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Caso Clínico

Lipoid Congenital Adrenal Hyperplasia: An Uncommon Cause of Adrenal Insufficiency

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A B S T R A C T

Lipoid congenital adrenal hyperplasia (CAH) is a rare autosomal recessive disorder caused by defective synthesis of all steroids. Typical features include disorder of sex development, early-onset adrenal crisis and enlarged adrenal glands with fatty accumulation. Glucocorticoid and mineralocorticoid replacement therapy enables long-term survival. We report a case of lipoid CAH caused by mutation in the steroidogenic acute regulatory protein (*StAR*) gene. The patient had typical early-onset adrenal crisis at 2 months of age, normal-appearing female genitalia and a karyotype of 46, XY. Genetic analysis revealed a homozygous mutation at c.505G>A (p.Glu169Lys) in exon 5 of the *StAR* gene. To our knowledge this is the first case of classic lipoid CAH reported in the Portuguese population. *StAR* mutations should be considered in the differential diagnosis of newborn babies and infants with primary adrenal insufficiency with atypical presentation, allowing genetic counselling, guidance of follow-up and prevention of complications.

Palavras-chave:
Hiperplasia Suprarrenal Congénita;
Insuficiência Adrenal/congénita.

Hiperplasia Congénita da Suprarrenal Lipóide: Uma Causa Rara de Insuficiência Adrenal

R E S U M O

A hiperplasia congénita da suprarrenal (HCSR) lipóide é uma doença hereditária rara resultante de um bloqueio da fase inicial da esteroidogénese. O quadro clínico à apresentação é tipicamente o de uma crise adrenal grave, de início precoce, aliada a distúrbios do desenvolvimento sexual e hipertrofia das glândulas suprarrenais por acumulação lipídica. A terapia hormonal de substituição permite uma sobrevida a longo prazo. Relatamos um caso de HCSR lipóide causada por uma mutação no gene da proteína reguladora da esteroidogénese (steroidogenic acute regulatory protein - StAR). A apresentação clínica foi de uma crise adrenal grave aos 2 meses de idade, objetivando-se genitais femininos normais e cariótipo 46,XY. O estudo molecular revelou uma variante patogénica c.505G>A (p.Glu169Lys) em homozigotia no exão 5 do gene *StAR*. Até à data, este é o primeiro caso de HCSR lipóide relatado na população portuguesa. As mutações do gene *StAR* devem ser consideradas no diagnóstico diferencial de recém-nascidos e lactentes com insuficiência adrenal primária com apresentação atípica, possibilitando o aconselhamento genético, e permitindo antecipação e precocidade de atuação.

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Introduction

Lipoid congenital adrenal hyperplasia (CAH) is an extremely rare and the most severe form of CAH. This disorder is characterised by severe adrenal and gonadal steroidogenesis impairment due to a defect in the conversion of cholesterol to pregnenolone, the precursor of all steroids (Fig. 1). The defect in lipoid CAH

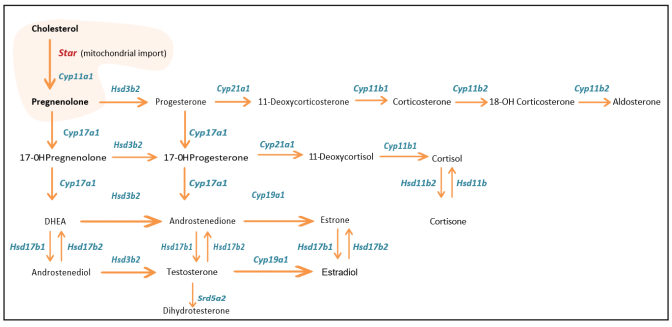

Figure 2. Simplified scheme of the classic steroid biosynthetic pathway.

CYP, cytochrome p; HSD, hydroxysteroid-dehydrogenase; SRD, 5α-reductase.

is mainly due to steroidogenic acute regulatory protein (*StAR*; OMIM 600617) gene mutations. *StAR* regulates the transfer of cholesterol from the outer to inner mitochondrial membrane, where it becomes the substrate for the cholesterol side-chain cleavage enzyme, P450scc, also called CYP11A1 (encoded by the *CYP11A1* gene). The clinical features of lipoid CAH include salt wasting crisis from impaired mineralocorticoid and glucocorticoid synthesis. All affected individuals with classic lipoid CAH are phenotypically female regardless of their gonadal sex, due to a severe defect in fetal testicular steroidogenesis, reflecting an absence of testosterone synthesis between 6 and 12 weeks of gestation in 46,XY genetic male.[1-4] Hormone replacement enables long-term survival for these patients.

Currently, more than 83 different mutations of the *StAR* gene have been reported in approximately 200 patients.[4]

To our knowledge, no case of lipoid CAH has been described in the Portuguese population. We report a case of classic lipoid CAH with early onset during first infancy, and a severe clinical presentation.

Case Report

A 2-month-old phenotypic female infant was admitted to the pediatric intensive care unit (PICU) of a Portuguese tertiary children's hospital in the sequence of a cardiopulmonary arrest due to a salt wasting crisis. She was born full-term, by caesarean delivery, with a birth weight of 2990 g (appropriate for gestational age) and the Apgar score at the 1st and 10th min of life was 7 and 10, respectively. The infant did not have neonatal hypoglycemia or respiratory distress. She was the second child of consanguineous parents (second cousins), both Caucasian of Portuguese ancestry and healthy. The older brother of 5 years old was healthy too. There was no family history of disorders of sex development (DSD) or sudden death. She had a poor weight gain since birth and was diagnosed with an *Escherichia Coli* pyelonephritis at 1-month-old. One month later (2-month-old), at the time of the PICU admission, she presented with severe dehydratation (13% of birth weight loss), hypothermia (<35ºC), and the initial laboratory workup revealed severe hypoglycemia (< 10 mg/dL), metabolic acidosis (pH 7.17; pCO2 53.2; HCO3 19.3 mmol/L), hyponatremia (128 mEq/L) and hyperkalemia (5.9 mEq/L). Physically she presented with normal female external genitalia (normal clitoris and normal urethral and vaginal orifices), and she was found to have mucosal and cutaneous hyperpigmentation. After initial stabilization, and behind the suspicion of a classic CAH, a hormonal screening was performed. The serum adrenocorticotropic hormone (ACTH) level was greater than 4000 pg/mL, renin level was also high (1029 uU/mL), with low levels of cortisol (2.3 µg/Ll) and aldosterone (4.21 pg/mL). The levels of all adrenal steroids, including dehydroepiandrosterone-sulfate (DHEA-S), androstenedione and 17-hydroxyprogesterone (17-OHP), were also low. She was diagnosed with primary adrenal insufficiency and intravenous therapy with stress doses of hydrocortisone and posteriorly fludrocortisone was started, in conjunction with sodium chloride supplementation, with progressive clinical improvement. During hospitalization, she undergoes further investigation. Abdominopelvic ultrasonography revealed normal size adrenal glands and the presence of testes-like gonads in the pelvic cavity. Neither ovaries nor a uterus were identified. The karyotype revealed a 46,XY. After almost one month of hospital stay, the infant was discharged on oral hydrocortisone (15 mg/m^2), fludrocortisone (0,1 mg daily), and salt supplementation, and she was followed up regularly by pediatric endocrinology. Her hyperpigmentation resolved progressively in the first year of life, and she had no adrenal crisis episodes thereafter. At the age of five the patient underwent an exploratory laparoscopy with bilateral gonadectomy. Pathological results confirmed the presence of testicular parenchyma with marked interstitial fibrosis, epididymis, and ductus deferens. At the age of 12, she began estrogen replacement therapy. She had regular growth, and at the age of 15 she almost reached her final height. At the last visit, with 17 years, her height (- 0,16 SD), weight, and body mass index (1,32 SD) were adequate considering her genetic potential. She was doing well under replacement therapy with hydrocortisone, fludrocortisone and ethinylestradiol. A molecular study was performed at Laboratoire d'Endocrinologie Moléculaire et Maladies Rares - Hospices Civils de Lyon, where pathogenic variants which seemed to be involved in the patient's pathology were checked by Sanger sequencing. It has been identified a homozygous c.505G>A or p.Glu169Lys in exon 5 of the *StAR* gene, which allows the diagnosis of lipoid CAH. Unfortunately, the parents were not genetically studied.

Discussion

Lipoid CAH is inherited as an autosomal recessive disorder,[1-4] and the only consistent genetic clusters identified to date include *StAR* gene mutation in Japanese and Korean populations,[1] probably reflecting a founder effect, since the genetic defect in the *StAR* gene is highly homogeneous in both. Approximately 65%-70% of affected Japanese alleles and virtually all affected Korean alleles carry the mutation *Q258X*. Other genetic clusters were found among Palestinian Arabs, carrying the mutation *R182L*,[2] in eastern Saudi Arabia, carrying the mutation *R182H*,[1] and in Switzerland, carrying the mutation *L260P*.[1] Most disease-causing *StAR* mutations are in the C-terminal region between exon 5 and 7, encoding for *StAR* related lipid transfer domain.[2] These do not have measurable activity and cause classic lipoid CAH when homozygous or in compound heterozygosity with mutations of similar activity. A milder form, related to mutations retaining 10%-25% of normal *StAR* activity, is defined as "non-classic" lipoid CAH.[1] These patients typically experience adrenal insufficiency after infancy, mineralocorticoid secretion is minimally affected and the 46,XY

individuals may masculinize normally.[5,6]

To our knowledge, this is the first case of lipoid CAH described in the Portuguese population and it was caused by the homozygous p.Glu169Lys mutation in the *StAR* gene. This mutation has already been described and studied in vitro.[2] In an unbiased Turkish nationwide cohort of almost 100 children with primary adrenal insufficiency (PAI) of unknown etiology,[7] which represents the largest nationwide study of the molecular genetics of childhood PAI undertaken, the p.Glu169Lys was reported in homozygous state only once (within a total of 11 StAR gene mutations identified). It has already been reported in a compound heterozygous state in two 46,XY patients, one from Japan and the other from Turkey, both with normal female external genitalia and adrenal failure.[2,5,8] Similar to our case, these patients also presented in early infancy with severe adrenal insufficiency and complete sex reversal, reflecting a complete inactivation of the *StAR* function, consistent with classical lipoid CAH presentation.

The typical ultrasonography features of lipoid CAH are enlarged adrenal glands with cholesterol ester deposits.[9] However, a suspected diagnosis of lipoid CAH in the absence of adrenal enlargement cannot be ruled out. Huang *et al* [10] studied images of the adrenal glands from lipoid CAH patients and found that 7 of 9 cases had enlarged adrenal glands, one had normal-sized adrenal glands with fatty deposits, and one had normal adrenal glands as described in our case. Only two lipoid CAH cases with small-sized adrenal glands have been reported previously.[9] The physiological mechanism for small adrenal glands remains unclear.

In 46,XX patients with a *StAR* mutation, a wide clinical spectrum of disorders is observed, from no puberty at all to normal puberty with regular menses. Thus far, pregnancy has been reported in only few women with a *StAR* gene mutation who presented with spontaneous puberty and menarche. These pregnancies were facilitated using two different types of intervention (clomiphene citrate treatment and in vitro fertilization).[11] The natural course of gonadal steroids and histology in 46,XY lipoid CAH individuals is currently uncertain as most patients, similar to ours, have been gonadectomized. To our knowledge, there is only one report on a human placental-like alkaline phosphatise positive testicular carcinoma in situ in a 15-year-old patient.[12] In general, gonads with testosterone biosynthetic defects without testicular dysgenesis should not be prone to neoplasia.[13] Whether gonadectomy is necessary in every 46,XY lipoid CAH case remains therefore questionable. It would be also interesting to assess gender dysphoria in 46,XY individuals with this disorder, since information on the psychosexual outcome of individuals with DSD will be of great importance for sex assignment at birth.

In summary, we report the first known Portuguese case of lipoid CAH with early onset and severe clinical presentation of adrenal insufficiency and complete sex reversal. There is a key-message that should be kept in mind: in a newborn female phenotype with severe salt loss, an abnormality of the first stage of steroid biosynthesis should be suspected, especially in a context of consanguinity and, of course, if the karyotype is 46,XY. This is one of the biggest differences from the mostly common 21-hydroxylase deficiency (21-OH) deficiency, in which patients have higher level 17-OHP, and affected 46,XX (not the 46,XY) patients are virilized. The description of this case gives strength to the future consideration of *StAR* mutations in the differential diagnosis of newborn babies and infants with primary adrenal insufficiency with atypical presentation. Molecular identification will allow genetic counselling, guidance of follow-up and prevention of complications.

Contributorship statement / Declaração de contribuição:

MIL: Conceptualization, data collection, writing original draft, and final approval.
RBS: Conceptualization, data collection, review and final approval.
AM and RC: Conceptualization, methodology, supervision, review and final approval.

Responsabilidades Éticas

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