Hypopituitarism: a review on the diagnosis and management of central hypoadrenalism and hypothyroidism

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Educational aims

- To identify best practices in the management of patients who have central hypoadrenalism and/or hypothyroidism
- To outline the necessary tests needed for the diagnosis of central hypoadrenalism and hypothyroidism
- To understand the rationale for supplementation therapy with glucocorticoids and thyroxine
- To better appreciate the role of patient education and proper advice as an essential part of management
- To highlight the monitoring requirements needed for proper titration of supplementation dosages

Key words
Hypopituitarism, central hypoadrenalism, secondary hypothyroidism, TSH deficiency, ACTH deficiency.

Abstract

A variety of conditions can result in hypopituitarism and this article focuses on the diagnosis, treatment and management of central hypoadrenalism and hypothyroidism. Central hypoadrenalism, if untreated, can potentially prove to be fatal and thus it is imperative that a timely diagnosis is done and life long supplementation instituted. Different glucocorticoid supplementation regimes together with possible side effects are discussed. Life long thyroxine replacement is needed for central hypothyroidism. Particular aspects regarding the diagnosis and management of central hypothyroidism are tackled. Important elements in the management of these patients, so as to ensure suitable supplementation are proper clinical and biochemical monitoring together with effective patient education.

Introduction

The pituitary gland is situated at the base of the brain and is divided into the anterior and posterior lobes. The anterior pituitary is responsible for the synthesis and secretion of adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), growth hormone (GH) and prolactin. It has a crucial role in the control of the hypothalmo-pituitary-adrenal axis through its secretion of ACTH, released under the influence of hypothalamic corticotropin-releasing hormone (CRH), ACTH being responsible for the control of cortisol secretion by the adrenals. Control of thyroid hormone production by the thyroid through the secretion of TSH, released under the influence of hypothalamic thyrotropin-releasing hormone (TRH) is another key role of the anterior pituitary. Partial or complete insufficiency of anterior pituitary hormone secretion termed hypopituitarism may result from pituitary or hypothalamic disease. A variety of conditions can result in hypopituitarism besides developmental and genetic causes, including various tumours such as pituitary adenomas and craniopharyngomas, head trauma, irradiation, pituitary infarction, empty sella syndrome and infiltrative diseases. In acquired hypopituitarism, failure of pituitary hormones usually follows a particular order with loss of GH first, followed by LH and FSH, than TSH and lastly ACTH. This order may reflect their relative importance for survival and in fact the more severe clinical condition occurs with ACTH deficiency which if left untreated can be fatal.[1] This review will focus on the diagnosis and management of ACTH and TSH deficiencies (central hypoadrenalism and hypothyroidism respectively).

Central hypoadrenalism

Diagnosis of central hypoadrenalism

Since serum cortisol levels usually reach a peak value at about 0800h, a level less than 100nmol/L at this time is taken to mean that there is cortisol deficiency.[2] Levels of serum cortisol taken at other times of the day are not very significant in terms of the diagnosis of hypoadrenalism. Hence a number of dynamic function tests have been devised to assess whether a patient can mount a suitable elevation in serum cortisol in response to stress as happens physiologically in a normal person. The test which has been available for many

years and still considered to be the gold standard is the insulin tolerance test (ITT) in which an insulin dose is given to induce a hypoglycaemic episode and repeated measurements of serum cortisol are taken.[3] Due to the nature of the test, it needs to be carried out under medical supervision and has some important contraindications such as a history of epilepsy, ischaemic heart disease or cardiac dysrhythmias. A peak value of 550nmol/L or above has to be achieved for the test to indicate adequate cortisol stress response.[1] A test which is simpler and shorter to do and for most cases provides adequate results which correlate well with an ITT, is the short synachten test (SST). In this test 0.25mg of ACTH[1-24] [tetracosactrin (Synacthen®)] are injected intramuscularly (i.m.) or intravenously (i.v.) and serum cortisol levels are measured at 0, 30 and 60 minutes. Since the use of the SST for evaluation of central hypoadrenalism works on the principle that adrenal glucocorticoid producing cells will have their cortisol producing ability attenuated as a result of chronic ACTH deficiency, there is a time lag until this develops and thus this test should not be used to assess patients in their early stages after a pituitary insult.[4,5] Another alternative test which could be used when an ITT is contraindicated, is the glucagon test where 1mg of glucagon is injected subcutaneously and measurements of serum cortisol are carried out every half hour for 4 hours.[1,6-8]

Treatment of central hypoadrenalism

In the acute setting when central hypoadrenalism is present or suspected, the treatment of choice is hydrocortisone given through the i.v. or i.m. route. Before administering the first dose of hydrocortisone, if possible a serum sample for estimation of cortisol level is taken. Usually the dose is 100mg every 6-8 hours, together with i.v. saline infusion. After 24 hours the dose of hydrocortisone can be reduced to 50mg 6 hourly and then, if clinically tolerated, changed to oral hydrocortisone.[1,9]

Long term treatment involves lifelong supplementation of glucocorticoids. Previously most patients used to be given hydrocortisone 20mg as soon as they wake up and 10mg in the late afternoon. Following studies[10] that determined that the average daily dose of cortisol secreted is 5.7mg/m^2 per day or 9.9 ± 2.7 mg/day, which is equal to a daily delivered dose of 15-20mg, usual supplementation dosages were revised down to this level. With the knowledge that mimicking the normal circadian cortisol rhythm has proven to be very difficult, different approaches were adopted by various experts: either starting with a twice daily dose of hydrocortisone and if on clinical assessment, the patient is still feeling unwell going up to thrice daily dosing or advocating that the replacement dose of hydrocortisone be divided into 3 doses from the start with typical dosages being a 10mg dose taken on rising, 5mg at midday and 5mg in the early evening.[1,11-13] Some experts advocated that this thrice daily regime be further fine tuned by adopting a weight adjusted dosage.[11] It is important to note that the first morning dose of hydrocortisone is best taken as soon as the patient wakes up with a glass of water and the last dose should be taken in the late afternoon rather than the evening to prevent unphysiological high levels of cortisol in the evening and possibly insomnia.[1,12] Studies on the relation between hydrocortisone dosage and health-related quality of life suggest that a twice daily regimen is superior to a once daily dose and perhaps a thrice daily better than twice daily although the evidence here is not as strong.[12,13] In a large study[14] on 2424 hypopituitary patients of whom 1186 were on hydrocortisone, it was shown that while patients who were on hydrocortisone had higher levels of total cholesterol, triglycerides, HbA1c and a higher waist circumference, compared to ACTH-sufficient patients, those who were taking a dose of hydrocortisone less than 20mg/day did not have statistically significant differences in the metabolic parameters mentioned when compared to patients who had an intact hypothalamic-pituitary-adrenal axis. To try to mimic the physiological cortisol circadian rhythm better, modified release oral formulations of hydrocortisone are currently being developed. The total replacement dose needed might be less for those patients who have some residual pituitary function as evidenced by a subnormal peak response on a stimulation test but a normal basal level of cortisol. Some patients would even just require steroid cover for periods of increased stress.[1] Mineralocorticoid replacement (Ex. Fludrocortisone) is not needed in central hypoadrenal patients.

An important dimension of the assessment of proper glucocorticoid replacement treatment is regular clinical assessments aiming to highlight symptoms/signs of under or over treatment, although one has to appreciate that minor degrees of over/under treatment might prove very difficult to diagnose on clinical grounds.[12,13] In this context the role and value of cortisol day curves is debated by various experts, though they may have a role in monitoring adequate replacement and avoiding over treatment of patients[1] or in those who are on other drugs which interfere with the metabolism of hydrocortisone.[13] Another method advocated by some experts to help assess adequate glucocorticoid replacement is taking a serum cortisol level 4 hours after ingestion and comparing this level to a dosing nomogram.[11] Although the effect on bone mineral density of patients who are on glucocorticoid is debatable, there are some studies which suggest a lower bone density in such patients particularly in post-menopausal women. Hence it is reasonable to suggest that patients are to be kept on the lowest dose of hydrocortisone possible and have their bone mineral density followed up.[12,13]

An important dimension in the management of patients who are glucocorticoid deficient is their education. Patients who are on replacement steroids are advised to carry a Steroid Card with them at all times and emphasis made on the fact that they should not stop taking this treatment unless advised otherwise by their doctor. On a practical level, patients should be advised to think ahead so that they do not run out of the replacement steroid tablets. They are also provided with a phial of hydrocortisone 100mg to be available for administration in emergency settings and adequately educated on how this is given if the need arises. These patients are advised that they should double their usual dose of hydrocortisone if they have a major stressful event such as a febrile illness unless they are severely ill when they might need hydrocortisone administration through the i.v. route.[1,9,12]

Central hypothyroidism

Diagnosis of central hypothyroidism

The biochemical diagnosis of central hypothyroidism is done when a low thyroxine (T4) level is noted together with an inappropriately normal or low TSH level. It is worth noting that tri-iodothyronine (T3) levels often remain within normal limits even when T4 levels are low and thus the measurement of its level might not be helpful for diagnosis. A high index of suspicion should be maintained in

Key points

- A combination of basal serum cortisol levels and various dynamic function tests have been devised to establish whether a patient has an adequately functioning hypothalamo-pituitary-adrenal axis.
- Typical daily glucocorticoid supplementation dose is 15-20mg hydrocortisone divided into twice or thrice daily doses.
- The first morning dose of hydrocortisone is best taken when the patient wakes up and the last dose should be taken not later than in the late afternoon.
- Vital to educate patients on the importance of drug compliance and what to do during major stressful events.
- Biochemically patients with central hypothyroidism have low thyroxine levels with an inappropriately normal or low TSH level.
- Serum TSH level is not a good indicator of adequate thyroxine supplementation dosages in central hypothyroidism and changes in dose should be done according to serum thyroxine levels and on clinical grounds.

those patients who have conditions which could result in hypopituitarism and thus central hypothyroidism, such as a history of pituitary tumours, previous cranial irradiation or cranial injuries.[15,16]

Treatment of Central Hypothyroidism

The treatment of central hypothyroidism is life long thyroxine. It is important to ascertain before starting T4 treatment in a patient, that the possibility of coexistent hypoadrenalism has been excluded or if present is adequately replaced since it is well known that T4 increases cortisol clearance and thus an adrenal crisis might be precipitated in patients who are cortisol deficient. Usually it is advisable to start with low doses of T4 such as 25-50µg daily and than titrating the dose every few weeks until the correct dose is found. Elderly patients and those with a history of ischaemic heart disease deserve special attention in titrating the dose of T4. Several drugs including iron, calcium, mineral supplements, aluminium hydroxide and sucralfate are known to interfere with T4 absorption. Adverse reactions to T4 treatment have to do with over replacement of T4 and thus will include symptomatic or subclinical thyrotoxicosis. It is important to note that in central hypothyroidism TSH levels cannot be used as an indicator of correct dosage as is done in primary hypothyroidism since the TSH response is inappropriate. Thus changes in dosages should be done on clinical grounds and according to serum T4 levels, aiming to keep these in the upper half of the normal reference range.[15,16]

Conclusion

While not very common, hypopituitarism, especially central hypoadrenalism and hypothyroidism need to be promptly diagnosed and appropriately treated. While aiming to restore normal physiological hormonal levels, a structured monitoring system, both clinically and biochemically is needed to determine the most appropriate drug supplementation dosages for a particular patient. Patient information is a key component of the management of these patients in order to ensure drug treatment compliance and minimise potential problems.

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