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Original article

An observational study on adrenal insufficiency in a French tertiary centre: Real life versus theory

Étude observationnelle sur l'insuffisance surrénalienne dans un centre specialisé : de la théorie à la pratique

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Abstract

Background. – Patients suffering from adrenal insufficiency, whether primary (PAI) or secondary (SAI) have an increased mortality risk and increased morbidity. There are no guidelines on hydrocortisone replacement therapy and little is known on patients' management in current practice. We described patients' profiles and treatment in a tertiary referral centre. *Methods.* – Data were collected retrospectively from medical charts. PAI and SAI patients were described and compared. *Results.* – Two hundred and one patients (79 PAI + 122 SAI) were included. They had a mean duration of disease of 11.2 years. Main causes of PAI were autoimmune diseases (31%) and adrenalectomy (26%). SAI was caused primarily by pituitary tumors (61%) and irradiation (20%). Mean dose of daily hydrocortisone (HC) was 27.5 and 19.9 mg/day in PAI and SAI patients respectively, with a majority of patients dividing the dose into 2 intakes (46.8 and 72.2% in PAI and SAI groups, respectively). SAI patients exhibited more cardiovascular risk factors than PAI patients. The HC daily dose was slightly higher in patients with dyslipidemia (in both PAI and SAI groups) and in those with high blood pressure (in the SAI group only). One third of patients were out of work, due to unemployment, sick leaves, or disability. *Conclusions.* – The management of AI is far from standardized, and individual tailorization is difficult with currently available means of treatment. Under- and overdose of hydrocortisone likely leads to complications, and altered quality of life reflected by a high rate of "out of work" patients.

Keywords: Primary adrenal insufficiency; Secondary adrenal insufficiency; Hydrocortisone replacement therapy; Dyslipidemia; High blood pressure; Occupational status

Résumé

Introduction. – Les patients porteurs d'une insuffisance surrénalienne primaire (ISP) ou secondaire (ISS) présentent une surmorbidité et une surmortalité. Il n'existe pas de consensus sur le schéma optimal d'hydrocortisone, et peu de données sur le traitement substitutif dans la vraie vie. *Méthodes.* – Nous rapportons ici les données épidémiologiques, cliniques et thérapeutiques concernant les patients suivis dans notre centre pour une ISP ou une ISS. Les données ont été recueillies rétrospectivement, et comparées en fonction de l'origine (primaire ou secondaire) de l'insuffisance surrénalienne. *Resultats.* – Deux cent un patients (79 avec ISP et 122 avec ISS) ont été inclus. La durée moyenne de suivi par rapport au diagnostic était de 11,2 ans. L'ISP était principalement liée à une autoimmunité (31 %) ou à une surrénalectomie bilatérale (26 %). L'ISS était principalement liée à des tumeurs hypophysaires (61 %) et à la radiothérapie hypophysaire (20 %). La dose moyenne d'hydrocortisone était de 27,5 (ISP) et 19,9 mg/jour (ISS). La majorité des patients prenaient leur dose en 2 prises (46,8 % dans l'ISP, 72,2 % dans l'ISS). Les patients avec ISS présentaient plus de facteurs de risque cardiovasculaires que les patients avec ISP. La dose d'hydrocortisone était plus élevée chez les patients avec dyslipidémie et avec HTA. Un tiers des patients ne travaillaient pas à la dernière évaluation.

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Conclusions. – La prise en charge de l'insuffisance surrénalienne n'est pas standardisée, et l'individualisation du traitement est complexe. Le sous- ou sur-dosage en hydrocortisone conduit probablement à une altération de la qualité de vie, reflétée par le taux important d'inactivité au sein de notre population.

Mots clés : Insuffisance surrénalienne primiare ; Insuffisance surrénalienne secondaire ; Hydrocortisone ; Dyslipidemia ; Hypertension artérielle

1. Background

Adrenal insufficiency (AI) can result from lesions of the adrenal glands (primary AI, including Addison disease) or from insufficient ACTH secretion by the pituitary gland (secondary AI). Both are rare conditions. However, the incidence of primary AI (PAI) has increased over the last decades [1] and its prevalence ranges from 93 to 140/million [2]. Secondary AI (SAI) prevalence was estimated at 150 to 280/million [2] but the disease is probably under diagnosed and might concern up to 400 individuals/million [3]. The prognosis of the disease was dramatically improved when the live-saving glucocorticoid replacement therapy was introduced more than 60 years ago. Despite this outstanding progress, mortality rates remain higher than those of the general population in both Addison disease [4,5], especially in younger and male patients [6] and SAI [7,8], although in the latter, many confounding factors cannot be excluded, namely other hormone deficiencies.

Patients with AI also have an increased risk of morbidity: adrenal crisis [9], impaired health-related subjective health status and quality of life [10,11], poor metabolic profile [12] and reduction of bone mineral density (BMD) [13]. These data suggest that hormone replacement therapy in these patients is not optimal.

Actually, some experts' opinions have been published [14], but there is no consensus on the practical modalities of treatment (total daily dose, number and distribution of intakes), except for the subgroup of patients with congenital adrenal hyperplasia [15], and little is known on the management of AI patients in routine practice. We showed in a previous study that, in a cohort of 50 patients (20 PAI and 30 SAI) treated in one centre, up to 13 different dosing regimens were used [16].

We reviewed the medical records of patients with PAI or SAI treated in our department to describe their characteristics and treatment, to compare both populations, and to try and find factors associated with AI complications, such as HC dose. We showed primarily that PAI and SAI subjects differ in many ways, in particular metabolic profiles and HC daily dose, but a relationship between this daily dose and complications could not be clearly established. From these data, we aimed to discuss main issues in the management of AI patients.

2. Methods

The study was conducted in a single centre, namely the Department of Endocrinology and Metabolic Diseases in La Timone Hospital, Marseille, France. We performed a comprehensive search in the hospital database to identify all patients treated for AI diagnosed or hypopituitarism from January 2000 to June 2013. From these medical charts, we selected those of patients with a confirmed diagnosis of PAI or SAI. All patients had given informed consent for the use of anonymous personal data extracted from their medical records for scientific or epidemiological purposes as approved by the Internal Review Board of our institution. Primary adrenal insufficiency was defined by 08:00 am cortisol level inferior to 360 nmol/L, and inferior to 550 nmol/L after 250 μg synacthen stimulation test, associated with increased ACTH levels. Secondary adrenal insufficiency was defined by cortisol level inferior to 360 nmol/L, and inferior to 550 nmol/L after insulin induced hypoglycemia (with blood glucose level < 0.3 g/L), associated with low or normal ACTH level. Insulin induced hypoglycemia was not performed when cortisol level was inferior to 100 nmol/L at 08:00 am, and associated with at least one other pituitary hormone deficiency. Other pituitary deficiencies were defined as follows: gonadotroph deficiency was defined by low plasma testosterone with non elevated gonadotrophin levels in men, amenorrhoea with low plasma estradiol and low or normal gonadotrophins in non-menopausal women, and a lack of increased gonadotrophins in post-menopausal women. Somatotroph deficiency was defined by subnormal response of GH to an insulin tolerance test (peak below 3 ng/mL). The diagnosis of thyrotroph deficiency was based on low free T4 level with normal or diminished TSH.

The following data, reported at the last visit, were collected and analyzed: age, sex, duration and etiology of the disease, body mass index (BMI), systolic (SBP) and diastolic (DBP) blood pressure, plasma lipid levels, HbA_{1c}, associated deficiencies (diabetes insipidus, panhypopituitarism) and treatment with fludrocortisone or levothyroxine, hydrocortisone (HC) dosing regimen, comorbidities (diabetes mellitus, dyslipidemia, high blood pressure defined as blood pressure superior to 140 and/or 90 mm Hg, osteoporosis, depression), and occupational status.

2.1. Statistics

Quantitative variables were expressed as mean, standard, median and range; categorical variables were expressed as counts and percentages. Comparisons between PAI and SAI subgroups, and between comorbidity subgroups were performed using Student *t*-test or Chi^2 test as appropriate. Correlation analysis was performed by linear regression analysis. All statistical tests were performed with XLStats v2013.4.05 (Paris, France). All tests were bilateral with a level of significance set at 0.05.