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Case Report

Frasier syndrome: A rare syndrome with WT-1 gene mutation

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ABSTRACT

Frasier syndrome is a rare disorder of sex development. It is caused by mutation in Wilms' tumor suppressor gene (WT-1) located in 11p23. This gene encodes a transcription factor involved in the development of kidney and gonads. The syndrome is characterized by female external genitalia in 46, XY patients, streak gonads with a higher risk of gonadal tumors, mainly gonadoblastoma. Nephropathy consists of nephrotic syndrome (NS) mainly due to focal segmental glomerular sclerosis (FSGS). NS presents early in childhood and responds poorly to steroid and immunosuppressive agents. Progression to End Stage Renal Disease (ESRD) usually occurs by second or third decade of life. We present a 6 years old female child with insignificant past medical history diagnosed as steroid resistant nephrotic syndrome. Renal biopsy showed FSGS. CT Abdomen showed streak gonads with rudimentary uterus. Further genotype showed WT-1 mutation with Karyotype of 46XY. Elective bilateral gonadectomy was done and histopathology showed bilateral dysgerminoma. After a year, her disease progressed to ESRD and she succumbed to the illness.

Keywords: Frasier syndrome, Gonadoblastoma, Nephrotic syndrome

INTRODUCTION

Frasier syndrome (FS) is characterized by gonadal dysgenesis and nephropathy. Wilms' tumor suppressor gene (WT-1) located in 11p23 encodes a zinc finger transcription factor involved in development of kidney and gonads.[1] Mutations in the WT1 gene were identified in patients with WAGR (Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation), Denys-Drash syndrome (DDS), and Frasier syndrome (FS). In contrast to DDS there is no known predisposition to Wilms's tumor, but gonadoblastoma is far more common in FS than in DDS.[2]

Usual presentation is persistent proteinuria in the first decade and subsequently nephrotic syndrome (NS) that progresses to end-stage renal failure by second or third decade.[3] NS responds poorly to steroid and immunosuppressive agents.[4] Primary amenorrhea is due to dysgenetic gonads. FS phenotype includes 46 XY karyotype with pure intersex state or 46 XX karyotype with normal gonadal development. Typical FS phenotype is 46, XY with female external genitalia, gonadal dysgenesis and development of renal failure in the second decade of life. There is higher level of risk of gonadal tumor in FS that cannot be ignored, hence Elective gonadectomy is indicated.[5-7] Many genetic mutations have been identified in subjects with steroid-resistant nephrotic syndrome and focal segmental glomerulosclerosis.[8]

CASE REPORT

A 6-years-old female child born of non- consanguineous parentage with insignificant past medical history presented to outpatient department with facial puffiness and decreased urine output. External genitalia was normal. Investigations confirmed the diagnosis of

nephrotic syndrome. She was initially treated with prednisolone 2mg/kg/day for 8 weeks. She did not attain remission after completion of steroids. She was started on cyclophosphamide after which an increment in albuminemia and a decrease in proteinuria was observed. She relapsed after withdrawal of the drug. Renal biopsy was performed which showed FSGS.

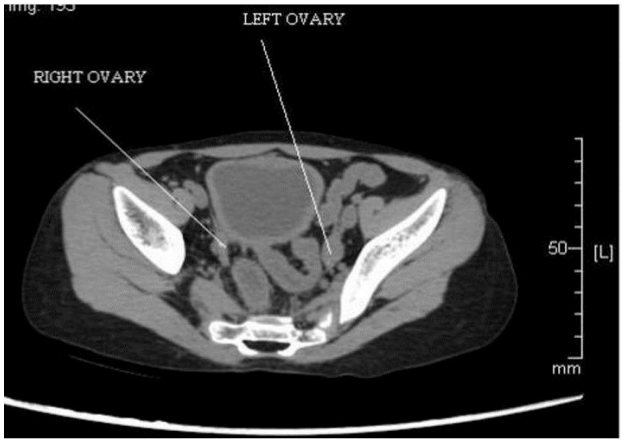

Figure 1: CT Abdomen shows rudimentary uterus with streak gonads.

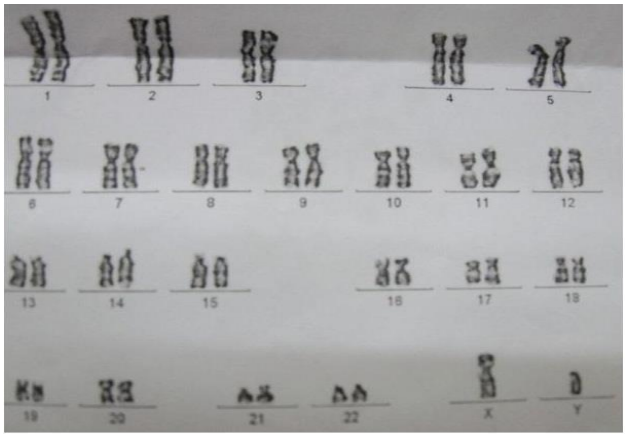

Figure 2: Karyotyping shows 46 XY.

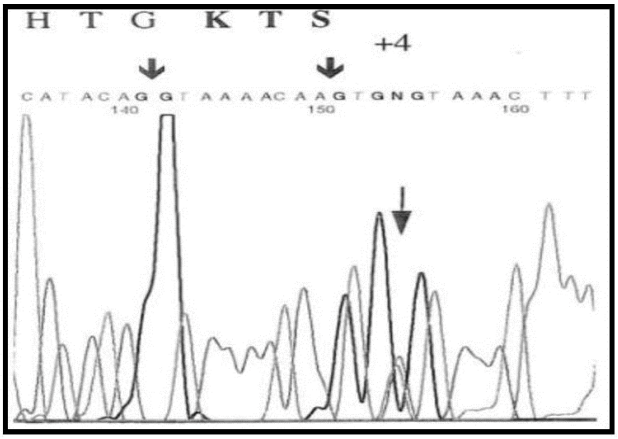

Figure 3: Automated sequencing shows IVS9+4C T> mutation.

CT Abdomen showed streak gonads with normal kidneys (Figure 1). Karyotyping revealed 46, XY (Figure 2). Automatic sequencing identified the IVS9+4C >T heterozygous mutation in the WT1 gene (Figure 3). Parents were counseled in detail about condition of the disease and child underwent elective gonadectomy in view of streak gonads. She underwent elective bilateral gonadectomy. Histopathological examination was suggestive of bilateral dysgerminoma. After a year, her disease progressed to Renal failure and she required regular dialysis for the same. She later succumbed to the illness.

DISCUSSION

There have been very few cases of FS reported in literature from India. Ezaki et al.[9] reviewed 88 patients with FS. Interestingly, both the clinical and phenotypical presentation was comparable. In Ezaki et al, 82% of the cases, had female external genitalia with karyotype of 46, XY, which is like our case.

Most common complaint was renal disorder (proteinuria) with mean age of 5.4± 4.3 years. Our patient also presented with nephrotic syndrome at 6 years of age. The number of patients with IVS9 +5G→A mutation was larger than IVS9 +4C→Tr mutation. Our case had mutation in IVS9 +4C→T. our case underwent elective gonadectomy at 7 years in contrast to mean age of 15 years in Ezaki et al.

Guaragna et al.[10] compared 4 cases of FS. Three cases among them are young patients with FS and bilateral gonadoblastoma associated with dysgerminoma and submitted to bilateral gonadectomy, with neither resurgence nor metastasis appearing during follow-up. Unfortunately, two patients had kidney transplantation before gonadectomy. 1case had horseshoe kidney, which is one of the most common congenital anomalies of the genitourinary system which is unlike our case. This paper also emphasizes the importance of screening patients with SRNS for WT1 mutations.[8]

CONCLUSION

FS is a rare disorder. High index of suspicion is needed to diagnose FS in children with steroid resistant nephrotic syndrome. These patients are less likely to respond to immunosuppressive treatment, although the risk of relapse after renal transplant is low. Karyotype is essential in girls with FS where an intersex state may be missed until the patient presents with a primary amenorrhea in adolescence. Elective Gonadectomy is indicated due to higher risk of gonadoblastoma of dysgenetic gonads.

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