Disponible en ligne sur ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Annales d'Endocrinologie 71 (2010) 309–313

Annales d'Endocrinologie
Annals of Endocrinology

Clinical case

Adrenal hypoplasia congenita – an uncommon reason of primary adrenal insufficiency

Hypoplasie surrénalienne congénitale – une cause rare d'insuffisance surrénale

M. Fichna [a,*,b], M. Żurawek [b], P. Gut [a], J. Sowiński [a], J. Nowak [b]

[a] *Department of Endocrinology and Metabolism, Poznań University of Medical Sciences, 49 Przybyszewskiego, 60355 Poznań, Poland*
[b] *Institute of Human Genetics, Polish Academy of Sciences, Strzeszyńska 32, 60479 Poznań, Poland*

Available online 12 June 2010

Résumé

L'hypoplasie surrénalienne congénitale (HSC) est une maladie héréditaire rare qui associe l'insuffisance surrénale primitive à un hypogonadisme hypogonadotrope. La plupart des cas résultent de mutations dans le gène *NR0B1* (Xp21.3) qui code pour un récepteur nucléaire orphelin DAX-1. Un patient âgé de 20 ans est diagnostiqué comme porteur d'une HSC. L'insuffisance surrénale avait été diagnostiquée et traitée dès la naissance. À l'adolescence un retard staturo-pondéral était noté. Sa puberté et l'âge osseux étaient retardés. Aucun dysfonctionnement somatotrope ni thyréotrope n'était mis en évidence. La DHEA-S et la testostérone restaient indécelables. Les taux des gonadotropines, effondrés, n'ont pas augmenté après stimulation, sans aucune anomalie hypothalamo-hypophysaire détectable à l'IRM. La supplémentation en androgènes a permis le développement des caractères secondaires sexuels, amélioré sa croissance et avancé son âge osseux. Au niveau moléculaire a été trouvée une transversion C > A dans *NR0B1* qui introduit un codon stop prématuré (Y399X). La même mutation a été identifiée dans une famille écossaise mais les différences phénotypiques suggèrent le rôle d'autres facteurs qui modifient la présentation clinique. Quoique le dépistage moléculaire ne change pas la thérapie, il permet un conseil génétique dans la famille. Évidemment l'auto-immunité reste une cause majeure de l'insuffisance surrénale, mais il faut toujours considérer d'autres affections plus rares.

Mots clés : Hypoplasie congénitale des surrénales ; Insuffisance surrénale ; Hypogonadisme hypogonadotrope ; NROB1

Abstract

Adrenal hypoplasia congenita (AHC) is a rare inherited condition characterised by primary adrenal failure and hypogonadotropic hypogonadism. Most cases arise from mutations in the *NR0B1* gene (Xp21.3), which encodes an orphan nuclear receptor DAX-1. A 20-year-old patient was recently diagnosed with AHC. Adrenal failure had been recognized and treated since his infancy. During adolescence, gradual decrease in growth velocity and low body mass were noted. Lack of puberty and skeletal immaturity were observed. Serum DHEA-S and testosterone were undetectable. Low gonadotropin levels failed to rise after stimulation. Neither dysfunction of the somatotropic nor pituitary-thyroid axis was found and no hypothalamo-pituitary pathology was visible on MRI. Androgen replacement therapy induced the development of secondary sexual characteristics, remarkably improved patient's growth and advanced his bone age. *NR0B1* mutation screening revealed nucleotide transversion C > A, resulting in premature stop codon (Y399X). Same mutation was previously identified in a Scottish family, however, phenotypic differences suggest the role of additional factors modifying the disease course. Although it does not change therapeutic strategy, accurate molecular diagnosis allows genetic counselling in family members. Autoimmunity remains the major cause of adrenal failure; however, other rare conditions should always be considered.

Keywords: Adrenal hypoplasia congenita; Adrenal insufficiency; Hypogonadotropic hypogonadism; NROB1

1. Introduction

Adrenal hypoplasia congenita (AHC, OMIM #300200) is a rare inherited condition characterised by primary adrenal fail-

* Corresponding author.
E-mail address: marfichna@netscape.net (M. Fichna).

0003-4266/$ – see front matter © 2010 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ando.2010.04.003

ure and hypogonadotropic hypogonadism [1]. Most cases are due to mutations in the *NR0B1* gene (nuclear receptor subfamily 0, group B member 1) located on the chromosome Xp21.3. *NR0B1* encodes 470-amino acid orphan nuclear receptor DAX-1, expressed in adrenal cortex, gonads, hypothalamus and anterior pituitary [2]. The protein was shown to repress the function of steroidogenic factor (SF-1), responsible for transactivation of numerous genes involved in biosynthesis of steroid hormones, development of adrenal glands and sexual differentiation [3].

AHC may present isolated or as part of a contiguous gene syndrome, together with glycerol kinase deficiency (GKD) and/or Duchenne muscular dystrophy, which result from deletions in the Xp21.3-p21.1 region [1,4]. Females are asymptomatic mutation carriers, although a case of skewed inactivation of the normal paternal allele in a symptomatic girl with 46,XX karyotype has been described [5]. As *NR0B1* mutations impair the development of the permanent adult cortical zone, acute symptoms of adrenal insufficiency usually appear in the neonatal period [1,6,7]. The complete clinical picture of the disease typically manifests with delayed puberty [6]. Gonadotropin deficiency seems to result from combined functional abnormalities at the hypothalamic and pituitary level [8]. There are also reports on late-onset AHC forms with incomplete loss of hormonal function [6,7,9,10].

2. Case report

Here, we describe a 20-year-old patient, recently diagnosed with AHC, although adrenal failure was observed and treated since his infancy. He was born at term (Apgar 8-10-10) to non-consanguineous parents following an uncomplicated pregnancy. Three weeks later he presented acutely to the local hospital with failure to thrive and severe dehydration. According to his mother's statement, the symptoms reminded her of her older son, who had died of a fulminant infection on the 21st day of life. The patient was immediately referred to the specialized clinic where the following results were obtained: serum Na^+ 124 mmol/l, K^+ 7.6 mmol/l, serum cortisol 52 nmol/l. Chest X-ray revealed bilateral inflammatory lesions. Acute adrenal crisis precipitated by pneumonia was diagnosed and treatment with i.v. hydrocortisone and saline together with antibiotics was initiated. A diagnosis of congenital adrenal hyperplasia was made, although his plasma 17alpha-hydroxyprogesterone remained within the reference range (1.51 nmol/l) and 24 h urine collection for 17-ketosteroids also revealed normal (2.70 μmol/24 h). By contrast, 24 h urine excretion of 17-hydroxycorticoids was slightly decreased (5.78 μmol/24 h). After successful treatment of infection, the patient was commenced on oral hydrocortisone and fludrocortisone.

In his early childhood, the patient timely reached all motor milestones, however, speech was delayed till the age of 4 years. His school performance remained poor and psychological tests situated his mental development within the lower limit of normal. At 13 years, gradual decrease in growth velocity and low body mass were noted but the observation continued for the following years with no further diagnosis (Fig. 1). Aged

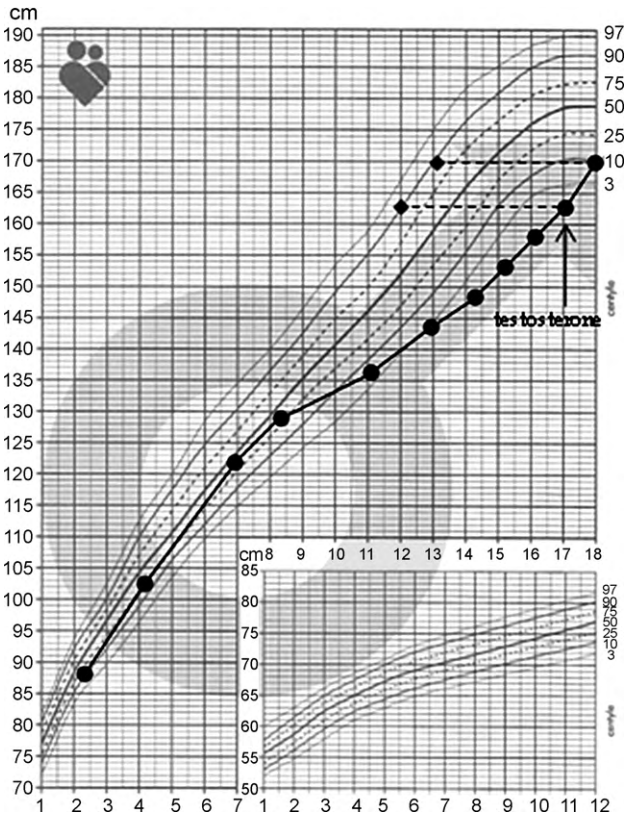

Fig. 1. Growth curve of the proband [11]. The introduction of testosterone replacement is indicated by an arrow. Relevant bone ages are also marked (diamonds).
Courbe de croissance du patient étudié. L'introduction de la thérapie de remplacement par la testostérone est indiquée par une flèche. La progression de l'âge osseux est également indiquée (losanges).

17 years, the patient was admitted to the endocrine department. His height (162 cm) and weight (42 kg) were below the 3rd percentile of the normal development curves. Testes were descended bilaterally, without pathology on ultrasonography, but no pubertal development was observed. Patient's bone age was 12 years. MRI evaluation demonstrated no abnormalities in the hypothalamo-pituitary region and the patient was normosmic. Studies revealed serum IGF-1 462 ng/ml and basal hGH 1.6 μIU/ml, increasing to 18 μIU/ml at sleep and to 25.8 μIU/ml after stimulation with insulin. No thyroid dysfunction was noted. Serum gonadotropins were low (FSH 1.9 mIU/ml, LH 0.4 mIU/ml), with no rise after LH-RH injection (FSH 2.0 mIU/ml, LH 1.0 mIU/ml). Dehydroepiandrosterone sulfate (DHEA-S) and testosterone were virtually undetectable in serum. A stimulation test with Synacthen showed insufficient increase in cortisol levels (36–61 nmol/l) and very low 17alpha-hydroxyprogesterone (0–0.2 ng/ml). Testosterone enanthate was prescribed: 50 mg i.m. every 4 weeks for 6 months, increased afterwards to 100 mg per month, and DHEA supplementation was added. One year later the patient was 168 cm tall, weighted 49 kg, and his bone age advanced to 13 years. Some body hair appeared but without change in testicular volume. Stimulation with chorionic gonadotropin (hCG) revealed preserved Leydig cell responsiveness (Table 1). A 6-month therapy with hCG