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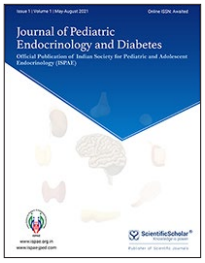

Case Report

Late presentation of lipoid congenital adrenal hyperplasia in a phenotypic male

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ABSTRACT

Lipoid congenital adrenal hyperplasia (LCAH) is a rare autosomal recessive disorder arising from a mutation in the steroidogenic acute regulatory (*STAR*) gene. In this case report, we present a 9.5-year-old male child who presented with hyperpigmentation and normal male external genitalia. He was diagnosed with primary adrenal insufficiency and whole exome sequencing revealed a homozygous mutation in the *STAR* gene consistent with LCAH and clinically fitting into the non-classical category corresponding to >10–20% residual enzymatic activity. It is noteworthy to see that our case had a much later presentation in childhood compared to the usual presentation between 2 and 4 years of age.

Keywords: Lipoid congenital adrenal hyperplasia, Steroidogenic acute regulatory protein, *STAR* gene

INTRODUCTION

Lipoid congenital adrenal hyperplasia (LCAH) (OMIM #201710) is a rare autosomal recessive disorder arising from a mutation in the steroidogenic acute regulatory (*STAR*) gene.[1] Complete and partial defects in steroidogenesis due to differing amounts of *STAR* activity are categorized as classical lipoid congenital adrenal hyperplasia (CLCAH) and non-classical lipoid congenital adrenal hyperplasia (NCLCAH), respectively.[2] The literature review revealed only <50 cases of NCLCAH reported so far, of which 58% of the cases had 46,XY karyotype.[2]

CASE REPORT

A 9-year and 6-month-old male child, firstborn to a second-degree consanguineously married couple, presented to the pediatric endocrinology outpatient clinic with diffuse hyperpigmentation of nail beds and knuckles. He was born at full term through cesarean section with a birthweight of 3.8 kg and an uneventful neonatal period. There was no history of previous hospitalizations or family history of similar complaints.

On anthropometric assessment, his weight was 33.2 kg, with a weight age of 10.8 years and a weight z-score of +1.04, and his height was 149 cm with a height age of 12 years and a height z-score of +2. His mid-parental height was 185.5 cm with a z-score of +2.02. On examination, his blood pressure was 98/62 mmHg, and he had hyperpigmented gums, knuckles, and nail beds. He had normal male external genitalia (Quigley grade 1) (External masculinization score 12/12)

with a sexual maturity rate of A1, P1, testicular volume of 2/2 mL, and stretched penile length of 5 cm.

Investigations showed thyroid-stimulating hormone 5.04 μIU/mL (0.5–4.3 μIU/mL), free thyroxine 1.38 ng/dL (0.9–2.3 ng/dL), serum sodium 140 mEq/L, serum potassium 4.13 mEq/L, 8 am cortisol 4.9 μg/dL (3–21 μg/dL), and adrenocorticotropic hormone (ACTH) 1555 pg/mL (pre-pubertal: 7–28 pg/mL). A standard dose ACTH stimulation test (performed in another center) with 250 μg of synacthen (tetracosactide acetate) showed serial cortisol levels of 5.92 μg/dL, 5.99 μg/dL, and 6.23 μg/dL at 0, 30, and 60 min, respectively.

With a diagnosis of primary adrenal insufficiency, the child was started on oral hydrocortisone at 10 mg/m^2/day and fludrocortisone at 0.1 mg/day. A karyotype was done, which showed 46,XY. Whole exome sequencing revealed a homozygous likely pathogenic variant, c.815G>A (p.Arg272His), in exon 7 of the *STAR* gene (ENST00000276449.9), consistent with LCAH. Sanger sequencing was done for the parents, and both were heterozygous for the same variant.

DISCUSSION

Steroid acute regulatory protein (StAR), is a cytoplasmic protein encoded by the *STAR* gene, comprising 285 amino acids, and is located on chromosome 8p11.2.[2] LCAH can be clinically classified into two groups: The classic form and the non-classic form. CLCAH is typically characterized by lipid accumulation in the adrenal glands, primary adrenal insufficiency in the neonatal period or early infancy, and female external genitalia, irrespective of the karyotype. NCLCAH usually presents with primary adrenal insufficiency later on in childhood and completely masculinized or minimally undervirilized external genitalia in XY males.[2,3]

NCLCAH can be defined as one of the three: (1) Age ≥1 year at the time of onset of primary adrenal insufficiency, (2) no salt-wasting crisis, and (3) Quigley grade 1 in 46, XY karyotype.[3] The clinical phenotype is related to the residual enzymatic activity, in which the enzymatic activity of <10% and >10–20% is generally considered as CLCAH and NCLCAH, respectively.[2] The variant of *STAR* gene mutation noted in our case has been reported previously in literature in two male children from different families who were diagnosed with NCLCAH at the age of 4 and 5 years, respectively.[2] A key learning point from this case is the importance of the performance of genetic tests in cases of probable "idiopathic" Addison disease (based on logistic and financial considerations) for a proper underlying diagnosis.

CONCLUSION

STAR gene mutation is usually paralleled to a phenotypic female with severe salt-wasting crisis regardless of the karyotype corresponding to CLCAH. It is noteworthy to see that our case was of NCLCAH, who presented much later in childhood at 9.5 years of age with hyperpigmentation and completely masculinized external genitalia, while the usual presentation is between 2 and 4 years of age with varying degrees of masculinization.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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