trastornos autonómicos, disfunción bulbar, atrofia óptica o ataxia.

El síndrome triple A es debido a mutaciones patológicas en el gen *AAAS*, el cual codifica para la nucleoporina ALADIN. Estas mutaciones alteran el transporte de proteínas necesarias para la reparación del ADN (apraxatina, DNA ligasa I), lo que provoca hipersensibilidad al estrés oxidativo. Este incremento en el estrés oxidativo a nivel nuclear parece ser responsable de la progresión clínica en el síndrome triple A.

Se han descrito más de 75 mutaciones en el gen *AAAS* sin encontrarse asociación genotipo-fenotipo. De hecho, el fenotipo es variable incluso entre individuos con el mismo genotipo[11]. Por ello, aunque el estudio genético es imprescindible para el diagnóstico, no aporta información sobre el fenotipo o el pronóstico del paciente. Algunos pacientes no presentan mutaciones en dicho gen, por lo que pueden existir otros genes implicados.

El caso descrito es único no sólo por ser el primero asociado a la variante c.1058T >C, sino por la afectación precoz neurológica/digestiva y aparición tardía de insuficiencia suprarrenal de mecanismo fisiopatológico desconocido.

Financiación

Este trabajo no ha recibido ningún tipo de financiación.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

Bibliografía

1. Capataz Ledesma M, Méndez Pérez P, Rodríguez López R, Galán Gómez E. Síndrome de Allgrove (triple A). Hallazgo de una mutación no descrita en el gen AAAS. An Pediatr (Barc). 2013;78:109–12.
2. Grant DB, Barnes ND, Dumic M, Ginalska-Malinowska M, Milla PJ, von Petrykowski W, et al. Neurological and adrenal dysfunction in the adrenal insufficiency/alacrima/achalasia (3A) syndrome. Arch Dis Child. 1993;68:779–82.
3. Kilicli F, Acibucu F, Senel S, Dokmetas HS. Allgrove syndrome. Singapore Med J. 2012;53:e92–4.
4. Luigetti M, Pizzuti A, Bartoletti S, Houlden H, Pirro C, Bottillo I, et al. Triple A syndrome: A novel compound heterozygous mutation in the AAAS gene in an Italian patient without adrenal insufficiency. J Neurol Sci. 2010;290:150–2.
5. Nakamura K, Yoshida K, Yoshinaga T, Kodaira M, Shimojima Y, Takei Y, et al. Adult or late-onset triple A syndrome: case report and literature review. J Neurol Sci. 2010;297:85–8.
6. Polat R, Ustyol A, Tuncez E, Guran T. A broad range of symptoms in allgrove syndrome: single center experience in Southeast Anatolia. J Endocrinol Invest. 2020;43:185–96.
7. Roucher-Boulez F, Brac de la Perriere A, Jacquez A, Chau D, Guignat L, Vial C, et al. Triple-A syndrome: a wide spectrum of adrenal dysfunction. Eur J Endocrinol. 2018;178:199–207.
8. Meyer A, Catto-Smith A, Crameri J, Simpson D, Alex G, Hardikar W, et al. Achalasia: Outcome in children. J Gastroenterol Hepatol. 2017;32:395–400.
9. Messina MF, Autunno M, Koehler K, Russo M, Arrigo T, Crisafulli G, et al. Upper and lower motor neuron involvement as presenting manifestation of Triple A syndrome. J Endocrinol Invest. 2009;32:482–3.
10. Dumić M, Barišić N, Rojnić-Putarek N, Kušec V, Stanimirović A, Koehler K, et al. Two siblings with triple A syndrome and novel mutation presenting as hereditary polyneuropathy. Eur J Pediatr. 2011;170(3):393–6.
11. Leveille E, Gonorazky HD, Rioux MF, Hazrati LN, Ruskey JA, Carnevale A, et al. Triple A syndrome presenting as complicated hereditary spastic paraplegia. Mol Genet Genomic Med. 2018;6:1134–9.

María Eugenia López Valverde[a,*],
María Isabel Rebollo Pérez[a],
Eva María Martínez Fernández[b],
Eva Murillo Espejo[b] y Pilar Carrasco Salas[c]

[a] *Servicio de Endocrinología y Nutrición, Hospital Juan Ramón Jiménez, Huelva, España*
[b] *Servicio de Neurología, Hospital Juan Ramón Jiménez, Huelva, España*
[c] *Servicio de Genética, Hospital Juan Ramón Jiménez, Huelva, España*

* Autor para correspondencia.
Correo electrónico: eukane_lpz@hotmail.com
(M.E. López Valverde).

https://doi.org/10.1016/j.endinu.2021.03.006

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 (5α-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 5α-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 5α-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 5α-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/m^2). 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 hypoplasic 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 5α-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 5α-RD2 deficiency in 1961 by Nowkowski and Lenz[5] 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 (Sanlucar, 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-Diosdado[8] there were ambiguous 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 approach[9] because the biochemical diagnosis is not reliable enough. The 5α-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 5α-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 described[10] 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]

Bibliografía

1. Belchetz PE. The testis. In: Besser GM, Cudworth AG, editors. Clinical endocrinology. 1st ed. Philadelphia: JB Lippincott; 1987. p. 1–18.
2. Cohen-Kettenis PT. Gender change in 46, XY persons with 5a-reductase-2 deficiency and 17beta-hydroxysteroid dehydrogenase-3 deficiency. Arch Sex Behav. 2005;34:399–410.
3. Cheon CK. Practical approach to steroid 5 alpha-reductase type 2 deficiency. Eur J Pediatr. 2011;170:1–8.
4. Wilson JD, Griffin JE, Russell DW. Steroid 5 alpha-reductase 2 deficiency. Endocr Rev. 1993;14:577–93.
5. Nowakowski H, Lenz W. Genetic aspects of male hypogonadism. Rec Prog Horm Res. 1961;17:53–89.
6. Griffin J, McPhaul M, Russell D, Wilson J. The androgen resistance syndrome: steroid 5a-reductase 2 deficiency, testicular feminization, and related disordes. In: Scriver CRBA, Sly WS, Vale D, editors. The metabolic and molecular bases of inherited disease. 7th ed. New York: McGraw-Hill; 1995. p. 2967.
7. Costa EM, Domenice S, Sircili MH, Inacio M, Mendonca BB. DSD due to 5 alpha-reductase 2 deficiency—from diagnosis to long term outcome. Semin Reprod Med. 2012;30:427–31.
8. Aguilar-Diosdado M, Gavilán-Villarejo I, Escobar-Jimenez L, Beitrán J, Giron JA. Male pseudohermaphroditism with 5-α-reductase deficiency: Report of two new familial cases. The importance of early diagnosis. J Pediatr Endocrinol Metab. 1995;8:67–71.
9. Maimoun L, Philibert P, Cammas B, Audran F, Bouchard P, Fenichel P, et al. Phenotypical, biological, and molecular

heterogeneity of 5alpha-reductase deficiency: an extensive international experience of 55 patients. J Clin Endocrinol Metab. 2011;96:296–307.
10. Wigley WC, Prihosa JS, Mowszowicz I, Mendonca BB, New MI, Wilson JD, et al. Natural mutagenesis study of the human steroid 5 alphareductase 2 isozyme. Biochemistry. 1994;33:1265–70.

Mikel González Fenández[a], Isabel Esteva de Antonio[b], Idoia Martínez de la Piscina Martín[c], Jorge Soler Martínez[d], María Cruz Almaraz Almaraz[b,*]

[a] *Endocrinology and Nutrition Department of University Hospital Miguel Servet, Zaragoza, Spain*
[b] *Endocrinology and Nutrition Department, Gender Identity Unity, Regional University Hospital of Málaga, IBIMA, CIBERDEM, Málaga, Spain*
[c] *Biocruces Bizkaia Health Research Institute, Cruces University Hospital, UPV/EHU, CIBERER, CIBERDEM, ENDO-ERN, Plaza de Cruces 12, 48903 Barakaldo, Spain*
[d] *Urology Department, Regional University Hospital of Málaga, Málaga, Spain*

* Corresponding author.
E-mail address: mariac.almaraz.sspa@juntadeandalucia.es (M.C.A. Almaraz).

https://doi.org/10.1016/j.endinu.2021.04.003