P1-19

Heterozygous mutations in CYP11A1 gene can cause life-threatening salt wasting and failure to thrive

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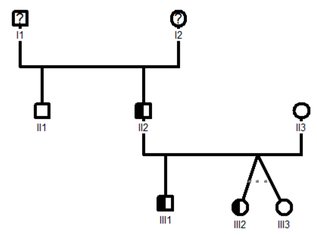
Background:

Cytochrome P450 side-chain cleavage enzyme (CYP11A1 gene) catalyses the conversion of cholesterol to pregnenolone in steroidogenic cells, the first step in the biosynthesis of all steroid hormones. SCC deficiency has been established as an autosomal recessive disorder caused by inactivating homozygous or compound heterozygous mutations in the CYP11A1 gene, with a wide phenotypic spectrum ranging from prematurity, complete underandrogenization and severe early-onset adrenal failure, to term birth with clitoromegaly and later-onset adrenal failure. No patient with P450scc deficiency has been described with the massive adrenal enlargement typical of congenital lipoid adrenal hyperplasia.

Figure 1: Family tree with the 3 affected members



Objective and hypotheses:

The first child of the family **(P1)** a 46, XY boy, presented with early onset adrenal insufficiency and life-threatening failure to thrive the first months of life, with low adrenal androgens but normal external genitalia and a girl, 46 XX, **(P2)** with severe adrenal crisis the first hours of life. The father **(P3)**, but not his only male sibling, was stated to suffer from failure to thrive during the neonatal period, had normal external genitalia and, obviously, was fertile. According to his mother sayings, his survival was achieved due to the intensive feeding, namely every hour for several months, which obviously prevented hypoglycemia, critical dehydration and hyponatremia. The situation was ameliorated as months went by and practically was resolved around 18 months of age.

This is, to our knowledge the first report of severe adrenal insufficiency during the first year of life caused by a heterozygous mutation.

P1 was first admitted to our center at the age of 3 months with extreme failure to thrive and marked hyponatremia 126 mmol/l - hyperkalemia 7.5 mmol/l. ACTH was elevated 137 pg/ml with normal but disproportionate cortisol levels 22.2 ng/dl, whereas DHEA-S was non-detectable and gonadotrophins suboptimal for male mini-puberty: LH 0.8 IU/L, FSH 1.75 IU/L with low normal testosterone 0.62 ng/ml. 17-OH-progesterone was normal for age at 4 ng/ml, while plasma renin activity was clearly elevated 7.2 ng/ml/h with only high normal aldosterone 462.4 pg/ml.
Ultrasound revealed normal adrenal size. The baby was started immediately on fludrocortisone 100 μg x 2 p.o., which resolved within hours his critical situation as he started gaining weight fast. Two months later, despite optimal electrolytes and adequate feeding, catch-up growth was not as expected. After repeated random measurements of cortisol levels around 3 μg/dl, a low-dose ACTH test (1 μg) showed a suboptimal response at 12 μg/dl. At that point hydrocortisone 25 mg/m^2/day was started, and catch-up growth was resumed. At the age of 3 yrs hydrocortisone was successfully discontinued and fludrocortisone reduced at 50 μg x 3 p.o. At 4.75 yrs fludrocortisone was gradually reduced and stopped, which resulted in a sustained reduction in height velocity similar to that observed in primary hypoaldosetronism when mineralocorticoids are discontinued. Despite normal electrolytes elevated renin persisted for over 6 months after fludrocortisone withdrawal which led us to advice restarting of fludrocortisone treatment at the minimum dose of 50 μg x 2 p.o.

After 5 years of the first child's birth the parents decided to have children with in vitro fertilization (IVF) and the result was twins, two fraternal girls. Few hours after birth and while in the maternity, the second of the girls presented acute adrenal crisis with marked hyponatremia 132 mmol/l, hyperkalemia 7.9 mmol/l, elevated plasma renin activity 27.1 ng/ml/h and lower than expected for the acute stress ACTH 11.5 pg/ml and cortisol 12 μg/dl levels. She was started immediately on fludrocortisone 100 μg x 2 p.o. and 3 g/day NaCl p.o., which resolved completely her situation within hours. Unlike her brother DHEA-S was in the high normal range, and a low-dose ACTH test showed a borderline cortisol response to 17 μg/dl. Thus we decided to advice hydrocortisone supplementation only on stress and illness. The girl's evolution was uneventful and she has a normal growth.

Method: Direct sequencing of the entire coding region and all the intron-exon boundaries of the CYP11A1 gene was performed.

Results: A novel heterozygous CYP11A1 c.235G>A missense variant was identified in exon 1 leading to the substitution of a valine by an isoleucine on amino acid position 79 to the patient, to one of his sisters and his father who suffered from failure to thrive during the first year of life and survived, according to his mother, grace to intensive feeding. Despite the fact that all available software-based prediction models show a non-deleterious effect for this heterozygous mutation, the segregation of 3 affected members in this family with early onset adrenal insufficiency and failure to thrive, proves it's pathogenic role.

Conclusion:

A novel heterozygous mutation in CYP11A1 gene can cause early onset adrenal insufficiency with life-threatening failure to thrive.

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