

# Octreotide: A therapeutic option for idiopathic intracranial hypertension

Panagopoulos GN<sup>1</sup>, Deftereos SN<sup>1</sup>, Tagaris GA<sup>1</sup>, Grillia M<sup>1</sup>, Kounadi T<sup>2</sup>, Karamani O<sup>2</sup>, Panagiotidis D<sup>3</sup>, Koutiola-Pappa E<sup>3</sup>, Karageorgiou CE<sup>1</sup>, Piadites G<sup>2</sup>

<sup>1</sup>Department of Neurology, Athens General Hospital "G. Gennimatas", Athens, Greece

<sup>2</sup>Department of Endocrinology, Athens General Hospital "G. Gennimatas", Athens, Greece

<sup>3</sup>Department of Ophthalmology, Athens General Hospital "G. Gennimatas", Athens, Greece

Corresponding Author: Dr Spyros N Deftereos, Eirinis 67st, Ag. Paraskevi, 15341, Athens, Greece;  
Email: deftereo@gmail.com

## ABSTRACT

**PURPOSE:** To study the effects of octreotide, a somatostatin analogue, in patients with Idiopathic Intracranial Hypertension (IIH). **METHODS:** We performed a prospective, open-label study of the effect of Octreotide on 26 patients with symptoms and signs of IIH, investigated by brain MRI and lumbar puncture. Octreotide was administered subcutaneously, at an initial dose of 0.3 mg/day; and was gradually increased until headache was relieved (upper-dose limit: 1 mg/day). Treatment with octreotide at 1 mg/day was administered for a maximum of six to eight months and afterwards the dose was gradually tapered. Patients were followed prospectively every month for three years. CSF opening pressure was measured before the treatment was started and again in the first follow-up examination, on month one. In all follow-up visits the presence of papilledema was evaluated by fundoscopy; visual fields and visual acuity were also examined. **RESULTS:** Overall 24/26 patients improved significantly (92%). Headache was relieved within days (1-10, median 7 days). Papilledema subsided in all 24 patients, in up to two months (35 to 68, median 45 days). Visual disturbances, initially presenting in 20 of our patients, improved in 18 (90%). The mean reduction in CSF pressure after treatment was  $20.72 \pm 10.7$  cmH<sub>2</sub>O (range 2 to 48). Patients were followed for three years after cessation of treatment. No recurrence of papilledema, or any other symptoms, has been observed. **CONCLUSIONS:** Octreotide resulted in a significant and sustained improvement of IIH in our patients. These results suggest that it may be an effective alternative to existing treatments for IIH.

Search Terms: Idiopathic Intracranial Hypertension, Treatment, Octreotide, Somatostatin

## INTRODUCTION

The pathogenesis of idiopathic intracranial hypertension (IIH) is unknown. It has been attributed to cerebral edema (Sahs, 1956), cerebral hyperaemia (Mathew, 1975), increased resistance to CSF drainage (Johnstone, 1973) and increased venous sinus pressure (King, 1995) but it remains unclear which element is the primary pathogenic factor.

Although the pathophysiology of IIH is controversial, it seems likely that growth hormone (GH) might play a significant role in the onset of the disease. Indeed, the majority (80%) of children treated with recombinant GH for various reasons (e.g. growth hormone deficiency, chronic renal failure, Turner's syndrome and Prader-Willi syndrome), as well as adults with tumor-induced hypoglycemia, developed IIH (Malozowski, 1993). Moreover, patients refractory to GH treatment when treated with insulin-like

growth factor I (IGF-I), which is the primary mediator of the actions of GH, also developed IIIH (Malozowski, 1993; Price, 1995). The hypothesis that changes in hormonal status may be involved in the pathogenesis of IIIH is supported by studies demonstrating that octreotide, a somatostatin analogue that exerts potent inhibitory effects on the GH/IGF-I axis (Plewe, 1984, Tauber, 1989) has been very effective in the relief of severe chronic headache associated with acromegaly (Sandler, 1987) as well as headache associated with pituitary tumors (Williams, 1987).

In a previous study, octreotide was administered to three patients suffering from IIIH and produced promising result (Antaraki, 1993). In the present study, we evaluated the use of octreotide in a larger group of patient with IIIH.

## METHODS

We recruited our study subjects from patients admitted to our Department (Neurology Department, “G. Gennimatas” General Hospital, Athens, Greece) between January 1996 and April 2003 with symptoms and signs of increased intracranial pressure (headache, dizziness, blurred vision). Further inclusion criteria where: 1) unilateral or bilateral papilledema, 2) CSF pressure greater than 200 mmH<sub>2</sub>O, 3) normal CSF composition, 4) absence of enlarged ventricles or an intracranial mass in brain MRI and 5) absent focal neurological signs. We excluded patients with intracranial hypertension secondary to cerebral venous occlusion or intracranial mass (evidenced by MRI), meningeal diseases or increased CSF protein (evidenced by CSF examination) and toxic or endocrine disorders (disclosed by history and blood screening).

Twenty-six patients were finally enrolled and 51 were excluded: 38 due to the presence of an intracranial mass, 5 due to cerebral venous occlusion, 4 due to carcinomatous meningitis, 3 due to hypothyroidism and 1 due to tetracycline toxicosis.

Patients underwent a complete ophthalmologic evaluation that included the examination of visual acuity and visual fields. Fluoroangiography was also performed. CSF opening pressure was measured on admission by lumbar puncture. Patients were placed in the lateral decubitus position. Octreotide (Sandostatin<sup>®</sup>), a long-acting somatostatin analogue was administered subcutaneously at an initial dose of 0.3 mg/day. The dose was increased slowly (by 0.1 mg every third day) until the headache was relieved or a maximum dose of 1 mg/day was reached. This dose was sustained for six to eight months. Afterwards it was slowly tapered.

Patients were followed prospectively every month for three years. CSF opening pressure was measured again in the first follow-up examination, on month one. In all follow-up visits the presence of papilledema was evaluated by fundoscopy; visual fields and visual acuity were also examined.

The study protocol was approved by the Institutional Committee on human research and all patients gave informed consent. Statistical analysis was performed using the SPSS 10.0 statistical software package (SPSS Inc., Chicago, Illinois). Continuous variables are expressed as mean  $\pm$  standard deviation. Student's *t* test was used to compare variables. A *p* < 0.05 was considered statistically significant.

## RESULTS

Mean patient age was 27.5 $\pm$ 5.1 years. Twenty-three were females (88.5%). Eighteen of the 26 patients (69%) were overweight (Body Mass Index > 25). Mean body mass index was 26.65 $\pm$ 2.25. Headache and papilledema were presenting symptoms in all patients. The headache was usually gradual in onset, but

some (2/26) experienced acute severe headache. Most patients (20/26) experienced transient visual obscurations. These occurred several times a day and were provoked by postural changes. Double vision, sometimes intermittent, was observed in 5 out of 26 patients. In most of cases (16/26), visual field disturbances (2-4 dioptre) could be demonstrated, while visual acuity was reduced in 6.

Overall 24/26 patients improved significantly (92%). Headache was relieved within days (1-10, median 7 days). Papilledema subsided in all these 24 patients, in up to two months (35 to 68, median 45 days). Visual disturbances, initially presenting in 20 of our patients, finally improved in 18 (90%). Figures 1 and 2 show improvement of papilledema and visual field defects in two of our patients.

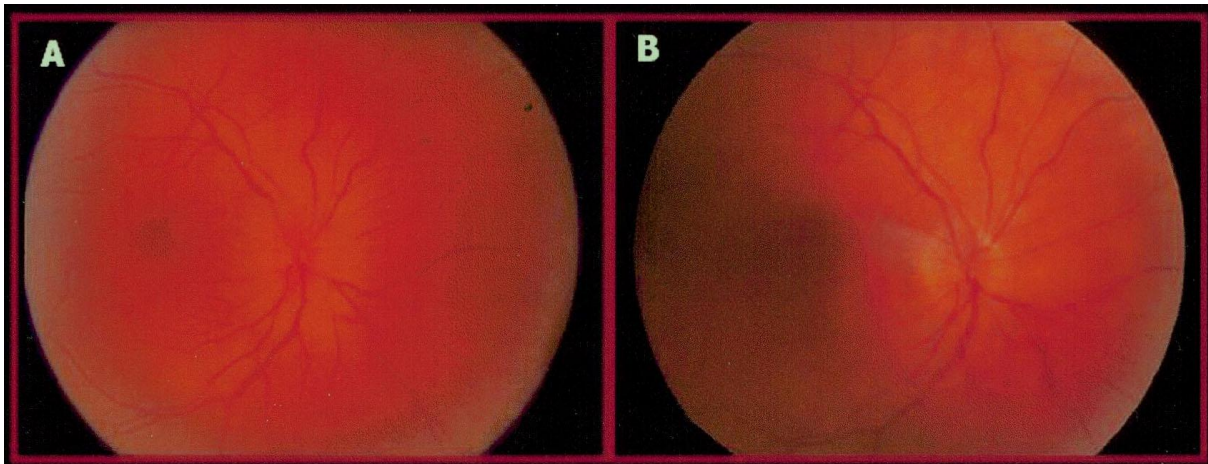


Figure 1. (A) Papilledema in patient No.3 before treatment with octreotide. (B) Remission of papilledema two months after treatment with octreotide (0.4 mg/day)

The mean value of CSF opening pressure before treatment with Octreotide was  $34.4 \pm 12.5$  cmH<sub>2</sub>O (range 21 to 66). After treatment mean CSF pressure was  $14.68 \pm 4.52$  cmH<sub>2</sub>O (range 8 to 23). The difference of the two means was statistically significant ( $p < 0.001$ ). The mean reduction in CSF pressure after treatment was  $20.72 \pm 10.7$  cmH<sub>2</sub>O (range 2 to 48). The median duration of the treatment was 42 weeks (range 15-130) and the median total dose was 112.5 mg (range 31.4-290.4 mg).

Two of our patients have not responded to treatment. In these cases, a very small reduction in CSF opening pressure was noted, namely 3 and 2 cmH<sub>2</sub>O, after 15 weeks of treatment, while headache, papilledema and visual disturbances did not improve. Octreotide was discontinued and conventional therapy with acetazolamide and corticosteroids was initiated, but it failed to control the high intracranial pressure as well; ultimately the insertion of a lumboperitoneal shunt was required.

Nausea (5 patients, 19%) and diarrhea (4 patients, 15%) were the most common side effects. The symptoms were mild and did not require interruption of the treatment.

Patients were followed for three years after cessation of treatment. No recurrence of the papilledema, or any of the other symptoms, has been observed.

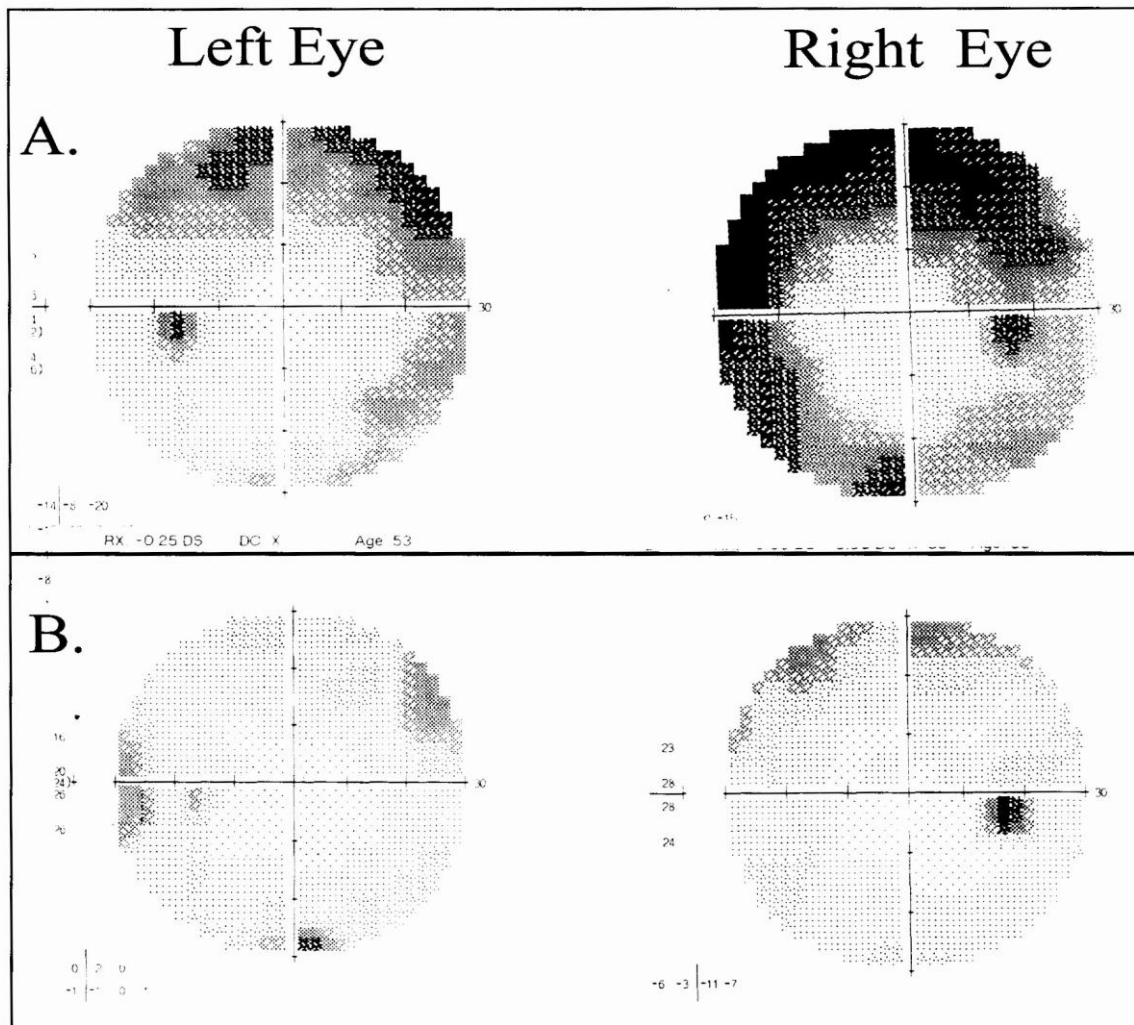


Figure 2. (A) Visual field defects in patient No.16 before treatment with octreotide. (B) Improvement four months after treatment with octreotide (0.4 mg/day).

## DISCUSSION

The medical management of IIH currently includes the carbonic anhydrase inhibitor acetazolamide, corticosteroids and diuretics. Repeated lumbar punctures and surgical procedures, such as ventriculoperitoneal/lumboperitoneal shunts and optic-nerve-sheath fenestration are used in those not responding to medical management and who present visual deterioration (Lueck, 2005, Alex, 2006). To date, there have been no sufficiently large studies of any treatment modality in idiopathic intracranial hypertension so the evidence base for management decisions is poor (Lueck, 2005, Alex, 2006).

We treated 26 patients suffering from IIH with octreotide, and we followed them prospectively for three years. Overall, 92% of the patients were relieved of the signs and symptoms of intracranial hypertension and this remission lasted at least three years after cessation of the treatment. Visual

disturbances improved in 90%. These results suggest that octreotide may be an effective alternative to existing treatments for IIH. In addition, these results were long-lasting, since none of these patients relapsed within the three-year follow-up period.

There is a wide spectrum of potential therapeutic application for somatostatin analogues, including acromegaly and secretory pancreatic and carcinoid tumors (Lamberts, 1996). Much effort has been directed toward developing synthetic peptides, which resist enzymatic degradation and have a longer half-life than the native one. Octreotide is a somatostatin analogue that is used successfully in the clinical setting; its pharmacodynamic properties are qualitatively similar to those of the endogenous peptide hormone but differ in terms of potency, antihormonal specificity and duration of activity (Battershill, 1989, Lamberts, 1996).

The mechanism of action of octreotide in IIH is not clear, while its determination is hindered by the fact that the pathogenesis of IIH itself is currently unknown. Indeed, the view that IIH is a result of increased resistance to CSF absorption and of increased CSF production has been disputed (Digre, 2001). In other studies (Corbett, 2002), IIH has been attributed to increased venous sinus pressure, but even this hypothesis has been challenged. King et al. (2002) suggested that increased venous sinus pressure is a result rather than the cause of intracranial hypertension. Their view is supported by evidence of a reduction in venous sinus pressure following the reduction of CSF pressure after CSF drainage.

On the other hand, several lines of evidence suggest that octreotide may play a role in the pathogenesis of IIH. Firstly, IIH is a well-recognized side effect of treatment with GH (Malozowski, 1993). Secondly, insulin-like growth factor I receptors, which are the mediators of the effects of GH, are abundant in the choroid plexuses, the site of production of cerebrospinal fluid (Ichimiya, 1988). Finally, a decrease in the production of GH has been reported in patients that underwent shunting operation for hydrocephalus (Lopponen, 1998). These observations support the view that intracranial pressure and the production of GH are associated.

Treatment with octreotide relieved headache in our patients; although this effect may be mediated solely by the reduction of intracranial pressure, it seems that additional mechanisms are operative. Indeed, it has been suggested that long acting somatostatin analogues inhibit serotonin, bradykinin, prostaglandins, substance P and vasoactive intestinal peptide, which are involved in the development of several types of headache (Kapicioglu, 1997, Matharu, 2004). In two previous reports, octreotide has been found to be an effective treatment for migraine and cluster headache (Kapicioglu, 1997, Matharu, 2004).

A limitation of our study is that we were not blinded and did not compare octreotide with other available treatments for IIH. However, we have shown that this drug is effective and produces a sustained result. Improvement of the symptoms and signs of IIH for a three-year follow-up period has not been reported so far, in studies of the other available medications. Our aim here was to report our encouraging results and stimulate further studies on this important issue.

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