An update on diagnosis and treatment of adult growth hormone deficiency

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Adult growth hormone deficiency (AGHD) is nowadays recognized as a distinct clinical entity and replacement therapy has become a standard practice. The benefits of GH treatment seem to outweigh its potential risks but issues concerning long term efficacy and safety are still a subject of debate. More research is needed in some key areas and it remains essential to monitor patients by means of longitudinal surveillance studies.

Mise à jour sur le diagnostic et le traitement de la déficience en hormone de croissance chez l'adulte

La déficience en hormone de croissance de l'adulte (AGHD) est reconnue aujourd'hui comme un syndrome clinique à part entière et son traitement est devenu une pratique courante. Les bénéfices du traitement l'emportent sur les risques potentiels mais certains sujets concernant l'efficacité du traitement à long- terme et la sécurité restent débattus. Dans certains domaines clés, de nouvelles études sont nécessaires et une surveillance longitudinale des patients traités par hormone de croissance est indispensable.

MOTS-CLÉS

Déficience en Hormone de croissance, insuffisance antéhypophysaire, adultes avec déficit en GH

INTRODUCTION

The isolation and purification of cadaveric pituitary derived growth hormone (GH) occurred in the late 50's (1). In 1959 Raben reported the results of the first trial showing the effects of human GH on growth (2). During the two next decades GH was used primarily for the treatment of childhood growth retardation and its use was restricted by the limited supply of the pituitary-extracted hormone. A valid radioimmunoassay for detection of plasma GH was published in 1963, which identified significant amounts of circulating GH in healthy adults, thereby supporting the idea of a meaningful biological role (3). After the withdrawal of the pituitary extracted native hormone in 1985, following alarming reports of several cases of Creutzfeldt-Jakob disease (4), the introduction of recombinant human GH (rhGH) in 1985 provided an opportunity for further studies of its effects in adults. The first double-blind, randomized placebo controlled trials investigating the effects of GH in adults were completed in 1989 (5,6) and gave the impetus to a huge scientific craze leading to a plethora of publications on a new syndrome called 'Adult Growth Hormone Deficiency' (AGHD).The rational use of GH as replacement therapy in the adult was thus progressively established and today AGHD is universally recognized as a true clinical syndrome and its treatment has become standard practice (7).

Although rhGH has been used for almost 30 years and the benefits of treatment seem to outweight its potential risks, issues concerning long term efficacy and safety are still a subject of debate. With this in mind we will discuss here the main aspects of AGHD 25 years after its first use in our country and try to answer when and why it is still worth to treat adults with this GHD syndrome.

KEY WORDS ▶ Growth Hormone Deficiency, Hypopituitarism, GH deficient adults

AETIOLOGY

Growth hormone deficiency (GHD) can develop due to a variety of conditions and may present during childhood or adulthood (**Table 1**).The aetiologies of adult GH deficiency are almost identical to those of hypopituitarism. More than two-thirds of cases are caused by pituitary adenomas or other tumors of the sellar region, or result from the treatment of such tumors (8, 9). Congenital GHD may be isolated or associated with other pituitary hormone deficiencies. In the majority of cases, no cause can be identified and they are classified as idiopathic (10). Idiopathic GH deficiency arising in adult life is rare and its diagnosis requires rigorous testing (11). Traumatic brain injury (TBI) has been recently documented as a frequent cause of GHD (12). Childhood onset GH deficiency due to an organic cause will almost always persist into adulthood while patients with idiopathic isolated GHD could often have no more biochemical criteria for AGHD when retested in adult life and therefore will not need to restart GH treatment as adults (13, 14).

Table 1. Main causes of adult growth hormone deficiency (AGHD)

Childhood onset
Congenital - Idiopathic - Genetic - Associated with embryologic defects
Cranial irradiation for brain tumor, lymphoma, leukaemia
Head trauma
Central nervous system tumors
Infiltrative diseases
Adulthood onset
Pituitary/hypothalamic tumors and their treatment
Peri-sellar tumors (craniopharyngioma, meningioma, chordoma, etc...)
Brain injury/subarachnoid haemorrhage
Sheehan's syndrome
Autoimmune lymphocytic hypophysitis or any other cause of hypophysitis (IgG4-related, ipilimumab-related…)
Infiltrative/ granulomatous/infectious diseases
Empty sella syndrome
Idiopathic

DIAGNOSIS OF ADULT GH DEFICIENCY

AGHD should be investigated in patients with a high pre-test probability of having the disease and in whom there is a medical intention and patient willingness to start treatment if needed (7). True AGHD syndrome should not be confused with states of functional and relative GH insufficiency, such as obesity and aging. It is important to mention that the normal progressive decrease of GH secretion with aging (the so called "somatopause") is not a recognized indication for GH treatment and substantial evidence suggests that GH use in the healthy elderly is associated with little benefits and increased rates of adverse events (15,16).

Therefore, the investigation of adult patients for GH status should be limited to specific cohorts of GHD candidates(7,11).

- Young adult patients with a history of childhood GHD should be retested to confirm GHD after completion of growth. However, retesting during the transition period is not mandatory in patients expected to have lifelong severe GHD owing to causes such as genetic mutation, structural lesions or multiple pituitary hormone deficiencies (17,18).
- Patients harboring a known organic hypothalamic-pituitary lesion.
- Patients with a history of surgery or radiation therapy of a pituitary or brain lesion. Total body irradiation even at low doses (10-12 Gy) can induce GHD several years later (19).
- Patients with a history of head trauma or subarachnoid hemorrhage.
- Patients with clinical and/or biochemical evidence of other pituitary hormone deficits - (as these can be diagnosed lately after an initial asymptomatic pituitary disease such as Sheehan's syndrome)

BIOCHEMICAL TESTING FOR AGHD

The symptoms and signs of GH deficiency in adults are non specific (**Table 2**). Biochemical testing to assess GH production is therefore essential for diagnosis. Because GH secretion is pulsatile (20), a single serum GH measurement will not accurately reflect appropriate somatotropic function (11,21). On the other hand IGF-I has a long half-life in the circulation, but measurements of IGF-I are of limited utility in diagnosing GH deficiency in adults because of considerable overlap in plasma IGF-I levels between individuals with and without GHD (22). However in patients with organic or genetic cause of severe GHD, a very low serum IGF-I associated with deficiencies in three or more other pituitary hormones is as specific for the diagnosis of GH deficiency as any available provocative test (18).

The diagnosis of growth hormone deficiency must be confirmed by an abnormal hormonal response to one or more provocative tests. Several tests have been studied and the insulin tolerance test (ITT) is still the'gold standard" or reference test but it requires medical surveillance and is contraindicated in patients with ischemic heart disease, seizure disorders and is a potential risk in elderly patients (7,17). The glucagon test and the combined GHRH-arginine test are considered valid alternatives. The cut-off values for optimal sensitivity and specificity vary

Table 2. Main symptoms and signs of adult growth hormone deficiency (AGHD)

• Chronic fatigue/psychosocial problems/decreased quality of life
• Fine and dry skin
• Increased truncal adiposity/decreased lean body mass
• Reduced muscle strength and exercise capacity/ impaired cardiac function
• Decreased bone mineral density (BMD) and increased risk of fracture
• Atherogenic lipid profile/increased pro-inflammatory markers/increased intima-media thickening/insulin resistance

among the commonly used tests (23). For the insulin and glucagon tests, the threshold value defining severe GH deficiency is 3 μg /L, whereas partial deficiency is defined by a peak between 3.01 and 5 μg/L. For the GHRH-arginine test different threshold according to BMI have been proposed: <11.5 μg/L for BMI<25kg/m^2, <8 μg/L for BMI of 25-30 kg/m^2 and 4.2 μg/L for those with a BMI >30 kg/m^2. (24). Recently a lower threshold of 1 μg/L has also been proposed for glucagon test in overweight/obese subjects, as obesity naturally blunts GH response to glucagon stimulation (25).

TREATMENT OF GH DEFICIENCY

BENEFITS OF GH REPLACEMENT THERAPY

During the past 30 years, many clinical studies have investigated the short- and long-term effects of GH replacement in patients with AGHD.

The most consistent finding across studies of GH replacement therapy is improvement in body composition with an increase in lean body mass (LBM) and a decrease in total body fat (BF) (26, 27). These effects are rapid, occurring during the first 3 months of treatment and are maintained over 15 years (28), even though the treatment cannot prevent the modifications of body composition related to ageing (29, 30). Results on long-term effects on BMI appear to be inconclusive (27). As GH replacement increases lean body mass one might expect an improvement of muscle function as well, but data are rather conflicting (31,32).

The positive effects of GH therapy on bone mass and bone mineral density (BMD) in AGHD patients are undeniable and are only observed after at least 18-24 months of treatment. GH replacement therapy results in a biphasic change in BMD, with an initial 6-12 month period of increased bone resorption followed by an overall increase in bone mass (27). These effects are affected by gender, age and treatment duration (33). Prospective studies of long duration show that GH replacement for up to 15 years leads to a significant increase in BMD in the lumbar spine, particularly in men, and to stabilization of BMD values at the femoral neck (34, 35). However there is still scarce evidence that prolonged AGHD replacement ultimately reduces the risk of fractures (36-38). In particular, randomized controlled clinical trials with fracture end points are still not available and would be needed in order to definitively establish a protective effect of GH therapy.

Patients with hypopituitarism have reduced life expectancy, with a 2-fold higher risk of death from cardiovascular disease compared with healthy controls (39, 40). GH deficiency is the most likely explanation for this finding (41) although other factors such as underlying pathology, previous radiotherapy, and over- or under-replacement of other pituitary hormones may also been implicated (39, 40). There is growing body of evidence indicating that patients with adult GH deficiency are characterized by a cluster of different cardiovascular risk factors and markers, which can significantly increase their cardiovascular morbidity and mortality (42-44).

Prolonged GH therapy improves several cardiovascular risk factors, particularly the lipid profile. A meta-analysis of blinded, randomized, placebo-controlled trials showed that GH replacement has beneficial effects on body composition, total and LDL cholesterol levels as well as on diastolic blood pressure (45). We nowadays know that these effects are sustained and persist after 15 years of treatment (28). Furthermore, additional benefits on serum lipid levels may be achieved by a combination therapy of GH and statin (46). GH may also have beneficial effects on other cardiovascular risk factors, such as fibrinogen and inflammatory parameters, and reduce the intima-media thickness of the carotid arteries (45, 47, 48). The effects of GH on cardiac function have also been investigated and the most consistent effects are increases in left ventricular lass, wall thickness, left ventricular telediastolic diameter and volume of blood ejected at each systole (49). However, the global benefit of GH replacement on clinical endpoints, such as cardiovascular disease morbidity and mortality remains to be determined in larger prospective and long-term studies.

The effects on glucose metabolism are more complex. As expected GH acutely reduces insulin sensitivity but these deleterious effects are not maintained after prolonged therapy and after a few years of treatment insulin resistance improves, probably as a consequence of the favorable modifications of the body composition (45, 50). Nonetheless, a proportion of GHD patients will develop type 2 diabetes with increasing duration of GH replacement and increasing age, especially in the presence of predisposing conditions such as obesity or pre-existing glucose intolerance (28, 51) .

Growth hormone deficiency in adults causes distress and poor well-being. Patients with AGHD often complain of chronic fatigue and feel less energetic and less healthy than normal subjects of the same age (52). A disease

specific questionnaire (AGDA-QoL) has been developed and validated for evaluating the quality of life in AGHD patients (53). It comprises 25 items based on the symptoms most frequently reported by GHD adults. Numerous placebo-controlled, double blinded studies as well as cohort studies have documented significant improvements in QoL scores and psychological well-being under GH therapy in most, but not all, adults with GH deficiency who had impaired QoL at baseline assessment (27,54-56). Most of the improvement in QoL occurs during the first year of treatment and data from long term trials demonstrate a sustained improvement for at least 10 years, with the most marked improvements in GHD women and in patients with low baseline QoL (57, 58). In addition GH replacement therapy results in a significant decrease in the number of days of "sick leave", the number of days at hospital and the number of visits to the doctor (59). This indirectly demonstrates an improvement in the overall health state of GH-treated adult subjects, and should be considered when calculating the socio-economic cost of treatment.

OPTIMAL DOSE AND MONITORING OF GH THERAPY

Initially, GH doses were determined based on weight or surface area, in analogy with the experience gained from pediatric practice (5, 6). This approach resulted in GH doses of approximately 25 μg/kg that were associated with supra-normal levels of serum IGF-I and high rates of side effects (60). Current treatment regimens use individualized, weight independent dose-titration approach, taking into account the patient's age, sex and estrogen status (7). In order to avoid adverse events, treatment is initiated with low doses which are progressively up-titrated to attain normal IGF-I levels (7). Although serum IGF-I cannot be assumed to reflect the overall effect of GH in all tissues, it remains the most useful serum marker for GH dose titration in adults (7, 60, 61). The common target used for IGF-I is the upper half of the reference range, unless side effects are present but in elderly patients the target IGF-I range could considerably be reduced (7, 61). Daily subcutaneous injections might be responsible of poor adherence that increases over time and compromises therapeutic efficacy. In the last few years new long-acting GH preparations have been developed, showing similar clinical effects in comparison with daily GH injections (62,63). However, a recent review by an expert panel (64) concluded that, as these formulations have different pharmacokinetics and pharmacodynamics, long-term safety issues need to be addressed and that no comparison can be really made with those effects related to daily GH injections. The main safety concerns are the maintenance of supraphysiological elevation of GH throughout the day and non physiological tissue distribution. Besides, their potential advantages in terms of cost and compliance still need to be addressed in future clinical trials.

Theoretically GH replacement should be a lifelong treatment but the duration of treatment is still a matter of debate. However if benefits are being achieved without any side-effect, there is no particular reason to stop treatment at a given age. On the other hand, regardless of the patient's age and condition, if no apparent benefit of treatment has been observed after 1 year, treatment withdrawal should be considered as the cost-effectiveness ratio becomes unbalanced (7,17,61).

SAFETY

1. SIDE EFFECTS

Most of the reported side effects are the result of GH-induced fluid retention and include edema, arthralgia, myalgia, paresthesia and carpal tunnel syndrome. They are observed early after GH therapy is initiated, they are more frequent with higher doses, and they subside following dose reduction. They occur in 5-18% of patients, more frequently in elderly, overweight and female patients (49, 65).

2. LONG TERM SAFETY

Given the potential role of GH and IGF-I in cell proliferation (66), the long-term safety of GH replacement therapy has been a concern and has therefore been well studied in several large epidemiological studies and post-marketing registries (67-69).

There is no evidence that treatment with GH increases the risk of recurrence of pituitary tumors (68-70), therefore the presence of a stable remnant of pituitary tumor is not a contraindication to GH treatment. Also, accumulating data do not suggest that GH administration to survivors of childhood cancer is associated with an increased risk of recurrence of the primary malignancy (71,72). However, it appears that there might be a slight excess risk of second neoplasia in GH treated patients compared with non GH treated cancer survivors, but the risk decreases with increasing length of follow-up (73). On the other hand results from large database are reassuring showing that there is no increased risk of "de novo" cancers in GH treated patients (68, 69). Although preliminary data from the French cohort of the 'Safety and Appropriateness of GH treatments in Europe' (SAGhE) study indicated an increased risk of overall mortality in adults treated with GH during childhood (74), the recent final results do not support that GH treatment affects the risk of cancer incidence or mortality and a causal relation is unlikely (75). Moreover, a recent review of available published data from GH registries, compiling data from real-life clinical practice and covering over 150,000 patients, provides reassurance on the long term safety of GH treatment (67). Nevertheless, continued surveillance of people exposed to GH is essential both during treatment and in the years thereafter, especially in the older people who elect to continue therapy (76). Moreover, an active neoplasia remains so far an absolute contra-indication to start or continue GH administration.

CONCLUSIONS

Adult patients with a confirmed GHD syndrome should be considered for replacement therapy. During the last 30 years, a large body of literature has accumulated and supports many important beneficial effects of GH on body composition, exercise capacity, skeletal mineralization and QoL. Treatment also improves several cardiovascular surrogates but has not been proved yet to reverse the increased vascular mortality associated with hypopituitarism. Most of the above results are sustained in the long-term (10-15 years) and the prevalence of serious adverse events is low. Based on the results from observational research studies, we can nowadays conclude that GH therapy has a good safety profile when used for approved indications and at recommended doses.

However, a warning must be made here. With our better knowledge of the anabolic effects of growth hormone and the wider availability of unrestricted hormone quantities, including uncontrolled material provided by the black market and internet, its use (or misuse) is inevitably broadening, bypassing its so far evidence-based, well-accepted indications. Areas such as doping, body-building and anti-aging medicine are heavily contaminated by the fraudulent or inappropriate use of growth hormone or growth factors, and no one can predict today what will be the future consequences of this misappropriation of an otherwise safe and beneficial therapy.

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