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Frasier syndrome diagnosed in a 4-year-old girl

Case report

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Abstract: The authors present the case of a girl with Frasier syndrome that was diagnosed at the age of 4 years. At 3.5 years, she was diagnosed a steroid-resistant nephrotic syndrome associated with focal segmental glomerulosclerosis. The girl presented with female phenotype and male genotype (46XY) as well with gonadal dysgenesis. Genetic analysis confirmed the +2T>C mutation in the intron 9 of the WT1 gene. She developed end-stage renal disease at 14 years, culminating in renal transplantation. The liver biopsy revealed a post-transplantation lymph-proliferative disease.

Keywords: *Frasier syndrome • Rare mutation • Post-transplantation lymph-proliferative disease*

1. Introduction

Frasier syndrome is a clinical entity comprising nephrotic syndrome resulting from focal segmental glomerulosclerosis, progressive renal failure, male pseudohermaphrodism, karyotype 46 XY with gonadal dysgenesis, and a significant risk of the development of gonadoblastoma. Frasier syndrome is a rare disease caused by mutation of the Wilms' tumor suppressor gene WT1 [1,2]. First reports of this syndrome were published in 1991; its incidence remains uncertain. The final diagnosis is established on the basis of genetic analysis [3,4].

2. Case report

The girl was hospitalized for the first time at our Department at the age of 3.5 years with the diagnosis of steroid-resistant nephrotic syndrome. A percutaneous kidney biopsy finding pointed to a focal segmental glomerulosclerosis. Prior to the administration of cyclophosphamide therapy (for possible changes in chromosomes during therapy), the karyotype – 46 XY was determined upon suspicion of Frasier Syndrome, which was confirmed by the following investigations. An ultrasound scan of internal genitals showed an infantile uterus and ovaries of similar structure. Genetic analysis detected mutation +2T>C in intron 9 of the WT1 gene. Because cyclophosphamide therapy did not lead to the remission of the renal disease, therapy by cyclosporine was attempted until the establishment of final diagnosis, which also failed to produce adequate results. There was a gradual progression of chronic renal failure. During the further course of the disease, the girl was receiving ACE inhibitor therapy. At the age of 11, she underwent endocrinological investigations to either confirm or negate the presence of active ovarian tissue. The condition of hypergonadotrophic hypogonadism was detected: FSH>200, IU/L (<1–3); LH>200, IU/1 (20–75); estradiol 10.47 pg/ml (19–140): testosterone, <0.2 ng/ml (2–8.5).

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Hormone substitution therapy was introduced, resulting in the development of secondary sex characteristics (breast development, female type hairiness).

The same year, explorative laparoscopy was performed because of high risk for the development of gonadoblastoma; at this time, the bilateral absence of ovarian and testicular tissue was verified. The uterus was in the normal position, and was of normal size and appearance for the girl's age. The histopathologic finding of the adnexa registered only ovarian tube tissue but no presence of gonadal tissue.

She developed the end stage renal disease at the age of 14 years that culminated in renal transplantation; the living donor was the girl's mother. The liver biopsy revealed a post-transplantation lymph-proliferative disease (PTLD), which developed 8 months following the transplantation. A polymerase chain reaction to Epstein-Barr virus was positive. She was treated by antiviral therapy (ganciclovir) and rituximab with prednisone. Gradually, the PTLD went into remission, and polymerase chain reaction (PCR) to Epstein Barr virus became negative. Through the next year she was treated with corticosteroids only (20 mg prednisone per day) to combat the lymphopenia caused by the rituximab therapy. She has had no signs of graft rejection. The girl has been again treated with immunosuppressive therapy (rapamune) during the last 5 months.

3. Discussion

The case of a girl with Frasier syndrome diagnosed as early as the age of 4 years is presented in this study. In all presented cases of Frasier syndrome up to now, the diagnosis had been established at older ages, most frequently between 10 and 20 years during investigations for missing menarche or infertility [1]. There was a progression of chronic renal failure in our case, so that the 14-year girl entered the terminal renal insufficiency, with the following renal transplantation.

The WT1 gene located at chromosome 11p13 has a significant role in the development of the kidneys and gonads. Frasier syndrome is most often characteristic of a heterozygous point mutation of an alternative splice donor site in intron 9, leading to disorders in the ratio of the WT1 isoforms (+KTS/-KTS, 2:1 →1:2) necessary for normal development of kidneys and gonads. WT1 (-KTS) is essential for differentiation of podocytes, whereas WT1 (+ KTS) is essential for determination of male sex, but not for the formation of female sex. Our patient presented with a relatively rare mutation in the intron 9 of WT1 gene: +2T>C [3,4,5].

There is a question whether Denys-Drash and Frasier syndromes are different entities or, alternatively, a different spectrum of the same disease. In Denys-Drash syndrome, the mutations located in exon 9 cause early development of renal insufficiency for mesangial sclerosis, male pseudohermaphroditism, and increased risk of nephroblastoma. Having in mind the previous condition and availability of a live donor, our patient underwent a pretransplantation bilateral nephrectomy. Most authors do not agree concerning the increased risk of nephroblastoma in the Frasier syndrome patients; therefore, they do not find the bilateral pretransplantation nephrectomy indicated [1,2].

During the usual timing of puberty, the hormonal status of the patients with Frasier syndrome is characterized by dominant hypergonadotrophic hypogonadism, pointing to the primary dysfunction of gonads. Patients with Frasier syndrome have a 44% risk for the development of gonadal tumors, particularly gonadoblastomas. Therefore, these patients require a removal of nonfunctional gonads [6,7].

In conclusion, Frasier syndrome is diagnosed in girls with nephrotic syndrome resulting from focal segmental glomerulosclerosis, chronic renal insufficiency, and delayed puberty; they present with female genotype and male karyotype. Final diagnosis is established by genetic analysis.

Although FS is a rare disease, we nevertheless recommend determination of the karyotype and ultrasonography of internal genitals in each female child with resistant nephrotic syndrome and FSGS. Early diagnostics of Frasier syndrome enables the avoidance of cytotoxic-nephrotoxic drug treatment: these drugs do not give an adequate therapeutic response in the treatment of nephrotic syndrome. Early diagnosis also allows adequate control of these patients, first of all given the high risk of the development of malignant alteration of dysgenetic gonads [8, 9].

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