

*Case Report***Absent pubertal development in a child with chronic renal failure: the case of Frasier syndrome**Anselm Bönnte<sup>1</sup>, Willibald Schröder<sup>2</sup>, Erick Denamur<sup>3</sup> and Uwe Querfeld<sup>1</sup><sup>1</sup>University Children's Hospital, Cologne, <sup>2</sup>Department of Gynecology, RWTH Aachen, Aachen, Germany and <sup>3</sup>Laboratoire de Biochimie Génétique and INSERM U458, Hôpital Robert Debré, Paris, France**Keywords:** Denys-Drash syndrome; Frasier syndrome; gonadoblastoma; pubertal development; WT1 mutations**Introduction**

Disturbances of pubertal development are commonly encountered in adolescent patients with chronic renal failure (CRF) [1]. However, the absence of pubertal development may be falsely attributed to CRF in patients with Frasier syndrome [2,3]. Frasier *et al.* first described the association of nephrotic syndrome and gonadoblastoma in a patient with XY gonadal dysgenesis [4]. Further case reports have confirmed this association and established that Frasier syndrome is a clinical entity consisting of nephrotic syndrome occurring in late childhood (age approximately 10–20 years), associated with focal segmental glomerulosclerosis (FSGS), progressive CRF, a female phenotype with absent pubertal development, a male karyotype (46 XY) and gonadal dysgenesis (streak gonads) predisposing to gonadoblastoma [2]. The diagnosis can now be confirmed by demonstrating splice-site mutations in the WT1 gene [5–7].

**Case**

Patient M. G., born 1981, was first seen in December 1990 at the age of 9 years in an outside hospital after developing diabetes mellitus type 1. During the workup for diabetes, she was noticed to have the nephrotic syndrome. She was then referred to our hospital for a renal biopsy which showed minimal glomerular changes, but only three glomeruli were biopsied.

The patient proved to be steroid resistant and developed arterial hypertension and growth arrest at the 25th percentile. Cyclosporin A therapy also had

no effect on proteinuria. A second renal biopsy performed after 6 months showed FSGS with global sclerosis in eight and FSGS in four out of a total of 13 glomeruli. At this time, renal function was 75 ml/min/1.73 m<sup>2</sup>. Cyclosporin A was stopped and a trial of cyclophosphamide was initiated. Because of persistent proteinuria, therapy with captopril was started 2 months later. Cyclophosphamide was without effect and stopped after 3 months. In 1992, a pericardial effusion was noticed on echocardiography and later proved to be resistant to therapy. During the following 2 years the patient was lost to follow up but was referred again in October 1994 because of chronic renal insufficiency with a GFR of 64 ml/min/1.73 m<sup>2</sup> and apparent growth failure with a height of 147 cm (3rd percentile). At this outpatient visit, absent puberty was diagnosed for the first time (puberty stage Tanner B1, P1). On ultrasound, an infantile uterus could be seen with bilateral ovary-like structures. Further clinical workup disclosed hypergonadotropic hypogonadism (FSH > 150 mIU/ml, LH 73.3 mIU/ml, oestradiol 13 pg/ml). Chromosomal analysis showed a normal male karyotype (46 XY). The patient was started on hormonal substitution therapy with oestrogen and gestagens. Because of the high risk of malignancy, exploratory laparotomy was performed in August 1995 and revealed bilateral streak gonads which were removed (Fig. 1). The histology showed no evidence of malignancy. A marked growth spurt along with some pubertal development (puberty stage Tanner B2, P2) could be initiated with hormonal substitution and the patient reached a final height of 164 cm (25th percentile).

Renal function progressively diminished over the next 3 years. The patient continued with insulin treatment with a total of 30 units/day. Arterial hypertension was treated with carvedilol, nitrendipin and quinapril. Haemodialysis had to be initiated in 1998. According to the family's urgent wish, the patient was transferred to an outside maintenance haemodialysis programme. We were informed in 1998 that the patient had died suddenly at home without an apparent cause. An autopsy was not granted.

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Fig. 1. Intraabdominal situs of streak gonad in a patient with Frasier syndrome.

## Discussion

We describe a phenotypically female patient with steroid resistant nephrotic syndrome associated with focal segmental glomerulosclerosis, progressive CRF, streak gonads, and a 46 XY karyotype. In addition, the patient had diabetes mellitus type I and an unexplained chronic pericardial effusion; these findings have not been described in other patients with Frasier syndrome reported in the literature.

Since the development of gonadoblastoma is a typical complication of gonadal dysgenesis, removal of the non-functional streak gonads has been recommended, preferably before renal transplantation is performed. It is possible that some cases with malignant metastatic dysgerminoma after renal transplantation reported in the literature were in fact cases of Frasier syndrome [8].

Mutations of the Wilms' tumor suppressor gene, WT1, cause different pathologies of the urogenital system, including the Denys-Drash syndrome and Frasier syndrome. Previous studies of the sex determining gene SRY and of the WT1 gene in patients with Frasier syndrome had failed to detect mutations [9,10]. However, it could recently be shown that Frasier syndrome is in fact due to mutations in the WT1 gene which had been missed in previous studies because only exons of the WT1 gene had been screened. Frasier syndrome is caused by mutations in the donor splice site in the intron 9 of the WT1 gene resulting in a decrease in the KTS+ isoform of the protein coded

by the WT1 gene leading to a decrease in the KTS+/KTS- ratio, which is responsible for the glomerular and genital abnormalities [5-7]. In our patient, the search for mutations within WT1 exon 8 and 9 and intronic flanking regions identified the 1228+4 C→T heterozygous mutation. This point mutation is commonly reported in Frasier syndrome [11].

In conclusion, Frasier syndrome should be considered in girls with chronic renal failure associated with focal segmental glomerulosclerosis and absent pubertal development. Patients have a male karyotype and the definite diagnosis can now be made by genetic methods. Removal of streak gonads should be performed early because of the high risk of gonadoblastoma. It should be noted that singular cases of Frasier syndrome have recently been reported in female patients with renal disease (karyotype 46 XX) but with normal pubertal development and intact reproductive function, respectively [12,13].

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