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Challenges in the management of caudal duplication syndrome

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ABSTRACT

Caudal duplication syndrome (CDS) is a rare developmental anomaly in which embryonic cloaca and notochord structures are duplicated [1]. Due to the diverse clinical manifestation and rarity of CDS, it is crucial to report every case and to share experience and outcomes of individually adjusted management plans.

We report here the case of a 2-year-old girl born with duplication of the urogenital (bladder, urethra, uterus, vagina, vulva) and gastrointestinal (gallbladder, appendix vermiformis) systems. Additionally, coccygeal agenesis, lipomyelomeningocele and vertical talus were present. A thorough examination and urological reconstructive surgery were performed.

While there may be a desire from patients, parents and healthcare specialists to modify all malformations to an anatomically correct state, the current opinion is that only anatomical variants that influence function should be modified. Consent from patients should be sought for decisions regarding more sensitive matters such as vulva surgery for cosmetic reasons or correction of anatomical variants without functional consequences.

1. Background

Caudal duplication syndrome (CDS) is a rare developmental anomaly (ORPHA:1756) in which structures derived from the embryonic cloaca and notochord are duplicated to varying extents [1]. The prevalence of the syndrome is less than 1 per 100,000 births, with female predominance at a ratio of 2:1 and no familial and racial predilection or other notable risk factors [2,3].

CDS manifests as duplicative anomalies of the hindgut (includes the distal third of the transverse colon and splenic flexure, descending colon, sigmoid colon and rectum), bladder, urethra, genital organs, spinal cord and vertebrae [4]. Depending on the organs involved, the spectrum of anomalies can be variable. In some cases, even complete agenesis has been reported, also known as caudal regression syndrome. It is important to be aware that distal organ duplication can be partial or complete, and sometimes exstrophy of the colon or bladder is present. Single, partial or multiorgan fusion and atresias are also sometimes found [5]. Patients often have other associated anomalies outside the caudal region [4].

Due to anatomical variability, diverse functional manifestations and limited knowledge of this rare syndrome, devising a patient management plan is always a challenge. Multistage surgical treatment predominantly focuses on achieving excellent functional results rather than attaining cosmetic effects [6,7].

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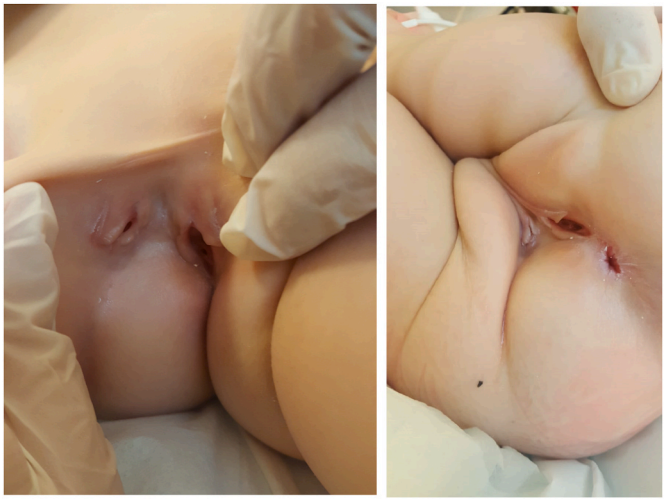

Fig. 1. Perineal examination showed two separate vulvas and one anus.

2. Case presentation

A 2-year-old girl presented with vulvar abnormalities (two vulvas), recurrent urinary tract infections and urinary incontinence. The child was born in the United Kingdom, where the diagnostic procedure was initiated. However, due to the COVID-19 pandemic, the investigation plan was delayed and the patient relocated to her parents' country of origin (Latvia). Various diagnostic tests had been performed, including confirmation of a normal karyotype (46,XX), but a clear diagnosis of CDS was not established until she presented at our centre (Children's Clinical University Hospital). The patient was the mother's sixth pregnancy. The mother's unfavourable reproductive history was as follows: one legal abortion (twins from a previous marriage), three missed abortions (in the first trimester) and one medical abortion (due to chromosome 18 trisomy). Prenatal ultrasound revealed a right hydroureter and a slightly smaller right kidney, but otherwise the pregnancy and delivery were uneventful.

Upon admission, physical examination revealed thickening of the subcutaneous tissues of the lower side of the back; the patient had previously been diagnosed with lipomyelomeningocele. Furthermore, asymmetrical gluteal folds, shortening of the right leg with hypoplastic muscles and a smaller foot were found. The patient had previously been diagnosed with congenital vertical talus, that had been surgically corrected and addressed with an orthosis, and congenital hip dysplasia. Perineal examination showed two separate vulvas (Fig. 1). One vulva was positioned almost along the midline, the labia were properly formed and the urethral and vaginal openings were visualized. The second vulva was positioned laterally to the right side and it was smaller with one common opening for the urethra and vagina – urogenital sinus. Constant leakage of urine from the right-sided vulva was found. During the examination, one anus was visualized; however, later examinations suggested the possibility of an anal fistula.

The patient suffered recurrent urinary tract infections and urinary incontinence. Her mother disclosed that her daughter was very upset about her incontinence because she had already mastered using a potty. The patient had adequate bowel movements with no faecal incontinence. The development of the child's motor skills and psychosocial functions was assessed as age appropriate.

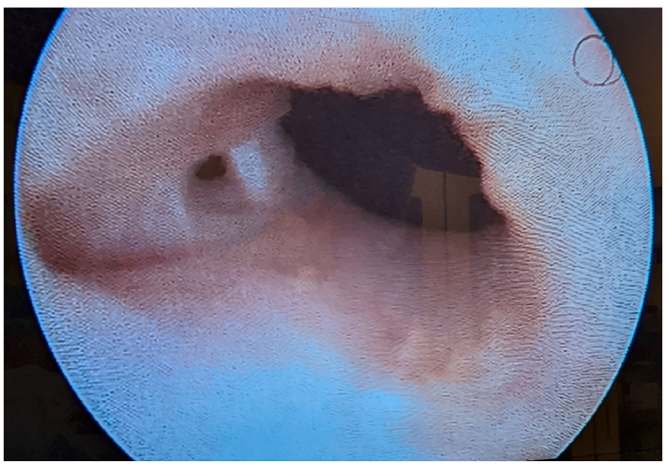

Fig. 2. Cystovaginoscopy revealed an approximately 1.5-cm long urogenital sinus in the vulva localized to the right side. Proximally from vaginal and urethral confluence, a normal vagina and cervix were seen.

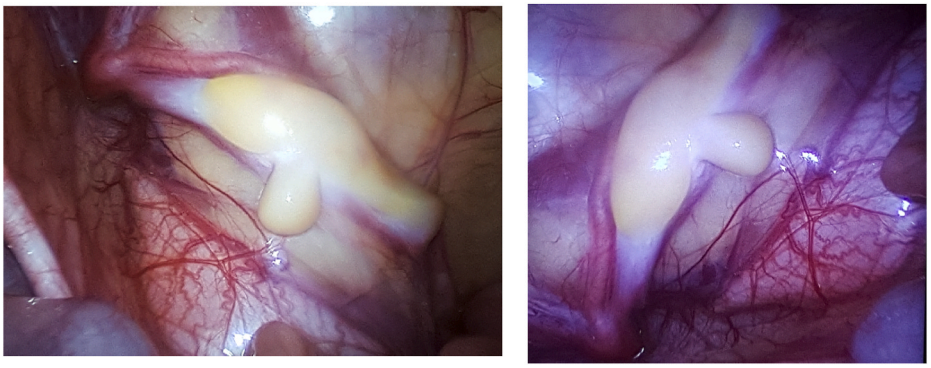

Fig. 3. Diagnostic laparoscopy. Small duplex unicornuate uterus with one fallopian tube from each. Ovarian appearance corresponded to prepubertal age.

2.1. Investigations

Cystovaginoscopy confirmed complete urogenital duplication:

- Examination of the vulva along the midline revealed normally formed vaginal and urethral openings. The midline bladder had a normal capacity, the left ureter opened into the left ostium inside the urinary bladder and a normal bladder neck was visualized. The vagina and uterine cervix were properly formed.
- The vulva localized to the right side was smaller and had one common opening for the vagina and urethra. Examination revealed an approximately 1.5-cm long urogenital sinus (Fig. 2). The right bladder was smaller and sickle shaped. A dystopia of the second ureteral ostium was revealed – visualized in the urethra slightly distal to the ipsilateral bladder neck. The vagina and uterine cervix were properly formed.

Retrograde cystourethrogram showed two independent bladders and a grade II–III vesicoureteral reflux of the right side.

Examination with a **Pena muscle stimulator** revealed that the anal sphincter was located 2 cm posterior from the existing anal opening, suggesting the possibility of an anal fistula. Additionally, the anal sphincter was found under the vulva on the right side, causing suspicion of two colons. However, **barium enemas** did not reveal any colonic anatomic defects.

Diagnostic laparoscopy showed two vermiform appendixes and a duplex unicornuate uterus with one fallopian tube and ovary from each (Fig. 3).

Magnetic resonance imaging of the brain and spine showed sacral dysraphism with lipomyelomeningocele at S1–S4 level, low spinal cord termination with conus medullaris fixation at S1 level and coccygeal agenesis (Fig. 4).

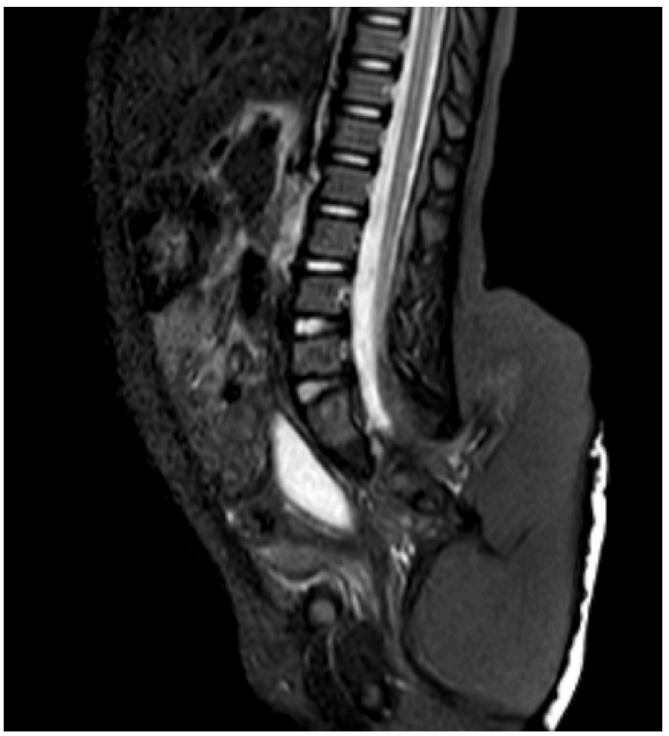

Fig. 4. Magnetic resonance imaging showed lipomyelomeningocele at S1–S4 level.

Next-generation sequencing analysis of an anorectal malformation gene panel and the *AXIN1* gene did not reveal any alterations. Methylation analysis of the *AXIN1* gene promoter has not yet been performed.

2.2. Differential diagnosis

Although each malformation was individually identified early on in the diagnostic process, it took longer to contemplate the notion that they were not isolated pathologies but instead may indicate caudal duplication syndrome. Involvement of a multidisciplinary team and a thorough search of the literature were necessary to identify this rare syndrome.

2.3. Treatment

Urologic reconstructive surgery was performed to address the patient's vesicoureteral reflux, recurrent urinary tract infections, and physical and emotional discomfort due to urinary incontinence. She underwent extirpation of the right-sided dysplastic urinary bladder at the proximal urethral level. During the same surgery, ureteral reimplantation using the Politano-Leadbetter technique was performed, whereby the ureter of the right side was reimplanted on the left urinary bladder following ureterostomy (Fig. 5). The treatment plan was approved by the European Reference Network on urogenital diseases and conditions (ERN eUROGEN) Clinical Patient Management System (CPMS) panel.

2.4. Outcome and follow-up

Seven days after reconstruction, the bladder catheter was removed and controlled urination resumed. There was normal urinary continence during the postoperative period, indicating functional improvement. The patient will attend regular follow-up appointments at the urology clinic to monitor her urinary system functions.

Based on the recommendations of our team's neurosurgeon, the patient's lipomyelomeningocele will be surgically corrected in the near future.

When the patient is older, she should be closely monitored by a paediatric gynaecologist to assess the development of her genital system and any potential problems in adolescence. At present, there are no indications for reconstructive surgery of her genital system.

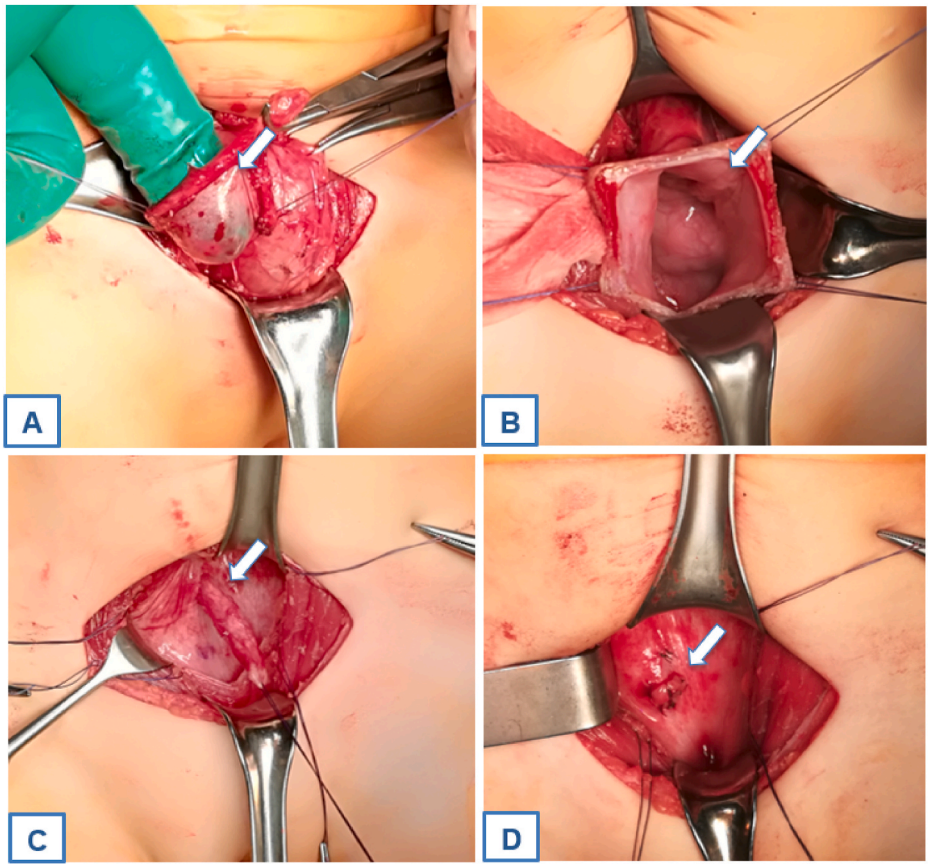

Fig. 5. Urologic reconstructive surgery included extirpation of the right-sided dysplastic urinary bladder (A), visualization of the midline bladder cavity (B) and right-sided ureteral reimplantation (C, D).

The patient's opinion and consent should be sought for decisions regarding vulva surgery for cosmetic reasons. Thus, it is advised to wait until she reaches an age when she can express her own concerns and preferences.

3. Discussion

Although the etiopathogenesis of CDS remains unclear, an unfavourable reproductive history of the patient's family suggests a strong genetic basis. Over the years, several authors have proposed theories for the development of the syndrome:

- In 1993, Dominguez et al. proposed the first theory. They claimed that **damage to the caudal cell mass of the 23–25-day embryo** can result in incomplete regression of the neurenteric canal and fibrous tissue could divide the notochord, mesoderm and endoderm leading to caudal duplication [5].
- Bannykh et al. presented the theory that CDS originates from **conjoined twins** and the phenomenon could be explained by the incomplete fusion of early embryos [8].
- **Adherence between the ectoderm and endoderm** resulting in the formation of two hemineural plates has been suggested as the main pathogenetic component by Pang et al. [7].
- Sur et al. postulated that the syndrome is related to misexpression of one or more of the distal *HOX* genes, potentially *HOX10* or *HOX11*, leading to **abnormal proliferation of caudal mesenchyme** [9].
- The most recent theory – **a duplicated caudal cell mass with hyperplasia of the intervening central caudal mesenchyme** – has been proposed by Yang et al. Via a molecular interaction, an insult causes late gastrulation phase problems, resulting in ectopic primitive streak formation and thereby inducing a duplication of the caudal cell mass [10].

There is a growing debate about the specific genes that may be involved in the development of CDS. One candidate is the *AXIN1* gene; a mutated form of this gene has been found in mice with caudal duplication [11]. Although no mutations in the *AXIN1* gene have been found in humans with CDS, Oates et al. described an interesting clinical case of a monozygotic twin pair discordant for a caudal duplication anomaly where the *AXIN1* gene promoter region of the affected twin was significantly more methylated than that of the unaffected twin [12]. In the case of our patient, analysis of the *AXIN1* gene did not reveal any alterations. Methylation analysis of the *AXIN1* gene promoter will be performed in the near future.

Reconstructive surgery for CDS patients should be performed to address altered functionality only, as in our patient with vesicoureteral reflux, recurrent urinary tract infections and incontinence. In the literature, opinion regarding the necessity for reconstruction varies. However, there is an increasing number of reports that interventions only provide real improvement in symptomatic patients [4,10]. For instance, Abrahamson's report on different types of lower urinary tract duplications concluded that complete reduplication (as in our patient) is quite consistent with normal life and treatment is not recommended unless necessary [13]. Furthermore, Gastol et al. reported on three CDS patients who did not undergo urologic reconstruction because no dysfunction was present [14]. Indeed, individual reconstructive therapy should only be considered in cases where the child voids urine in two simultaneous streams and displays features of urinary tract obstruction, infection and vesicoureteral reflux with failing renal function [13,15]. In cases where duplication of the urinary tract was repaired, treatment ranged from combining the two bladders with ligation of one urethra to complete unilateral cystectomy [16,17]. Our patient underwent a unilateral cystectomy because the bladder of the right side was significantly smaller and underdeveloped. It is likely that connection of both bladders in this case would not have provided the desired functional effect. Future follow-ups to monitor the neurogenic bladder development of our patient are very important as she also has a lipomyelomeningocele and coccygeal agenesis.

If there are no other serious complaints, the patient's opinion and consent should be sought for decisions regarding vulva surgery for cosmetic reasons. Thus, it is advised to wait until she reaches an age when she can express her own concerns and preferences. In a recent review, Radu-Iulian et al. reported that CDS is more commonly diagnosed in females, with both internal and external duplicated genitals being generally well developed and ovarian function unimpaired [4]. In most cases, the genital system functions adequately, so there is no absolute indication for reconstructive surgery. Active intervention should be undertaken in cases where complications can be expected, such as menstrual flow obstruction if one of the sides is hypoplastic or impenetrable [18]. At present, there are only a few reports of CDS in adult patients and in the main they have normal menstruation, the ability to have sexual intercourse and the possibility to become pregnant; however, a case of infertility has been reported [4,19]. An effective reproductive function is demonstrated by the case of an adult woman with CDS whose obstetric history evinces functional use of both vaginal openings from which she conceived three pregnancies and had three subsequent live births via caesarean section [2]. Radu-Iulian et al.'s review also reported that all pregnant CDS patients carried their pregnancies to full term and underwent a caesarean section due to altered anatomy and possible complications. At the same time, Greenberg and Hendren reported the case of a woman with CDS and cloacal malformation that had a vaginal delivery after reconstructive surgery [4,20]. At present, our patient's gynaecological intervention plan is uncertain; however, there will probably be more clarity when she reaches puberty. Nevertheless, concerns have currently been raised regarding the possible function of our patient's uterus and vagina (especially on the right side) and unfavourable reproductive outcomes, e.g. ectopic pregnancy, in the future. From the cases described in the literature, some of the women had sexual intercourse in both vaginas. However, without additional intervention, this would be difficult for our patient due to the urogenital sinus on the right side. Counselling regarding these issues will be necessary when the patient is old enough. Uterine anatomy and function (endometrial thickness) should be monitored during puberty and beyond.

Reconstructive surgery of our patient's gastrointestinal tract was not required as her bowel movements and faecal continence were adequate despite the presence of anus dystopia and a suspected anal fistula detected by a Pena muscle stimulator. This is in line with the viewpoint in the literature that it is not necessary to make all anomalies anatomically normal. In their review, Radu-Iulian et al.

recommended a delay to further treatment until such a time that a complete assessment of the types and extents of malformations can be conducted and an individually tailored treatment plan can be devised with input from both the family and multidisciplinary team [4].

Our patient's good neurological condition has allowed us to postpone lipomyelomeningocele correction until the most appropriate time. This is a rare situation because spine and spinal cord duplication syndromes are often associated with moderate to severe neurological deficits [21]. It has been reported that CDS can sometimes coexist with the features of caudal regression syndrome, i.e. lumbosacral hypogenesis and anomalies of the lower gastrointestinal tract, genitourinary system and limbs [18]. Coccygeal agenesis suggests that our patient may have an overlap of both syndromes. Going forward, her neurological status will be regularly assessed and surgical correction of the lipomyelomeningocele is planned for the near future as it can lead to lower limb paralysis.

As CDS is a very rare pathology and most case reports do not describe long-term follow-up, there is a lack of information regarding the quality of life and long-term prognosis of CDS patients [4]. Therefore, it is very important to not only diagnose the syndrome and treat it appropriately but also ensure long-term follow-up and a successful transition from paediatric to adult care.

4. Conclusions

- CDS is such a rare and clinically variable pathology that there is currently insufficient global experience to provide common recommendations for examination and treatment. The patient approach should be individually tailored.
- The desire to transform malformations into anatomically correct structures should be precluded in the treatment of CDS. Instead, the sole focus should be on gaining functionality.
- It is recommended that cosmetic treatment is postponed until the patient can express their concerns and make their own decisions.
- It is very important to involve a multidisciplinary team in the care of the patient and to provide long-term follow-up in order to observe changes in organ systems as the child grows.
- As the pathogenesis of CDS and most appropriate management plan remain unclear, it is vital to continue research on this syndrome and report all relevant observations.

The perspective of the patient's parents

"As parents, we hope our daughter is now able to grow up and enjoy life like other children. Before surgery, the greatest difficulty and discomfort she encountered was urinary incontinence. This began after the age of one and significantly disrupted her potty training. Since the surgery, there has been a marked improvement and we are able to focus on rigorous potty training again.

The greatest difficulty we encountered was the lack of an explanation for our daughter's congenital anomalies. Receiving the specific diagnosis of CDS has reduced our anxiety and allowed us to establish a daily routine and be supportive of the necessary treatment."

Statement of ethics

Patient's family gives permission for patient information and photograph to be published in scientific journal anonymously.

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Author contributions

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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