Scientific Research Publishing

Open Journal of Endocrine and Metabolic Diseases, 2020, 10, 18-23
https://www.scirp.org/journal/ojemd
ISSN Online: 2165-7432
ISSN Print: 2165-7424

Bilateral Macronodular Adrenal Hyperplasia

Annelie Kérékou Hodé*, Hubert Dédjan

Endocrinology, Metabolism and Nutrition Department, CNHU-HKM, Cotonou, Bénin
Email: *kerekouannelie@yahoo.fr

How to cite this paper: Hodé, A.K. and Dédjan, H. (2020) Bilateral Macronodular Adrenal Hyperplasia. *Open Journal of Endocrine and Metabolic Diseases*, **10**, 18-23.
https://doi.org/10.4236/ojemd.2020.102003

Received: January 25, 2020
Accepted: February 24, 2020
Published: February 27, 2020

Abstract

Cushing's syndrome is the set of clinical manifestations secondary to a chronic excess of glucocorticoids. Bilateral macronodular adrenal hyperplasia with subclinical cortisol secretion is the most common, but its prevalence remains unknown. We describe a case of bilateral macronodular adrenal hyperplasia. This is a 36-year-old female patient who had been consulting for secondary amenorrhea and developing asthenia for 4 months. The clinical examination noted an overweight patient with high blood pressure, facio-trunk obesity, hirsutism and purple stretch marks in the abdomen and thighs. Biologically, hypokalemia at 2.9 meq/l (3.5 - 5.4), normal calcemia at 90 mg/l (85 - 104), fasting blood sugar was 0.84 g/l (0.7 - 1), the tests for minute, low and high dexamethasone suppression test revealed insufficient suppression of cortisol. The cortisoluria collected from the second day to the third day of the high dexamethasone suppression test was at 186 µg/24 h (<60), the ACTH (Pg/ml) was undetectable (6.4 - 49.8). The diagnosis of an independent adrenocorticotrophin (ACTH) Cushing syndrome was made and the adrenal CT scan revealed bilateral macronodular hyperplasia. A bilateral adrenalectomy was performed and a complete remission of Cushing syndrome was achieved. We prescribed to her, hydrocortisone 20 mg/day and alpha-fludrocortisone 25 to 50 µg/day, This medical observation showed that macro-nodular adrenal hyperplasia with overt Cushing syndrome can occur in the third decade of life. Bilateral adrenalectomy has resulted in a complete cure for Cushing's syndrome, but may be fraught with complications.

Keywords

Hyperplasia, Macronodular, Adrenal, Cushing's Syndrome, Adrenalectomy, Dexamethasone

1. Introduction

Cushing's syndrome is the set of clinical manifestations secondary to a chronic

excess of glucocorticoids. Its origin may be dependent on the adrenocorticotropic hormone (ACTH) in 80% of cases or independent of adrenocorticotrophin ACTH, therefore adrenal in 20% of cases. The adrenal origin can be bilateral in less than 2% of cases and in this case it can be bilateral macronodular or micronodular hyperplasia of the adrenals [1] [2] [3] [4]. Bilateral macronodular hyperplasia (BMAH) with subclinical cortisol secretion is the most common, but its prevalence remains unknown [5] [6] [7]. We describe a case of bilateral macronodular adrenal hyperplasia.

2. Observation

A 36-year-old patient who has been consulting for secondary amenorrhea and asthenia evolving since four months.

At the clinical examination, we observe an apyretic and asthenic patient, a body mass index (BMI) at 26.44 kilos/m^2, high blood pressure at 160/100 mmHg, pulse at 80 beats/minute, facio-truncal obesity with a lunar facies, the roots of the pelvic limbs are slender, a hirsutism in the chin and cheeks evaluated at 7/36 according to the score of Ferriman and Galway, purple stretch marks on the abdomen and thighs, thin and ecchymotic skin.

Laboratory test revealed normal blood count with a hemoglobin level of 13 g/dl (12 - 16), leukocytes at 5 G/l (4 - 8 G/l), hypokalemia at 2.9 meq/l (3.5 - 5.4), the normal calcemia at 90 mg/l (85 - 104), the fasting blood sugar was at 0.84 g/l (0.7 - 1), the overnight dexamethasone suppression test revealed insufficient suppression of cortisol with a cortisolemia at 24.5 µg/100ml (5.6 - 15.2), the low dexamethasone suppression test (0.5 mg/6hours for 48 hours) revealed insufficient suppression of cortisol with a cortisolemia at 18.5 µg/100ml (5.6 - 15.2), the high dexamethasone suppression test (8 mg/day for 48 hours) revealed an insufficient suppression of cortisol with a cortisolemia at 24.5 µg/100ml (5.6 - 15.2) and the cortisoluria collected from the second day to third day was 186 µg/24 h (<60), ACTH (Pg/ml) was undetectable (6.4 - 49.8); TSH = 0.72 µIU/ml (0.25 - 4), prolactinemia at 17.6 ng/ml (<20).

The diagnosis of an independent ACTH Cushing syndrome was retained and the adrenal CT scan revealed bilateral macronodular hyperplasia with adrenals that measured on average 8 cm in diameter and descended to the renal hilum. Iodocholesterol scintigraphy was not performed. Bone densitometry was not performed. The medical preparation for surgery had consisted of the administration of nizoral (ketoconazole) 600 mg/day but stopped a week later before the occurrence of significant hepatic cytolysis with transaminases increased to more than four times the normal upper. She was then put on OP'DDD (mitotane) 3 g/day for a month later combined with orimetene (aminogluthetimide) 1000 mg/day for a week. The medical preparation was stopped two days before surgery. Bilateral laparoscopic adrenalectomy was retained but converted to laparotomy intraoperatively before rupture of the splenic pedicle complicated by profuse hemorrhage. This first intervention was limited to the left adrenalectomy and a caudal

splenopancreatectomy. Secondly, the right adrenalectomy was performed without incident. An anatomopathological examination of the operating parts was in favor of nodular hyperplasia of the adrenal cortex. The 8 h postoperative cortisol level is less than 1 µg/100ml (5.6 - 15.2) (Table 1). It has been brought to life on hydrocortisone 20 mg/day and on alpha-fludrocortisone 25 to 50 µg/day depending on serum potassium and blood pressure. She had an addissionnary card and was educated to double the doses of hydrocortisone in case of fever, infection and trauma. The evolution was marked by a complete remission of Cushing syndrome for twenty four years.

3. Discussion

Our patient's age was lower than that described in the literature. Indeed, Cushing syndrome secondary to bilateral macronodular adrenal hyperplasia is diagnosed between the fifth and sixth decade of life, but a careful history often revealed a diagnostic delay of 7.8 years [8]. Recent publications have shown a female predominance with an M/F sex ratio of 1:2—3 in sporadic cases and parity in family cases [3] [4] [6] [9] [10] [11] [12] [13].

Physiologically, ACTH by binding in the fasciculated zone on its receptor coupled to protein G (melanocortin type 2), induces an enzymatic cascade leading to the synthesis of cortisol.

In BMAH, the synthesis of cortisol is dependent on illegitimate receptors coupled to the protein G. These latter under the influence of several hormones such as the gastric inhibitory polypeptide (GIP), catecholamines, vasopressin, glucagon, serotonin, angiotensin 2, luteinizing Hormone (LH) or human chorionic gonadotrophin (HCG) stimulate cortisol synthesis [14]. In BMAH with Cushing's syndrome, 80% of patients have an illegitimate receptor and 55% of patients have several [9] [10] [15]. These illegitimate receptors are responsible for the formation of adrenal

Table 1. Laboratory tests result.

Tests	Value	Normal Value
hemoglogbin	13 g/dl	12 - 16 g/dl
leukocytes	5 G/l	4 - 8 G/l
kalemia	2.9 meq/l	3.5 - 5.4 meq/l
calcemia	90 mg/l	85 - 104 mg/l
glycemia	0.84 g/l	0.7 - 1 g/l
Cortisolemia after overnight dexamethasone suppression	24.5 µg/100ml	5.6 - 15.2 µg/100ml
Cortisolemia after low dexamethasone suppression	18.5 µg/100ml	5.6 - 15.2 µg/100ml
Cortisolemia after high dexamethasone suppression	24.5 µg/100ml	5.6 - 15.2 µg/100ml
Cortisoluria after high dexamethasone suppression	186 µg/42h	<60 µg/24 h
ACTH	undetectable	(6.4 - 49.8)
TSH	0.72 µUI/ml	0.25 - 4 µUI/ml
Prolactinemia	17.6 ng/ml	<20 ng/ml

macronodules [3]. Autocrine synthesis by the hyperplastic adrenals of ACTH, the regulation of which does not depend on the corticotropin releasing hormone (CRH), has also been described in recent studies [13].

In the molecular test, several genes are linked to the occurrence of BMAH. The mutation of the armadillo repeat containing 5 gene (ARMC5) is found in 50% of BMAH [11] [16]. It is a tumor suppressor gene. The mutation of the following genes has also been described: multiple endocrine neoplasia gene (MEN1), adenomatous polyposis coli gene (APC), stimulatory G-Protein alpha subunit gene (GNAS), melanocortin 2 receptor gene (MC2R), 11 phosphodiesterase isoform gene (PDE11A), familial adenomatous polyposis gene (FAP) [4].

As a prelude to surgery, steroidogenesis inhibitors such as ketoconazole, mitotane, aminogluthetimide, metopirone,etomidate and glucocorticoid antagonists (mifepristone) could be used [4] [17]. Likewise, certain illegitimate receptors may be the subject of targeted therapies. Beta blockers, analogs of the gonadotropin releasing hormone (leuprolide acetate), analogues of somatostatin (octreotide LAR, pasireotide) could be used [4] [14].

Surgical treatment for BMAH depends on the severity of the hypercortisolism and their complications. When cortisoluria/24 h is greater than 2 times the normal upper value, a bilateral laparoscopic adrenalectomy is indicated [4] [10] [18] [19]. The constraint of bilateral adrenalectomy is the lifelong substitution of hydrocortisone and mineralocorticoid. De Venanzi *et al.* did not record deaths in 45 patients suffering from BMAH and who have been treated by bilateral adrenalectomy [4]. Bilateral adrenalectomy in all-cause Cushing syndrome is responsible for 17% mortality according to Ritzel *et al.* [18]. In our case, the conversion of laparoscopic adrenalectomy to laparotomy occurred after the rupture of the splenic pedicle, which testifies that this surgery is not without complications.

When cortisoluria is less than twice the normal value, a unilateral adrenalectomy of the largest adrenal gland or the one which has the most fixed marked iodocholesterol is indicated [10]. Sheikh Ahmad et al analyzed 71 cases of unilateral adrenalectomy performed for bilateral macronodular adrenal hyperplasia. They found a remission (improvement of clinical signs, sufficient cortisol minute braking test, normal cortisoluria/24 hour) of 94.4% of Cushing syndrome over a period of 61.1 ± 41.7 months. Relapse in 19% of cases was observed [20].

4. Conclusion

This medical observation has shown that macro-nodular adrenal hyperplasia with patent Cushing syndrome can occur in the third decade of life. Bilateral adrenalectomy has resulted in a complete cure for Cushing syndrome, but it can be punctuated by complications.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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