Case Report

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Frasier Syndrome: A Rare Disorder in a Patient With Nephrotic Syndrome

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Abstract

Frasier syndrome is a rare genetic disorder characterized by the association of progressive renal glomerulopathy and 46,XY complete gonadal dysgenesis with a high risk of developing gonadoblastoma. Mutations in the Wilms' tumor suppressor gene (WT1) located in 11p23 are responsible for this syndrome. Patients with this syndrome commonly present with normal female genitalia, streak gonads, and a 46, XY karyotype. Nephropathy in Frasier syndrome is in the form of nephrotic syndrome (NS) with proteinuria that begins early in childhood and progressively increases with age, mainly due to nonspecific focal segmental glomerular sclerosis (FSGS). We herein present a 4-year-old girl who presented with steroid-resistant nephrotic syndrome and was later diagnosed with Frasier syndrome.

Keywords: Frasier syndrome; Nephrotic syndrome; Gonadal dysgenesis.

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Introduction

Frasier syndrome is an uncommon genetic syndrome characterized by steroid-resistant nephrotic syndrome, gonadal neoplasm, and female external genitalia with a 46, XY genotype (1). Frasier et al (2) first described this syndrome in 1964 in a pair of monozygotic twins in whom WT-1 mutation was found. Izaki et al classified this syndrome into three types according to external genitalia, sex chromosome, and clinical phenotype. The foremost common type is type 1 characterized by female external genitalia with a 46, XY genotype. Type 2 is described as male external genitalia with a 46, XY genotype, and type 3 is defined as female external genitalia with a 46,XX genotype (1).

WT-1, a tumor suppressor gene located in 11p23, encodes a zinc finger transcription responsible for the development of kidneys and gonads (4).

Mutations in the WT1 gene have been observed in patients with Denys-Drash syndrome (DDS), WAGR (Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation), Wilm's tumor, and Frasier syndrome (FS). Unlike Denys-Drash syndrome, gonadoblastoma is more common in Frasier syndrome (4).

Case Report

Case scenario: A 4-year-old girl, the 1st issue of non-consanguineous parents, presented with generalized edema and was diagnosed with nephrotic syndrome in March 2018 in view of nephrotic range proteinuria, hypoalbuminemia, and hypercholesterolemia (300 mg/dl). She was initially treated with prednisolone 60 mg/m^2/day for 8 weeks; however, she failed to attain remission. She also developed hematuria and

hypertension. Therefore, a biopsy was done in August 2018, which was suggestive of focal segmental glomerulosclerosis (FSGS with focal tubular necrosis, IgM 1+, C_3 3+). Cyclosporine was initiated in August 2018 but it was discontinued due to a rise in the creatinine level and mycophenolate mofetil was started in September 2018. She was also hypertensive, which was controlled by several antihypertensive drugs including prazosin, nifedipine, and clonidine. As proteinuria continued despite receiving steroids and MMF, tacrolimus was added and the first dose of rituximab was injected in February 2019 at a dose of 500mg/m^2. During this period, her USG showed a rudimentary uterus with streaky ovaries without any tumors. Although she had normal-looking female genitalia, a karyotype and clinical exome sequencing were requested. However, she was unfortunately lost to follow-up. In March 2020, she again presented with severe respiratory distress with a high creatinine level (13.4 mg/dl) and an eGFR of 11 ml/min/1.73m^2. Tacrolimus was discontinued after 6 months of initiation but she still used MMF and prednisolone. The karyotype report revealed a male karyotype (46, XY) (Figure 1) and exome sequencing showed WT-1 mutation in intron 9 (c.1432+4C>T variant), which is likely pathogenic, indicating a diagnosis of Frasier syndrome. The parents were counselled regarding the chance of future gonadal tumors and they agreed to proceed with surgical treatment. A pediatric surgeon was consulted and she underwent elective gonadectomy in August 2020. Histopathologic report showed no features of gonadoblastoma. She is now on regular hemodialysis trice a week.

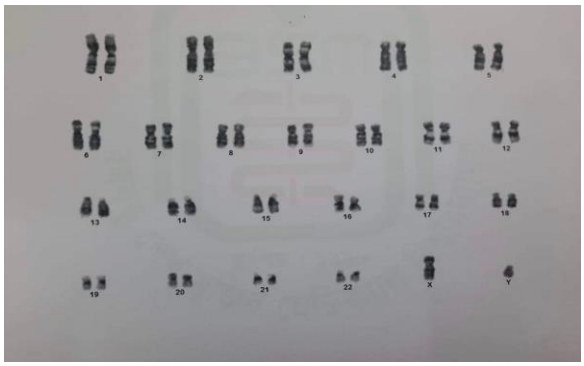

Figure 1. Karyotype of the patient

Discussion

Frasier syndrome is an autosomal dominant disorder rarely reported from Bangladesh. This rare syndrome affects both males and females. Ezaki et al (1) studied 88 cases in a systematic review and found that 82% of the patients had female external genitalia with a 46,XY karyotype, which is similar to our patient. Patients with Frasier syndrome mostly present with renal symptoms (65%) at a mean age of 5.4±4.3 years. Our patient presented with the features of nephrotic syndrome at the age of 4 years. Another retrospective study found that 94% of the patients with WT-1 mutation presented with proteinuria at a median age of 4 years, which is similar to our case (5). In our case, renal biopsy showed FSGS, which is similar to a study by Vidhiya et al (6). Gurgana et al reported four cases of Frasier syndrome that had FSGS on renal biopsy (7), which is also consistent with our findings. Steroid resistant nephrotic syndrome and FSGS are linked to various genetic mutations. Santin S et al suggested WT1 gene analysis in patients with steroid-resistant nephrotic syndrome with female external genitalia who are negative for mutation in the nephrosis 2 gene causing idiopathic steroid-resistant nephrotic syndrome (podocin; NPHS2) (8).

Kumar et al found *WT1* mutation in intron 9 (IVS 9 + 4 C>T, 2; IVS + 5 G>A, 1) in three SRNS cases (9). Izaki et al reviewed 88 cases with Frasier syndrome and found that 23 cases had (IVS 9 + 4 C>T) heterozygous mutation in the WT-1 gene (1). A case report from India and one from Japan also showed point mutation (IVS 9 + 4 C>T) in the WT-1 gene (6,10). This same heterozygous mutation (IVS 9 + 4 C>T) was found in our case.

Our patient had a 46,XY karyotype with female genitalia, which is consistent with the results of studies by Aditi et al and Matuszczak et al who both found a 46,XY genotype with a female phenotype (11,12) .

There are many case report of gonadoblastoma with WT-1 mutation and ESRD in female adolescents and adults (13-16). A previous study recommended early gonadectomy in patients with Frasier syndrome without a gonadal tumor (17). Bilateral gonadectomy was performed in our patient once a diagnosis of Frasier syndrome

was confirmed. Aditi et al achieved partial remission of nephrotic syndrome with cyclosporine in their study (11). Cyclosporin was discontinued in our patient due to a rise in the creatinine level.

Renal replacement therapy increases the chance of survival in children with Frasier syndrome suffering from ESRD. Nephrotic syndrome does not recur after kidney transplantation (1,18).

Conclusion

Frasier syndrome is a rare disorder; however, it should be suspected when a female child presents with steroid-resistant nephrotic syndrome. Screening for WT-1 mutation ought to be performed in suspected cases. Preemptive gonadectomy might have beneficial effects in Frasier syndrome. Management is multidisciplinary. Renal transplant or dialysis can increase the life expectancy of the patients with Frasier syndrome who have ESRD.

Ethics

Authors had signed informed consent from parents for reporting of the patient.

Conflict of interest

The authors declared no conflict of interest.

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