

sensitivity to oxidative stress. This increase in oxidative stress in the nucleus seems to be responsible for clinical progression in triple A syndrome.

More than 75 mutations have been described in the AAAS gene, without finding any genotype-phenotype association. In fact, the phenotype is variable even among individuals with the same genotype.¹¹ Therefore, although the genetic study is essential for diagnosis, it does not provide information on the patient's phenotype or prognosis. Some patients do not have mutations in this gene, so there may be other genes involved.

The case described is unique not only because it is the first associated with the c.1058T>C variant, but also because of the early neurological/gastrointestinal involvement and late onset of adrenal insufficiency with unknown pathophysiological mechanism.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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5-Alpha-reductase type 2 deficiency. A new case in the Spanish population



Déficit de la 5-alfa-reductasa tipo 2. Un nuevo caso en la población española

The 5-alpha-reductase type 2 deficiency (5 α -RD2) is a rare autosomal recessive 46, XY disorder of sexual development (DSD), resulting in the inability to convert testosterone (T) to dihydrotestosterone (DHT), an NADPH dependent process catalysed by the membrane-bound steroid 5 α -RD2.¹ Individuals are usually identified as female in childhood but undergo virilisation at puberty. For this reason gender dysphoria in individuals raised as female is very prevalent, reaching 63% according to Cohen et al.²

Although the disease is rare among Caucasians, there is a high prevalence in the population of Dominican Republic due to consanguineous marriages. It is also prevalent in other regions like Papua New Guinea.³

Clinical presentations are much broader than the original phenotype. Many people with 5 α -RD2 deficiency are usually identified in the neonatal period because of ambiguous genitalia and some are misdiagnosed with androgen insensitivity syndrome. During puberty, an increase in male sex hormones leads to the development of some secondary sex characteristics.

We report a 16-year-old woman from Almeria (Spain), born and raised as a female, suffering from 5 α -RD2 deficiency, and who presented with tall size and primary amenorrhoea. There was no history of personal or familiar significant medical illness. There was no history

of consanguinity between her parents. On examination, blood pressure was 123/69 mmHg. She weighed 91.5 kg, height was 184 cm (body mass index of 27 kg/m²). General physical examination was within normal limits (no features suggestive of hypothyroidism, Cushing's syndrome or acromegaly). External genitalia examination revealed clitoromegaly. Gonads were palpable in the inguinal canal bilaterally, there was neither breast development (Tanner stage I) nor signs of hirsutism. She underwent a gynaecological ultrasound examination which showed a 1 cm blind vaginal pouch. Magnetic resonance shows no remnants of female genital organs or prostatic organs, a suggestive image of small cavernous sinuses with a hypoplastic penis and an image of both rounded inguinal undescended testicles.

Laboratory investigations showed normal hemogram, glucose, renal and liver function tests, and serum electrolytes. In view of tall size and primary amenorrhoea, we measured; serum total testosterone 4.5 ng/ml (raised considering female reference intervals (FRI) 0.1–0.8) (male RI (MRI) 2.8–8), estradiol 51 pg/ml (MRI 7.63–42.6), LH 6.22 mUI/ml (MRI 1.4–7.7), FSH 3.95 mUI/ml (RI 1.5–14). 17-OH progesterone, DHEAS, thyroid profile, ACTH, cortisol, IGF-1 and prolactin were all normal. Chromosomal study revealed a 46 XY karyotype. The diagnosis of 5 α -RD2 deficiency was suspected based on clinical and biochemical findings. DSD targeted gene panel sequencing identified a homozygous T to G change at c.271 in exon 1 of the coding SRD5A2 sequence, which is predicted to result in a p.Tyr91Asp alteration. Parents were both carriers of the same heterozygous variant. This pathogenic mutation has been previously described by Wilson et al.⁴

After the diagnosis treatment was initiated with cutaneous estradiol and GnRH analogues. The gonads were recently removed and nowadays only needs cutaneous estradiol and vaginoplasty is pending.

The diagnosis of DSD in a 46 XY individual is a complex process due to the broad spectrum of phenotypic manifestations and the vast number of causes that can originate them. From the first case reported of a 5 α -RD2 deficiency in 1961 by Nowkowsky and Lenz⁵ to date, the number of gender role changes is higher than in other intersex conditions. There are several factors that may determine whether these individuals, who were raised as girls, change to a male social sex after puberty.

The tendency to the male gender identity and role can be explained by the prenatal exposure of the brain to androgens, coupled with postnatal and puberty virilisation. It is possible that androgen exposure is more important than sex of rearing or sociocultural influences.⁴ However cultural advantages of the male role, family desire and genital appearance might be other factors in the decision. In three cohorts including 136 affected individuals the predominant sex of rearing was female and the rate of social sex change differs. In Sao Paulo and in Dallas cohorts the prevalence of social sex change was around 50%.^{4–6} In the French cohort,⁷ the percentage was 12%. These differences are possibly due to differences in the age of diagnosis.

This case is a novelty because there are only two cases reported in the Spanish population (Sanlúcar, Cadiz) and there was no data about the genetics. Although the age of the diagnosis was very similar, there are several differences between the cases. In Aguilar-Diosdado⁸ there were ambig-

ous genitalia, and the diagnosis was made biochemically with elevated ratios of serum T to DHT. In contrast, in our case there was female genitalia and the diagnosis was made locating the mutation. The final difference is that in the case we report, female identity was maintained, whereas in the other cases they change to male identity.

Nowadays the mutational analysis of the SRD5A2 gene is indicated as the first approach⁹ because the biochemical diagnosis is not reliable enough. The 5 α -RD2 gene is located on the short arm of chromosome 2p23. It contains four introns and five exons and encodes a 254 aminoacid protein.⁹ Mutations have been found in all five exons of the coding regions. To date, around 90 mutations have been described. Although correlation between the type of mutation and change to male social sex in adulthood was not established, mutations result in a variability of enzymatic disfunctions and phenotype.¹⁰ The Tyr91Asp mutation causes impaired 5 α -RD2 activity in genital skin fibroblasts.⁴ A correlation between the severity of the clinical manifestations and the degree of the impairment of enzyme activity has been described¹⁰ though, the same mutation can result in phenotype variability ranging from female phenotype to partially virilised external genitalia. Indeed, phenotype variability has been described in siblings with the same compound heterozygous mutation.⁹ This may indicate that other factors, such as environmental elements contribute to the varying clinical manifestations of the disease.¹⁰

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