

Clinical Case Seminar

A5 (1-4)

Familiar inheritance of X-linked Congenital Adrenal Hypoplasia: even genetic counseling may sometimes fail!

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Abstract

Congenital Adrenal hypoplasia (CAH) is a rare genetic disorder which can present two distinct modalities of transmission: recessive X-linked or recessive autosomal modality. That linked to the X chromosome is generally associated with hypogonadotropic hypogonadism (HH). In this case, the gene responsible is DAX-1. We report the history of an infant 36-days old who was admitted to our clinic complaining of acute adrenal insufficiency (AAI), salt wasting and metabolic acidosis. He was the nephew of one of our patients with X-linked CAH. The main causes of early onset AAI were excluded and on the basis of family history we suspected diagnosis of X-linked CAH. Therefore, replacement therapy with gluco- and mineral-corticoids was started immediately. Molecular analyses confirmed the occurrence of DAX-1 gene mutation F449fsX461. His maternal uncle was already recognized to suffer from this disorder, while his mother, grandmother and maternal aunt carried the *DAX-1* mutation in heterozygosis. This case report stress the role of genetic counseling in families with DAX-1 gene mutation

Key-words: congenital adrenal hypoplasia, acute adrenal insufficiency, salt-wasting dehydration, genetic counseling, DAX-1 gene

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Introduction

X-linked CAH is a disorder which causes adrenal insufficiency in infancy and occurs in less than 1:12,500 live births (1). Clinical signs and symptoms appear early, during the first month of live and include the features of adrenal insufficiency: hyperpigmentation, vomiting, poor feeding, failure to thrive, convulsions, vascular collapse and sudden death. Biochemical findings include hyponatremia, hyperkalemia, hypoglycemia, metabolic acidosis, reduced serum cortisol and aldosterone, and increased plasma ACTH.

Case Report

Case presentation: An Italian male infant, born at term after a physiological pregnancy and with postnatal poor weight gain, was admitted to our clinic at the age of 36 days for extreme somnolence, dehydration with salt-wasting (Na^+ 121 mEq/l; K^+ 7.3 mEq/l) and metabolic

acidosis (Arterial blood gas analysis: pH 7.30, HCO₃⁻ 15.9 mmol/l, EB -8.7 mmol/l). Physical examination showed body temperature of 35.7°C, heart rate 140 bpm, height 53.9 cm, body weight 3.360 kg (-210 g than birth weight). Fasting glucose concentration was 46 mg/dl. The infant appeared lethargic, pale and dehydrated. Both testes were present in the hyperpigmented scrotum.

Differential diagnosis: The endocrine evaluation suggested acute adrenal insufficiency (AAI). Serum cortisol and aldosterone levels were subnormal (4.6 µg/dL and 17.30 pg/ml). Plasma ACTH levels and plasma renin were markedly elevated (1430.0 pg/dl and >320 pg/ml respectively). Basal 17-OH-progesterone level was normal (1.1 ng/ml). On the basis of hormone evaluation, congenital adrenal hyperplasia due to 21-hydroxylase deficiency and ACTH deficiency due to congenital defects of hypothalamus or pituitary gland were excluded. The ultrasound evaluation of adrenal glands did not show adrenal hemorrhage. Adrenoleukodystrophy was excluded on the bases of the absence of neurological features and of normal very long-chain fatty acids levels.

Family history: Our patient was a third-son of non-consanguineous parents. His brother and sister were apparently healthy. In 1999, his maternal uncle was recognized to suffer from X-linked Congenital Adrenal Hypoplasia (CAH) (2). The family genetic study showed that mother, grandmother and maternal aunt of our patient harbored a *DAX-1* mutation in heterozygosis, but the mother of our patient omitted to inform us about this data (fig. 1).

Diagnosis confirmation: The family history of our patient indicated diagnosis of X-linked CAH. Molecular studies confirmed the presence of mutation F449fsX461 in *DAX-1* gene.

Treatment: Replacement therapy with gluco- and mineral-corticoids (hydrocortisone 21.4mg/m²/day and fluorocortisone 100 mcg/day) was rapidly started and induced resolution of the clinical picture.

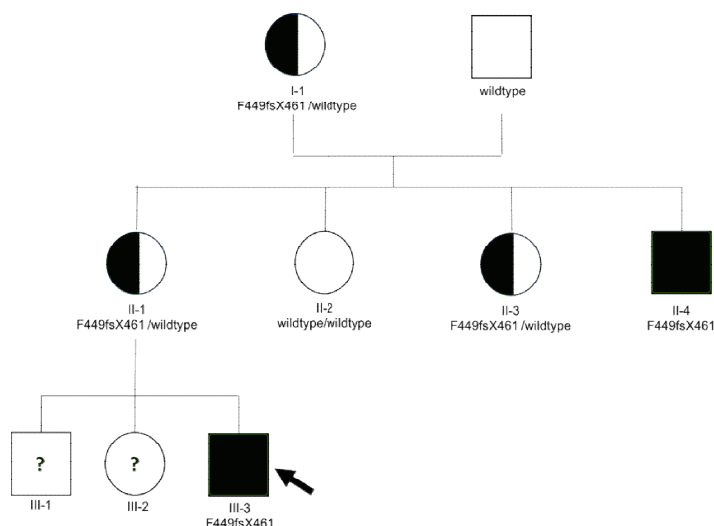


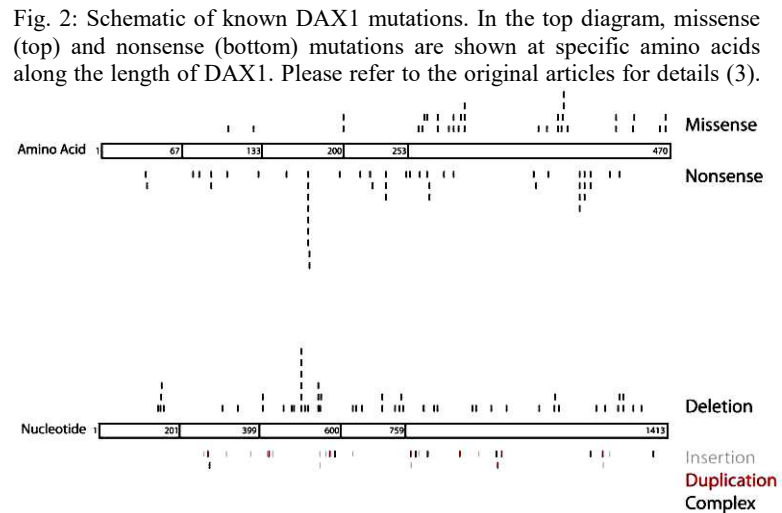
Fig. 1: Pedigree of an Italian Family with AHC X-linked and mutation analysis of *DAX-1* gene. The arrow indicates the proband

Discussion

X-linked CAH is a rare inherited disease caused by mutations or deletions in *DAX-1* gene. CAH is usually characterized by primary adrenocortical failure in early infancy or childhood and hypogonadotropic hypogonadism (HH) with impaired or arrested pubertal development during adolescence. More than 60 years after the first description of CAH, the molecular mechanisms of this rare disorder appear more precisely defined.

The human *DAX-1* gene (on chromosome X, gene 1) consists of two exons and encodes a 470-amino acid protein (1, 3). Over 215 mutations were reported in this gene, most of them are frameshift or nonsense, but some missense mutations were also found (Fig 2). The gene is expressed in the adrenal gland, testis, ovary, pituitary gonadotropes and hypothalamus and plays a key role in the development and function of the adrenal gland and of hypothalamic-pituitary-gonadal axis (4). An autosomal-recessive form of CAH is due to a mutation or deletion in *NR5A1* gene, placed on chromosome 9q33, that codes for steroidogenic factor 1 (SF-1) and is also associated with HH (5). Despite these advances, the well-known clinical heterogeneity of the adrenal syndrome associated with *DAX-1* insufficiency remains unclear. Majority of the patients presents AAI within few days after birth, while some of them may develop adrenal insufficiency during the childhood and adulthood (6).

We present an Italian family with a novel X-linked CAH due to a frameshift *DAX-1* mutation and the clinical features of a young boy with AAI diagnosed at the age of 36 days, in order to underline the role of genetic counseling. As demonstrated by the family tree (fig. 1), there were 3 potential female carriers of the deletion. Proband (III-3) is the only affected male offspring from 2 different heterozygotes sisters (II-1 and II-3). Proband's brother did not present signs of CAH (III-1). The F449fsX461 mutation in *DAX-1* gene is a frameshift mutation in codon 449 (TTC), leading to a deletion of one single thymidine nucleotide and to premature truncation of codon 461 with consequent premature stop codon. The predicted truncated *DAX-1* protein is a



loss of function molecule which may be responsible for the severe adrenal phenotype of our patient. To our knowledge, the mutation detected in this family was not reported until now. This case highlights both the importance and the difficulties of molecular diagnosis and genetic counseling. Indeed, proband's mother, although she was heterozygotes for the DAX-1 mutation, did not perform the genetic analysis during pregnancy and omitted of reporting family history to her son's doctors. If the mother had disclosed the information about the family genetic study, CAH could be early detected in her son preventing severe AAI with salt-wasting.

In conclusion, this study describes a large family carrying a frameshift DAX-1 mutation that demonstrates X-linked transmission of the defect over several generations. We underline utility of genetic counseling in families with CAH X-linked. The genetic diagnosis of *DAX-1* is not only a differential diagnosis method for patients with CAH but also the best method to allow earlier instauration of life-saving glucocorticoid and mineralcorticoid therapy in affected male offspring.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

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