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ABSTRACT

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MULTIFACETED CLINICAL PRESENTATION OF CAUDAL REGRESSION SYNDROME: A CASE REPORT AND LITERATURE REVIEW

The purpose of the study is to analyze modern scientific achievements in the field of anomalies of the caudal spine and syndromic diseases that are most common in medical practice, and compare them with our clinical observations.

Materials and methods: A rare clinical case of caudal regression syndrome in a child was investigated. Medical history was studied by interviewing the parents, reviewing outpatient and inpatient records, and analyzing the results of clinical and laboratory tests. The primary method of examination was X-ray. For more accurate diagnosis, ultrasound, and contrast-enhanced computed tomography (with Tomohexol-350) in 3-D format were used. Our findings were compared with the results of other studies conducted over the last ten years.

Results of the study and discussion: A 15-year-old girl, G., was under our observation. Her weight was 50 kg, and her height was 167 cm. A month prior to admission, she had experienced pain in the lower abdomen and lumbar spine. She became fatigued quickly, could stand and run only for short periods. The spinal axis deviated to the right in the lumbar region, with the apex of the curvature at the third lumbar vertebra, and a fixed deformity. Plain radiographs of the lumbar spine revealed multiple vertebral malformations. An ultrasound of the abdominal cavity showed a cyst on the left ovary, agenesis of the left kidney, and multiple malformations of the lumbar spine. The uterus was deformed – "bicornuate uterus". A diagnosis of caudal

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regression syndrome was made, and the course of the condition and treatment were described.

Conclusions: A defect that develops in the early stages of embryogenesis typically leads to multiple malformations of nearby anatomical structures. This phenomenon is known as sequencing – the sequence of congenital multiple malformations, which is supported by our findings. It is clear that caudal regression syndrome may have several variants, which require further study.

Keywords: caudal regression syndrome; renal agenesis; bicornuate uterus; ovarian cyst; spine; case report.

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БАГАТОГРАННА КЛІНІЧНА ПРЕЗЕНТАЦІЯ СИНДРОМУ КАУДАЛЬНОЇ РЕГРЕСІЇ: ВИПАДОК З ПРАКТИКИ ТА ОГЛЯД ЛІТЕРАТУРИ

Мета дослідження – проаналізувати дані сучасних наукових досягнень у галузі аномалій хвостового відділу хребта та синдромних захворювань, які найбільш поширені у практиці лікарів та порівняти їх з нашими клінічними спостереженнями.

Матеріали та методи. Ми досліджували рідкісний клінічний випадок синдрому каудальної регресії у дитини. Вивчено історію хвороби шляхом опитування батьків, уважно вивчено дані амбулаторних та стаціонарних документів, результати клінічних та лабораторних досліджень. Основним методом дослідження була рентгенографія. Для більш точної діагностики захворювання використовували ультразвуковий метод, контрастну комп'ютерну томографію (з томогексолом-350) у форматі 3D. Наші дані порівнювали з результатами інших досліджень, отриманих за останні десять років.

Результати дослідження та їх обговорення. Під нашим спостереженням перебувала дівчинка Г. 15 років. Маса тіла 50 кг, зріст 167 см. За місяць до госпіталізації з'явилися болі внизу живота, в поперековому відділі хребта. Вона швидко втомлюється, може недовго стояти і бігати. Відхилення осі хребта вправо в поперековому відділі, вершина викривлення 3-го поперекового хребця, фіксована деформація. На оглядовій рентгенограмі поперекового відділу хребта виявлені множинні вади розвитку хребців. При ультразвуковому дослідженні органів черевної порожнини виявлена кіста лівого яєчника, відсутність (агенезія) лівої нирки, множинні вади розвитку поперекового відділу хребта. Матка була деформована – «дворога». Поставлено діагноз: синдром каудальної регресії, описано перебіг та лікування.

Висновки. Вада, що розвивається на ранніх етапах ембріогенезу, як правило, сприяє множинним вадам

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розвитку найближчих анатомічних структур. Це явище називається секвенуванням – послідовністю розвитку вроджених множинних вад розвитку, що підтверджується нашими даними. Очевидно, що синдром каудальної регресії може мати кілька варіантів, які підлягають подальшому вивченню.

Ключові слова: синдром каудальної регресії, агенезія нирок, дворога матка, кіста яєчника, хребет, клінічний випадок.

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INTRODUCTION

Approximately 20% to 30% of children born with birth defects experience the presence of multiple major anomalies affecting various organ systems, commonly termed as multiple congenital anomalies (MCAs). Around 3% of live births, totaling 120,000 cases among the approximately 4 million annual births in the United States, involve major developmental defects, alternatively known as major congenital anomalies. These anomalies are characterized by being life-threatening, necessitating significant surgical intervention, or resulting in substantial disabilities [1, 2]. Many multiple disabilities need to be studied as they have specific characteristics and educational support needs. Students with severe and multiple disabilities are often low in development and daily life activities, and they may have emotional and behavioral issues. Multiple disorders of newborns have been the focus of study and research. Newborn screening has expanded to include over 60 disorders, allowing for early identification and treatment. Avery's Diseases of the Newborn provides comprehensive coverage of diseases affecting newborns [3, 4]. Multiple disorders of newborns, particularly in the field of medicine, are studied under the branch of syndromology. Neonatal hypotonia is a common clinical presentation in neonatal medicine, and a systematic approach involving history-taking and neurological examination can help identify the underlying diagnosis. Newborn screening plays a crucial role in the early identification and treatment of disorders that may go unrecognized without screening [5, 6].

In practice, syndromic diseases can be diagnosed when a child has three or more minor developmental anomalies in addition to one severe congenital defect. Here are some key points to consider:

1. Syndromic hypermobility in children and adolescents presents challenges in diagnosis and management due to the multiorgan involvement, evolving classification criteria, and heterogeneous presentation [7]
2. Syndactyly, a common upper limb congenital anomaly, can occur alone or in association with other abnormalities [8]. It is important to note that syndactyly is not specifically mentioned in the context of the query.
3. Infants referred for developmental dysplasia of the hip may have concomitant syndromic pathology, highlighting the need for thorough evaluation and identification of risk factors [9].

Caudal Regression Syndrome (CRS), or Caudal Dysplasia Syndrome, is a rare congenital pathology characterised by malformations of the caudal spinal cord, pelvic bones and lower extremities. CRS is a complex disorder with various types and associated anomalies. It can be divided into three types: sirenomelia, complete absence of the sacrum, and partial absence of the sacrum. Genitourinary and gastrointestinal anomalies are common in CRS, with neurogenic bladder and bowel incontinence. Treatment of CRS is complex and multidisciplinary, involving orthopedic management for spinal deformities, spinopelvic instability, and lower limb deformities [10, 11].

The incidence of CRS is 0.1 per 10,000 normal births. However, the incidence of CRS in fetuses whose mothers have diabetes mellitus increases 200 to 250 times compared to the healthy population. Maternal diabetes is significantly linked to CRS, although the exact cause is unknown. The association between diabetes and CRS is well-established, and it is important for appropriate management to diagnose CRS early [12, 13].

The type of inheritance has not been definitively established; in most cases, it is a sporadic disease. Clinical signs of the disease depend on the number and severity of malformations of the lumbar, sacral vertebrae and coccyx. Lower extremity muscular

atrophy and various malformations of the pelvis and lower extremities, congenital dislocation of the hips, flexion contractures of the hip and knee joints, and clubfoot are characteristic. The lower body is narrowed and deformed, the trunk and limbs are shortened [14, 15].

Neurological symptoms are characterised by lower paraparesis, muscle hypotonia, and suppression of tendon reflexes. The pelvic floor muscles and sphincters are underdeveloped, so children often have urinary and faecal incontinence [16, 17]. There are isolated cases of malformations of the urinary system and gastrointestinal tract, thallium gene.

The aim of the study is to analyse the data of modern scientific achievements in the field of developmental anomalies of the caudal spine and syndromic diseases that are most common in the practice of doctors and compare them with our clinical observations.

MATERIALS AND METHODS: We investigated a rare clinical case of CRS syndrome in a child. The history of the disease was studied by interviewing the parents, the data of outpatient and inpatient documents, the results of clinical and laboratory examinations were carefully studied. The basic method of examination was X-ray. For a more accurate diagnosis of the disease, we used the ultrasonographic method, contrast tomography (with Tomohexol 350) in 3-D format. Our data were compared with the results of other researchers' studies obtained over the past ten years.

RESULTS AND DISCUSSION

Clinical case. Girl G. age 15 years. Body weight 50 kg, height 167 cm. From the second pregnancy, premature birth, she grew and developed normally. A month ago, she developed pain in the lower abdomen, in the lumbar spine. She gets tired quickly, can stand and run for a short time.

On examination. Body proportion is preserved. Movements in the joints of the legs are not restricted, not painful, and the muscle tone of the limbs is reduced. Lumbar lordosis is flattened, spinal mobility at this level is limited. Deviation of the spinal axis to the right in the lumbar spine, the top of the curvature is the 3rd lumbar vertebra, the deformity is fixed.The body proportion is preserved, movements in the joints of the lower extremities are not restricted, not painful, not stiff, and the muscle tone of the extremities is reduced. The child complains of occasional back pain during flexion and extension in the lumbar spine, lasting up to several minutes with radiation to the left buttock, so the girl deliberately avoids such movements. At rest, the back pain is not disturbing. The lumbar lordosis is flattened, and spinal mobility at this level is limited. Deviation of the spinal axis to the right in the lumbar spine, the top of the curvature is the third lumbar vertebra, the deformity is fixed. On palpation, there is pain in the paravertebral zones on the left at the level of the middle third of the lumbar spine, which increases with flexion and extension movements and turns of the trunk. The pain spreads to the left buttock and the upper part of the left lower limb along the posterior surface. No sensory disorders or atrophy of the muscles of the buttocks and lower extremities were detected. The abdomen is soft, somewhat painful on the left during palpation. A left ovarian cyst was suspected.

Complete blood count: Red blood cells – 3.7 x 10/12, haemoglobin – 120, colour index – 1.0, leukocytes – 7.1 x 10/9, erythrocyte sedimentation rate – 3 mm/h, rods – 2%, segmented – 28%, eosinophils – 3%, lymphocytes – 64%, monocytes – 3%. General urine analysis – specific gravity 1024, protein, sugar not detected, 2–4 leukocytes in the field of view. General faecal analysis and scraping for enterobiosis were normal.

Biochemical blood test. Total protein – 73 g/l. Creatinine – 0.084%. Total bilirubin – 13.3 μmol/l. Total Ca – 2.0 mmol/l. AlAT – 0.200 mmol/l. ACAT – 0.200 mmol/l. Blood group B (III), Rh +.

Abdominal ultrasound revealed a cyst of the left ovary, absence (agenesis) of the left kidney, multiple malformations of the lumbar spine. The uterus was deformed – "bicornuate uterus".

Contrast CT scan (with Tomohexol 350) in 3-D format. The only right kidney with preserved full morphological structure and function (Fig. 1).

CT scan of the spine revealed multiple malformations of the lumbar spine (Fig. 2). Moderate wedge-shaped deformity of the right half of the body of the 3rd lumbar vertebra, similar counter-lateral deformity of the body of the 5th lumbar vertebra. The fourth lumbar vertebra consists of two wedge-shaped parts connected by the posterior part of the vertebra. Partial longitudinal split of the body of the first sacral vertebra, marked leftward deviation of the sacral axis.

The first sacral vertebra is not fused with the body of the sacrum (normally fused), complete longitudinal splitting of the body of the 2nd sacral vertebra along the anterior surface. The deviation of the lumbar spine axis according to the Koba method is 10 degrees, the sacral axis – 30 degrees (Fig. 3). The left half of the sacrum is underdeveloped. The coccyx is underdeveloped, consists of bone fragments of different sizes and shapes, and is deviated to the left at an angle of 45 degrees. The entrance to the pelvic cavity is asymmetrical and narrowed.

The right kidney is normal, the left kidney is absent. The blood supply network of the right kidney is normal, on the left – absent (Fig. 4).

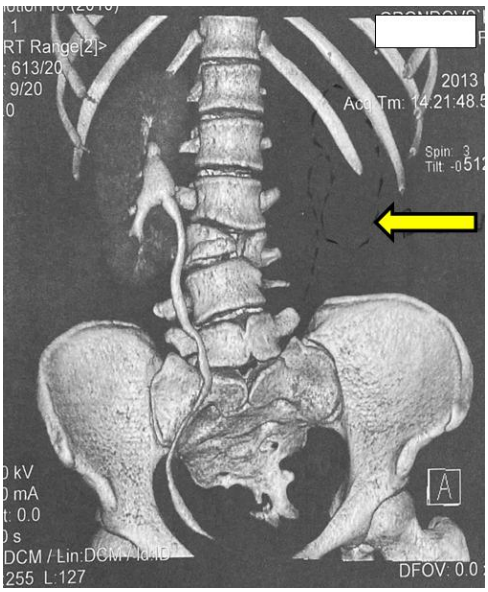

Fig. 1. Contrast CT (with Tomohexol 350) in 3-D format. Agenesis of the left kidney (arrow). Hypertrophied right kidney with full ureter

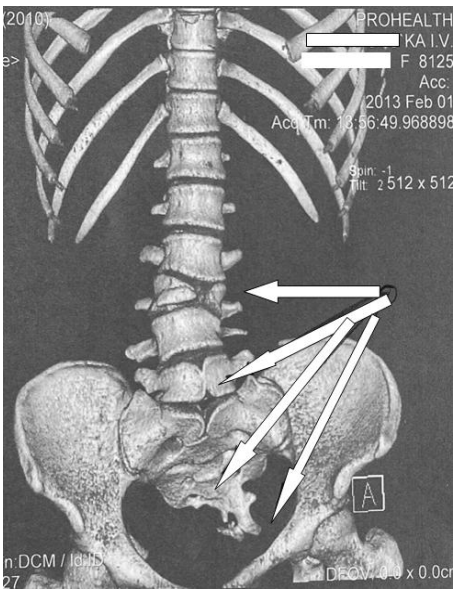

Fig. 2. Contrast CT (with Tomohexol 350) in 3-D format. Multiple malformations of the lumbar, sacral and coccygeal spine. Explanation in the text

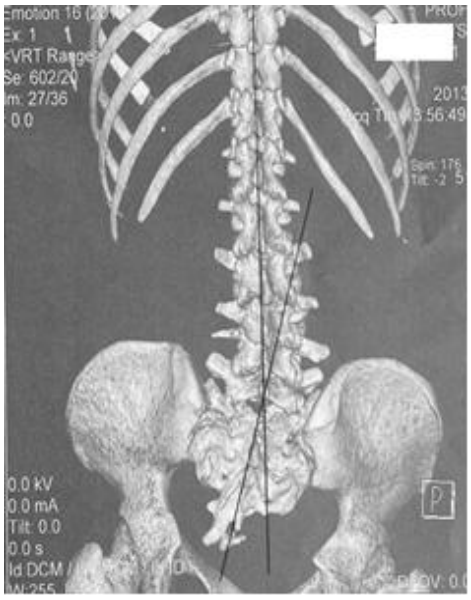

Fig. 3. Contrast CT (with tomogexol 350) in 3-D format. Abnormal development of the caudal part of the spine. Scoliosis (marked by lines), pelvic cavity distortion

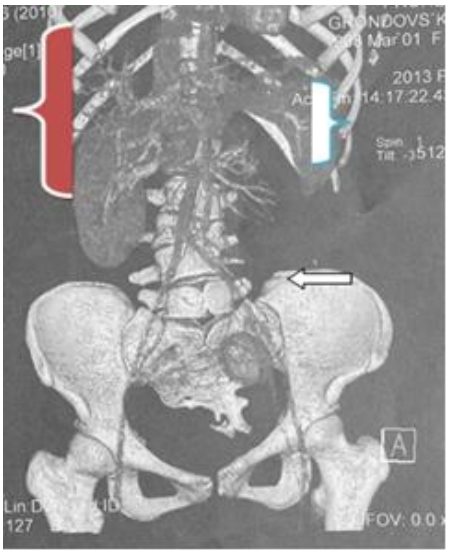

Fig. 4. Contrast CT (with Tomohexol 350) in 3-D format. Normal blood supply network of the hypertrophied right kidney (red curly bracket). Agenesis of the left kidney – no blood supply (white curly bracket). Excessive blood supply to the left ovary (arrow)

Caudal regression syndrome. Agenesis of the left kidney. Cyst of the left ovary. Malformation of the uterine body – bicornuate uterus uterus. Congenital scoliosis of the lumbar spine of the II degree. Multiple malformations of the lumbar and sacroiliac spine with functional disorders. Hypoplasia of the left half of the sacral spine. Chronic cystitis. Lower limb muscle hypotonia.

The patient was consulted by the country's leading paediatric orthopaedist at the National specialized children's hospital «Ohmatdyt» Ministry of Health of Ukraine Ministry of Health of Ukraine, where the diagnosis was confirmed. It was found that surgical treatment was contraindicated at this stage due to the severity of the diagnosis.

She was prescribed comprehensive physiotherapy treatment. The complex of physical therapy was aimed at strengthening the muscle tone of the lumbar spine – creating a so-called 'muscle corset'. Massage, ozokerite applications, electrophoresis with a solution of calcium

salts of the lumbar spine. A complex of B vitamins. The corset, tightly fitting to the back muscles, slightly reduced lumbar lordosis, reduced the angle of inclination to the front, increasing the stability of the back due to six elastic stiffening rods mounted in the corset. Part of the load was borne by the corset, while the other part was distributed to the healthy part of the back, increasing its stability.

The tightening of the anterior abdominal wall muscles by the corset slightly increased the intra-abdominal pressure, which took part of the load from the body weight, relieving the spine. The corset, made of durable, synthetic and porous material, did not interfere with sports activities, created an additional warming and massage effect, helped to relax the muscles, and protected them from hypothermia. The unloading and corrective effect was also achieved when lying on the back with a hard and flat bed surface. A similar effect was observed when swimming in the pool, where body weight is reduced by almost half, which helps to relax the spinal column. Water procedures in the pool helped to harden the child and had a great positive emotional stimulus. Given the presence of one kidney, the child had certain restrictions, did not eat canned, smoked food, confectionery fats, drinks containing preservatives and other artificial substances. After the treatment, the child's muscle tone improved and his back pain significantly decreased.

Congenital defects are divided into different categories based on their frequency. Congenital defects are a significant cause of mortality and morbidity in infants, with major structural defects being present in 2–3% of newborns and increasing to 3–4% by the age of one year [18]. Multiple congenital anoMCAs) occur in 20–30% of infants with birth defects, providing insights into underlying causes and developmental pathways [19]. The incidence of CRS is 0.1 per 10,000 normal births, which is 10 cases per 100,000 pregnancies, i.e. the disease is on the verge of extremely rare and rare diseases [20, 21].

According to the classification, there are three types of CRS [10, 11].

Type A. Agenesis of 1–2 lumbar vertebrae. Fusion of the iliac bones or a small gap between them, the sacral vertebrae are connected to the pelvis in the middle.

Type B. Absence of several lumbar vertebrae, complete fusion of the iliac bones. The sacral vertebrae are fused with the iliac bones.

Type C. Total agenesis of the lumbar vertebrae, a large distance between the pelvis and the thoracic spine.

The extreme severity of CRS is called sirenomelia. Sirenomelia is characterized by fusion of the lower extremities, along with other abnormalities such as pelvic-sacral dysplasia, genital anomalies, renal dysplasia, colon atresia, and imperforate anus. It is the most severe form of CRS and is a rare and lethal congenital malformation. The prevalence of sirenomelia is reported to be 0.8–1 cases in 60,000–100,000 deliveries, with a male/female ratio of 2.7–3:1. The etiology of CRS and sirenomelia remains unknown, but they are believed to be different entities [22].

CRS can be a component of other syndromic complexes – VACTERL anomaly and is represented by the association of several developmental anomalies. Its name is formed by the first letters of the developmental defects that make up the syndrome – VACTERL [11, 23].

V (vertebral anomalies) – spinal anomalies (70%). A (anal atresia) – atresia of the anus (55%). C (cardiovascular anomalies) – septal defects and other heart defects (75%). TE (tracheo-esophageal fistula) – tracheo-oesophageal fistula with esophageal atresia (70%). R (renal defects) – renal abnormalities, agenesis, dysplasia, hydronephrosis, single umbilical artery (50%). L (limb defectes) – defect of the radius, hypoplasia of the thumbs or radius, polydactyly, syndactyly (70%). The cause of the disease has not been definitively established and is sporadic.

Recently, several other types of VACTERL syndrome have been identified. VACTERL-H – syndrome, hydrocephalus is added to the above defects. The type of inheritance is not known. There is also VACTERL-H syndrome X-linked, which is caused by a mutation of the Z/C3 gene on chromosome Xq26.

The diagnosis is made if there are three of the seven congenital malformations listed. Diagnosis of CRS is complemented by instrumental examination methods.

Radiography of the spine. The most affordable diagnostic method that allows to assess anatomical changes in the skeleton of the spinal column.

CT. A more accurate diagnostic method for examining the bone structures of the spine, which are not visible in a classical X-ray examination.

Magnetic resonance imaging. It helps to detect bone changes in detail and more accurately assess the condition of the spinal cord and other soft tissues.

Ultrasound diagnostics (ultrasound). An affordable and informative method of recognising the disease at any age. The value of the examination is that the diagnosis can be carried out before the birth of a child (prenatal). If severe CRS is detected, it is advisable to terminate the pregnancy.

The most typical signs of CRS are the absence of several lumbar vertebrae, close positioning of the iliac wings, reduced distance between the femoral heads, reduced size (or complete absence) of the sacrum. Such changes are considered early ultrasound signs of caudal regression syndrome.

Treatment is comprehensive and permanent. The type of treatment depends on many factors, is selected strictly individually and is aimed at improving the child's quality of life [24].

Conservative therapy is necessary to correct complex disorders caused by abnormal organs and systems. Surgical correction should be active to eliminate pelvic-spinal instability in order to prevent deformation of internal organs. It is aimed at fixing the pelvic bones to the spinal column using various metal structures. Such operations involve the elimination of spinal canal stenosis and other defects to improve nerve function.

Elimination of hip dislocations in the hip joints. Such surgical interventions are performed on patients who have a chance to walk, as well as to facilitate sitting in a wheelchair. At an early age, open reduction of hip dislocations is performed, and at an older age, palliative surgery (subluxation corrective osteotomy of the hips) is performed.

Elimination of knee joint contractures with the help of plastic surgery of tendons and muscles of the knee joints. Sometimes hardware methods of eliminating contractures are used – the Ilizarov apparatus and other devices. Such contractures are difficult to correct and are prone to frequent relapses.

Correction of atypical clubfoot. As a rule, triple arthrodesis of the foot joints is performed. Such severe foot defects require frequent, long-term, ineffective surgical interventions, so sometimes it is considered more rational to perform amputation of the defective feet with subsequent prosthetics.

An ovarian cyst is a benign, fluid-filled tumour of small size. They are formed from ovarian follicles. Most often, they do not pose a threat to the female body and disappear without additional treatment. Therefore, such a cyst is called temporary, follicular. Large cysts that have grown to 10–12 cm are subject to surgical treatment. The causes of ovarian cysts are not known for certain. It can be hormonal disorders, chronic inflammation of the ovaries, endocrine disorders of the body, and hereditary predisposition.

A bicornuate uterus is a malformation of the uterus and is rare, occurring in about 5% of girls. It has an irregular shape, i.e. it is divided into two so-called "horns", two separate cavities that converge into one in the lower part. The size and dimensions of the 2 cavities can be different. The main reason is intrauterine disorders of the development of the female embryo in the first months of pregnancy.

The basis for the formation of the internal female genital organs – uterus, vagina, fallopian tubes – are the Müllerian ducts. Normally, the Müllerian ducts merge with each other to form a uterus with a single cavity, and the membranes between the ducts dissolve before the baby is born. By the age of 12 months, the uterus acquires a regular, pear-shaped shape. The entire process of formation of the girl's genitals is completed by the 22-nd week of development, resulting in the formation of two fallopian tubes, one uterus, cervix and vagina.

Various developmental defects can occur in case of disorders of the morphogenesis of the child's genitals. From complete uterine agenesis (absence) to other anomalies, which are divided into certain categories: saddleback uterus; bicornuate uterus; uterus with a complete or incomplete septum; double uterus; one-horned uterus.

With a double uterus, reproductive function is usually preserved and rarely requires surgical correction. According to other sources, this uterine defect causes heavy and painful menstruation, cyclical disruptions, amenorrhoea, and in the future, pregnancy termination and infertility.

A bicornuate uterus uterus increases the likelihood of congenital deformities due to mechanical factors: uterine stiffness; fetal hypokinesia.

Single kidney agenesis is quite common among patients with renal anomalies and is usually combined with other defects of the urinary and reproductive systems.

Renal agenesis is a rare condition characterized by the absence or failure of development of one or both kidneys [25]. The incidence of renal agenesis in the pediatric population is estimated to be 1:500 to 1:2000 children [26].

There are three types of renal agenesis [27].

Type 1. Bilateral agenesis.

Type 2. Unilateral agenesis with ureteral involvement.

Type 3. Unilateral agenesis without ureter.

Unilateral renal agenesis accounts for about 5% of renal malformations. Right kidney agenesis – mostly occurs in girls. Agenesis of the left kidney is a rare condition that is more severe. Agenesis, when a kidney and ureter are absent, is often accompanied by genital malformations, which coincided with our clinical observation [28, 29].

Unilateral agenesis may not manifest itself even before reaching adulthood and is often detected by chance during an examination for another disease. Throughout life, the second kidney, which increases in size in the fetal period, takes over the entire blood purification process. This is called "compensatory hypertrophy" [30]. Such people live quite normally without ever having to see a doctor. However, if the kidney begins to fail to cope with its functions and the effects of renal failure begin to increase, dialysis or organ transplantation is indicated [31].

A defect that develops in the early stages of embryogenesis, as a rule, contributes to multiple malformations of nearby anatomical structures (Fig. 5). This phenomenon is called sequencing – the sequence of development of congenital multiple malformations [32]. Such defects can have a minimal clinical picture or the most pronounced. The longer the gestation period, the lower the probability of sequence [33, 34, 35].

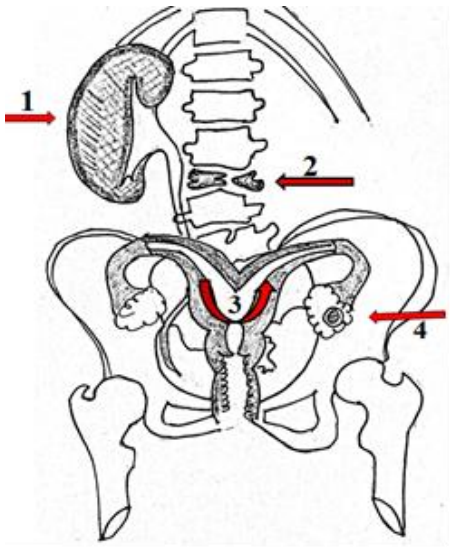

Fig. *5. Schematic representation of the sequencing phenomenon in caudal regression syndrome. Arrows indicate. 1. One right kidney with ureter. 2. Abnormal development of the lumbar, sacral and coccygeal spine. 3. Bicornuate uterus. 4. Cyst of the left ovary*

There are three main causes that contribute to disorders of morphogenesis of organs and systems: mechanical causes; congenital malformations; functional causes [36, 37]. In our clinical case, the patient, the expectant mother, has the following risks of having a child with defects: mechanical cause – bicornuate uterus; congenital defects – agenesis of the kidney, ureter, hypoplasia of the caudal part of the spine; functional causes – congenital hypotension.

Other negative factors, such as infection, radiation, medications, teratogens, amniotic cords, and vascular factors, must also be taken into account. This phenomenon is called disgrouping [38, 39]. The main mechanisms of vascular disgrouping in the embryo and fetus and the most common defects include persistence of embryonic vessels – clubfoot, underdevelopment of the forearm and lower leg bones, premature amputation of embryonic vessels – Poland, Klippel-Feil, and Mobius syndrome, gastroschisis, and horseshoe kidney. Disorders of vascular maturation – capillary haemangiomas, aneurysms, arteriovenous fistulas. Vascular occlusions (external compression) – two-horned uterus. Vascular occlusion (embolic thrombus) – macrocephaly, gallbladder atresia, distal syndactyly, skin aplasia.

CONCLUSIONS

A defect that develops in the early stages of embryogenesis, as a rule, contributes to multiple malformations of nearby anatomical structures. This phenomenon is called sequencing – the sequence of development of congenital multiple malformations, which is confirmed by our data.

In our clinical observation, there are data that do not fit into the classical picture of caudal regression syndrome, as there was partial hypoplasia of the fourth lumbar vertebra, no bony fusion of the iliac bones, and agenesis of the sacrum against the background of agenesis of the left kidney, bicornuate uterus, and left ovarian cyst. The caudal regression apparent syndrome may have several variants that are subject to further study.

PROSPECTS FOR FUTURE RESEARCH

Further research is needed to better understand all possible clinical forms of caudal regression in childhood, which will improve the effectiveness of diagnosis, treatment and prevention of this disease in each case.

AUTHOR CONTRIBUTIONS

(I) Conception and design: Protsailo M. D., Dzhyvak V. H.
(II) Provision of study materials or patients: Protsailo M. D., Khlibovska O. I., Nikitina I. M.
(III) Literature review: Protsailo M. D., Dzhyvak V. H.
(IV) Collection and assembly of data: Protsailo M. D., Mudryk U. M.
(V) Data analysis and interpretation: Dzhyvak V. H., Bidzilya P. V., Hudak P. S.
(VI) Manuscript writing: All authors
(VII) Final approval of manuscript: All authors

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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