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Growth Hormone Deficiency in Children and Adult Patients with Hypopituitarism: Challenges in the Diagnosis and Management

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Abstract

Hypopituitarism is the decreased (hypo) secretion of one or more of the eight hormones normally produced by the pituitary gland at the base of the brain.If there is decreased secretion of one specific pituitary hormone, the condition is known as selective hypopituitarism. If there is decreased secretion of most or all pituitary hormones, the term panhypopituitarism is used.

Hypopituitarism is a complex medical condition associated with increased morbidity and mortality, requires complicated treatment regimens, and necessitates lifelong follow up by the endocrinologist.

Keywords

Hypopituitarism, Growth hormone deficiency, Pituitary hormone replacement therapy, endocrine Replacement Therapy

Introduction

Aetiology

Of the various causes of hypopituitarism in adults (see box), pituitary adenoma or its treatment by surgery and/or radiotherapy is by far the commonest. Macroadenomas (greater than 1 cm) are associated with one or more trophic hormone deficits in 30% of cases direct compression and destruction of the surrounding normal pituitary leads to hyposecretion. Other postulated mechanisms include primary mass effect of the tumour on the vascular portal system/pituitary stalk, raised intrasellar pressure affecting portal circulation, and focal pituitary necrosis secondary to prolonged interruption of portal blood supply. While microadenomas (less than 1 cm) rarely affect pituitary function, prolactin producing microadenomas often present with hypogonadism because of the suppressive action of a high prolactin (PRL) level on gonadotrophins' (follicle stimulating hormone FSH and luteinising hormone LH) secretion. Among the peripituitary tumours causing central endocrine dysfunction, craniopharyngioma is the commonest.

Occurrence of hypopituitarism after pituitary surgery is influenced by tumour size, extent of invasion into surrounding structures, remaining viable normal pituitary, and the skill of the neurosurgeon. Transient postoperative diabetes insipidus (DI) is seen in 5% of cases but permanent DI occurs less frequently. At least partial recovery of pituitary function in 40%–65% of patients has been reported after surgery but postoperative deterioration has also been reported.Patients should be made aware of the possibility of hypopituitarism before surgery. Post-surgical endocrine assessment is mandatory.

Anterior hypopituitarism may follow cranial radiotherapy used in treating various intracranial tumours, acute lymphoblastic leukaemia (prophylactic cranial radiotherapy), and those receiving total body irradiation. The impact is dependent on the total dose, fractionation, duration of treatment, and time elapsed since radiation exposure to the hypothalamic-pituitary axis.

In one series after a radiotherapy dose to the hypothalamic-pituitary axis of 37.5 to 42.5 Gy, after five years all patients were growth hormone (GH) deficient, 90% gonadotrophin deficient, 77% adrenocorticotrophic hormone (ACTH) deficient, and 42% were thyroid stimulating hormone (TSH) deficient. Gamma knife surgery for pituitary adenoma has recently been reported to affect pituitary function less than conventional radiotherapy although these are preliminary findings and require long term studies to determine if this is the case. Congenital isolated/multiple pituitary hormone deficiencies (MPHD) have been described. Growth hormone gene GH-1[1]and growth hormone releasing hormone receptor gene GHRH-Rmutations can result in isolated growth hormone deficiency whereas KAL gene defect is implicated in the X-linked form of Kallman's syndrome (isolated hypogonadotrophic hypogonadism plus hypo/anosmia).

Causes of hypopituitarism

Deficient pituitary gland function can result from damage to either the pituitary or the area just above the pituitary, the hypothalamus. The hypothalamus contains releasing and inhibitory hormones which control the pituitary. Since these hormones are necessary for normal pituitary function, damage to the hypothalamus can also result in deficient pituitary gland function. Injury to the pituitary can occur from a variety of insults, including damage from an enlarging pituitary tumor, irradiation to the pituitary, pituitary apoplexy, trauma and abnormal iron storage (hemochromatosis). With increasing damage there is a progressive decrease in function. There appears to be a predictable loss of hormonal function with increasing damage. The progression from most vulnerable to least vulnerable is usually as follows: first is growth hormone (GH), next the gonadotropins (LH and FSH which control sexual/reproductive function), followed by TSH (which control thyroid hormone release) and finally the last to be lost is typically ACTH (which controls adrenal function).

Growth Hormone Deficiency

Growth hormone is necessary in children for growth, but also appears necessary in adults to maintain normal body composition (muscle and bone mass). It may also be helpful for maintaining an adequate energy level, optimal cardiovascular status and some mental functions. Symptoms of GH deficiency in adults include fatigue, poor exercise performance and symptoms of social isolation. GH is only available in injectable form and must be given 6-7 times per week.

Antidiuretic Hormone deficiency causing diabetes insipidus

This problem arises from damage to the pituitary stalk or the posterior pituitary gland. It may occur transiently after transsphenoidal surgery but is rarely permanent. Patients with diabetes insipidus have increased thirst and urination. Replacement of antidiuretic hormone resolves these symptoms. Antidiuretic hormone (ADH) is currently replaced by administration of DDAVP (also called Desmopressin) a synthetic type of ADH. DDAVP can be given by subcutaneous injection, intranasal spray, or by tablet, usually once or twice a day.

ACTH deficiency

A basal (9 am) cortisol less than 100 nmol/l in untreated patients, or greater than 450–500 nmol/lobviates the need for provocative tests of ACTH reserve without compromising patient care. If cortisol insufficiency is clinically suspected, particularly in an unwell patient, basal cortisol and ACTH samples are taken but cortisol replacement started awaiting results. The ITT remains the gold standard for assessing the entire hypothalamic-pituitary-adrenal (HPA) status and has been cross validated historically against a physical stress (major surgery), with a normal peak cortisol response of 580 nmol/l.In response to hypoglycaemia (less than 2.2 mmol/l), a cortisol level greater than 500 nmol/l is considered to be consistent with normal ACTH status. An ITT however is not without contraindications or morbidities and hence several authors advocate the short synacthen test (SST) with appropriate cut offs as the first line test. While controversy exists about the cut offs and diagnostic reliability, the potential for missing subtle HPA defects remains a possibility; a 30 minute cortisol (after intramuscular synacthen 250 µg) of greater than 550 nmol is considered to represent a “pass”. An ITT should be performed in those who fail the screening SST.

Gonadotrophin deficiency

This is associated with low serum testosterone in the presence of normal or low gonadotrophin levels in men and low serum oestradiol concentrations in pre-menopausal women without appropriately increased gonadotrophins, and in post-menopausal women the absence of the normal rise of gonadotrophin concentrations.

Subjects and Methods

Subjects

One hundred and one hypopituitary patients (46 males and 55 females; age, 16–73 yr) and 35 healthy subjects (15 males and 20 females; age, 18–70 yr) entered this study after their informed consents had been obtained. None of the subjects of this study had taken any drug or medication known to affect skeletal or mineral metabolism. In addition, none of the 136 subjects had habitual ingestion of coffee greater than 4 cups/day or more than 2 alcohol containing beverages/day. Seventy-six patients and 19 controls were nonsmokers, and the remaining subjects were mild smokers (<15 cigarettes/day). Furthermore, none of the patients had active peptic ulcer disease or abnormal renal and/or hepatic function. All patients had been previously operated on via the transsphenoidal and/or transcranic route for nonfunctioning pituitary adenoma, meningioma, or craniopharyngioma, and 17 of them had also been irradiated. A variable degree of pituitary insufficiency was found in the 101 patients, as shown in Table 1. Hormone replacement therapy with l-T_4 (50–100 µg daily, orally), cortisone acetate (25–37.5 mg/day), and intranasal desmopressin (5–20µ g/day) was given where appropriate.

Males with hypogonadism were treated with testosterone enanthate (250 mg monthly, im), whereas premenopausal females were given estro-progestinic replacement. The adequacy of hormone replacement therapy was periodically assessed by means of serum free thyroid hormones, testosterone, urinary free cortisol, and serum and urinary Na^+ and K^+ measurements. At study entry, these hormonal parameters were in the normal range for age in all patients. None of the patients had ever received GH treatment.

Table 1.

Clinical characteristics of the 101 patients grouped on the basis of the GH response after ARG plus GHRH and of the 35 controls

GH peak after ARG + GHRH:	Patients				Controls, GH >16.5 µg/L
	GH < 3 µg/L	GH 3.1–9 µg/L	GH 9.1–16.5 µg/L	GH >16.5 µg/L	
Mean (±sem) µg/L	0.9 ± 0.08	4.7 ± 0.4	11.0 ± 0.3	28.3 ± 4.3	40.7 ± 2.2
No. of patients	41	25	18	17	35
Females/males	16/25	15/10	12/6	12/5	20/15
Age range (yr)	18–70	16–65	21–53	21–56	18–70
Mean (±sem) age	44.4 ± 1.8	37.1 ± 2.8	36.7 ± 2.6	36.3 ± 3.2	47.1 ± 2.7
Disease duration (yr)	11.1 ± 0.8	9.4 ± 1.3	7.1 ± 1.9	2.8 ± 0.4	
Pituitary deficiencies (no. of patients)	38	22	7	7	0
Pituitary deficiencies (%)	92.7	88	39	41	0
FSH, LH	78	72	17	17	0
TSH	73	60	11	0	0
ACTH	73	68	0	12	0
Diabetes insipidus	24	0	11	12	0

Study protocol

At study entry, serum calcium, phosphorus, and creatinine and circulating alkaline phosphatase, intact PTH, and osteocalcin (OC) were assayed twice in a single sample. Urinary cross-linked N-telopeptides of type I collagen (Ntx), calcium, phosphorus, and creatinine were assayed in the 24-h urinary collection the day before the study. Assay of IGF-I and IGF-binding protein-3 (IGFBP-3) levels and assessment of BMD measured at the lumbar spine and femoral neck levels were performed in all patients. All subjects were tested with ARG+GHRH. ARG (arginine hydrochloride, Damor, Naples, Italy) was administered at a dose of 0.5 g/kg up to a maximal dose of 30 g slowly infused from 0–30 min; GHRH (1–29, Geref, Serono, Rome, Italy) was given at a dose of 1µ g/kg as an iv bolus at time zero. Blood samples were taken every 15 min from −15 to 90 min. According to recent studies (9–12), showing that adult patients with a GH peak after an insulin tolerance test of less than 3 µg/L had a GH response to ARG+GHRH below 9µ g/L, whereas normal subjects had a GH response after ARG+GHRH always greater than 16.5 µg/L, we classified the GH response after ARG+GHRH in our 101 subjects as follows: very severe GHD (GH peak, <3 µg/L), severe GHD (GH peak, 3.1–9 µg/L), partial GHD (GH peak, 9.1–16.5µ g/L), and normal (GH peak, >16.5 µg/L).

Assays

All hormone measurements were performed using the same reagents in two laboratories at the Department of Molecular and Clinical Endocrinology and Oncology, University Federico II of Naples, and the Department of Endocrinology, University of Turin. Assay performances were similar in the two laboratories. Serum GH levels were measured by immunoradiometric assay (IRMA) using commercially available kits. The sensitivity of the assay was 0.2 μg/L. The intra- and interassay coefficients of variation (CVs) were 4.5% and 7.9%, respectively. Plasma IGF-I was measured by IRMA after ethanol extraction. The normal ranges in 20- to 30-yr-old, 31- to 40-yr-old, 41- to 50-yr-old, and over 50-yr-old men were 108–458, 92–483, 100–316, and 78–213μ g/L, respectively, whereas in women these values were 118–523, 112–506, 96–288, and 78–268 μg/L, respectively. The sensitivity of the assay was 0.8 μg/L. The intraassay CVs were 3.4%, 3.0%, and 1.5% for low, medium, and high points of the standard curve, respectively. The interassay CVs were 8.2%, 1.5%, and 3.7% for low, medium, and high points of the standard curve. Plasma IGFBP-3 was measured by RIA after ethanol extraction. The normal ranges in 20- to 30-yr-old, 31- to 40-yr-old, 41- to 50-yr-old, and over 50-yr-old subjects were 2.1–7.6, 1.7–7.3, 2.1–4.3, and 2–4 mg/L, respectively. The sensitivity of the assay was 0.5 μg/L. The intraassay CVs were 3.9%, 3.2%, and 1.8% for low, medium, and high points of the standard curve, respectively. The interassay CVs were 0.6%, 0.5%, and 1.6% for low, medium, and high points of the standard curve. PTH was assayed by the IRMA method; the normal range was 9–55 pg/mL. Serum OC levels were measured by RIA; the normal range was 3.0–13.0 μg/L. Urinary Ntx levels were measured by enzyme-linked immunosorbent assay; the normal ranges were 23–110 and 13–96 nmol bone collagen equivalent (BCE)/mmol in males and females, respectively.

Results

On the basis of the GH response to ARG+GHRH, 41 patients had very severe GHD (GH peak, 0.9 ± 0.08 μg/L; group 1), 25 patients had severe GHD (GH peak, 4.7 ± 0.4 μg/L; group 2), 18 patients had partial GHD (GH peak, 11.0 ± 0.3 μg/L; group 3), and 17 patients had normal GH responses (GH peak, 28.3 ± 4.3 μg/L; group 4). In the 35 controls (group 5), the GH response after ARG+GHRH was 40.7 ± 2.2 μg/L.

Plasma IGF-I concentrations in patients in groups 1 (76.5 ± 7.6μ g/L) and 2 (80.3 ± 7.5 μg/L) were similar and lower ($P < 0.001$) than those in groups 3–5, which were not different from each other (170.9 ± 40.6, 186.5 ± 20.1, and 188.8 ± 11.1 μg/L, respectively). IGF-I concentrations were below the normal range for age in 28 patients in group 1 (68.3%), 15 in group 2 (60%), and 2 in group 3 (11.1%) and were normal in all subjects in groups 4 and 5. Similarly, IGFBP-3 concentrations in groups 1 (2.1 ± 0.3 mg/L) and 2 (2.2 ± 0.3 mg/L) were similar and lower than those in groups 3 (3.5 ± 0.7 mg/L; $P< 0.05$), 4 (3.6 ± 0.8 mg/L), and 5 (3.8 ± 0.2 mg/L; $P < 0.05$). Plasma IGFBP-3 concentrations were below the normal range for age in 24 patients in group 1 (58.3%), 10 in group 2 (40%), and 1 in group 3 (5.5%) and were normal in all subjects in groups 4 and 5.

Management of hypopituitarism

The treatment of hypopituitarism includes therapies directed at the underlying disease process, and endocrine replacement therapy. The pituitary tumours may be treated with medical therapy, surgery, radiotherapy, or a combination of these modalities. A macroprolactinoma, for instance, is amenable to treatment with dopamine agonists, there is a high surgical cure rate for GH secreting microadenoma by skilled surgeons.

Hormone Replacement Therapy

The goals of HRT in hypopituitarism are to achieve normal levels of the circulating hormones, to restore normal physiology as closely as possible, and to avoid the symptoms of deficiency with minimal side effects.

Discussion

GHD in adults is associated with increased fat mass, reduced lean mass, osteopenia, impaired fibrinolysis, altered cardiac structure and function, unfavorable glucose and lipid metabolism, reduced exercise capacity, and reduced quality of life (3, 13, 14). Reduced BMD has been widely reported in hypo pituitary patients (3, 4–8), although the roles of individual pituitary hormone deficiency and/or of replacement therapy in the development of bone loss have not been firmly elucidated.

Conclusion

Hypopituitarism is associated with increased mortality and morbidity, necessitates complicated treatment regimens, and significantly affects the economy of the healthcare system. Strategies to limit the use of conventional radiotherapy may well lead to a reduced incidence of hypopitutarism. It is probable that hormonal treatment that approaches normal physiology might have a favourable influence on the adverse outcomes; therefore optimising replacement and lifelong follow up is appropriate.

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