

P R A C E K A Z U I S T Y C Z N E
*ginekologia*Frasier syndrome in 17-year-old girl
– case report

Zespół Frasiera u 17-letniej dziewczynki – opis przypadku

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Abstract

The authors present a case of Frasier syndrome in a 17-year-old girl with nephrotic syndrome and male pseudohermaphroditism. Due to the existing risk of developing tumors in dysgenetic gonads, the patient was admitted to the clinic for prophylactic gonadectomy. The operation was then postponed as a result of rapid progression to end-stage renal failure, and the patient was placed on hemodialysis. During subsequent laparoscopy, both ovaries and dysgenetic gonads were resected. Histopathological examination revealed the presence of both seminal ducts and epididymis. Early prophylactic resection of dysgenetic gonads, such as was undertaken in this patient, is indicated in children with Frasier syndrome to prevent the development of germ cell tumors.

Key words: **Frasier syndrome / pseudohermaphroditism / ambiguous genitalia / renal failure / nephrotic syndrome**

Streszczenie

Autorzy prezentują przypadek 17-letniej dziewczynki z zespołem nerczycowym i obojnactwem rzekomym męskim. Z powodu ryzyka nowotworu wywodzącego się z dysgenetycznych gonad dziewczynka została przyjęta do Kliniki Chirurgii Dziecięcej do profilaktycznej gonadektomii. Planowany zabieg został odroczone z powodu pogorszenia funkcji nerek aż do ich schyłkowej niewydolności. Po wdrożeniu leczenia nerkozastępczego i wyrównaniu parametrów gospodarki azotowej wykonano laparoskopową gonadektomię obustronną z usunięciem obu jajowodów. W badaniu histopatologicznym w gonadach stwierdzono struktury najądrza i przewodów nasiennych. Wczesne profilaktyczne usunięcie dysgenetycznych gonad jest wskazane u dzieci z zespołem Frasiera w celu zapobiegania powstania guza wywodzącego się z komórek germinalnych.

Słowa kluczowe: **zespół Frasiera / obojnactwo rzekome / zaburzenia różnicowania płci / niewydolność nerek / zespół nerczycowy**

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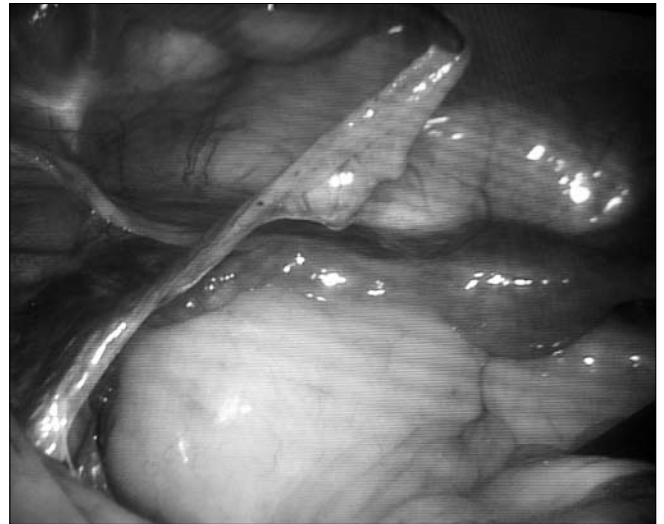
Frasier syndrome was first described by Frasier et al. in 1964 as an association between glomerulosclerosis, male to female sex reversal, and dysgenetic gonads in a pair of monozygotic twins [1]. Further reports have described this syndrome in association with the risk of dysgenetic gonads, as a predisposing factor for gonadoblastoma [2, 3, 4, 5]. Polymerase chain reaction amplification testing can confirm such a diagnosis, generally by demonstrating mutation in the WT1 gene. Mutations of the WT1 gene are also present in a minority of patients with Wilms' tumor, as well as children with Denys-Drash and/or WAGR syndromes. WT1 gene acts as a tumor suppressor gene and has four different isoforms. Patients with Frasier syndrome display mutations in intron 9 [2, 6, 7, 8].

Case report

A 17-year old girl was referred to the gynecological outpatient clinic, because of primary amenorrhea. The girl's physical examination was consistent with Tanner 3 stage of development. Her weight was 57kg, height – 167cm (BMI:20.4). Prior medical history made mention of the fact, that at the age of 7, she developed hypertension because of nephrotic syndrome and segmental glomerulosclerosis. As a result of the aforementioned, the patient was prescribed Encortone, Amlodipinum, Enalapril, Furosemidum. Ultimately, she was admitted to the Department of Pediatric Surgery at the Children's University Hospital in Bialystok, for further investigation concerning her lack of menses.

Thyroid function was normal. In trans-abdominal pelvic ultrasound, neither the uterus nor the expected appendages were identified. Vaginoscopy showed a small vagina, with a lack of a visible cervix. Chromosomal analysis showed SRY sequences consistent with XY genotype. The DNA analysis attested to a mutation in the WT1 gene, consistent with Frasier syndrome. The cytohormone vaginal smear revealed features of active estrogen function. The patient was subsequently subject to an oral hormone replacement, in the form of an estrogen-progesterone pill (Cyclo-Progynova). Following the introduction of such treatment, the girl began to menstruate regularly.

The diagnosis of Frasier syndrome may be based on the presence of specific mutation in the WT1 gene, nephrotic syndrome associated with diffuse mesangial sclerosis that lead to chronic renal failure, and a 46XY karyotype in a phenotypic female. Due to the risk of developing tumors in dysgenetic gonads, a laparoscopic evaluation of the abdomen with subsequent gonadectomy was planned. Laboratory tests showed elevated levels of serum urea (122mg/dl) and creatinine (6,96mg/dl). The laparoscopy was then postponed, and the patient underwent hemodialysis. Once serum levels of both urea and creatinine diminished, the laparoscopy was undertaken. Prior to the operation, the colon was emptied with an enema, and a Foley catheter was inserted. The operation was performed under general anesthesia with endotracheal intubation, in the supine position. Open access was attained through the use of a blunt trocar, placed at the rim of the umbilicus. Two other trocars were introduced under visual guidance, into the right and left iliac fossa respectively. Pressure of 12 mmHg of carbon dioxide was used. Three cannulas were sufficient for this procedure, an umbilical one for the telescope, and 2 other ones (in the right and left lower quadrants) for instrumentation. In the right lower



Picture 1. Small uterus with obliterated Fallopian tubes and dysgenetic gonads.

quadrant, we used a 10mm cannula for both instrumentation and removal of the specimen, while in the left lower quadrant; a 5mm cannula was inserted. During the operation, a small uterus and two obliterated Fallopian tubes were visualized. Both gonads spread as a strand along the Fallopian tubes. The ovaries and the dysgenetic gonads were both resected. Hemostasis was reached with electrocoagulation and staples. Histopathological examination then revealed seminal ducts and epididymis along the obliterated Fallopian tubes. The patient was discharged from the hospital on the second day post-hoc. Diffuse mesangial sclerosis is a rare cause of end-stage renal failure. It usually presents as nephrotic syndrome with rapid progression to end-stage renal failure [6]. In children with early onset of proteinuria, rapid deterioration of renal function and female phenotype or ambiguous genitalia, both a karyotype and a WT1 gene analysis ought to be performed [3, 6, 7, 8]. It is of utmost importance to correctly differentiate all of the syndromes associated with WT1 mutations, as each one predisposes towards a different type of tumor [6]. The inclusion of nephropathy within the context of Frasier syndrome remains a poor prognostic factor, although the mortality rate has decreased significantly in the last decade. Vast advances in hemodialysis and living-donor transplantations have both allowed for an improved quality of life and a prolonged lifespan. [4, 9].

Dysgenetic gonads can be unilaterally or bilaterally undescended. Persistent Mullerian structures may link the gonads together, causing one gonad to migrate to the contralateral side [1, 2, 3, 10]. In patients with dysgerminoma, computed tomography or magnetic resonance imaging is indicated. Tumor staging includes examination of the abdominal cavity, diaphragm, omentum, paracolic gutters, paraaortic, and pelvic lymph nodes. Serum alpha-fetoprotein and human chorionic gonadotropin levels can serve as markers of unresected or recurrent disease [3, 6, 9]. Sometimes patients do not live long enough to develop the cancers associated with these syndromes, and this may account for the missed diagnosis in patients with the female phenotype. It is important to determine the presence of a genetic alteration in

order to offer familial genetic counseling [9] further knowledge within the field may also be used by the patients themselves, possibly as part of a biopsychosocial model of adjustment when it comes to their daily dealings with the disease.

Conclusion

Early prophylactic resection of dysgenetic gonads is indicated in children with Frasier syndrome to prevent the development of germ cell tumors. It may also serve a potential future role in the development and/or improvement of genetic and psychological familial counseling.

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