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СИНДРОМ ЦИННЕРА: СЕРИЯ СЛУЧАЕВ И ОБЗОР ЛИТЕРАТУРЫ

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Zinner Syndrome: Case Series and Literature Review

Резюме

Синдром Циннера — редкая врожденная аномалия развития мезонефрального протока, характеризующаяся триадой признаков: наличием кист семенных пузырьков, ипсилатеральным почечным агенезом и обструкцией эякуляционных протоков, приводящая к тяжелому осложнению — олигозооспермии/азоспермии, что в последующем может вызвать бесплодие. Широкое использование методов медицинской визуализации способствует увеличению частоты обнаружения этих изменений, в свою очередь именно магнитно-резонансная томография (МРТ) является наиболее эффективным методом для постановки диагноза. **Цель исследования:** оптимизация маршрутизации пациентов с синдромом Циннера, а также минимизация риска постановки ошибочного диагноза или пропуска патологии, с помощью обобщения результатов методов визуализации. **Материалы и методы:** Приведены 2 клинических случая синдрома Циннера: осложнённого течения у 25-летнего пациента, а также случайно выявленного у пациента 27 лет. Пациентам было выполнено комплексное диагностическое исследование, включающее: ультразвуковую диагностику (УЗИ), компьютерную томографию (КТ), магниторезонансную томографию (МРТ). Полученные результаты были проанализированы в соответствии с данными литературных источников. **Результаты:** В большинстве случаев синдром Циннера является случайной находкой при обследовании пациентов. Точность диагностической оценки на основании данных методов визуализации и верная тактика маршрутизации, позволила своевременно поставить верный диагноз и принять правильное решение о дальнейшей тактике лечения. **Заключение:** Синдром Циннера является редким заболеванием и зачастую устанавливается на основании данных методов визуализации. Врачу-рентгенологу и врачу клинической практики необходимо знать о диагностических критериях данного синдрома, с целью успешной диагностики и определения оптимальной тактики лечения.

Ключевые слова: *Синдром Циннера, компьютерная томография, магниторезонансная томография, обзор литературы*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract
Zinner syndrome is a rare congenital anomaly of the mesonephric duct, characterized by a triad of symptoms: seminal vesicle cysts, ipsilateral renal agenesis and ejaculatory duct obstruction. This leads to a severe complication — oligozoospermia/azospermia, which can subsequently cause infertility. The widespread use of medical imaging increases the probability of incidental detection. Namely, magnetic resonance imaging (MRI) is the imaging modality of choice for making a diagnosis. **Study purpose**: to optimize patient routing in Zinner syndrome, as well as to minimize the risk of misdiagnosis or missed pathology, by providing strong and weak points for each modality. **Materials and methods**: we present two clinical cases of Zinner syndrome. The first one is a complicated course in a 25-year-old patient, and the second one is accidentally discovered in a 27-year-old patient. The patients underwent a comprehensive diagnostic panel, including: ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI). The results obtained were analyzed in the light of available literature data. **Results:** in most cases, Zinner syndrome is an incidental finding during. The diagnosis based on these imaging methods and the correct patient routing allowed us to make a timely and correct diagnosis, followed by decisions on further treatment tactics. **Conclusion:** Zinner syndrome is a rare disease and is often diagnosed based on imaging findings only. A radiologist and clinician need to know about the diagnostic criteria for this syndrome in order to successfully diagnose and determine the optimal treatment tactics.

Key words: *Zinner's syndrome, CT scan, magnetic resonance imaging, literature review*

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Introduction

Zinner syndrome is an extremely rare urologic congenital abnormality in males, which is characterised by seminal vesicular cysts, ipsilateral renal agenesis and seminal duct obstruction. For the first time, the disease was described in 1914 by A. Zinner [1]. Zinner syndrome is very rare, therefore, there are only a few references in the literature to this condition [1, 10]. Currently, there are approximately 300 registered cases of this disease [2].

Very often this syndrome is asymptomatic; however, with the growth of cysts and also depending on the functional status of the contralateral kidney and reproductive activity of the patient, the following symptoms can be observed: dysuria, frequent nocturnal enuresis, haematuria, groin pain, and painful ejaculation because of the mass effect of seminal vesicular cysts [6]. Later, long-lasting seminal duct obstruction results in oligospermia/ azoospermia. Since the clinical presentation is ambiguous, diagnosis is dependent on imaging [1]. Therapy depends on the severity of the patient's condition, urinary tract anatomy, and whether the patient wants to preserve the reproductive function or not.

The article describes two clinical cases, where MRI results allowed making a correct diagnosis and, thus, selecting an adequate management approach.

The objective of this review is to summarise the visualisation results for the changes in Zinner syndrome in order to draw urologists and radiologists' attention to this abnormality, so that the risk of an incorrect diagnosis or pathology negligence is minimised, and the routing of such patients is optimised.

Materials and methods. Two case studies of Zinner syndrome are presented: complications in a 25-year-old patient and an occasionally diagnosed disease in a 27-year-old patient. The patients underwent a comprehensive diagnostic examination, which included an ultrasound examination, computed tomography (CT), magnetic resonance imaging (MRI).

Methods of Source Search

The article presents an overview of publications for the last 5 years. Literature sources were analysed in PubMed, Google Scholar, Russian Science Citation Index (RSCI). The following keywords were used for the search in foreign publications: *Zinner's syndrome, CT scan, magnetic resonance imaging, literature review.*

Case Study No. 1

Patient K., 25 years old, was admitted to the Urology Department complaining of repeated episodes of drawing pain in the groin area; elevated body temperature to 37.8 °C. According to the medical record, since

2017 the patient has been complaining of drawing pain in the small pelvis area with radiation to the right leg, he underwent abdominal and pelvic ultrasound: right kidney aplasia, varicose veins of the pelvic cavity.

As the complaints persisted, in 2018 the patient was referred to lumbar MRI, which found an oval cyst formation at the pelvic level with changes in tubular structures. On the same date, the patient consented to pelvic MRI in order to study the changes in more detail. MRI results showed an oval cyst formation up to 34x30x35 mm in the right pelvic area, on the outside of the bladder and rectum, changing into a ball of tubular structures of up to 8 mm in diameter, with thick contents in the orifice and signs of seminal duct obstruction to the right. Once coronary T2-weighted images of the lumbar area were reviewed, right kidney aplasia was confirmed, and the following conclusion was made: Zinner syndrome (spermatocyst cyst, seminal duct obstruction, right kidney aplasia).

Taking into account the impact of this syndrome on the reproductive function, the patient was offered to perform a semen analysis, which showed a slightly elevated WBC level up to 1,200,000 c/mL (normal value: < 1,000,000 c/mL); 35 % active and inactive sperms (normal value: ≥ 32 %).

Up to February 2020, the patient was followed up (ultrasound, MSCT, MRI) by the urologist at the place of the patient's residence. Urinary system CT showed an increase in the size of periprostatic cyst formations vs. initial MRI.

Since February 2020, the patient has been having periodic groin pain radiating to the scrotum, lasting for up to one week. In January 2022, the patient started complaining of acute pain after ejaculation in the area of the right spermatic cord with episodes of elevated body temperature to 37.8 °C; therefore, the patient was hospitalised to the Urology Department for further examination and selecting a therapeutic approach.

Physical examination: the prostate gland is enlarged, symmetric, with clear contours, tightly elastic, painless when palpated. Laboratory blood tests (complete blood

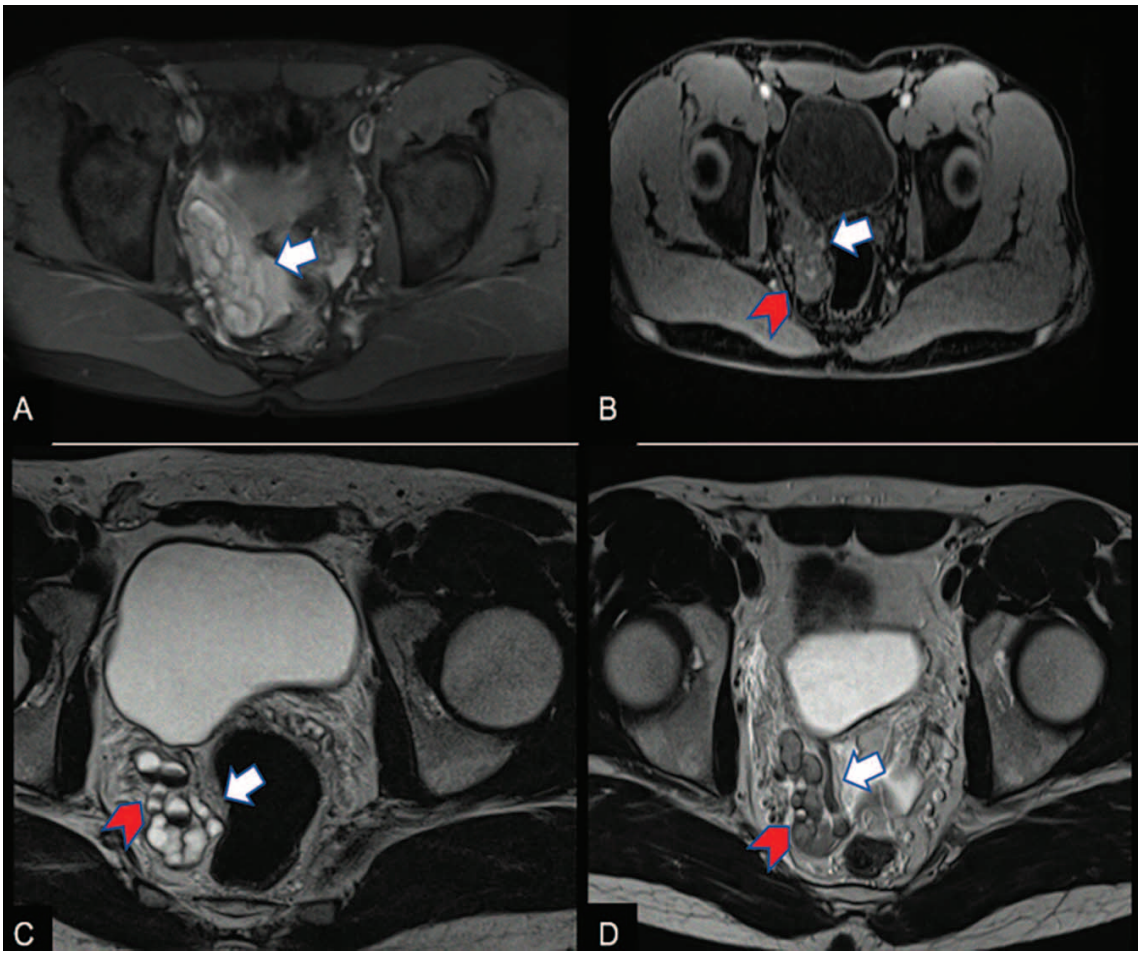

Figure 1. *(A, B) Axial T1 and T1 FS MRI: cystic dilatation of tortuous seminal vesicles on the right (white arrow), with a weakly hyperintense signal on T1-weighted images, and fluid levels (red arrow). (C, D) Axial isotropic T2 and routine T2 MRI: dilated tortuous seminal vesicles on the right (white arrow), in the form of T2 hypointense intraluminal content changes with fluid levels (red arrow)*

count and blood biochemistry): unremarkable. The semen analysis showed oligospermia.

A follow-up pelvic MRI showed a negative trend in the form of a complicated cyst in spermatocysts: the size of the cyst to the right increased, and the orifice contents changed to non-homogenous (T2-weighted images) and slightly hyperintense (T1-weighted images), with signs of restricted diffusion and borderline formation. Also, there were signs of changes in the signal characteristics of adjacent dilated coiled spermatocysts to the right in the form of slightly hyperintense (T1-weighted images) and hypointense (T2-weighted images) changes in the orifice contents; homogenous pelvic effusion (Fig. 1). According to the MRI results, the changes in the orifice contents of cysts were purulent and haemorrhagic (Fig. 2).

The patient underwent a conservative therapy with a positive trend: pain reduced, and the body temperature normalised.

Taking into account laboratory and instrumental data, the team decided to perform laparoscopic vesiculectomy to the right and remove the abdominal mass. The intraoperative laparoscopic examination confirmed the MRI diagnosis. The postoperative period was unremarkable; the patient was prescribed antibacterial, anti-inflammatory, infusion, haemostatic therapy.

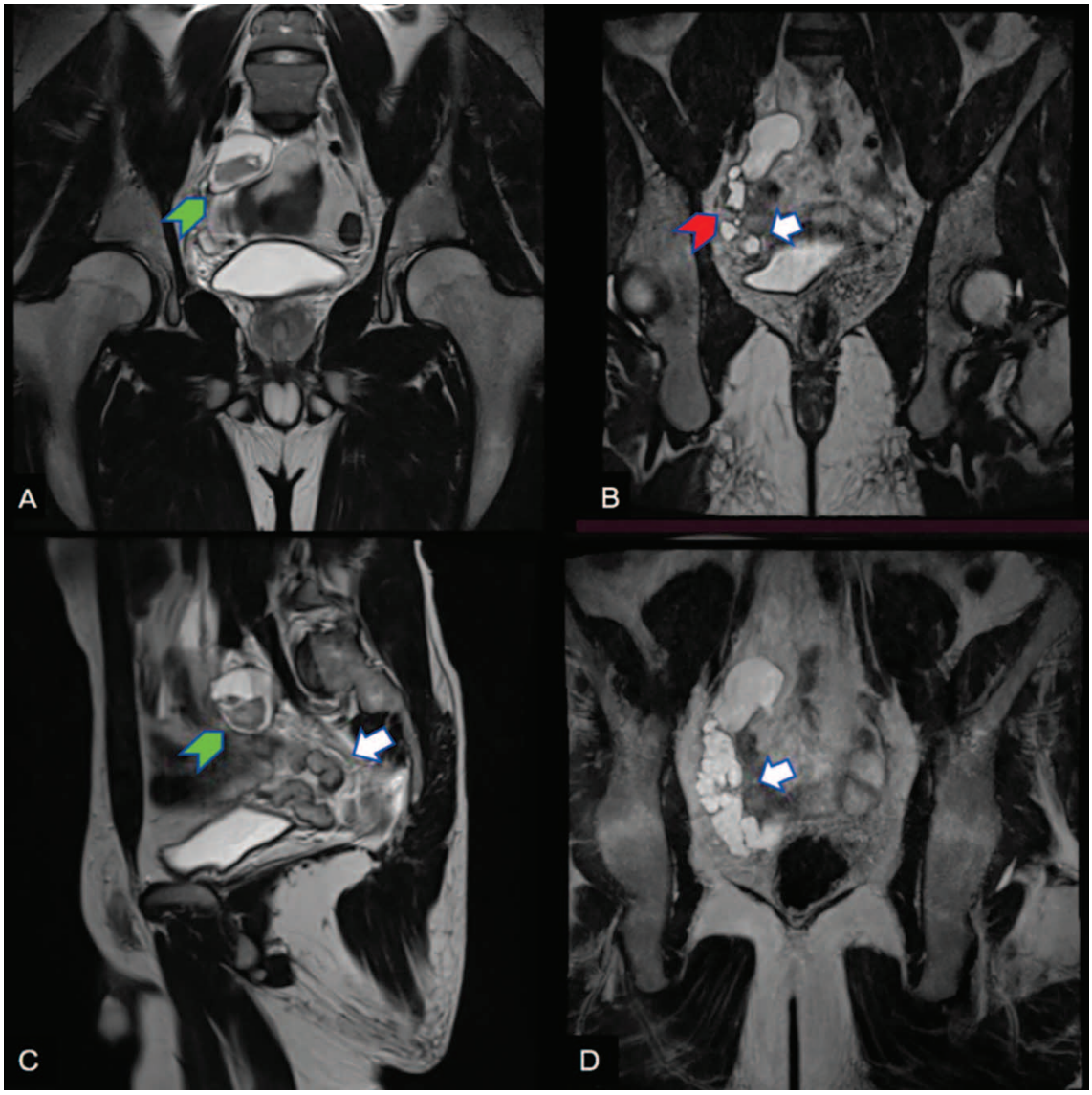

Figure 2. *(A, B, D) Coronal T2 and T2 MIP MRI: cystic dilatation of tortuous seminal vesicles on the right (white arrow), in the form of T2 hypointense intraluminal changes with fluid levels (red arrow). An increase in the size of the seminal vesicle cyst on the right with a change in the intraluminal contents to heterogeneous on T2 with fluid level (green arrow), indicating possible differential diagnosis between purulent and hemorrhagic (C) Sagittal isotropic T2 MRI: cystic expansion of convoluted seminal vesicles on the right (white arrow), heterogeneous intraluminal contents in enlarged seminal vesicles on the right (green arrow)*

The follow-up ultrasound did not show any pathological abdominal formations.

The histological examination of surgical material: no convincing evidence of purulent contents; cystic fibrosis masses were found in the orifice of dilated spermatocysts to the right, with a haemorrhagic component, thus confirming one of the origins of the cystic contents in pelvic MRI.

On the basis of the instrumental and histological data, the following diagnosis was made: Zinner syndrome, inflammatory disease of spermatocyst.

Case Study No. 2

Patient A., 27 years old, was referred to the medical organisation for pelvic MRI because he was complaining of scrotum pain after a trauma sustained during a sporting completion. The patient did not have any complaints of any problems with the urinary system. According to the medical records, when he was a child, the patient was diagnosed with right kidney agenesia.

Examination revealed damage to the soft tissues of the scrotum. Semen analysis, LH, FSH, total and free testosterone levels: unremarkable.For better pelvic organ imaging, the patient underwent MRI, which, in addition to the damage to the soft tissue of the scrotum, showed cyst dysplasia of spermatocysts to the right, with a highly intensive signal in spermatocysts to the right (T1-weighted image), most probably due to a high protein level because of the stasis (T2-weighted image) (Fig. 3).

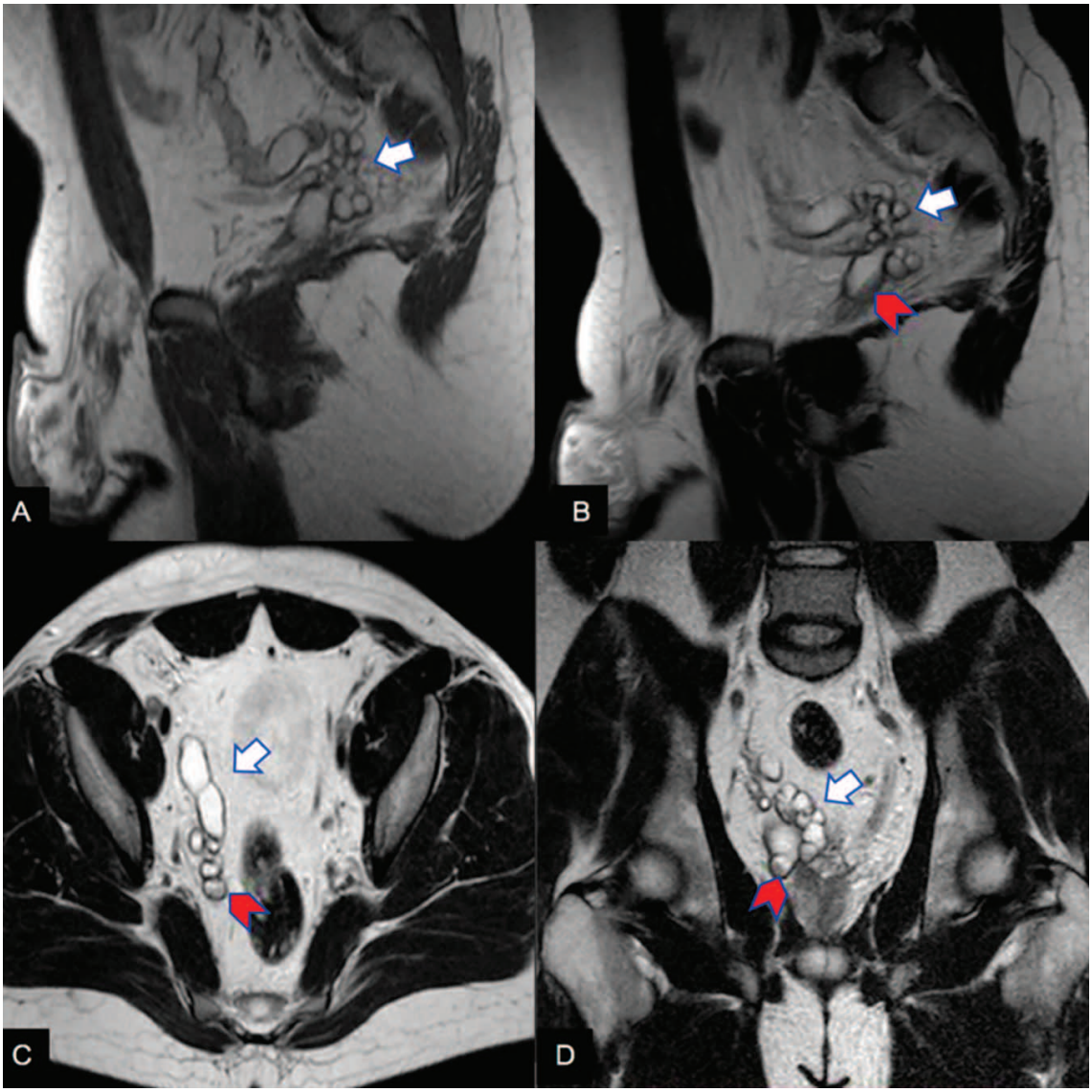

Figure 3. *(A) Sagittal T1 MRI: cystic dilatation of the right seminal vesicles (white arrow), with hyperintense signal on T1, indicating proteinaceous component. (B, C, D) Sagittal, axial, coronal T2 MRI: cystic dilatation of the right seminal vesicles (white arrow), with fluid levels in some of them (red arrow) located close to each other, extending caudally into the spermatic cord*

The data made it possible to diagnose Zinner syndrome. In this case, the disease was asymptomatic and was diagnosed accidentally.

Since the patient did not have any clinical symptoms and did not plan to have children in the foreseeable future, he was followed up, and the therapeutic approach was selected later.

Discussion

Zinner syndrome is a rare urologic pathology and is diagnosed on the basis of the following signs: the presence of seminal vesicular cysts, ipsilateral renal agenesis and seminal duct obstruction. These signs are caused by abnormal development of the mesonephric duct during embryogenesis. Normally, the urinary organs develop from intermediate mesoblast, which is differentiated into three sections during embryogenesis: forekidney, embryonic kidney and definite kidney. Soon forekidney regresses completely, while embryonic kidney divides into mesonephric tubes and mesonephric ducts (main sources of genital organs). For some time, the tubes act as kidneys, then they regress. A mesonephric duct is formed as a result of the fusion of segmental ducts of the mesonephric kidney and excretory ducts of forekidney opening to the cloaca [4]. An embryonic kidney and mesonephric ducts form a primitive renal body. Bulging (ureteral germ) is formed at the point where the mesonephric duct joins the cloaca [1].

During the second month of embryogenesis, the definite kidney forms (the main source of the definite kidney), which has a dual origin: from blastema and the distal part of the mesonephric duct. On week 5–6 of embryogenesis, an ureteral bud forms, which joins the definite kidney to start the formation of the calices-pelvis system of the kidney.

Aplasia of the distal part of the mesonephric duct and the lack of the ureteral bud cause unilateral kidney agenesia/dysgenesia and seminal duct atresia. Insufficient drainage function results in cystic fibrosis dilatation of spermatocysts [1].

However, despite the understanding the embryogenesis, the genetic background and genetic mechanisms of Zinner syndrome are still understudied. In some cases, there is genetic predisposition to this disease. A study by Pinhas et al. presents data on congenital urological abnormality in identical twins with polygenetic risk factors [15]. A study by Gabrielle et al. demonstrates the role of WNT9B gene variants in the development of family cases of bilateral kidney agenesia/hypoplasy and reproductive tract abnormalities [16], which was not confirmed in either of our case studies. Thus, apparently, Zinner syndrome can be caused by an array of genetic factors, and further studies should aim to assess other genes and molecular mechanisms associated with its origin.

Taking into account statistics presented in literature sources, this syndrome is usually asymptomatic [1], which was confirmed in both case studies in question; however, once cyst masses grow in size, clinical symptoms appear, which was observed in case study one [6]. Besides, the long-term mass effect of dilated seminal vesicular cysts on the seminal duct can result in obstructive oligospermia or azoospermia, which was observed in one study presented here [10, 13]. Also, haematospermia can be present in some cases [14]. Taking into account the impact of this syndrome on the reproductive function, the patients underwent laboratory tests, and no abnormal laboratory findings were observed in one of the cases. However, like the first case study, some literature sources describe abnormal semen analysis results in such patients [10]. Given that Zinner syndrome is often asymptomatic, in a majority of cases the diagnosis is made on the basis of instrumental results and often is accidental, which was confirmed in both cases.

Literature sources describe diagnostic criteria of this diagnosis: the primary method of examination is transrectal ultrasound, since it is an inexpensive and readily available method, also, it is not associated with exposure to radiation [1, 5, 7, 8]. The objective of examination is primary assessment of seminal vesicular cysts, that are seen as anechogenic cyst formations with some contents in the cyst cavity, with thick, uneven walls, some of which can have calcification in their structure [1]. Also, an ultrasound can find the signs of seminal duct obstruction. In some cases, seminal vesicular cysts can be isoechoic or hyperechoic due to protein contents in vesicles, like in the second patient.

On CT scans, this abnormality is diagnosed on the basis of the following signs: ipsilateral renal agenesis, cyst dilatation of spermatocysts with altered contents in some of them [7, 8]. CT allows assessing the collocation of changes vs. the nearest organ and providing information on possible complications.

MRI is a method of choice for patients with Zinner syndrome [2, 7]. MRI is a highly accurate method of male reproductive tract imaging; it is useful for clear assessment of spermatocysts and mesenterial duct abnormalities and unambiguous differential diagnosis of seminal vesicular cysts and other cyst formations in the small pelvis. Due to its high sensitivity, MRI allows differentiating between prostatic and seminal capsules and confirming that periprostatic cyst formations are indeed within the spermatocyst boundaries [5]. The typical periprostatic location makes it possible to accurately identify seminal cyst vesicles, which have a hypointense signal on T1-weighted images and hyperintense signal on T2-weighted images; however, the presence

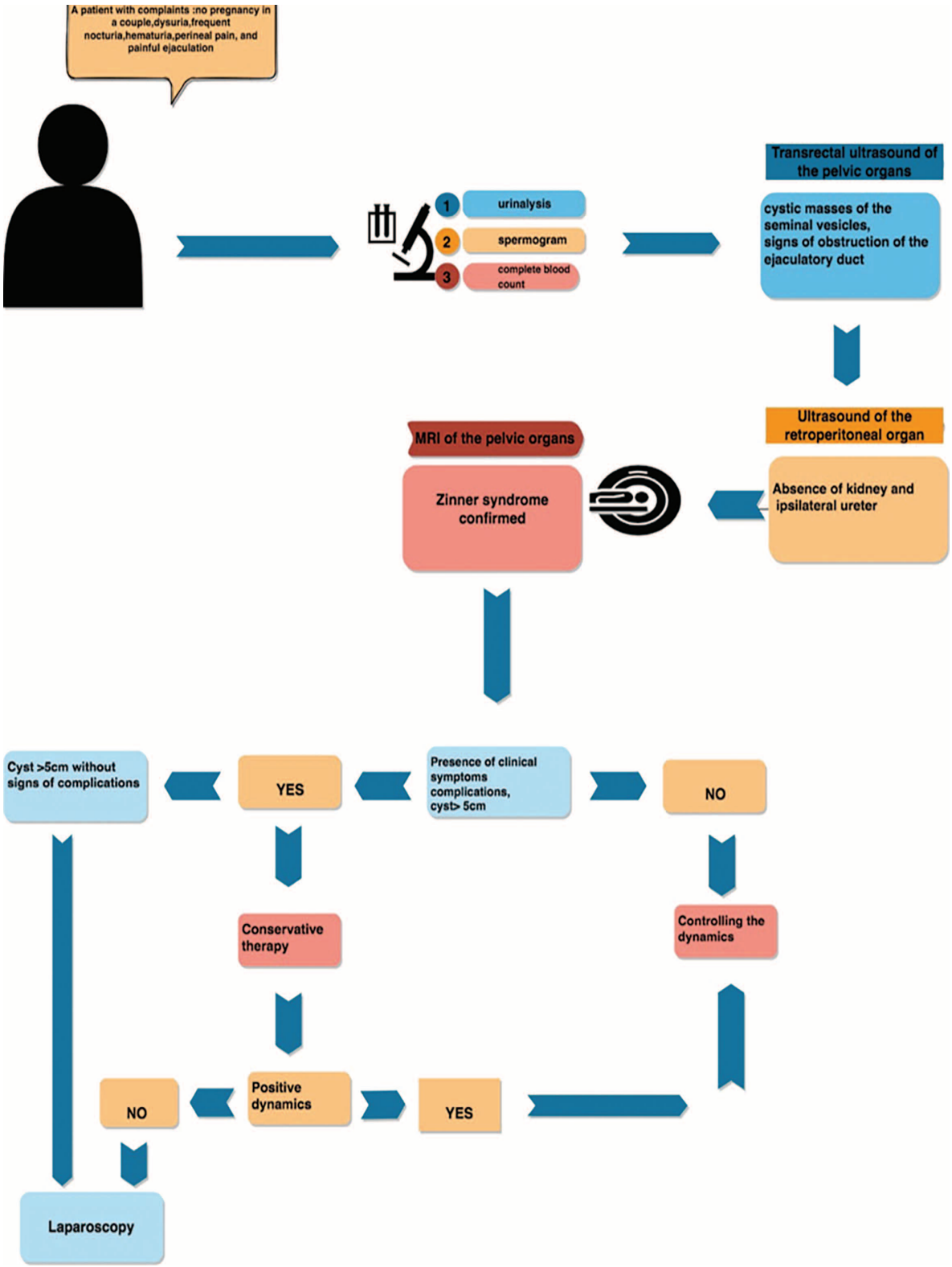

Figure 4. *Routing scheme for patients with Zinner syndrome.*

of protein, purulent or haemorrhagic material can boost the intensity on T1-weighted images similar to both our cases [5, 9].

One of the MRI advantages in detection of this disease is that MRI demonstrates the anatomic ratio between small pelvis organs and can identify the ureter. A study by Valerio Di Paola et al. presents data on the combination of Zinner syndrome with other abnormalities, such as ureter ectopy, ureter residues, which was not confirmed in the case studies in question [9].

Despite the fact that MRI is a preferred imaging method in this pathology, the primary diagnostic method is abdominal ultrasound and transrectal ultrasound, because it is a more readily available method [9].

One of the case studies describe complications of Zinner syndrome, which is a rare occurrence in literature sources [15]. Another quite rare complication is recurrent epididymitis [12].

The management of Zinner syndrome depends on the clinical course and changes during follow-up (Fig. 4). In asymptomatic disease, this diagnosis is treated conservatively with follow-up. However, literature sources describe some clinical cases where patients had minimally invasive transrectal aspiration of the cyst contents. Despite the minimally invasive nature of this procedure, there is a high risk of repeated cyst growth and infection [11]. Therefore, a full-fledged surgical intervention and sperm cryopreservation are the most efficient therapies [12].

For patients with clinical symptoms or cysts of over 5 cm, which can cause obturative azoospermia, and in case of complications, like in the first patient, and no response to conservative treatment, a surgery should be considered: currently, laparoscopic vesiculectomy is a method of choice [1, 9, 10].

One of the most technology-savvy methods is robot-assisted laparoscopy. This method used together with 3D imaging before the procedure ensures better preparation for surgery and a shorter period of early post-surgery recovery [11]. Nevertheless, this method has some limitations: it is hardly available compared to conventional laparoscopy.

Taking into account potential threat to the reproductive function in patients with seminal tract obstruction and secretory damage due to long-lasting sperm outflow impairment, a very important strategy to preserve fertility is sperm cryopreservation [17].

Conclusion

Urinary system abnormalities are often neglected by healthcare providers when there are ambiguous clinical urinary symptoms. Clinicians should be aware of the diagnostic criteria of Zinner syndrome for successful diagnostics and an optimal management strategy in occasionally detected symptoms of this congenital abnormality.

Given that Zinner syndrome is a rare condition, very often it is diagnosed on the basis of imaging results, sometimes it is an occasional finding; X-ray specialists should understand the mechanisms of urinary abnormalities in case of ipsilateral changes, as it helps to make a correct diagnosis. Currently, the main imaging method for this syndrome is pelvic MRI.

Key Points

- Zinner syndrome has three signs: seminal vesicular cysts, ipsilateral renal agenesis and seminal duct obstruction.
- Zinner syndrome is a rare congenital abnormality of the mesonephric duct and should be suspected in young patients with renal agenesia and non-specific pelvic pain.
- The first line of diagnostic examination is physical examination and transrectal ultrasound.
- The second line and a method of choice is pelvic MRI. MRI allows confirming the diagnosis as it can detect dilated spermatocysts located in the periprostatic area.
- MRI is more useful in male reproductive tract imaging and accurate differential diagnosis of seminal vesicular cysts and other cyst formations in the small pelvis.
- Asymptomatic patients should be followed-up with further conservative therapy. Patients with clinical symptoms should have surgery — currently, it is laparoscopicvesiculectomy, with robot assistance, where possible.

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