Bilateral adrenalectomy for severe hypertension in congenital adrenal hyperplasia due to 11β-hydroxylase deficiency: Long term follow-up

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Résumé

La surrénalectomie bilatérale comme option chirurgicale pour le traitement des patients avec hyperplasie congénitale des surrénales (HCS) secondaire au déficit en 21-hydroxylase a été récemment proposée. Il y a cependant peu de données documentées concernant l’efficacité à long terme et les effets secondaires potentiels de ce traitement. Des patients présentant un déficit en 11β-hydroxylase (11βHD) ont été également concernés par cette nouvelle approche thérapeutique.

Objectif. – Décrire notre expérience de la surrénalectomie bilatérale comme traitement de l’hypertension grave chez un patient présentant un déficit en 11βHD et rapporter les résultats et le suivi à long terme (72 mois) après la chirurgie.

Patient et intervention. – Le cas rapporté est celui d’un patient de 22 ans, élevé en tant que garçon et présentant un pseudo-hermaphrodisme féminin secondaire à une insuffisance en 11βHD. Son hypertension est demeurée mal contrôlée par le traitement substitutif et antihypertenseur, l’exposant ainsi à des complications graves. La surrénalectomie bilatérale lui a été proposée.

Résultats. – L’intervention a été suivie de la normalisation immédiate de la pression artérielle. Au cours du suivi, aucune crise d’insuffisance surrénalienne n’a été rapportée grâce à une bonne compliance thérapeutique. Un taux modérément élevé de 11-deoxycortisol a persisté après l’intervention ; il serait dû à la présence de tissu ectopique.

Conclusion. – La surrénalectomie bilatérale est une méthode sûre et efficace pour contrôler l’hypertension artérielle de l’HCS secondaire à un déficit en 11βHD. Le suivi clinique et biochimique à long terme des patients avec HCS traités par surrénalectomie bilatérale est nécessaire.

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Abstract

Context. – Bilateral adrenalectomy has been recently proposed as a surgical treatment option for patients with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. There is however little documented data about the long-term efficiency and potential side effects of this treatment. Patients with 11β-hydroxylase deficiency (11βHD) have been also concerned by this new approach. Objective. – Our objective was to describe our experience with bilateral adrenalectomy as a treatment of severe hypertension in a patient with 11βHD deficiency and to report the long term follow-up (72 months) results after surgery. Patient and Intervention. – A 22-year-old genetically female patient with 11βHD deficiency was raised as a male because of severe pseudohermaphroditism. The patient has been managed by conventional steroid suppressive therapy and anti hypertensive drugs with limited success; hypertension remained uncontrolled and led to severe complications. Bilateral adrenalectomy was offered to him. Results. – The intervention was followed by immediate blood pressure normalization and resulted in remarkable clinical improvement. Good compliance with glucocorticoid and androgen substitutive therapies was noted. However, a high 11-deoxycortisol, presumably due to non-ovarian ectopic adrenal rests was noted 24 months after surgery.

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1. Introduction

Congenital adrenal hyperplasia (CAH) describes a group of inherited autosomal recessive disorders characterized by an enzymatic defect in cortisol (F) biosynthesis, with compensatory increase in corticotropin (ACTH) secretion [1,2].

Steroid 11β-hydroxylation deficiency (steroid 11βHD), the second most common cause of CAH, is related to mutations of the CYP11B1 gene. As in the most frequent steroid 21-hydroxylase deficiency, steroid 11βHD is characterized by an overproduction of adrenal androgens, which leads to a virilization of the female fetus causing ambiguous genitals in the majority of female infants. In the male cases, hyperandrogenism can induce pseudoprecocious puberty [1,3]. Growth is initially accelerated, followed by early epiphyseal closure and short stature in both genders.

Untreated steroid 11βHD-deficient patients have no salt loss. On the contrary, they frequently present low renin hypertension related to deoxycorticosterone overproduction (DOC) and possibly other precursors with mineralocorticoid activity [4]. This hypertension can be severe: left ventricular hypertrophy and retinopathy have been observed and deaths from cerebrovascular accidents have been reported [5].

Steroid 21-hydroxylase deficiency treatment consists of glucocorticoid-suppressive therapy and surgical correction of the ambiguous external genitalia in virilized female patients. Glucocorticoid replacement aims to substitute for cortisol deficiency and to reduce virilization by suppression of ACTH stimulation. Because complete hypothalamic–pituitary–adrenal axis suppression has proven difficult, replacement therapy has found only limited success. Treatment is complicated by the difficulty due to suppressing adrenal androgens with physiologically ranged glucocorticoid doses. Effective ACTH suppression requires physiologically glucocorticoid doses. However, alternating cycles of androgen and glucocorticoid excess in children often leads to an unacceptable degree of hypercortisolism, growth reduction, obesity, virilization, and precocious puberty. In adult life, women may suffer from loss of libido, irregular or absent cycles, and reduced fertility [6].

Steroid 11βHD’s treatment is similar to that of steroid 21-hydroxylase deficiency. It also aims at controlling excessive mineralocorticoid production [2,4]. Therefore, additional antihypertensive drugs may be required to lower blood pressure to the normal range.

Bilateral adrenalectomy treatment has been recently proposed as a surgical treatment option for inadequately controlled severe classic CAH with steroid 21-hydroxylase deficiency [7–13]. It has also been proposed as an alternative treatment modality for adult women presenting the inborn defect in the 21-

hydroxylase gene and who suffer from reduced fertility [14]. The advantages of this therapeutic alternative, the potential shortcoming and its possible practice use for children with the most severe cases of CAH are still being discussed [11,12].

In fact, bilateral adrenalectomy renders a patient Addisonian and increases susceptibility to adrenal crises. This surgical alternative was performed in only two CAH patients with 11βHD [15,16].

In this report, we present our experience in the use of bilateral adrenalectomy as a treatment of severe hypertension in a 22-year-old adult patient with steroid 11βHD, who had been managed with conventional steroid suppressive therapy and antihypertensive drugs with limited success.

2. Case report

The patient was born in 1980 and raised as a male. His case has been reported elsewhere [17]. At age 20, he underwent a renal ultrasonography for a recurrent urinary tract infection. Bilateral adrenal masses were seen and later confirmed by magnetic resonance imaging (MRI). The right adrenal mass approximately 160 mm × 80 mm × 70 mm in size was heterogeneous with posterior calcifications and evidence of hemorrhage. The left adrenal gland measured 60 mm × 50 mm × 40 mm.

The physical examination revealed an intelligent man with a final height of 145 cm, a weight of 45 kg, and a blood pressure of 190/100 mmHg. At initial laboratory tests, serum potassium level was 3.9 mmol/l, sodium was 140 mmol/l, and creatinine was 103 μmol/l. The external genitalia were completely masculinized; the penis was 6 cm in size with a first-degree hypospadias, the testes were not palpable.

Considering his short stature and history of precocious puberty as early as the age of six, detailed endocrinological measurements were performed and showed high levels of 11-deoxycorticisol (S), 17 OH progesterone (17 OHP) and ACTH.

Genitography revealed female internal genital structure. A chromosomal analysis showed a normal 46 XX female karyotype and lead to the diagnosis of CAH due to 11βHD with a pseudohermaphroditism (stage V of Prader).

Fundoscopy showed hypertensive retinopathy requiring laser photocoagulation. Electrocardiogram indicated left ventricular hypertrophy and the echocardiogram showed pronounced concentric ventricular hypertrophy (septum wall: 17–18 mm; posterior wall: 13–16 mm; n = 10 mm) consistent with long uncontrolled hypertension.

A first cerebral and hypothalamic pituitary MRI revealed a normal pituitary gland but demonstrated, on T2-weighted scan, paraventricular areas sequel of stroke. Suppressive therapy with
30 mg hydrocortisone was initiated. Nifedipine, 30 mg daily, was then added because of persistent high-level blood pressure. With this treatment, diastolic blood pressure was chronically around 100–110 mmHg and it proved very difficult to maintain a good control. Therefore, spironolactone 50 mg twice daily was first introduced alone and then combined with methylprednisolone 750 mg daily. Hydrocortisone replacement therapy was increased to 50 mg/day. With this treatment, blood pressure was still over 180/120 mmHg. Despite the frequent monitoring dose adjustments, suppressive treatment was difficult to balance with periods of high blood pressure. On March 2000 serum testosterone radio-immunoassay (RIA) was 2.4 μg/l (normal range less than 0.8 if female and 3–10 if male); plasma 17 OHP (RIA) of 42.6 ng/ml (normal range 0.5–2.4 ng/ml if male and 0.7–1.1 ng/ml if female during the follicular phase of the menstrual cycle) and elevated plasma ACTH on immunoradiometric assay (IRMA) of 97 ng/l (normal range 9–52 ng/l).

A bilateral adrenalectomy was suggested as an alternative treatment, in order to achieve a better blood pressure control, and permit an easier and less intensive medical therapy. The patient volunteered for surgery at age 22. On admission before surgery, his blood pressure was 220/140 mmHg. The patient was normokaliemic (4.2–4.7 mmol/l), and creatinine level was normal.

Investigation on replacement therapy had included morning plasma aldosterone (RIA) on supine position of 37 pg/ml (normal range 10–180 pg/ml). Plasma 17 OHP was 34.6 ng/ml. Plasma 11-deoxycortisol was measured by RIA after separation on a celite column to protect against cross-reactivity of cortisol antisemum with 11-deoxycortisol. Serum 11-deoxycortisol level was elevated: 7865 ng/ml. Testosterone was 3.2 μg/l; FSH (IRMA) 5.4 U/l; LH (IRMA) 4 U/l; and prolactin (IRMA) 10 μg/l (normal less than 20).

On April 2002 he underwent bilateral open adrenalectomy. High levels of blood pressure around 190/110 mmHg continued to be observed on the first postoperative day while medication included hydrocortisone and labelatalol on IV perfusion. On the second postoperative day, oral antihypertensive therapy with nifedipine (20 mg/day), methylprednisolone 500 mg and spironolactone 100 mg/day were reintroduced. This treatment reduced the blood pressure to 120/90 mmHg. Hydrocortisone was tapered to 30 mg/day orally. On the subsequent days, better levels of blood pressure continued to be observed. Antihypertensive drugs were reduced gradually. On the 15th postoperative day all antihypertensive treatments were stopped. Hydrocortisone was maintained to 30 mg/day. The patient did not require mineralocorticoid replacement therapy. Blood pressure remained at 120/80 mmHg. Plasma 11-deoxycortisol level decreased to 53 ng/ml. He was discharged from hospital under androgen substitutive therapy; testosterone heptylate (250 mg for 3 weeks) and the same dose of hydrocortisone. One month later, plasma 11-deoxycortisol level decreased to less than 5 ng/ml. Six months after surgery a new pituitary imaging (CT) showed no abnormalities. Compliance with the substitutive therapy was good and no adrenal crisis was reported.

After repeated psychological evaluations, the patient showed some degree of anxiety due to persisting menstrual bleeding, and still wanted to be considered as a man. Therefore, a bilateral salpingo-oophorectomy and a hysterectomy were performed. The patient was then evaluated at 3-month intervals. He didn’t require mineralocorticoid treatment and serum potassium level remained normal. Eighteen months after the adrenalectomy, a new echocardiogram showed marked reduction of the left ventricular hypertrophy: septum wall 13–18 mm; posterior wall 12–14 mm, left ventricular mass 166 g, left ventricular mass index 112 g/m². Plasma 17 OHP, 11-deoxycortisol were also measured; their values were respectively less than 0.1 and 328 ng/ml. A new MRI showed no adrenal tissue and no ectopic adrenal rests in the abdomen. Six months later, the patient was re-admitted for a new hormonal evaluation; the baseline hormone levels are depicted in Table 1. Forty-eight months after adrenalectomy, blood pressure was still normal. Adrenal scintigraphy using ¹³¹I-norcholesterol imaging showed no tracer uptake while 11-deoxycortisol remained elevated.

**Table 1**

<table>
<thead>
<tr>
<th>Hormonal status of study patient 24, 48 and 72 months after bilateral adrenalectomy.</th>
<th>Postoperative 24 months</th>
<th>48 months</th>
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<td>8 h</td>
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<td>ACTH (ng/l) (N: 9–52)</td>
<td>244</td>
<td>86</td>
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<td>17 OHP (ng/ml) (N: 0.7–1.1)</td>
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<td>11-deoxycortisol (ng/ml) (N &lt; 10)</td>
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<td>11-deoxycortistosterone (pg/ml) (N: 40–200)</td>
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OHP: OH progesterone. The patient received hydrocortisone 30 mg/day; 20 mg at 8 h and 10 mg at 20 h. Samples at 8 h and 20 h were taken before hydrocortisone administration.
Active renine (RIA) (normal range 0.32–1.22 pmol/l in supine position and 0.04–0.6 in upright position) was 0.19 pmol/l in supine position and 0.22 pmol/l in upright position. Seventy-two months after, blood pressure, 17 OHP was still normal while plasma 11-desoxycorticosterone (RIA) was slightly elevated 238 pg/ml (normal range 40–200 pg/ml).

2.1. DNA amplification and sequencing

Peripheral blood samples of the index case were obtained with informed consent. Six relatives (mother, father, one of his aunts, and three sisters) accepted to give blood samples, which allowed performing a familial genetic analysis. All were anatomically normal. The DNA were amplified by PCR with CYP11B1-specific primers and sequenced on an automated sequencer (PR Morel Y., Lyon, France). It was determined that the propositus was homozygous for the G379 V mutation, which was responsible of the total loss of 11βHD activity.

2.2. Pathologic findings

On macroscopic examination, both adrenal glands were dark and brown; numerous nodules deformed their usual shape. The right adrenal gland measured 80 mm × 60.5 mm × 30 mm, a hemorrhagic cyst of 35 mm was found within. The left adrenal gland measured 60 mm × 40 mm × 20 mm (Fig. 1).

Microscopic examination showed diffuse and nodular hyperplastic cells of the zona fasciculata in both adrenals. The cells had a dark green cytoplasm containing lipofuscin pigment. The adrenals also contained scattered nests of cells with compact eosinophilic cytoplasm. Abundant lymphocytic infiltration was noted between and within hyperplastic cortical nodules. Numerous intermixed lobules composed of adipose tissue and haematopoietic foci separated the cortical cells (Fig. 2). A calcified large fibrohyaline capsule delimited the hemorrhagic cyst noted in the right adrenal gland. The adjoining zona glomerulosa observed in the periphery of the adrenal was thin but normal.

The removed ovaries were multicystic and showed no adrenal rests on histological examination.

3. Discussion

The case reported here, illustrates the difficulties with suppressive therapy and the potential interest of bilateral adrenalectomy that allowed effective treatment of severe hypertension in an adult with CAH due to 11βHD deficiency. Bilateral adrenalectomy treatment has been recently proposed as a surgical treatment option for severe classic CAH due to 21-hydroxylase deficiency [8], and within a short period of time, this procedure has been adopted by numerous medical centers [13,18]. As steroid 11βHD is relatively rare, bilateral adrenalectomy for patients with this steroid deficiency has been reported in only two cases [15,16]. There are several published cases that document problems with patients treated for steroid 11βHD, including advanced puberty, short final height and cardiovascular complications in both sexes [17,19]. 11βHD-deficient patients are precisely those who may benefit more from adrenalectomy, mainly difficult-to-control cases that illustrate the problem with suppressive therapy and who also develop severe hypertension. 11βHD was diagnosed too late and in later life in this patient’s case. The very short final stature is the result of androgen precocious bone maturation in this pseudohermaphroditic patient raised as a male. Pronounced left ventricular hypertrophy, retinopathy and cerebrovascular accident are extremely severe complications due to untreated hypertension. Before surgery the patient’s poor compliance is not to be excluded. Suppressive treatment might have been dropped because it induced regular menses and a lesser degree of virilization. We also believe that the macronodular hyperplasia that has developed during the years of unsuppressed ACTH secretion in both adrenals and the calcifications after the spontaneous hemorrhage probably were the cause of the suppressive treatment’s inefficiency. As a result, the patient developed pronounced levels of hypertension. It must...
be noted, however, that after adrenalectomy the patient complied totally with the substitutive therapy and during the period of follow-up no adrenal crises were observed.

The only document that mentions the short-term course of blood pressure levels after bilateral adrenalectomy in case of 11βHD is that of Chabre et al. [15]. In that article, antihypertensive medications continued to be prescribed after surgery and were stopped only one year later. But what is interesting to mention in our case is the rapid normalization of the blood pressure levels within 15 days after surgery. Postoperative course was marked by 11-deoxycortisol levels normalisation, indicating no small secreting rests of adrenocortical tissue. Indeed, normal children may present multiple locations of adrenal ectopic tissue from the diaphragm to the pelvis [20,21]. Ectopic adrenal tissue has been discovered in testes in males with CAH [22–24] and has been found in ovaries in females [25,26]. In our case the presence of an ectopic adrenal tissue in the ovaries was unlikely because of the persistence of normal levels of blood pressure and levels of 11-deoxycortisol measurements before oophorectomy. This was later confirmed by the pathologic study of the removed ovaries.

Long-term follow-up confirmed the normalization of blood pressure by surgery. However, despite persistent normal 17 OHP level, a marked elevation of 11-deoxycortisol level has been observed. Presumably this circulating steroid came from an adrenal rest, not shown by MRI and by the adrenal scintigraphy. ACTH levels were also elevated in early morning but showed a decrease during the rest of the day.

In the case reported by Chabre et al., despite the excellent clinical result, the levels of 11-deoxycortisol and DOC remained above normal after surgery, indicating small rests of secreting adrenocortical tissue [15].

This patient with the classical form of 11βHD has a mutation that totally destroys the expression or the activity of CYP11B1. In steroid 21-hydroxylase deficiency, it has been advocated that female patients with deleted or completely non-functional genes are the first to be considered for adrenalectomy. [9,18].

No abnormalities were found in the pituitary imaging before medical treatment despite years of undiagnosed disease. After adrenalectomy, imagery remained normal.

The other interesting findings in this case were the pathologic features of both adrenals, which showed myelolipomatous foci. The latter may explain the spontaneous hemorrhage observed in the right adrenal gland [27,28]. So far, about 12 cases of myelolipomas and CAH have been reported [29]. All the cases described were due to 21-hydroxylase deficiency and only two cases were associated to 17-hydroxylase deficiency [30,31]. All those patients were either untreated or had discontinued long-term medications; this setting suggests excessive long-term ACTH secretion, causing hormonal stimuli in myelolipomatous changes.

Hence, bilateral adrenalectomy was a successful treatment for this patient with 11βHD; this procedure normalized blood pressure levels. A similar approach should be considered especially with difficult to control patients who present severe hypertensive complications. However, adrenalectomized patients will require lifetime close medical supervision and the present study reinforces the need for steroid precursor’s measurements. This is particularly important because many patients may develop adrenal rests that may nullify the beneficial effects of adrenalectomy.

References