Clinical case

Adrenal hypoplasia congenita – an uncommon reason of primary adrenal insufficiency

Hypoplasie surrénalienne congénitale – une cause rare d’insuffisance surrénale

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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.

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Mots clés : Hypoplasie congénitale des surrénales ; Insuffisance surrénale ; Hypogonadisme hypogonadotrope ; NR0B1

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.

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Keywords: Adrenal hypoplasia congenita; Adrenal insufficiency; Hypogonadotropic hypogonadism; NR0B1

1. Introduction

Adrenal hypoplasia congenita (AHC, OMIM #300200) is a rare inherited condition characterised by primary adrenal fail-
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 transcription 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). 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 some body hair were noted but the observation continued for the following years with no further diagnosis (Fig. 1). Aged 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 2.0 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

![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).](image)

**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).**
On admission, at 19 years and 9 months, his height and weight were 176 cm and 57 kg, respectively. He presented with hyperpigmentation, blood pressure 110/60 mmHg, scant body hair (P3 Tanner stage) and small (4 ml), soft testes. Bone age remained markedly delayed (14 years), and spinal bone mineral density (BMD) was decreased (77% of the peak BMD and 84% of the age-matched BMD). Repeated LH-RH test did not reveal any improvement in FSH and LH reactivity (basal FSH 1.93 raised to 2.18 mIU/ml, basal LH 0.57 increased to 1.11 mIU/ml). Free testosterone was 23 pg/ml and DHEA-S was 396 μg/dl, both on substitutive therapy. Hormones of the pituitary-thyroid axis, as well as hGH and IGF-1, all remained within the reference ranges. Plasma ACTH exceeded 1000 pg/ml and morning cortisol was 25.8 nmol/l. Serum autoantibodies to 21-hydroxylase were negative. Atrophic adrenal glands were visualised on computed tomography scans. Hydrocortisone replacement was performed yet. In view of previously published data, fertility in AHC is doubtful. Even after hormonal stimulation only scarce spermatogonia were detectable in testicular biopsies from those patients [6,12].

3. Discussion

Nowadays, autoimmunity is considered the main cause of primary adrenal insufficiency [13]. In the majority of cases, this is a complex disease, resulting from combined influence of genetic and environmental factors. Accordingly, autoimmune adrenal failure is usually diagnosed in adults, with a mean age at clinical presentation above 30 years [13,14]. In contrast, early onset of adrenal insufficiency in the first weeks of life evokes plausible monogenic origin. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency remains the most common cause of salt-wasting crisis in neonates. Infants with AHC are sometimes misdiagnosed with this condition, although serum adrenal steroid profiles in both disorders are fairly different [15]. Accurate distinction is crucial for further management of patients and for genetic counselling as well. A rare autosomal form of AHC has also been reported, being the effect of mutations in NR5A1 gene (chromosome 9q33), which encodes SF-1 receptor. However, these mutations are likely to associate with female phenotype in 46,XY individuals with gonadal dysgenesis [16].

To date, over 100 mutations in the NR0B1 gene have been identified. These are mainly frameshift and nonsense mutations resulting in truncation of the ligand-binding DAX-1 domain. Genetic variability may account for clinical heterogeneity observed among AHC patients [6,7,9,10]. Moreover, disparity in the age of diagnosis and various degree of hormonal deficiency are sometimes observed within a family, which indi-
In healthy boys, peak rise in testosterone levels (at G3/4 Tanner stage) is accompanied by an increase in the mean 24 h hGH serum concentration and correlates with pubertal growth spurt [20]. Studies in individuals with hypogonadotropic hypogonadism revealed amplified spontaneous and stimulated hGH secretion after exogenous testosterone administration [21]. Individuals with AHC are depleted of both adrenal and testicular androgen supply, therefore, their linear growth in this critical period may be impaired. Despite apparently normal hGH and IGF-1 secretion, our patient displayed progressive growth deterioration, which started around 9–10 years of chronological age. Since the introduction of testosterone replacement at the age of 17 years, his growth velocity remarkably improved, and remains in accordance with gradual maturation of the skeleton. The most recent data concerning the proband’s height (182 cm), referred to his current bone age (16 years), situate him above the 75th percentiles. An improvement in BMD is also expected and will require evaluation during future checkups.

In summary, autoimmune destruction remains the major cause of adrenal failure, however, other rare conditions should always be considered. Especially familial cases of early-onset adrenal insufficiency raise strong suspicion of a monogenic dis-

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Table 2
Principal monogenic causes of primary adrenal insufficiency [22,23].

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene involved (chromosome)</th>
<th>Coexisting disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune polyglandular syndrome type 1</td>
<td>AIRE (21q22.3)</td>
<td>Chronic mucocutaneous candidiasis and/or hypoparathyroidism, others autoimmune diseases, enamel hypoplasia, nail dystrophy</td>
</tr>
<tr>
<td>X-linked aldrinoleukodystrophy</td>
<td>ABD1 (Xq28)</td>
<td>Progressive neurologic symptoms of demyelination in brain and spinal cord, hypergonadotropic hypogonadism in males</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-Hydroxylase deficiency</td>
<td>CYP21A2 (6p21.3)</td>
<td>Virilised external genitalia in female infants, pseudo-precocious puberty in both genders, hirsutism in late-onset forms</td>
</tr>
<tr>
<td>11Beta-hydroxylase deficiency</td>
<td>CYP11B1 (8q21)</td>
<td>Virilised genitalia in female infants, pseudo-precocious puberty in both genders, hirsutism in late-onset forms, low-renin hypertension</td>
</tr>
<tr>
<td>3Beta-hydroxysteroid dehydrogenase deficiency</td>
<td>HSD3B2 (1p13.1)</td>
<td>Ambiguous external genitalia in male infants, mild virilisation at puberty in girls</td>
</tr>
<tr>
<td>17Alpha-hydroxylase/17,20-lyase deficiency</td>
<td>CYP17A1 (10q24.3)</td>
<td>Low-renin hypertension, ambiguous genitalia in males, lack of puberty in both sexes</td>
</tr>
<tr>
<td>Cytochrome P450 oxidoreductase deficiency</td>
<td>POR (7q11.2)</td>
<td>Ambiguous genitalia in both sexes, multiple skeletal malformations as in Antley-Bixler syndrome</td>
</tr>
<tr>
<td>Lipoid congenital adrenal hyperplasia</td>
<td>STAR (8p11.2)</td>
<td>Female external genitalia in both genders at birth, hyaline membrane disease in neonates</td>
</tr>
<tr>
<td>Smith-Lemli-Opitz syndrome</td>
<td>DHCGR7 (11q12-q13)</td>
<td>Craniofacial anomalies, developmental delay, multiple malformations (limbs, heart, digestive tract, central nervous and urogenital system)</td>
</tr>
<tr>
<td>Adrenal hypoplasia congenita</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-linked form</td>
<td>NR0B1 (Xp21.3)</td>
<td>Hypogonadotropic hypogonadism in males; may be associated with Duchenne muscular dystrophy and/or glycerol kinase deficiency</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>NR5A1 (9q33)</td>
<td>XY sex reversal</td>
</tr>
<tr>
<td>Kearns-Sayre syndrome</td>
<td>mtDNA</td>
<td>Cerebellar ataxia, external ophtalmoplegia, pigmented retinopathy, cardiac conduction defects, growth failure, diabetes</td>
</tr>
<tr>
<td>Wolman’s disease</td>
<td>LIPA (10q24-q25)</td>
<td>Malabsorption with severe diarrhoea, hepatosplenomegaly, hepatic cirrhosis</td>
</tr>
<tr>
<td>ACTH insensitivity syndromes</td>
<td></td>
<td></td>
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<tr>
<td>Familial glucocorticoid deficiency type 1</td>
<td>MC2R (18p11.2)</td>
<td>Tall stature</td>
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<tr>
<td>Familial glucocorticoid deficiency type 2</td>
<td>MRAP (21q22.1)</td>
<td></td>
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<tr>
<td>Allgrove syndrome (triple “A” syndrome)</td>
<td>AAAS (12q13)</td>
<td>Achalasia, alacrimia, neurologic disturbances</td>
</tr>
</tbody>
</table>

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The Y399X NR0B1 mutation was previously identified in two distant members of a large Scottish family [7,18]. In vitro transfection assays revealed impaired repression of SF-1-dependent transcription in the presence of Y399X variant, which implies that this mutation may reduce DAX-1 ability to silence gene expression in vivo [7,18]. Both affected subjects were diagnosed in their infancy but only one of them was subsequently followed till the age of 35 years, therefore more clinical data are available [18]. Interestingly, despite the presence of the same NR0B1 mutation, there are marked phenotypic differences in comparison to our patient, such as apparent recovery of adrenal function in adolescence and spontaneous puberty with subsequent decline in gonadal function [18]. These observations further support the role of additional factors, which may modify the disease course.

The patient’s history illustrates the crucial role of adequate androgen levels in pubertal growth. The onset of physiological puberty is characterized by an activation of the gonadotrophic axis and subsequent gradual increase in sex steroid secretion. Androgens enable the acquisition of secondary sexual characteristics but also promote somatotropic axis activity [19]. In healthy
ease. Symptoms of concomitant disorders may facilitate the differential diagnosis and guide the investigation of the genetic background (Table 2). Adrenal hypoplasia congenita has not been considered in our patient until several years after initial symptoms, when the complete clinical presentation became evident. Molecular analysis enabled the final diagnosis. Although it does not change therapeutic strategy, an accurate diagnosis allows for genetic counselling in other family members. One of the proband’s sister is disease-free, whereas the other one is now aware of the risk should she give birth to another male child.

**Conflict of interest**

The authors declare that there is no conflict of interest.

**References**


