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Original article

A monocentric experience of growth hormone replacement therapy in adult patients

Traitement substitutif par hormone de croissance chez l'adulte : une expérience monocentrique

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Abstract

Objectives. – To describe the results of growth hormone (GH) therapy in adult GH-deficient patients treated in a tertiary referral center, with a focus on quality of life and adherence. *Patients and methods.* – Retrospective study of patients followed over a total period of 11 years. Quality of life (QOL) was assessed by the QOL-Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) score and adherence to treatment was measured by a specific questionnaire. Clinical, biological, body composition and bone mineralization parameters were also analyzed. *Results.* – Data from 81 patients were analyzed. After a median treatment duration of 7 years, 2/3 of patients reported improved QOL (mean decrease of AGHDA score of 3.0 points, $P < 0.001$). A trend towards more frequent improvement was observed in middle-aged patients, women, childhood-onset GHD, and in patients with initially more impaired QOL. More than 60% of the patients reported continuing treatment without interruption. Seventy percent declared good adherence (≤ 2 missed injections/month). A majority reported enhanced well-being. Additionally, we observed a mean weight increase of 2 kg, while fat mass, waist/hip circumference ratio and lipids were unchanged. Bone mineral density was significantly increased at lumbar spine and femoral neck. *Conclusion.* – Our study confirmed a sustained improvement in quality of life and showed that majority of patients were still on GH treatment after a median duration of 7 years.

Keywords: Growth hormone deficiency; Growth hormone therapy; Adult patients; Quality of life; Adherence to treatment

Résumé

Objectif. – Décrire les résultats du traitement par hormone de croissance (GH) chez des patients adultes déficitaires en GH, traités dans un centre de référence, en particulier les effets sur la qualité de vie et l'adhésion au traitement. *Patients et méthodes.* – Étude rétrospective portant sur des patients suivis sur une période de 11 ans. La qualité de vie (QOL) a été évaluée par le score de l'échelle QOL-Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) et l'adhésion a été mesurée par un questionnaire spécifique. Nous avons aussi recueilli les données sur les paramètres cliniques, biologiques, la masse grasse et la minéralisation osseuse. *Résultats.* – Les données de 81 patients ont été analysées. Après une durée médiane de traitement de 7 ans, les deux tiers des patients ont rapporté une amélioration significative de la QOL (réduction moyenne de 3 points du score AGHDA, $p < 0{,}001$), plus fréquente (bien que non significativement) chez les patients d'âge moyen, les femmes, les patients ayant eu un GHD dans l'enfance et chez ceux ayant une QOL initiale plus altérée. Plus de 60 % des patients disaient poursuivre leur traitement sans interruption. Soixante-dix pour cent déclaraient une bonne adhésion (2 injections manquées ou moins/mois) et une majorité rapportaient une amélioration du bien être. Le poids moyen a augmenté de 2 kg alors que la masse grasse, le rapport tour de taille/tour de hanche et le bilan lipidique n'ont pas changé. La densité minérale osseuse a augmenté de façon significative au niveau du rachis et du col fémoral.

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Conclusion. – Notre étude confirme la persistance de l'amélioration de la QOL au long cours et a montré que la majorité des patients étaient toujours sous traitement après une durée médiane de 7 ans.

Mots clés : Déficit en hormone de croissance ; Traitement par hormone de croissance ; Adultes ; Qualité de vie ; Adhésion au traitement

1. Introduction

Growth hormone (GH) replacement therapy has been only used in children for decades, aiming exclusively at improving growth. Yet, GH deficiency (GHD) in adults is not rare, since the somatotropic cells are the most frequently affected in case of pituitary disease, and it is associated with many complications due to the pleiotropic effects of GH: modifications of body composition with increased fat mass, increased cardiovascular risk, decreased bone mineral density (BMD), impaired quality of life and probably increased mortality [1]. GH therapy in adults was licensed in Europe in the late 1990s and Health Authorities approved its reimbursement in 2003 in France. Guidelines for diagnosis and treatment have been issued and updated according to most recent publications [2,3]. The benefits of GH supplementation were demonstrated in several studies, with regard to quality of life, body composition, muscle strength, or BMD while effects on lipid profile, cardiovascular risk or mortality are more controversial [1,4–7]. However, most of these studies have a short follow-up period and cannot conclude on the persistence of benefits over time. Moreover, in chronic diseases with insidious complications and unspectacular treatment effects, real life management is probably far from that described in clinical trials. How many patients continue this supposedly lifelong treatment? For how many years? How adherent are they? Which benefits can be expected in daily practice? These questions are poorly documented and long-term follow-up is rarely reported. The objectives of our study were to describe a cohort of adult GHD patients treated in a tertiary referral center, focusing on quality of life, evaluated by the AGHDA questionnaire, patients' satisfaction and long-term adherence to therapy.

2. Patients and methods

We identified all adult GHD (AGHD) patients (16 years of age or above) treated with GH in the department of endocrinology, diabetes and metabolic diseases of the Hôpital de la Timone in Marseille. After an interim analysis in 2008 (data not shown), data were extracted from the medical files in 2012. The following information was reported: general characteristics of patients and disease [age, sex, diagnostic tests, age at diagnosis, etiology of GHD, etiological treatment (surgery, irradiation), other pituitary deficiencies), GH treatment (childhood or adult-onset, treatment duration in adulthood, initial and current dose, initial and subsequent IGF-1 levels), clinical examination (weight, body mass index, waist and hip circumference), paraclinical examination (body composition assessed by dual-energy X-ray absorptiometry (DEXA) or impedancemetry, serum triglycerides levels, HbA_{1c}, BMD, myocardial function estimated by left ventricular ejection fraction], quality of life evaluated by the AGHDA questionnaire, with lower scores reflecting better QOL. All this information is, in principle, recorded in routine practice since in France, the reimbursement of GH in adults had been conditioned on the provision of such data regarding treatment outcomes. For each parameter, we retrieved initial and last available values at the time of medical file examination. In addition, we investigated the adherence to treatment, using a home-made questionnaire comprising the questions on improvement of self-perceived health status, missing injections, treatment interruptions, and reasons for treatment discontinuation if appropriate. These questionnaires were sent to the patients along with a prepaid envelope for return.

These data were described using means, standard deviations, medians and ranges for quantitative variables, counts and percentages for categorical variables. Statistical tests used for comparisons were Chi^2 test or Fisher exact test for qualitative parameters and Student *t*-test or paired-samples *t*-test for quantitative parameters. All comparisons were bilateral, with a significance *P* value set up at 0.05. Statistical analysis was performed with the SPSS for Windows software, version 17.0.

3. Results

Main characteristics of the cohort ($n = 81$) are summarized in Table 1. Mean age at diagnosis was around 29 years. The most common etiology of GHD was pituitary tumors or craniopharyngioma. Among adenomas, the most frequent were non-functioning or gonadotroph adenomas ($n = 10$). Among other causes, the most frequent were Sheehan syndrome (8), pituitary stalk interruption syndrome (6), congenital GHD (5), germinoma (5), medulloblastoma (4), glioma (3), and Rathke's cleft cyst (3). Insulin tolerance test was by far the main diagnostic tool (76%) and GH peaks were below 10 UI/mL in all cases. Other pituitary deficiencies were associated in most cases, concerning mainly the thyrotroph axis.

For patients with both initial and last values available, mean IGF-1 levels increased from 101 ± 76 to 182 ± 77, $P < 0.001$. Among 36 patients with initial abnormal values, IGF-1 normalized in 29 (81%) and remained abnormal in 7 (19%). Time to IGF-1 normalization was 3.8 ± 2.1 months. Mean GH dose at the last visit was slightly higher in women (0.56) than in men (0.47).

AGHDA questionnaires from 67 (83%) patients could be analyzed. The questionnaire was filled 3 ± 6 and 45 ± 28 months after treatment initiation for the first and last evaluations, respectively. Mean and median AGHDA scores at baseline were 10.3 ± 6.6 and 12 (0–25), respectively. At last examination,