

Growth Hormone Treatment and Papilledema: A Prospective Pilot Study

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What is already known on this topic?

Growth hormone (GH) replacement therapy is a risk factor for secondary pseudotumor cerebri. The incidence of this complication can vary depending on different GH indications.

What this study adds?

Children with intracranial hypertension could be asymptomatic, so the diagnosis should be based on fundus examination and not on patient's symptoms. In our series, at risk patients had GH deficiency and hypothalamic-pituitary anatomic anomalies or genetic or chromosomal diseases. A previous history of pseudotumor cerebri should be investigated.

Abstract

Objective: To investigate the incidence of pseudotumor cerebri syndrome (PTCS) in children treated with growth hormone (GH) in a paediatric hospital and to identify risk factors for this complication.

Methods: Prospective pilot study of paediatric patients treated with recombinant human GH, prescribed by the Paediatric Endocrinology Department, between February 2013 and September 2017. In all these patients, a fundus examination was performed before starting treatment and 3-4 months later.

Results: Two hundred and eighty-nine patients were included, of whom 244 (84.4%) had GH deficiency, 36 (12.5%) had short stature associated with small for gestational age, six (2.1%) had a mutation in the *SHOX* gene and three (1.0%) had Prader-Willi syndrome. Five (1.7%) developed papilledema, all were asymptomatic and had GH deficiency due to craniopharyngioma (n = 1), polymalformative syndrome associated with hypothalamic-pituitary axis anomalies (n = 2), a non-specified genetic disease with hippocampal inversion (n = 1) and one with normal magnetic resonance imaging who had developed a primary PTCS years before.

Conclusion: GH treatment is a cause of PTCS. In our series, at risk patients had GH deficiency and hypothalamic-pituitary anatomic anomalies or genetic or chromosomal diseases. Fundus examination should be systematically screened in all patients in this at-risk group, irrespective of the presence or not of symptoms.

Keywords: Growth hormone treatment, pseudotumor cerebri syndrome, idiopathic intracranial hypertension, papilledema, risk factors

Introduction

Pseudotumor cerebri syndrome (PTCS) is a condition defined by elevated intracranial pressure (ICP) in the absence of clinical, laboratory or radiologic evidence of infection,

vascular abnormality, intracranial space-occupying lesion or hydrocephalus (1,2). It can be primary, or secondary if there are any identifiable risk factors. Primary PTCS most commonly occurs in obese adult women of childbearing age (12-32/100,000). However, it is a rare condition in childhood



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(0.5-0.9/100,000) with an identifiable risk factor in 53-77% of paediatric cases (3,4,5). Papilledema is a hallmark in PTCS, which is not a benign disorder; there is a risk of severe and permanent visual loss. Even patients with mild visual loss experience reduction in quality of life (6).

Growth hormone (GH) replacement therapy was first associated with PTCS by The Food and Drug Administration in 1993 (7). Since then, multiple publications have described this association. Reeves and Doyle (8) found that the prevalence in the GH treated population was approximately 100 times greater than in the general paediatric population. This complication usually occurs in the first weeks after initiating treatment (approximately 2-12 weeks) and the papilledema (optic disc swelling from raised ICP) resolves on stopping treatment (8,9).

Pseudopapilledema is an elevated optic disc with obscured margins that may occur in hyperopic eyes and in the presence of buried optic disc drusen, rather than from raised ICP. Optic disc drusen are acellular deposits located within the optic disc. Sometimes it can be very difficult to differentiate between pseudopapilledema and papilledema, requiring the opinion of a suitably experienced ophthalmologist and complementary tests (10).

The aim of this study was to investigate the incidence of PTCS in children treated with GH in a paediatric hospital and to identify risk factors for this complication. A secondary aim was to identify which children really need fundus examination during GH treatment in order to detect this complication.

Methods

A prospective pilot study was conducted in paediatric patients who started GH treatment from February 2013 to September 2017. Inclusion criteria were patients under 16 years of age prescribed GH by the Paediatric Endocrinology Department. Exclusion criteria were: absence of fundus examination prior to or at 3-4 months from starting treatment; severe optic disc atrophy where optic disc swelling would not develop; and cases where GH was prescribed by the Paediatric Nephrology Department. Predisposing pathology for intracranial hypertension was not considered an exclusion criterion, as fundus examinations were conducted before initiating treatment to rule out prior pathology of the optic nerve. The following variables were recorded: previous medical history; anthropometric data; and compliance with treatment.

Fundus was explored prior to and after 3-4 months of starting treatment or at any time when severe constant headache,

vomiting or other presenting symptoms suggestive of intracranial hypertension arose. Prior fundus examination identified possible cases of pseudopapilledema and avoided possible confusion between this entity and newly developed papilledema in subsequent fundus follow-up examinations.

Fundus examination was carried out with indirect ophthalmoscopy and retinography was taken in cases of pseudopapilledema to facilitate follow up. In cases when papilledema was detected, GH was stopped and fundus examination was repeated four weeks later. If papilledema persisted, the patient was referred for neurological assessment, lumbar puncture and possible medical treatment with acetazolamide. Once papilledema resolved, if GH treatment was still considered necessary, treatment was re-initiated at a lower dose and progressively increased until the objective dose was achieved, with monthly ophthalmology visits until four months were completed at the target GH dose.

Cerebral magnetic resonance imaging (MRI) of the hypothalamic-pituitary axis was performed in all patients with GH deficiency, prior to treatment. Initial GH doses were as indicated: 0.028-0.035 mg/kg/day for patients with GH deficiency and small for gestational age (SGA), 0.042 mg/kg/day for those with mutations in the *SHOX* gene and 1 mg/m²/day for patients with Prader-Willi syndrome (PWS).

Ethics approval was obtained from the Ethic Review Committee of the Hospital Universitario Vall d'Hebron (approval number: 383). All subjects (or their parents or guardians) gave their written informed consent.

Statistical Analysis

In this case series, simple descriptive statistics were sufficient to delineate our populations. Variables are expressed as number, mean and percent (%) or range, as appropriate.

Results

There were 306 patients to whom GH was prescribed by the Paediatric Endocrinology Department between February 2013 and September 2017. Only 289 patients were enrolled in this study, 17 were excluded because of loss of ophthalmological follow up.

The mean age was nine years (range 1-16) and 53% of the patients were male. The patients were categorized according to their indication for GH treatment: 244 patients (84.4%) with GH deficiency; 36 patients (12.5%) with short stature associated with SGA; six patients (2%) with a mutation in the *SHOX* gene; and three (1%) with PWS. Patients

diagnosed with chronic kidney disease were not included in the study as their indication for GH treatment and follow up was made by the Paediatric Nephrology Department.

In the first visit, prior to starting GH treatment, there were 546 eyes with normal optic discs, 16 eyes with pale optic discs, 11 eyes with pseudopapilledema, two eyes with optic disc and chorioretinal coloboma and one eye with dysplastic optic disc. Pale optic discs and optic disc and chorioretinal coloboma were secondary to the patient background pathology, suprasellar cerebral tumours and CHARGE anomaly respectively. In the follow up visit, five patients had optic disc swelling, suggesting papilledema, despite there being no symptoms of intracranial hypertension. None of the patients who presented with headache, who were visited urgently, presented with papilledema on fundus examination.

Table 1 outlines the characteristics of the five patients with papilledema. All these patients had GH deficiency: three had hypothalamic-pituitary axis abnormalities on brain MRI; two were congenital cases; and one was secondary to a suprasellar tumour. The patient with a suprasellar tumour had a ventriculoperitoneal shunt and was treated with external radiotherapy. The only patient with an isolated GH deficiency with normal MRI, had developed primary PTCS five years before and he was obese. The incidence of obesity in children without PTCS in our population is 10.3%.

The papilledema resolved on discontinuing GH treatment in four patients, whereas in the remaining patient, a lumbar

puncture confirmed the diagnosis and was also therapeutic. The opening pressure was 25 cm H₂O. The glucose was 61 mg/dL (38-82); protein 20 mg/dL (15-45) and there were neither leukocytes nor red blood cells present in the cerebrospinal fluid (CSF). Medical treatment was not required. In four cases GH treatment was reintroduced at a lower dose with progressive incremental doses, without the reappearance of papilledema.

Discussion

GH treatment is a risk factor for developing secondary PTCS although the mechanism is little understood. Two hypotheses have been proposed. The first is that GH could have a physiological antidiuretic effect, causing retention of sodium and water and expansion in blood volume, and reducing CSF resorption by the arachnoid villi. The second hypothesis proposes that GH would cross the blood-brain barrier, resulting in raised cerebral levels of GH and its mediator, insulin-like growth factor 1, and finally increasing CSF production (11,12,13,14).

GH was initially obtained from human pituitary gland, and was given at lower doses and frequency, and prescribed in fewer clinical situations. Since 1985, when recombinant human GH became commercially available, more patients were treated with larger doses and more often. Since then, indications for GH treatment have increased, as well as the potential adverse effects (15).

Table 1. Characteristics of patients treated with growth hormone who developed papilledema

Patients	Gender/age (years)	Papilledema onset time (months)	W (kg)/H (cm)	GH dose (mg/kg/week)	Other pathology/MRI anomalies	Risk factors PTCS	Treatment PTCS
1	M/14	2	71.4/144.7	0.20	--	PTCS 2010, obesity	GH stopped
2	M/3	3	11.4/86	0.23	Polymalformative syndrome, pituitary gland anomaly and partial agenesis of corpus callosum on brain MRI	None	GH stopped
3	M/11	3	26.5/128.3	0.21	PDR Dysmorphic phenotype Incomplete hippocampal inversion on brain MRI	None	GH stopped + LP
4	M/10	3	36.4/132	0.19	Craniopharyngioma, radiation therapy	None	GH stopped
5	F/4	3	10.7/80.4	0.32	Microcephaly Pituitary gland compression by an arachnoid cyst Hypoparathyroidism PDR	None	GH stopped

F: female, GH: growth hormone, H: height, LP: lumbar puncture, M: male, MRI: magnetic resonance imaging, PDR: psychomotor development retardation, PTCS: pseudotumor cerebri syndrome, W: weight

Table 2. Distribution of patients with growth hormone deficiency according to our classification in subgroups

GH deficiency subgroups		N° patients	N° papilledema
1	Isolated GH deficiency with normal H-P axis on MRI	164	1
2	GH deficiency (isolated or not) with abnormal H-P axis on MRI and/or RT	62	3
3	Genetic or chromosome disorders	18	1

GH: growth hormone, H-P: hypothalamic-pituitary, MRI: magnetic resonance imaging, RT: cranial radiotherapy

In our study, there were five patients with papilledema (1.7%), a higher incidence compared with the expected incidence in the general paediatric population (8,9,11,13). All of them had GH deficiency. Other indications for GH treatment did not appear to cause papilledema in this series, although these results may be biased due the small populations with these other indications.

As all the patients with papilledema were found to have GH deficiency, we analysed this group, classifying patients into three subgroups (Table 2):

1. Isolated GH deficiency (no other associated hormone deficiencies) with normal hypothalamic-pituitary axis anatomy on MRI.
2. Isolated GH deficiency or associated with other hormone deficiencies with altered hypothalamic-pituitary axis anatomy on MRI and/or past history of cerebral radiotherapy.
3. GH deficiency in patients with genetic or chromosomal diseases.

When considering patients who presented with papilledema, three completed criteria for subgroup 2, presenting with hypothalamic-pituitary axis abnormalities and external radiotherapy treatment in one case for a suprasellar tumour. These three patients in subgroup 2 had an intracranial hypertension, but not technically a PTCS, because the brain MRI was not normal. One other patient was classified as subgroup 3 for a non-specific genetic disease. Only one patient presented with an isolated GH deficiency with normal cerebral MRI, however this patient had had primary PTCS five years earlier. The patient with a suprasellar tumour also had a ventriculoperitoneal shunt, suggesting that the presence of a shunt is not protective against a rise in ICP induced by GH therapy.

For each GH indication, the incidence of this adverse effect can vary. Reeves and Doyle (8), reported higher incidences in patients with renal failure and Turner syndrome. Souza and Collet-Solberg (11), also detected a higher incidence in patients with chronic kidney disease. Darendeliler et al (16) proposed that patients with Turner syndrome, organic GH deficiency, PWS and chronic renal insufficiency might be more prone to develop papilledema when receiving GH. In our study, patients with renal disease were excluded, as

the GH was not prescribed by the Paediatric Endocrinology Department. However, we have conducted a retrospective study of these patients with renal disease on GH treatment during the same time period and have also detected a higher incidence of papilledema, as described in the literature.

The association between the dose of GH and the risk of PTCS is not clearly established. Malozowski et al (15) reported that higher doses and increased frequency of administration since the introduction of recombinant human GH in 1985 may be contributing to the development of PTCS in some patients. However, Reeves and Doyle found no relationship between the GH dose and PTCS development (8). One of our patients received GH at the usual dose without complications, later on it was withdrawn due to lack of therapeutic effect. Interestingly, papilledema appeared three months after restarting GH at a higher dose. Patients with PWS and mutations in the *SHOX* gene, who received higher doses of GH did not present with papilledema, although these subgroups were small in this study. Even though there is no evidence that the GH dose is directly related with this complication, we recommend starting at lower dose and increasing it progressively, in order to minimize this complication.

Patients with a previous history of PTCS may experience recurrence at rates reported to vary between 6-22% (4,17,18,19). There is usually a triggering factor, such as weight gain or the introduction of known medications associated with secondary PTCS (20). In our series, the only patient with a previous history of PTCS, presented with papilledema. This patient was obese, which could have been a further risk factor for primary PTCS recurrence, however his weight had remained stable prior to starting GH treatment, at one month and at two months of treatment, when papilledema was diagnosed. For this reason, we believe it is important to identify patients initiating GH therapy with a previous history of PTCS because of the risk of recurrence. Also, consideration should be taken for starting treatment at a lower dose with progressive increases, accompanied by with careful follow-up including fundus examination during the first months of treatment.

Headache is a common symptom in the general paediatric population, and is also relatively frequent in patients on GH

therapy, being the third most prevalent side effect described in KIGS (Pfizer International Growth study database) (16). On the other hand, headache is the main manifestation of intracranial hypertension at any age. However, in the paediatric population, headache is less common and 33% of children with PTCS may be totally asymptomatic (21,22), and diagnosis is only made on the observation of papilledema on fundus examination. It is important to highlight that papilledema is a cause of visual morbidity, including irreversible vision loss, independent of the patient symptoms. In our series, all patients with papilledema were asymptomatic, whereas no patients examined urgently for headache presented with papilledema.

Stopping GH is usually enough to treat this complication. Once papilledema has resolved GH can be reintroduced at a lower dose and progressively increased until the required dose is achieved to prevent recurrence and optimum growth. In the four patients where GH was reintroduced there were no recurrences of papilledema.

Study Limitations

The strengths of our study are the prospective design and the number of patients included in it. As children may be asymptomatic, prospective studies are the only way to establish the real incidence of this complication. The main limitation of our study is that patients with kidney diseases were not included and this group of patients has been reported to be at greatest risk of this complication in a different series.

Conclusion

In this study, we have shown that GH therapy is a risk factor for intracranial hypertension and the at-risk group were patients with GH deficiency and hypothalamic-pituitary axis abnormalities on MRI or genetic or chromosomal diseases. Patients may be totally asymptomatic, so fundus examination should be systematically implemented in this at-risk group, irrespective of the presence or absence of symptoms.

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Ethics

Ethics Committee Approval: Ethics approval was obtained from the Ethic Review Committee of the Hospital Universitario Vall d'Hebron (approval number: 383, date: 17.05.2019).

Informed Consent: All subjects (or their parents or guardians) gave their written informed consent.

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Authorship Contributions

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