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SHORT COMMUNICATION

Delayed onset of pseudotumor cerebri syndrome 7 years after starting human recombinant growth hormone treatment

A. VISCHI, S. GUERRIERO, G. GIANCIPOLI, V. LORUSSO, G. SBORGIA

Departments of Ophthalmology and ORL, Division of Ophthalmology, University of Bari - Italy

PURPOSE. *To report a case of pseudotumor cerebri (PTC) following treatment with human recombinant growth hormone (GH).*
METHODS. *A 42-year-old man who developed pseudotumor cerebri 7 years after starting human recombinant GH treatment is presented.*
RESULTS. *The patient's medical history was significant for hypophyseal dwarfism with a serious deficit of GH, hypogonadotropic hypogonadism, and hypothyroidism. In 1996 he started taking GH, testosterone, and l-thyroxine. Fundus examination showed disc edema in the left eye. GH was discontinued, and acetazolamide therapy was initiated. At the 3-month follow-up the acuity without correction was patch and the unilateral papilledema had resolved.*
CONCLUSIONS. *Pseudotumor cerebri or idiopathic intracranial hypertension is an uncommon and complex disorder. The diagnosis is possible when important criteria symptoms and signs are met. Several conditions and risk factors are associated with PTC. The most recently recognized risk factor is GH therapy. (Eur J Ophthalmol 2006; 16:178)*

KEY WORDS. *GH, Pseudotumor cerebri, Papilledema*

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INTRODUCTION

Pseudotumor cerebri (PTC), or idiopathic intracranial hypertension, is an uncommon and complex disorder. Several conditions and risk factors are associated with PTC. A most recently recognized risk factor is growth hormone (GH) therapy. The first published reports appeared in 1992 and 1993 (1, 2). Recombinant human GH became commercially available in late 1985. With this unlimited supply of GH, many more people were treated with much larger doses and with more frequent injections. Subsequently, reports of GH-associated PTC increased (3-7).

Case report

In October 2003, a 42-year-old man was seen in our department. He had nonspecific visual disturbances with headache for a few days. His medical history was significant for hypophyseal dwarfism with a serious deficit of GH, hypogonadotropic hypogonadism, and hypothyroidism. In 1996, he started taking GH (0.3 mg/d), testosterone (100 mg/mo), and l-thyroxine (50 mg/d). He had no known drug allergies. Slit-lamp examination results were normal with intraocular pressure of 15 mmHg in each eye by applanation tonometry. Visual acuity was 20/20 in the right eye and 20/40 in the left. He was orthophoric for distance and near. The cycloplegic refraction was +0.25 in each eye. Fundus examination in the right eye was normal but in the left eye showed a +3 disc edema, absent spontaneous venous pulsations, and increased tortuosity of the retinal vessels. Retinal hemorrhages were visualized. There was no evidence of sixth cranial nerve palsy. Fluorescein angiography showed hyperfluorescence of optic disk with late leakage and a hypofluorescent zone of the retina surrounding optic disk, related to hemorrhage (Fig. 1). Orbital echography showed optic nerve shadow expansion

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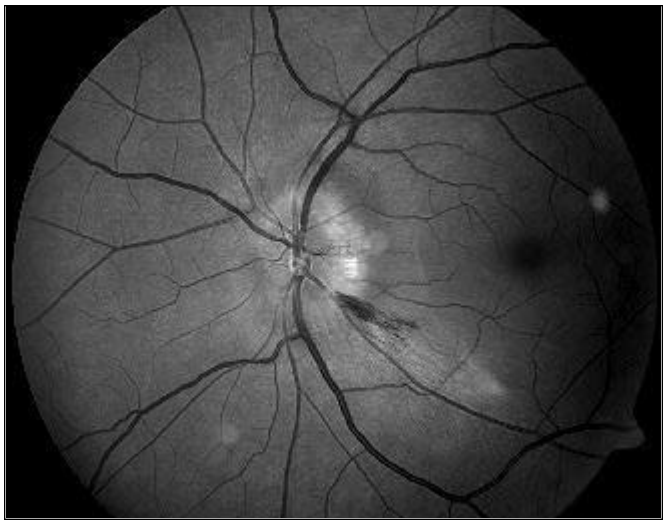

Fig. 1 - *Fluorescein angiography.*

with sheaths evidence in each eye (more evidence in the left) and papilledema in the left eye. Computerized axial tomography scan performed the same day showed normal ventricular size without evidence of mass, hemorrhages, edema, or midline shift. Visual fields (central 30-2 SITA-STANDARD) confirmed bilaterally enlarged blind spots. Significant laboratory values revealed LDH 71 U/L, total bilirubin 1.84 mg/dL. He had hypochromic microcytic anemia with hemoglobin and hematocrit of 12 g/dL and 38%, respectively. Antiphospholipid antibodies were normal, and negative p and c ANCA and normal inflammatory index were noted. Lumbar puncture revealed an elevated opening pressure of 36 cm water. Cerebrospinal fluid (CSF) composition was normal. GH was discontinued, and acetazolamide therapy was initiated. One month after presentation, visual acuity was 20/20 in the right eye and improved to 20/25 in the left eye. Slit-lamp examination results were normal with intraocular pressure of 15 mmHg in each eye. Dilated fundus examination showed marked reduction in optic nerve swelling in the left eye and absent papilledema in the left eye. Venous tortuosity and dilatation and retinal hemorrhages were minimal. At the 3-month follow-up examination, there was no complaint of headache. Visual acuity without correction was 20/20 in each eye. The papilledema in the left eye had resolved, and spontaneous venous pulsations were noted. Acetazolamide therapy was stopped. Six- and 9-month follow-up examination reconfirmed the findings of normal optic nerves with spontaneous venous pulsations. In September 2004, recombinant human GH was restarted at a dose of 0.15 mg/d by the primary endocrinologist.

DISCUSSION

We report an adult patient who met the criteria for PTC based on elevated intracranial pressure, normal CSF composition, and normal brain imaging. Treatment with rhGH had been started 7 years before presentation. The dosage of rhGH was 0.3 mg/d. This patient was a rare exception because the diagnosis of PTC was made 7 years after rhGH was started and the papilledema was unilateral. This makes the relationship between rhGH and PTC somewhat debatable in this case. Yet the papilledema resolved by the third month after the discontinuation of rhGH treatment. The clinical signs and symptoms in GH-treated patients with PTC were nonspecific; they included signs of intracranial hypertension of any cause. The most common symptom was headache, and papilledema was the most frequently observed sign. Visual disturbances were also very common. Patients with PTC may rarely be discovered incidentally when ophthalmoscopy reveals swollen optic discs and they have no symptoms or only nonspecific visual complaints with no headache. There is no clear correlation between the degree of elevation of the CSF pressure and the severity of the headache. Monocular or binocular transient visual obscurations are common. Blurring or total loss of vision lasts seconds, rarely longer, and is frequently precipitated by some change in posture or the Valsalva maneuver. Regarded by some as a harbinger of visual failure, transient visual obscurations may be alarming but have not definitely been proved to predict serious visual loss. Diplopia, a much less common symptom, is transient, almost always horizontal, and caused by sixth-nerve paresis. When persistent loss of vision is the presenting complaint, permanent severe visual loss is common. The causes of permanent visual acuity loss in IIH include optic disc infarction, macular lesions, subretinal hemorrhage, and a combination of ischemic and compression damage to the optic nerves. There has been an emergence of PTC cases since 1985, the year GH became plentiful with the commercial availability of recombinant human GH. A close temporal relationship between onset of GH treatment and onset of PTC has been reported, and almost always there has been a resolution of the signs and symptoms of PTC shortly after GH therapy is discontinued (7). An increase in the occurrence of PTC after insulin growth factor-I (IGF-I) therapy has also been reported (1). Recombinant human GH crosses the blood–brain barrier and increases the level of GH and IGF-I in the CSF (8). The choroids plexuses

contain GH receptors and a high concentration of IGF-I receptors. Thus, GH may cause excessive production of CSF. GH also causes sodium and water retention (9, 10). This retention may expand the blood volume, which may impair CSF absorption at the arachnoid villi. Neither excessive CSF production nor impaired CSF absorption explains the absence of ventriculomegaly. It is postulated that there is a loosening of the pial cells overlying the cerebral convexities, which permits a bidirectional flow of CSF between the ventricles and the extracellular and subarachnoid spaces (11). In most cases, PTC will begin within a few months after the start of GH treatment. There are occasional cases, however, when onset occurs a few years later. Patients with Turner's syndrome and renal failure may be at increased risk for PTC when they receive GH treatment.

Obesity may further increase the risk of PTC for renal failure patients. Papilledema and headaches are very common in adults with PTC; in almost all patients, they occur simultaneously. GH therapy should be discontinued as soon as PTC is suspected. In almost all patients, the increased intracranial pressure will resolve, usually within a few months. If GH therapy is resumed, the dose of GH should be reduced to 25–50% of the original dose. Although PTC may recur after the reintroduction of GH, most often it does not (11). Vision loss, which is the most important complication of PTC, may occur early or late in the course of treatment. Patients receiving hormone replacement often will complain of headaches. The headaches may be medication induced from the rhGH or related to the early development of pseudotumor. Although the pathophysiology for PTC is unknown, cessation of the drug is important in reversing the changes in the optic nerve. Permanent loss of visual function does occur in cases of PTC in the adult and pediatric general population, sometimes in as many as 10% of patients. Any patient who starts rhGH therapy and who is preverbal or cannot communicate adequately should undergo a baseline examination with routine follow-up. Otherwise, examinations should be performed immediately when visual symptoms or headaches arise.

The authors do not have proprietary interest in any product mentioned.

Reprint requests to:
Antonio Vischi, MD
Via Giuseppe Fanelli, 219
70124 Bari, Italy
anvischi@tiscali.it

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