2023 ANNUAL CONFERENCE
PESTOLA
PEDIATRIC ENDOCRINE SOCIETY
OF TEXAS, OKLAHOMA, LOUISIANA, AND ARKANSAS
FEBRUARY 3-5 | THE SKIRVIN HILTON
OKLAHOMA CITY, OK
A HYBRID EVENT

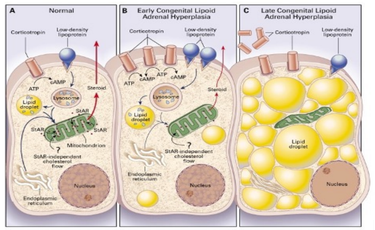
A Novel Single Allele Mutation in the Steroidogenic Acute Regulatory Protein Gene Resulting in Congenital Adrenal Insufficiency

1. S. Barclay, MS3, 2.J Meyer, MD, 3.C Sebastian, MD 4. J Tryggestad, MD
Section of Endocrinology, Department of Pediatrics
University of Oklahoma Health Sciences Center, Oklahoma City

2023 ANNUAL CONFERENCE
PESTOLA
PEDIATRIC ENDOCRINE SOCIETY
OF TEXAS, OKLAHOMA, LOUISIANA, AND ARKANSAS
FEBRUARY 3-5 | THE SKIRVIN HILTON
OKLAHOMA CITY, OK
A HYBRID EVENT

Introduction

- *Lipoid congenital adrenal hyperplasia (CAH) is a rare form of CAH caused by a deficiency in the steroidogenic acute regulatory protein (StAR), leading to a lack of cortisolproduction and increase in ACTH.*
- *StAR, a mitochondrial transport protein, is the first and rate limiting step in the adrenal pathway*
- *"Two Hit Hypothesis": inability to transport cholesterol into mitochondria along with build of cholesterol esters in the cell leading to damage and destruction of cytoarchitecture*



2: Two-Hit Model of Lipoid CAH. Hiranmoy S. Bose et. al 1996

Case Report

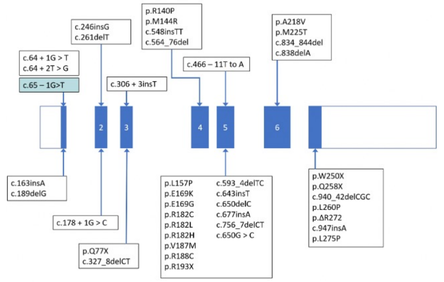
Patient is an AGA male born at 39 weeks with a 2.5cm penis and palpable testes in the scrotum without other obvious genital anomalies. He developed hyponatremia and hyperkalemia within first 48 hours of life, subsequent labs were consistent with severe adrenal insufficiency. Glucocorticoid, mineralocorticoid and salt replacement resulted in clinical and biochemical improvement. Hormonal labs at one month of age were suggestive of Leydig cell dysfunction. Most recently, at 12 years of age, testosterone levels were within normal limits, with an elevated luteinizing hormone level. Gene sequencing of DAX1 and NR5A1 were normal. At 10 years of age, exome slice revealed a heterozygous variant, c.65-1G>T(p.?) in the StAR gene. This patient's StAR variant is absent from the Genome Aggregation Database and was not found on literature review.

Findings

Age	Lab	Value	Reference Range
1 Month	Sodium	131 mEq/L	136-144
	Potassium	7.7 mEq/L	3.5-5.5
	Cortisol	<0.2 mcg/dL	6.9-21
	ACTH	712 ng/mL	0-46
	LH	74 mIU/mL	0.02-7
	FSH	8.4 mIU/mL	<0.3-4.1
	Testosterone	44 ng/dL	75-400
3 Months	LH	24.2 mIU/mL	0.02-7
	FSH	4 mIU/mL	0.16-4.1
	Testosterone	38 ng/dL	60-400
	Anti-Mullerian Hormone (at 2 months)	174 ng/dL	39.1-91.1
	Pregnenolone	<10 ng/dL	20-140
17 Months	Pregnenolone	12 ng/dL	20-140
	Aldosterone	<1 ng/dL	7-54
	Renin	1859 ng/dL/h	171-1115
	11-DOC	23 ng/dL	2-34
	Androstenedione	11 ng/dL	<10-17
	DHEA	<20 ng/dL	<68
12 Years	LH	13.2 mIU/mL	0.2-7
	FSH	3.4 mIU/mL	1.2-9.2
	★ Testosterone ★	538 ng/dL	18-620
	Anti-Mullerian Hormone	11.4 ng/mL	45.26-191.34
	Renin	7.8 ng/mL/h	0.5-3.3

Low
High
Normal

11-DOC, pregnenolone, and androstenedione were tested to assess for more common forms of CAH, caused by deficiencies in 3 β-HSD, 21-hydroxylase, and 11β-hydroxylase



1: Used with permission from C. Sebastian MD; adapted from Meimaridou et al. 2013

Discussion

- Four cases of Lipoid CAH caused pathogenic heterozygotes have been described in literature
- All four previous cases contained mutations that occurred in the first nucleotide of acceptor splice site of intron 1 (c.65-2A>G, c.65-2A>C), resulting in an in-frame loss of expression of exon 2. Our patient's variant (c.65-1G>T) occurred in the second nucleotide of the acceptor splice site of intron 1, also resulting in a loss of exon 2. Loss of exon 2 results in loss of the mitochondrial targeting sequence, and the variant StAR is not trafficked to the mitochondria
- All four previous cases had an XY karyotype and presented in first week of life with primary adrenal insufficiency (adrenal crisis or hypoglycemia) requiring glucocorticoids, as well as low cortisol and elevated ACTH. All four required mineralocorticoid therapy, with one being able to stop at puberty induction
- Three of the four had undervirilization of external genitalia, with one being assigned female at birth and undergoing gonadectomy at 3 years of age. The fourth had phenotypically normal male genitalia and later experienced hypogonadism at puberty.

Conclusions

The patient's heterozygous variant in the StAR gene, c.65-1G>T, is absent from both the Genome Aggregation Database and the literature. This patient has clear phenotypic findings of Lipoid CAH despite the fact that StAR deficiency is almost exclusively passed down as an autosomal recessive condition. Additionally, while Leydig cell dysfunction seemed certain early in life, it appears that this issue has improved considerably at the time of puberty. The unique combination of genetic and hormonal findings can add to our knowledge of Lipoid CAH.

Bibliography

1. Finn E, Kripps K, Chambers C, Rapp M, Meeks NJL, Xu F, Chen W, Larson AA, Nokoff NJ. A Novel Intronic Pathogenic Variant in *STAR* With a Dominant Negative Mechanism Causes Attenuated Lipoid Congenital Adrenal Hyperplasia. J Investig Med High Impact Case Rep. 2021 Jan-Dec;9:23247096211014685. doi: 10.1177/23247096211014685. PMID: 33966472; PMCID: PMC8114284
2. Ishii T, Hori N, Amano N, et al. Pubertal and adult testicular functions in nonclassic lipoid congenital adrenal hyperplasia: a case series and review. *J Endocr Soc*. 2019;3:1367-1374. doi: 10.1210/js.2019-00086
3. Baquedano MS, Guercio G, Marino R, et al. Unique dominant negative mutation in the N-terminal mitochondrial target- ing sequence of StAR, causing a variant form of congenital lipoid adrenal hyperplasia. *J Clin Endocrinol Metab*. 2013;98: E153-E161. doi:10.1210/jc.2012-2865
4. Kalinchenko NY, Chistousova GV, Petrov VM, et al. The rare form of congenital adrenal hyperplasia caused by an autosomal dominant form of STAR deficiency. *Prob Endocrinol*. 2018; 64:157-159.

printed by MegaPrint Inc. www.postersession.com