Case Report

Hypergonadotropic hypogonadism and renal failure due to WT1 mutation

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Introduction

Puberty is frequently delayed in adolescent patients with chronic renal failure, due to temporarily insufficient hypothalamo-pituitary stimulation of the gonads. In these patients, basal levels of gonadotropins are normal or slightly elevated due to increased plasma half-life of luteinizing hormone (LH) and follicle stimulating hormone (FSH) [1]. However, the response to gonadotropin releasing hormone (GnRH), LH and FSH stimulation is inadequate, confirming hypogonadotropic hypogonadism.

The exact mechanism of delayed pubertal development in chronic renal insufficiency is still unknown, but a reduced amplitude of pulsatile gonadotropin secretion, i.e. LH and FSH, is thought to play an important role [2]. In patients with chronic renal failure the onset of puberty is delayed on average by 2 years [2]. However, various other reasons may affect pubertal development in patients with chronic renal insufficiency, including gonadal disorders such as gonadal dysgenesis, Leydig cell hypoplasia, Turner syndrome and Klinefelter syndrome.

Case report

We report a male patient who underwent correction of glandular hypospadia and herniotomia at the age of 5 years. At that time, asymptomatic proteinuria (1.7 g/day) was first noted in the routine examination before surgical intervention, but no further diagnostic measures were taken.

At 10 years of age, gross proteinuria without oedema was confirmed. He was referred to our hospital for further evaluation. The serum creatinine was 0.7 mg/dl, urea 40 mg/dl, serum protein 58 g/l and albumin was 29 g/l, proteinuria was 6.3 g/day/m² body surface area showing a non-selective pattern, and urine sediment showed erythrocyte cylinders. A renal biopsy was performed which revealed focal segmental glomerulosclerosis (FSGS) with complete or subtotal sclerosis in eight and segmental sclerosis in two out of a total of 32 glomeruli. Despite treatment of proteinuria and hypertension by ACE inhibitor captopril, the patient progressed rapidly to end-stage renal failure and at the age of 15 years peritoneal dialysis therapy had to be started.

At this age, his height was 161.5 cm (height standard deviation score (SDS)-1.4) and his weight was 44.5 kg (body mass index (BMI) 17.1 kg/m²; BMI SDS-1.48). His bone age as radiologically determined was slightly delayed (14–14.5 years). Pubertal stage was PH3, according to Tanner, but the testicular volume was only 2 ml. Ultrasound examination of testes showed microcalcifications and normal vascular perfusion. A testicular biopsy was considered but rejected by the patient and his parents. Chromosomal analysis showed a normal male karyotype (46 XY). Serum levels of dehydroepiandrosterone sulfate (49.3 µg/dl), α-fetoprotein (0.9 U/ml) and β-human chorionic gonadotropin (<1.0 mU/ml) were normal. The basal testosterone level was very low, at 1.02 ng/ml. The basal levels of LH (19 U/l) and FSH (66.5 U/l) were extremely elevated. Thirty minutes after GnRH stimulation LH increased to 70.6 U/l and FSH to 125.8 U/l, confirming hypergonadotropic hypogonadism.

Hormonal replacement therapy was initiated due to the patient’s low testosterone levels, to induce secondary signs of puberty and prevent osteoporosis.

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Therapy was started with 50 mg testosterone enanthate i.m. every 4 weeks and the dose was gradually increased up to 250 mg every 4 weeks after 6 months. Testosterone levels rose to 4.06 ng/ml, while LH and FSH levels were suppressed to LH < 0.1 mU/ml and FSH 0.3 mU/ml. Consequently, testosterone dosage interval was extended from 4 to 5 weeks and subsequently LH and FSH increased while testosterone remained in the normal range. The patient’s pubic hair stage proceeded to PH5 and the young man started to shave.

Molecular analysis of the WT1 (Wilms’ tumour 1) gene revealed a heterozygous point mutation IVS9 + 5G > A, therefore a diagnosis of incomplete Frasier syndrome was made.

Two years later, the patient received a cadaveric kidney transplant with good graft function (serum creatinine 1.0–1.1 mg/dl) 18 months after transplantation. At the age of 19 years the patient agreed to a bilateral orchidectomy which he and his parents had refused before. On inspection, both testes were small (0.5 cm in diameter), and histologically, intratubular germ cell neoplasia with atypical Sertoli cells and intratubular microcalcification was diagnosed. Gonadoblastoma was excluded (Figure 1A and B).

**Discussion**

This phenotypically and genotypically male patient with focal segmental glomerulosclerosis (FSGS) had mixed gonadal dysgenesis with testicular atrophy and subsequent hypergonadotropic hypogonadism as well as male external genitalia with isolated glandular hypoplasia, defined as pseudohermaphroditism type 2 according to the Sinnecker classification of pseudohermaphroditism [3]. The molecular analysis of the WT1 gene showed a mutation IVS9 + 5G > A, one of the commonly reported mutations in typical Frasier syndrome [4]. The usual phenotype of Frasier syndrome in patients with male karyotype consists of female genitalia and hypergonadotropic hypogonadism due to severe gonadal dysgenesis [5,6]. However, a few patients with atypical phenotypes have been reported [4,7,8]. Gonadal development is impaired in varying degrees, resulting in a spectrum of male pseudohermaphroditism; all described phenotypically male patients had cryptorchism and hypospadias [4,7–9]. The degree of pseudohermaphroditism is determined by the ability to produce androgens by Leydig cells and anti-Mullerian hormone (AMH) by Sertoli cells. Obviously, our patient produced enough AMH to regress the female internal genitalia. This is noteworthy, since WT1 is especially expressed in Sertoli cells and mutations of WT1 are likely to impair AMH production. However, he was unable to produce enough testosterone to develop complete male external genitalia.

Pubertal and adult patients with Frasier syndrome are reported to have extremely high gonadotropin levels [4]. The patient described here also had elevated LH and FSH levels associated with decreased testosterone levels in the presence of atrophic testes. After testosterone replacement therapy, LH and FSH levels could be suppressed in our patient. This contrasts with other reports, which found a disturbed hypothalamo-pituitary-gonadal feedback regulation in patients with WT1 mutation [4].

Patients with Frasier syndrome develop renal failure due to FSGS and are at high risk for gonadoblastoma [4,6]. The latter was not seen in our patient. However, the intratubular germ cell neoplasia with intratubular microcalcifications can be regarded as a preneoplastic condition. The microcalcifications were already seen at ultrasound.

It is known that some malformation of the urogenital tract including Wilms’ tumour, WAGR [10], Denys–Drash and Frasier syndromes are associated with various mutations of the WT1 gene [11]. The WT1 gene is located on chromosome 11p13 and encodes for a zinc finger transcription factor [10], playing an important role in the development of kidney and gonads [12]. It is still a matter of debate whether Denys–Drash and Frasier syndromes are distinct entities or part of the same disease spectrum. However, the two syndromes have clinical and genetic

**Fig. 1.** Light microscopy (A and B) of the left testis. (A and B): Note microcalcification as well as intratubular germ cell neoplasia with atypical Sertoli cells and thickening of tubular basement membrane.
In Denys–Drash syndrome, WT1 mutations are typically located in exon 9, leading to the early development of renal failure due to mesangial sclerosis, increased risk of nephroblastoma and male pseudohermaphroditism [14]. In contrast, in the study of Melo et al. [4] that analysed all 27 patients with Frasier syndrome reported up to 2002, the WT1 mutations were in intron 9 of the WT1 gene: +4C>T (in 52% out of 27 analysed patients), +5G>A (in 26%), +2T>C, +5G>T and +6T>A (1 patient reported each); in addition 2 exonic mutations were seen [4]. These mutations obviously do not lead to the development of nephroblastoma [4]; therefore, bilateral nephrectomy prior to transplantation is not indicated in these patients.

We strongly recommend analysis for WT1 mutations in XY-patients with mild ambiguous genitalia and renal disease patterns, e.g. proteinuria. This is of particular importance since most of the patients described thus far had gonadal dysfunction due to dysgenesis and an increased risk for subsequent tumour development. Patients with Frasier syndrome have a risk of 44% for gonadal tumours, in particular, gonadoblastomas [4]. In addition, germ cell tumour, testosterone hilar cell adenoma, leiomyoma and dysgerminoma were also seen [4]. Thus, regular examinations of testes to rule out tumour development should be performed, and orchidectomy should be considered in patients with non-functional testes as well as gonadectomy in phenotypically female patients [15]. In our patient, the combination of FSGS and testicular atrophy prompted us to perform a genetic analysis of the WT1 gene which confirmed the diagnosis.

In conclusion, in patients with delayed puberty and chronic renal failure GnRH test may help to separate frequent hypogonadotropic from unusual hypergonadotropic hypogonadism, thus possibly detecting disfrequent hypogonadotropic from unusual hypergonadotropic. The chronic renal failure GnRH test may help to separate frequent hypogonadotropic from unusual hypergonadotropic hypogonadism, thus possibly detecting disfrequent hypogonadotropic from unusual hypergonadotropic.

Conflict of interest statement. None declared.

References


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