around 1 in 350 infants of diabetic mothers) [2]. Geoffroy Saint-Hilaire and Hohl first reported the spectrum of the clinical features of this condition in 1852 [3]. The syndrome was first proposed as a distinct clinical entity by Duhamel in 1960 [3]. This syndrome characteristically involves the lumbosacral vertebra and corresponding segments of the spinal cord, which innervate structures in the pelvis and lower limbs due to a developmental failure [4]. It is associated with urinary malformations such as neuropathic bladder, vesicoureteric reflux, hydronephrosis, ureter agenesis, and duplex ureters [5]. Anorectal malformation such as anorectal atresia and imperforate anus may combine the severe variants of the syndrome with the other associated spectrum of cardiovascular, pulmonary, gastrointestinal, and musculoskeletal abnormalities [6]. Severe forms can cause early neonatal death due to cardiac, renal, and respiratory problems. Prenatal ultrasound and fetal Magnetic Resonance Imaging (MRI) can be used for antenatal diagnosis, while radiographs and MRI of the vertebral column are imaging modalities used in children and adults [7]. There is no cure for this disorder because the primary pathology is irreversible. The usual aim of the management is supportive and symptomatic [8-10]. We reported our review of the clinical, radiological, management outcome and the family challenges of a series of cases with CRS to obtain a clue and understanding of this co-morbid pathology with its concomitant anomalies.

CASE SERIES

Case 1

A 4-month-old female child was referred to a pediatric surgical clinic for evaluation of multiple congenital abnormalities. She was

fifth born to consanguineous parents with three healthy elder siblings and one sister with a neural tube defect. Antenatal period the mother was treated for complicated gestational diabetes, and she was on folic acid supplementation as recommended, with no history of radiation exposure or ingestion of long-term medications apart from being on antidiabetic medications. Growth was age-appropriate. Physical examination revealed a flat buttock, bilateral knee flexion contractures, bilateral leg muscle atrophy, and bilateral congenital talipes equinovarus deformity, she had clinical evidence of bilateral hip dysplasia with positive Ortolani's and Barlow's tests (Figure 1A&B). She was arranged for an X-ray of the whole spine (Figure 1B&C). Un ultrasound of the lumbosacral spine revealed complete agenesis of the sacrum and L2-5 vertebrae, thickened conus medullaris with bilateral hip dysplasia with shallow acetabula. Overall, the findings were in keeping with CRS. An abdominopelvic ultrasound study revealed evidence of right renal agenesis, neurogenic bladder, and left vesicoureteric reflux. Renal function tests were within the normal range. Brain ultrasound was also normal. Echocardiogram was normal. Parents were counseled regarding available supportive treatment options and the long-term prognosis. Accordingly, Long-term follow-up was established with a multidisciplinary team; pediatric surgeons, pediatricians, urologists, and neurologists to monitor for growth, development, and screen for long-term health issues. The orthopedic surgeon was advised to design the protocol and the treatment options to improve pelvic stability of sitting stability despite the expectation of ambulation was low as she had bilateral hip dysplasia, leg muscle wasting, and fixed knee contractures resulting from an advanced lumbosacral vertebral defect.

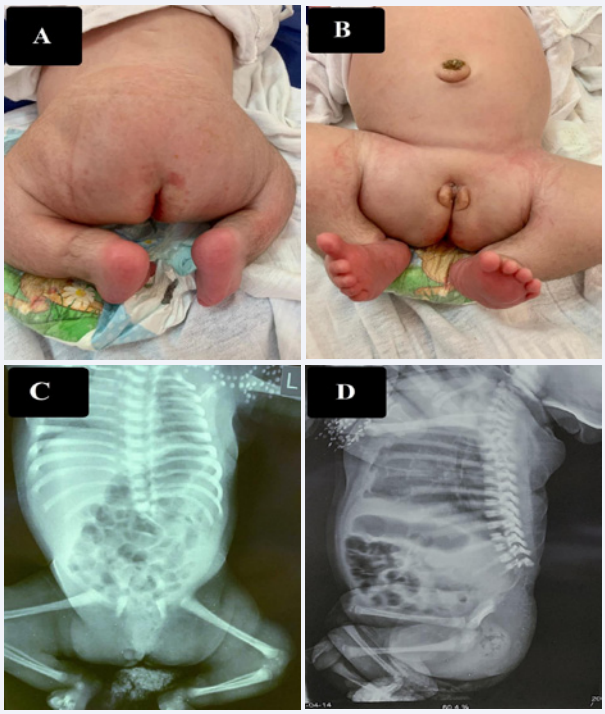

Figure 1 A, B, C and D: A&B; a flat buttock, bilateral knee flexion contractures, and bilateral congenital talipes equinovarus deformity. C&D; Anteroposterior and lateral plain roentgenograms of the whole spine revealed abrupt termination of the spinal column the L1 vertebra level , total sacral agenesis (Renshaw type 3), with the image of hip dysplasia by the shallow socket (acetabulum), and by displacement of the ball (femoral head) from the socket.

Case 2

A 6-years-old male child presented with poor urinary control since infancy with constant overflow incontinence. Since no organic cause could be found in previous examinations, the child was labeled as psychosomatic; a diagnosis that led faced the child to a great psychological trauma with stressful family domestic relationships. He was borne of consanguineous marriage, by normal vaginal delivery at term with the breech presentation following an uneventful pregnancy of a nondiabetic mother. There was no neuro-developmental delay. On examination, the patient's weight and height were appropriate for his age. The patient had a normal gait. There was continuous dribbling of urine, flat buttocks, and a dimple over the sacral area (Figure 2A&B). Nervous system examination was normal except for sluggish ankle jerk on both sides and anal sphincter hypotonia. The musculoskeletal examination was normal. A radiograph of the lumbosacral area of the spine showed an abnormal sacrum. MRI study revealed evidence of absent 2-5 sacral vertebrae and the coccyges (Figure 2C&D). Ultrasonography reported neurogenic bladder with residual urine (approx.250 ccs) in the bladder right vesicoureteral reflex (it was a grade 4 on voiding cystourethrogram VCUG study) (Figure 2E). Diuretic Reno gram (135MBq Tc99m MAG3), submitted poor function of right kidney, split function was 12% (Figure 2F). These images are along with anal hypotonia confirmed the presence of a mixed upper and lower motor neurogenic bladder with normal sensation. Lab investigations including complete blood count, renal function tests, and serum electrolytes were normal. Urine culture was negative even after 72 hours of incubation. The child was sent to a urologist for urinary diversion and re urodynamic assessments and follow-up.

Case 3

A 6 – years old female presented with dribbling of urine since birth and constipation with encopresis since 2 years of age. In antenatal history, the mother was treated for gestational diabetes. She was sixth born to consanguineous parents with two healthy elder siblings, one sister died because of birth asphyxia and she lost two brothers with birth defects. On examination, the patient's weight and height were appropriate for her age, flat buttocks, and a dimple over the sacral area (Figure 3A). A conventional radiograph of the vertebral column showed partial sacral agenesis. MRI of the vertebral column revealed the imaging findings were characteristic of caudal regression syndrome (Figure 3B&C). The family's challenges and concerns were how far they can encounter both the encopresis, dribbling, and their negative psychosocial outcomes as the patient is now enrolled in the school! At the age of 3 years she was toilet trained, at the age of 4 years she stopped going to the toilet to defecate and she experienced fecal incontinence occurring 3-5 times daily, occasionally even at night. Once every 2 weeks, she produced a large number of feces that clogged the toilet. Frequently she complained of abdominal pain and poor appetite, both clearly

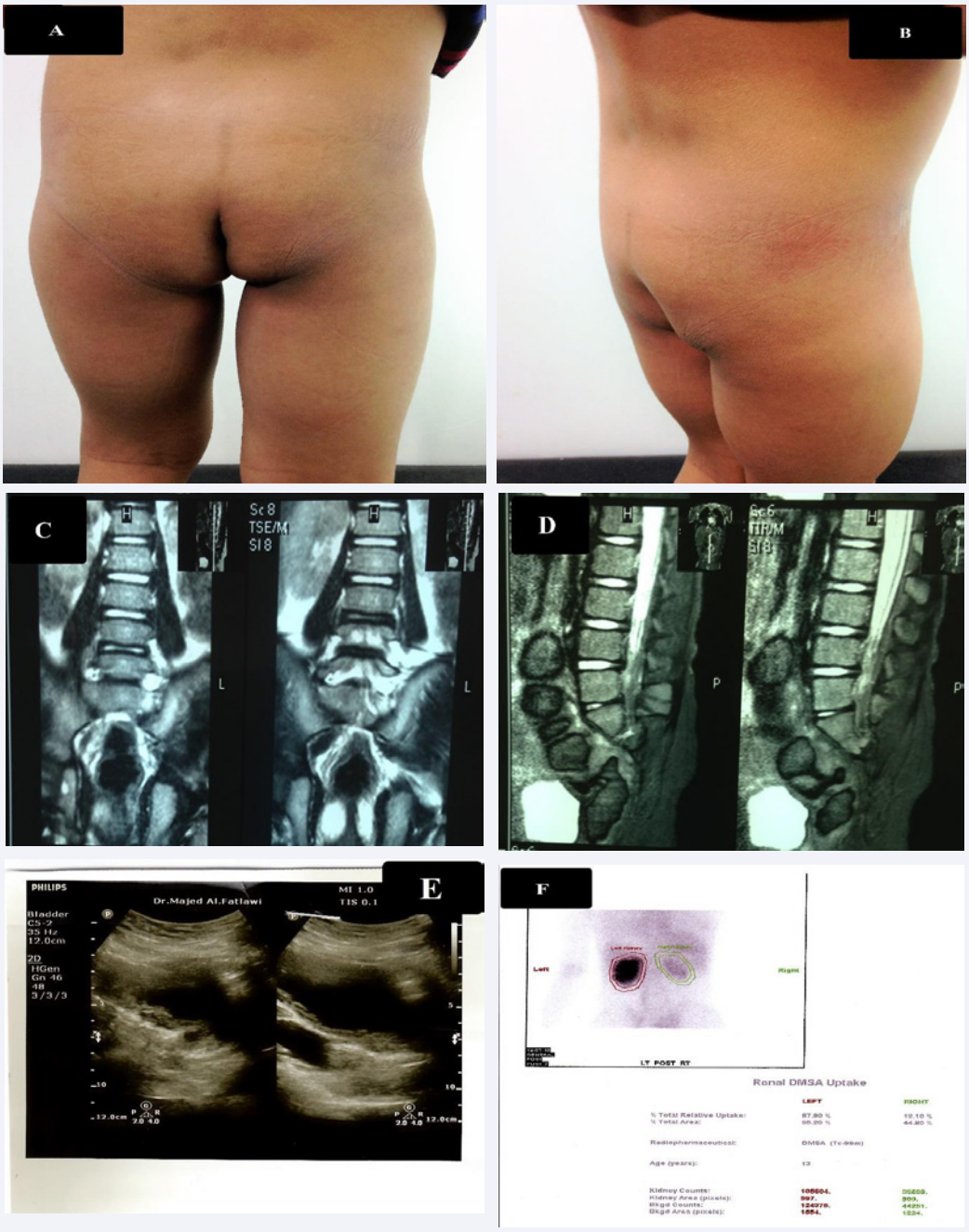

Figure 2 A, B, C, D, E and F; A&B: flat buttocks, and a dimple over the sacral area. C&D: MRI study revealed evidence of absent 2-5 sacral vertebrae and the coccyges (Renshaw type 2), Conus ends cephalic to the lower border of L1-2 vertebrae, and sacral deficit is large ending above S1 vertebrae. E: Ultrasonography reported thick wall with irregular trabeculated mucous membrane suggested neurogenic bladder). F: Diuretic Reno gram (135MBq Tc99m MAG3) submitted poor function of right kidney, split function was 12%.

related to her defecation pattern. Neurological assessments reported signs of motor and sensory dysfunction of the lower extremities with abnormal reflexes and abnormal anorectal sensation with ano- cutaneous reflex (anal wink). Abdominal and rectal examination revealed signs of fecal retention with perianal feces and in the rectal digital examination, a large fecal mass was found. She arranged for Colonic Transit Time with barium enema study where they revealed delayed distal colonic transits with abnormal defecation dynamics (Figure 3D&E). The workup focused on multidisciplinary team management, bowel management, and a pediatric psychologist advised educational interventions including child-friendly and family about the pathology and the outcome of CRS.

Case 4

A 7-year-old male with a history of chronic lower back pain, lower extremity weakness with paresthesia, fecal soiling (Figure 4A), and urinary incontinence since birth. He was the firstborn

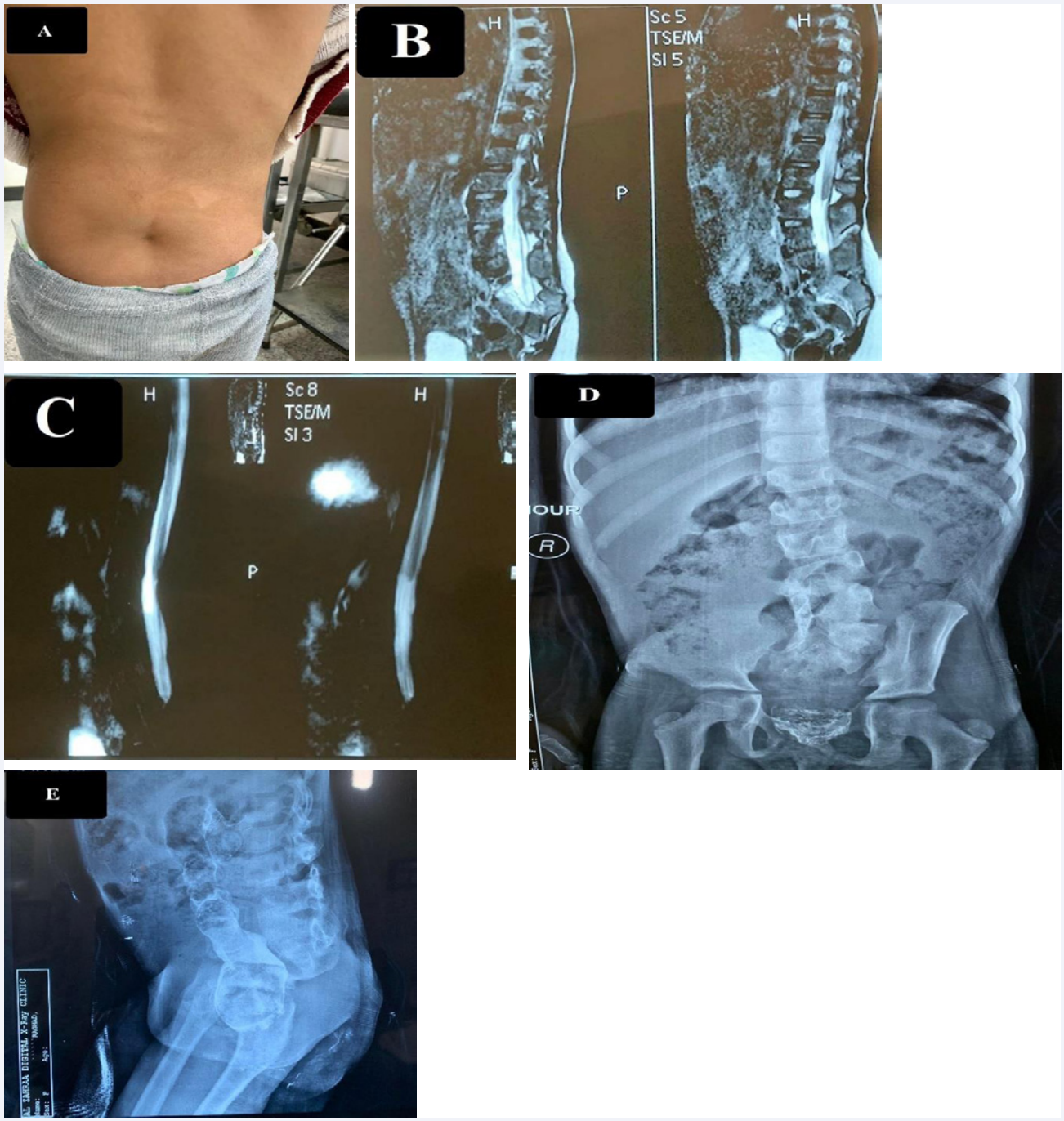

Figure 3 A, B, C, D and E; A: flat buttocks, and a dimple over the sacral area. B&C: MRI of the vertebral column revealed sacrococcygeal hypoplasia with a blunt-ending, club-shaped conus medullaris terminating at the T11-12 vertebral level. The caudal nerve roots were arranged in anterior and posterior bundles (Renshaw type 2). D&E: Barium enema revealed impacted stool filling the sigmoid colon and rectum, markedly distended recto sigmoid colon is obvious on these sequences, and signs of sacral agenesis.

to nonconsanguineous parents. Antenatal history the mother was treated for toxoplasmosis after two serial abortions with spiramycin and sulphonamide, no history of gestational diabetes was declared. The patient had 3-4 times casting of his feet for management of talipes equinovarus and one intervention for tenotomies. The patient underwent a plain radiograph of the lumbosacral spine revealing images suggested CRS (Figure 4B&C). Ultrasound assessments reported the images of the neuropathic bladder with evidence of reflex uropathy (Figure 4D). Voiding cystourethrogram revealed the evidence of a trabeculated bladder wall suggesting the image of a neuropathic bladder with bilateral vesicoureteral (grade 3 on the right side). Diuretic Reno gram (135MBq Tc99m MAG3), submitted poor function of right kidney (Figure 4E&F). The child was closely followed-up by a multidisciplinary team in order to observe all the outcomes and co-morbidities of this condition. Clean intermittent urinary

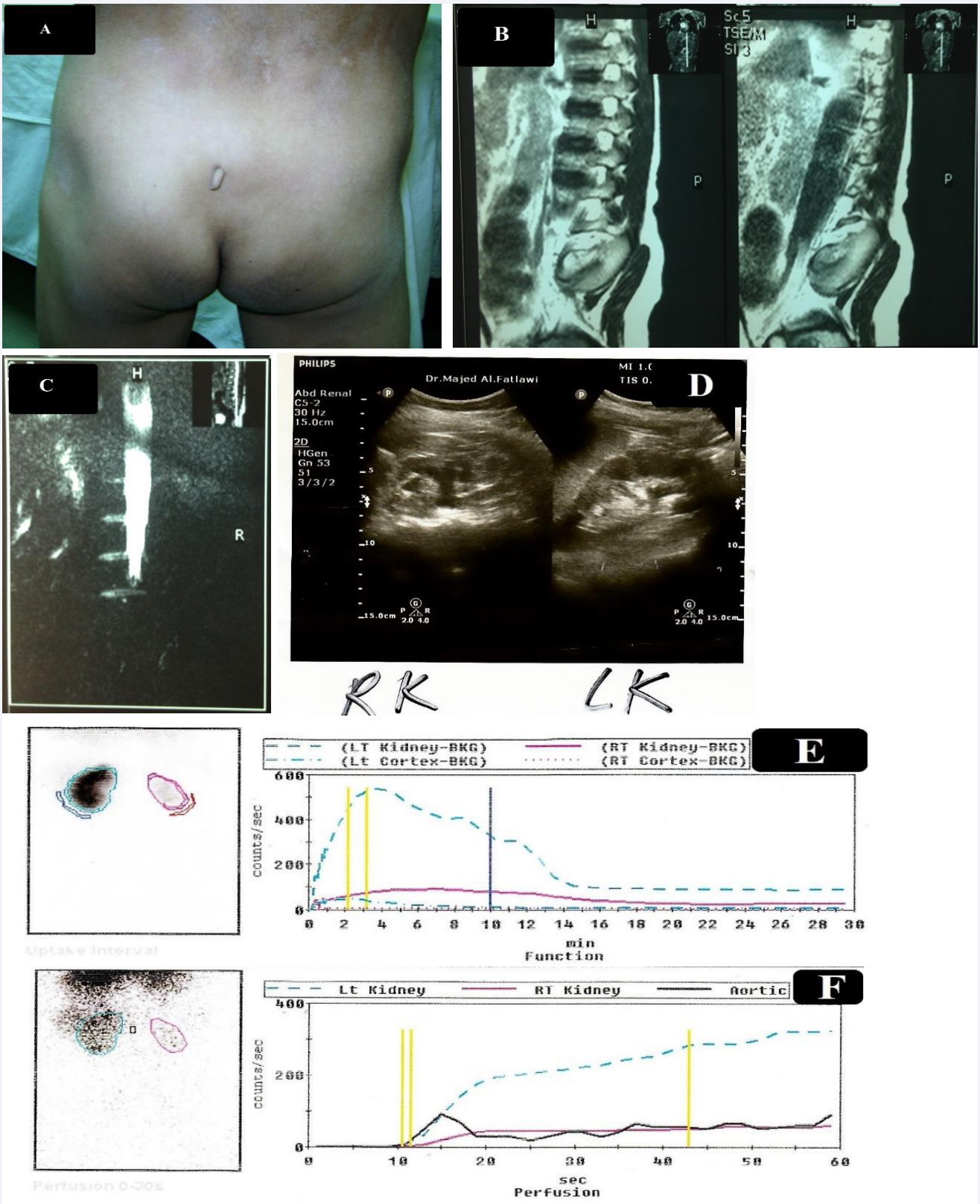

Figure 4 A, B, C, D, E and F; A: Flat buttock with sacral dimple. B&C: MRI of the lumbosacral vertebral column revealed an abruptly and high-ending conus, sacrococcygeal hypoplasia, including the absent S3–5 and coccygeal segments with dysplastic S1 and S2 (Renshaw type 1). D: Ultrasound image assessments reported the images of the neuropathic bladder with evidence of reflex uropathy, small right kidney with decrease in the parenchymal thickness and bilateral pyelonephritis changes. E&F: Diuretic Reno gram (135MBq Tc99m MAG3) submitted poor function of right kidney; the split function was 10%.

catheterization with an antibiotic cover according to the urine culture results and the family was instructed about the program of bowel management with tap water enemas.

Case 5

A 36.4-week gestation female infant was born via caesarean section to a 29-year-old diabetic mother (consanguineous marriage) with G4 P2+1, a weight of 3.7 Kg, an evident diabetic fetopathy with an APGAR score of 6/10 in one minute, and 9/10 in five minutes. There was no history of antenatal infections and the mother had been taking oral antidiabetic medication (Glipizide and Metformin combination).A routine prenatal ultrasound study revealed images of relatively low vertebral and sacral anomalies. On initial assessment, the infant was noted to have left clubfoot, imperforate anus (cloaca), and absent sacrum (Figure 5A&B). Other abnormal features included low set ears and bilateral cleft lip with depressed nasal bridge and high arched palate. An echocardiogram revealed a large ASD with a left to right shunt. Spinal ultrasound (US) revealed an absence of the sacrum with the conus having a blunt end at the tip at the L1-L2 disc space. The abdominal US reported bilateral hydronephrosis with evidence of obstructive uropathy (Figure 5C&D). At age of 2 months she arranged for MRI study of the spine, the images revealed signs of CRS (Figure 5E&F). She underwent a colostomy and antibiotics were initiated due to urinary tract anomalies. She had serial casting of her left foot because of her talipes equinovarus. Subsequent

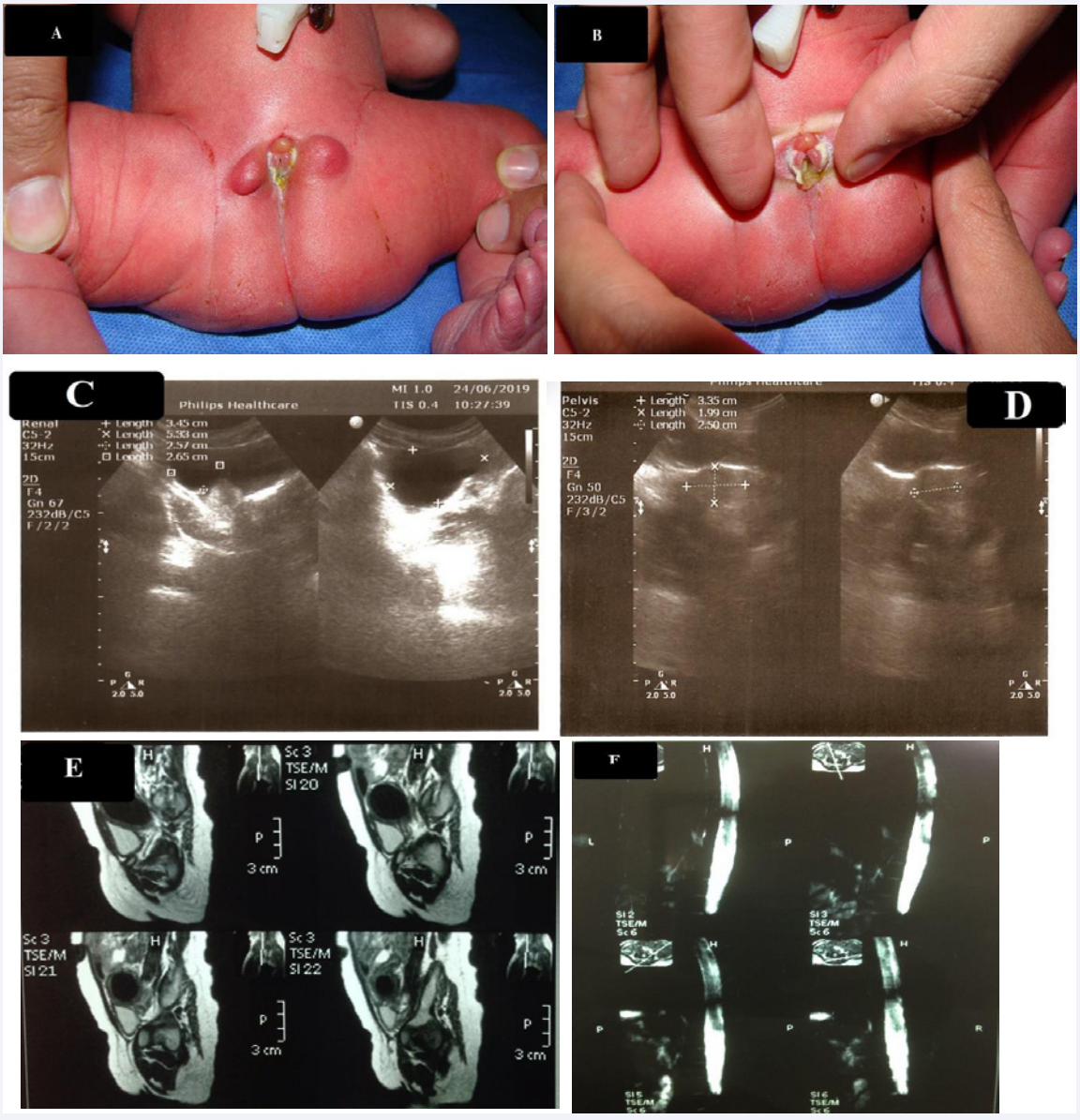

Figure 5 A,B,C,D,E and F; A&B: The perineum is spread identifying there is no anal opening. Then the labia are lifted up and out to reveal a single perineal orifice (cloaca). C&D: The abdominal US images revealed bilateral hydronephrosis, hydroureters with vesicoureteral reflex and hydrocolpus with evidence of obstructive uropathy. E&F: MRI of the spine revealed a rudimentary sacrum, absence of coccyx, and blunting of the spinal cord at L1 with the conus medullaris being truncated and nodular at the level of intravesicular T12, a rudimentary dysgenetic sacrum with a sagittal cleft in the median sacrum, and a thickened cauda equine was detected (Renshaw type 2).

repair of bilateral cleft lip and cloaca were done. During the 30 months period of serial follow, a multidisciplinary team arranges her for re urological, gynecological, and bowel management clinic assessments. At 26 months of age, the neurodevelopmental team assessment announced she had mild to moderate language, social, cognitive, and fine motor deficits and moderate to severe motor deficits especially related to ambulation. Subsequently, she had two tenotomies. On neurodevelopmental assessment at 18 and 24 months, she had mild to moderate language, social, cognitive, and fine motor deficits and moderate to severe motor deficits especially related to ambulation. Her last follow-up was at the age of 3 years.

DISCUSSION

Caudal regression syndrome is an uncommon malformation with a very low incidence characterized by abnormal development of the caudal spine of the developing fetus. It presents a spectrum of distal neural tube disruption, which may include incomplete development of the sacrum, to a lesser extent, the lumbar vertebrae, and, disruption of the distal spinal cord with extreme lack of growth of the caudal region [11,12]. During the embryologic period, the insult occurs at the mid posterior axis mesoderm and the lesion originates before the 28th day of the gestational period which interferes with the formation of the notochord, resulting in abnormal development of caudal structures [12-14]. Advances in the understanding of axial mesoderm patterning at early gestation reveal that a process of primary neuralization is compromised [14]. Aetiopathogenesis is complex, maternal diabetes, genetic predisposition, and vascular hypoperfusion have been declared as risk and possible causative factors [13,14]. In our cases (1, 3, and 5), the mothers were treated for gestational and old diabetes, authors announced this is due to the negative impact of hyperglycemia on oxidative stress and DNA structure which both can increase the risk of malformations in the fetus [15]. Those cases are a clear example of the wide range of alterations that can affect the fetus may be due to uncontrolled diabetes. CRS also occurs in non-diabetic women, as in our cases (2 and 4), with confounding etiologic factors. More recently has been suggested a drug-related etiology with trimethoprim-sulfamethoxazole and minoxidil. Familial cases suggest genetic cause with a recurrence risk of 5% in families that already had an affected child; this may explain its risk with diabetes in our first case [13]. CRS would be transmitted as either dominant or recessive characteristics, the dominant inherited sacral agenesis known as Currarino syndrome is correlated with the disease-causing HLXB9 gene, located at 7q36. In some cases, CRS may be associated with mutations in the VANGL1 gene [12]. In our community, there is a high incidence of consanguinity; many authors reported that inbreeding or consanguineous marriages have an effect on the rates of reproductive loss, congenital malformations, and genetic diseases, mainly autosomal recessive, and probably this made another aetiopathogenicity in our cases (1-3 and 5). We agree with the limitation of this series when resources did not allow the karyotype studies for our cases enrolled in this series [16,17]. Based on the type of vertebral defect and the nature of the attachment of iliac bones to the lowest vertebra, Renshaw 1978 classified CRS into four types [18]. Type 1 is characterized by either partial or complete unilateral sacral agenesis. Type 2 is the most common form, and in addition to partial sacral agenesis, there is a bilaterally symmetrical defect between the ilia and either normal or hypoplastic first sacral vertebra. Type 3 is characterized by total sacral agenesis and variable lumbar vertebral agenesis. Type 4 is the worst type and either fusion of iliac bones or iliac amphiarthrosis (a joint that has limited mobility). Severe sacral agenesis is associated with lower extremity neurologic compromise, especially the motor one. On another side, Pang divided patients with CRS into two groups [19]: Group 1: Conus ends cephalic to the lower border of L1 vertebrae. In these patients, the sacral deficit is large ending at or above S1 vertebrae. Group 2: Conus ends caudally to the lower border of L1 vertebrae. In these patients, the sacrum tends to be well preserved with identifiable portions of S1 or lower vertebrae. The associated orthopedic anomalies may range from deformities of feet (clubfeet or webbed skin on the back of the knees), flexion contractures of hips and knees, dislocation of hips, kyphoscoliosis, pelvic deformity, absence of ribs, and sirenomelia (fused lower extremities) [20,21]. Affected infants may also have. In our patient, the first abnormality clinically noticed was bilateral talipes equinovarus. On rare Occasions VACTERL defects (vertebral, anal, cardiac, tracheoesophageal fistula, renal, and limb) may associate with CRS, this occurrence may support the theory that these entities may be different manifestations of a single etiopathogenic factor (our case five had ARM with cloacal variant) [5,6]. Affected patients may also have a gastrointestinal obstruction and chronic constipation. Renal anomalies may occur including abnormal fusion of the two kidneys into a horseshoe shape, in several instances the patients may develop incontinence, recurrent urinary tract infections, abnormal backflow of urine from the bladder into the ureters (vesicoureteral reflux), and failure of the bladder to empty completely (neurogenic bladder) [9,22]. We followed these sequels in more advanced studies like diuretic Reno gram (135MBq Tc99m MAG3) to scan the renal function in our cases 2 and 4. The literature reported that even with intact perianal sensation there might be bladder or anal sphincter involvement because the motor deficit is always more pronounced than the sensory deficit [9]. Due to the state of anomalies, bowel or bladder deficiencies is quite common in CRS, both addressed the major concern in our series. Accordingly, avoiding cystourethrogram should be done routinely [23]. Intermittent clean self-catheterization along with uropharmacological support and manipulation are the preferred mode of treatment for those with neurogenic bladder.

To protocol the treatment pathways the multidisciplinary team; Pediatric surgeons, pediatricians, neurosurgeons, neurologists, urologists, orthopedists, orthopedist surgeons, cardiologists, nephrologists, and caregiver professionals should instruct the family; the standard management path is supportive and symptomatic. We should clarify the images of the pathology in a way that the affected child may not have all of the underlining pathology or symptoms and the symptoms vary from one to another usually the outcome and prognosis depends on the severity of spinal involvement and associated malformations. The early management of CRS should be started with an accurate prenatal diagnosis, and the parents' counseling regarding the potential sequelae should be considered. Recently a fetal ultrasound can detect some of the defects (a large nuchal translucency, a short crown-rump length, and abnormal appearance of the yolk sac)

that have been considered early ultrasonography signs of CRS [7]. In our case 5, fortunately the radiologist announced such pathology and the staff maximize the antenatal and post-natal care accordingly. This approach is important in view of the dismal prognosis and allows for earlier, less traumatic termination of pregnancy in the severely affected fetuses. In some literature, authors reported early detection of CRS at 11 weeks of gestational age by transvaginal ultrasound scanning [24]. MRI studies are implemented, which may be helpful in the evaluation of the fetal anatomy in cases with oligohydramnios [11]. In a rare instance, a single spectrum of segmental malformations of the spine and spinal cord in the body-wall complex (bladder exstrophy, omphalocele, and sacral myelomeningocele) with caudal defects and segmental spinal dysgenesis should be evaluated. The study considered one of the standard roles to categorize the severity of the spinal vertebrae and the cord defect. All our patients underwent an MRI images study as routine assessments. Many strategies should be implicated in the frame of patients care and treatments, a colostomy while incontinence may be managed by catheterization (any associated anomalies and urinary dysfunction should attract caregiver attention to the underlying possibility of sacral agenesis). Orthopedic care should be pointed to CRS patients with lower limb deformities, especially those with severe ones to enable more ease of mobility and better seating and state a rehabilitation program with a wheelchair or prosthetic mobilization despite no usual cognitive impairment is associated with this disability (Physical and occupational therapies should planned to improve quality of life). Psychosocial support for the life plan and cosmetic appearance should not be missed or neglected.

CONCLUSION

The target of this series is to highlight that the complex spectrum of CRS needs to be addressed and shaped for each case because of the variety of anomalies. Parents' counseling regarding the expected outcome should be considered. Implementation of periconceptional and antenatal assessments to control women with diabetes. Early workup and management strategies are very important to decrease the risk of complications and may improve the prognosis outcome. A multidisciplinary approach is a cornerstone, the purpose is not to correct all deformities but decrease the patients' long-term morbidity, increase the functionality of everyday life, and thus, survival is the role.

CONFLICT OF INTEREST

The authors declare that they have no competing interests. This work is original and not submitted with other publishers.

ETHICS STATEMENT

Written informed consents were obtained from the patients› parents who participated and managed in this report for publication and any accompanying images. The study conformed to the guidelines of the institutional review board of our Institution, which approved its ethical aspects.

ACKNOWLEDGMENTS

The author expresses sincere gratitude to all the pediatric surgery unit staff, pediatric outpatient's clinic, and the department of radiology at the Maternity and Child Teaching Hospital, Al Qadisiya- Al Diwaniya, Iraq, for their assistance. We are grateful to all colleagues in Iraqi-German Functional Imaging Clinic for their kind assistance to conclude the renal function results and images for these series.

REFERENCES

1. Caird MS, Hall JM, Bloom DA, Park JM, Farley FA. Outcome Study of Children, Adolescents, and Adults with Sacral Agenesis. J Pediatr Orthop. 2007; 27: 682-685.
2. Becerra JE, Khoury MJ, Cordero JF, Erickson JD. Diabetes mellitus during pregnancy and the risks for specific birth defects: A population-based case-control study. Pediatrics. 1990; 85: 1-9.
3. Adra A, Cordero D, Mejides A, Yasin S, Salman F, M J O'Sullivan, et al. Caudal regression syndrome: Etiopathogenesis, prenatal diagnosis, and perinatal management. Obstet Gynaecol Surv. 1994; 49: 508-516.
4. Singh SK, Singh RD, Sharma A. Caudal regression syndrome-case report and review of literature. Pediatr Surg Int. 2005; 21: 578-581.
5. Emami-Naeini P, Rahbar Z, Nejat F, Kajbafzadeh A, El Khashab M. Neurological presentations, imaging, and associated anomalies in 50 patients with sacral agenesis. Neurosurgery. 2010; 67: 894-900.
6. Duhamel, B. From mermaid to anal imperforation: The syndrome of caudal regression. Arch Dis Child. 1961; 36: 152-155.
7. Aslan H, Yanik H, Celikaslan N, Yildirim, G, Ceylan Y. Prenatal diagnosis of caudal regression syndrome: a case report. BMC Pregnancy Childbirth. 2001; 1-8.
8. Tortori-Donati P, Fondelli MP, Rossi A, Charlers AR, Armando C, Valeria C. Segmental spinal dysgenesis: neuro-radiologic findings with clinical and embryologic correlation. Am J Neuroradiol. 1999; 20: 445-456.
9. Torre M, Buffa P, Jasonni V, Cama A. Long-term urologic outcome in patients with caudal regression syndrome, compared with meningomyelocele and spinal cordlipoma. J Pediatr Surg. 2008; 43: 530-533.
10. Hentschel J, Stierkorb E, Schneider G, Goedde S, Siemer S, Gortner L. Caudal regression sequence: vascular origin? J Perinatol. 2006; 26: 445-447.
11. Boulas MM. Recognition of caudal regression syndrome. Adv Neonatal Care. 2009; 9: 61-69.
12. Kibar Z, Torban E, McDearmid JR, Reynolds A, Berghout J, Mathieu M, et al. Mutations inVANGL1Associated with Neural-Tube Defects. N Engl J Med. 2007; 356: 1432-1437.
13. Thottungal AD, Charles AK, Dickinson JE, Bower C. Caudal dysgenesis and sirenomelia-single centre experience suggests common pathogenic basis. Am J Med Genet Part A. 2010; 152: 2578-2587.
14. Kaygusuz EI, Eken MK, Sivrikoz ON, Cetiner H. Sirenomelia: A review of embryogenic theories and discussion of the differences from caudal regression syndrome. J Matern Neonatal Med. 2015; 29: 949-953.
15. Stroustrup A, Grable I, Levine D. Case 66: Caudal regression syndrome in the foetus of a diabetic mother. Radiology. 2004; 230:229-233.
16. Bener A, Mohammad RR. Global distribution of consanguinity and their impact on complex diseases: Genetic disorders from an endogamous population. Egyptian J Med Human Genetics. 2017; 18: 315-320.
17. Bittles AH, Black ML. Consanguinity, human evolution, and complex diseases. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107: 1779-1786.
18. Renshaw TS. Sacral agenesis. J Bone Joint Surg Am. 1978; 60: 373-383.

19. Pang D. Sacral agenesis and caudal spinal cord malformations. Neurosurgery. 1993; 32: 778-779.

20. Kjaer KW, Keeling JW, Opitz JM, Gilbert-Barness E, Hartling U, Hansen BF, et al. Sirenomelia sequence according to the distance between the first sacral vertebra and the ilia. Am J Med Genet Part A. 2003; 503-508.

21. Stocker JT, Heifetz SA. A morphological study of 33 cases and review of the literature. Perspect Pediatr Pathol. 1987; 10: 7-50.

22. Bohring A, Lewin SO, Reynolds JF, Voigtlander T, Rittinger O, Carey JC, et al. Polytopic anomalies with agenesis of the lower vertebral column. Am J Med Genet. 1999; 19: 99-114.

23. Moritoki Y, Kojima Y, Kamisawa H, Mizuno K, Kohri K, Hayashi Y. Neuropathic bladder caused by caudal regression syndrome without any other neurogenic symptoms. Case Report Med. 2012.

24. Unsinn KM, Geley T, Freund MC, Gassner I. US of the Spinal Cord in Newborns: Spectrum of Normal Findings, Variants, Congenital Anomalies, and Acquired Diseases. Radiographics. 2000; 20: 923-938.