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Research

Growth Hormone Treatment and Papilledema: a Prospective Pilot Study

Martín-Begué et al. GH and Papilledema

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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 chromosome diseases
- A previous history of pseudotumor cerebri should be investigated.

Abstract
Objective: To investigate the incidence of pseudotumor cerebri syndrome in children treated with growth hormone in a paediatric hospital and to identify risk factors of this complication.
Methods: Prospective pilot study of paediatric patients treated with growth hormone, 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: 289 patients were included: 244 had a growth hormone deficiency, 36 had short stature associated with small for gestational age, six had a mutation in the SHOX gene and three had Prader-Willi Syndrome. Five patients developed papilledema, all were asymptomatic and had a growth hormone deficiency: one had a craniopharyngioma, two a polymalformative syndrome associated with hypothalamic-pituitary axis anomalies, one patient a non-specified genetic disease with hippocampal inversion and one patient with normal magnetic resonance imaging who had developed a primary pseudotumor cerebri syndrome years before.
Conclusions: Growth hormone treatment is a cause of pseudotumor cerebri syndrome. In our series, at risk patients had growth hormone deficiency and hypothalamic-pituitary anatomic anomalies or genetic or chromosome 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

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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 (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 pseudotumor cerebri, 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. Reeve and Doyle found that the prevalence in the GH treated population was approximately 100 times greater than in the general paediatric population (8). This complication usually occurs in the first weeks after initiating treatment (approximately 2-12 weeks) and the papilledema (optic disc swelling from raised intracranial pressure) resolves on stopping treatment (9,8).

Pseudopapilledema is an elevated optic disc with obscured margins that may occur in hyperopic eyes and in the presence of buried optic disc drusen and not from raised intracranial pressure. Optic disc drusen are acellular deposits located within the optic disc. Sometimes it can be very difficult to differentiate between pseudopapilledema and papilledema requiring experienced ophthalmologist's opinion and complementary tests (10).

The aim of this study was to investigate the incidence of PTCS in children treated with GH in our paediatric hospital and to identify risk factors for this complication. We wanted to establish 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 included: 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 exclusion criteria 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 with this entity and papilledema in subsequent fundus controls.

Fundus examination was carried out with indirect ophthalmoscopy and retinography was taken in cases of pseudopapilledema to facilitate follow up. In case of detecting papilledema, GH was stopped and fundus examination was repeated 4 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 on the target 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 $1mg/m^2$/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). Subjects (or their parents or guardians) have given their written informed consent.

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 for loss of ophthalmological follow up. The mean age was 9 years old (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%) for GH deficiency, 36 patients (12.5%) for short stature associated with SGA, 6 patients (2%) with a mutation in the SHOX gene and 3 (1%) for 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 they had 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 pseudotumor cerebri in our population was 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 20mg/dL (15-45); there was neither leukocytes nor red blood cells. 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 despite its mechanism is little understood. Two hypotheses are considered: on one hand, GH could have a physiological antidiuretic effect, causing retention of sodium and water and expansion in blood volume, and reducing cerebrospinal fluid (CSF) resorption by the arachnoid villi. Whilst on the other hand, GH would cross the blood-brain barrier, then raising 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 been increased as well as the potential adverse effects (15).

In our study, there were five patients with papilledema (1,7%), a higher incidence comparing with the expected incidence in general paediatric population as described in the literature (9, 11, 8,13). All of them had GH deficiency. Other different indications for GH treatment did not cause papilledema in this series, given the fact that it could be biased due the small size of these other indications.

As all the patients with papilledema were found to have GH deficiency, we analysed this group, classifying patients into three subgroups (Table2):

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 chromosome diseases.

When considering patients who presented with papilledema, three completed criteria for subgroup 2, presenting 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 pseudotumor cerebri syndrome 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 before. The patient with a suprasellar tumour also had a ventriculoperitoneal shunt, suggesting that the presence of a shunt is not protective against a raise in intracranial pressure induced by GH therapy.

For each GH indication, the incidence of this adverse effect can vary. Reeves and Doyle, reported higher incidence in patients with renal failure and Turner's Syndrome (8). Souza and Collet-Solberg, also detected a higher incidence in patients with chronic kidney disease (11). Darendeliler F and col, described that patients with Turner syndrome, organic GH deficiency, PWS and chronic renal insufficiency might be more prone to develop papilledema when receiving GH **(**16). 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. 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 (15). 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 there is no evidence that the GH dose is directly related with this complication we recommend starting at lower dose and increase it progressively, in order to minimize this complication.

Patients with a previous history of PTCS may experience recurrence in 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 pseudotumor cerebri (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 the risk of recurrence. Also, consideration should be taken for starting treatment at a lower dose with progressive increasing with strict controls with fundus examination during the first months of treatment.

Headache is a common symptom in 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. 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 stablish 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 the highest risk for present this complication in the 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 chromosome diseases. Patients may be totally asymptomatic, so fundus examination should be systematically indicated in this at-risk group irrespective of the presence or not of symptoms.

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Authorship Contribution

All authors had substantial contributions to the conception and design of the work, data collection, analysis and interpretation of data, writing the manuscript and critical revision of the manuscript.

Disclosure statement

The authors have no conflicts of interest to declare.

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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 / RM 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: resonance magnetic 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	**Nº patients**	**Nº 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: brain radiation therapy