Three novel mutations of the StAR gene in five Algerian patients presenting with classical and non-classical lipoid adrenal hyperplasia.

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BACKGROUND- AIM

StAR deficiency is a rare cause of primary adrenal insufficiency (PAI), with fewer than 100 cases reported worldwide.

The first patients to be described suffered from severe forms of lipoid adrenal hyperplasia leading to marked undervirilisation in 46,XY foetuses.

More recently, however, less severe forms, known as “non-classical” or “atypical lipoid adrenal hyperplasia”, presenting with PAI with salt wasting (SW) syndrome and normal male genitalia have been reported.

The aim of the study is to present clinical and genetic data in five patients from three families with StAR deficiency and describe the genotype/phenotype correlation

METHODS

Clinical data were collected from all known patients with StAR deficiency in Algeria. Parental consent was obtained for genetic analysis to be performed.

Massively parallel sequencing (MPS) with a custom panel targeting candidate genes in adrenal insufficiency (*AAAS; CYP11A1; GPX1; MC2R; MCM4; MRAP; NNT; NR0B1; NR5A1; PRDX3; SAMD9; SGPL1; STAR; TXNRD2*) was carried out.

Mutations identified by MPS were confirmed in patients and their parents by Sanger sequencing

RESULTS

Between 2011 and 2018, of 277 patients referred for primary adrenal insufficiency in our centre, five patients from 3 families, were found to have StAR deficiency. Clinical and genetic data are summarized in the Table.
Age at diagnosis ranged from 1 day to 24 months, all but one patient presenting with salt wasting (SW).
Current median (range) age is 2.6 (0.6-7.4) years.
Of three patients with classical StAR protein deficiency (Patients 1-3), presenting aged < 6 months, karyotype was 46,XY karyotype in two both of whom had genital anomaly with complete sex reversal in one (patient 1) - external masculinisation score (EMS) 2/12: and severe undervirilisation in the other (patient 3) – EMS 6/12 (see Figure). The first patient was raised as a female. The second patient received testosterone 4 x 50 mg intramuscular injections during the first 4 months of life, resulting in a modest increase in penile length from 1 to 2 cm.
Two patients, a brother and sister (Patients 4 and 5), showed atypical presentation at an older age (> 1 year), with SW, pigmentation, and mild undervirilisation in the male (EMS 9/12)

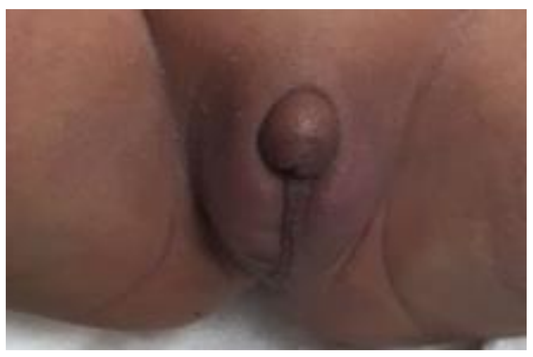

Figure: External genitalia of Patient 3
Severe micropenis, scrotal hypospadias, inguinal testis

Table: Clinical and genetic data of the patients

Patient (Pt)	Pt1	Pt2	Pt3	Pt 4	Pt 5
Consanguinity	Yes	Yes	Yes	Yes	Yes
Family history of adrenal insufficiency	Sister died at 2 months (SW)	Brother (Pt3)	Sister (Pt2)	Brother (Pt 5)	Sister (Pt4)
Age at presentation	23 days	5 months	1 day	19 months	24 months
Mode of presentation	SW	SW	Family history and DSD	SW Pigmentation	SW Micropenis
External genitalia	Female	Female	Severe hypospadias and micropenis	Female	Male Micropenis
Length of cliterophallus (cm) Testes Uterus	<0.5 Inguinal folds No	<0.5 No Yes	1 Inguinal folds No	<0.5 No Yes	1 Scrotal No
Karyotype	46,XY	46,XX	46,XY	No Y chromosome on multiplex PCR	Presence of Y chromosome on multiplex PCR
Sex of rearing	Female	Female	Male	Female	Male
Na/K at diagnosis (meq/l)	114/5.2	121/5.6	140/3.7	137/4.7 (on treatment)	126/6
ACTH (pg/ml)	1403	677	387	2000	2090
Renin (pg/ml)	76.8	8634		251	71180
Testosterone (nmol/l)	<0.05		0.41 (day 1)		
AMH (pmol/l)	359	-	209	-	
StAR gene mutation (homozygous)	c.306+2dupT in intron 3	c.64+480_c.167del in exon 2	c.64+480_c.167del in exon 2	c.73T>A p.Leu8Gln	c.73T>A p.Leu8Gln

CONCLUSIONS

StAR deficiency is a rare but important cause of PAI in consanguineous families. In this series, severe homozygous mutations, c.306+2dupT in intron 3 and c.64+480_c.167del in exon 2, resulted in severe undervirilisation and SW; while the milder c.73T>A p.Leu8Gln mutation caused an atypical form of StAR deficiency with mild undervirilisation and later presentation. This study demonstrates the phenotypic variability of StAR deficiency, and underlines the importance of testing for genes involved with steroidogenesis, including StAR, in unexplained PAI.

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Nothing to disclose concerning this presentation