

## Pseudotumor Cerebri Associated with Leuprolide Acetate for Central Precocious Puberty-Case Report

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Received date: Mar 23, 2015, Accepted date: Jun 27, 2015, Published date: Jun 30, 2015

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### Abstract

This article represents the fourth case in literature of an association between pseudotumor cerebri (PTC) and leuprolide acetate, the first with precocious puberty and severe visual loss. A 9-year-old girl with precocious puberty was treated with a once-monthly dose of leuprolide acetate (3.75 mg) for three months. In the 4th month of treatment, it was decided to increase the dosage of leuprolide acetate to 11.25 mg in once-quarterly doses. After 1 month, she complained of holocranial headache, transient visual obscuration followed by progressive visual loss. After 6 months, she persisted with holocranial headache and progressive visual loss associated with ocular deviation. Neuro-ophthalmological examination revealed severe visual loss and bilateral papilledema. Cerebrospinal fluid (CSF) analysis showed opening pressure of 45 cm H<sub>2</sub>O. The most likely diagnosis was PTC associated with leuprolide acetate. Treatment was started immediately with oral acetazolamide and leuprolide was discontinued. Acetazolamide was discontinued for having induced metabolic acidosis. A ventriculoperitoneal shunt was performed to control intracranial pressure as an alternative to acetazolamide treatment. The follow-up of 18 months showed CSF pressure of 14 cm H<sub>2</sub>O, stabilization of visual acuity and resolution of papilledema. There appears to be a causal relationship between the onset of leuprolide acetate with the development of PTC. Children should have a complete ophthalmic evaluation if they report headache or visual disturbances after administration of leuprolide acetate.

**Keywords:** Pseudotumor cerebri; Idiopathic intracranial hypertension; Leuprolide acetate; Precocious puberty

0.012% overall and increases to 0.028% among obese individuals (body mass index  $\geq 30$  kg/m<sup>2</sup>) [4].

### Introduction

Precocious puberty is the early activation of the biological maturation process triggered by increased pulsatile secretion of gonadotropin-releasing hormone (GnRH) that culminates in the appearance of secondary sexual characteristics.

Since 1980, GnRH analogues have been widely used as the treatment of choice in central precocious puberty. Reports of side effects of GnRH analogues are uncommon and may include local erythema, induration, and abscess as well as transient systemic effects such as headaches, hot flashes, weight gain, and depression [1,2].

Pseudotumor cerebri (PTC) is a syndrome associated to intracranial hypertension (IH) and no imaging evidence of ventriculomegaly or an intracranial lesion. PTC can be classified as either primary (when there is no clear causal factor) or secondary to cerebral venous thrombosis or changes in the composition of the cerebrospinal fluid (CSF). The primary PTC may be associated with obesity (also known as PTC idiopathic) and some pharmacological agents (such as vitamin A or derivatives and tetracyclines) [3]. The PTC idiopathic is the most common type of the disease and its incidence has been estimated at 1-3 per 100,000 in the general population, with an increase to 19 per 100,000 among overweight patients [4]. The prevalence of PTC idiopathic among Americans aged  $\geq 15$  years has been estimated to be

We present a case report of a female child with central precocious puberty who developed PTC with severe visual loss associated with the use of leuprolide acetate, a synthetic drug similar to GnRH.

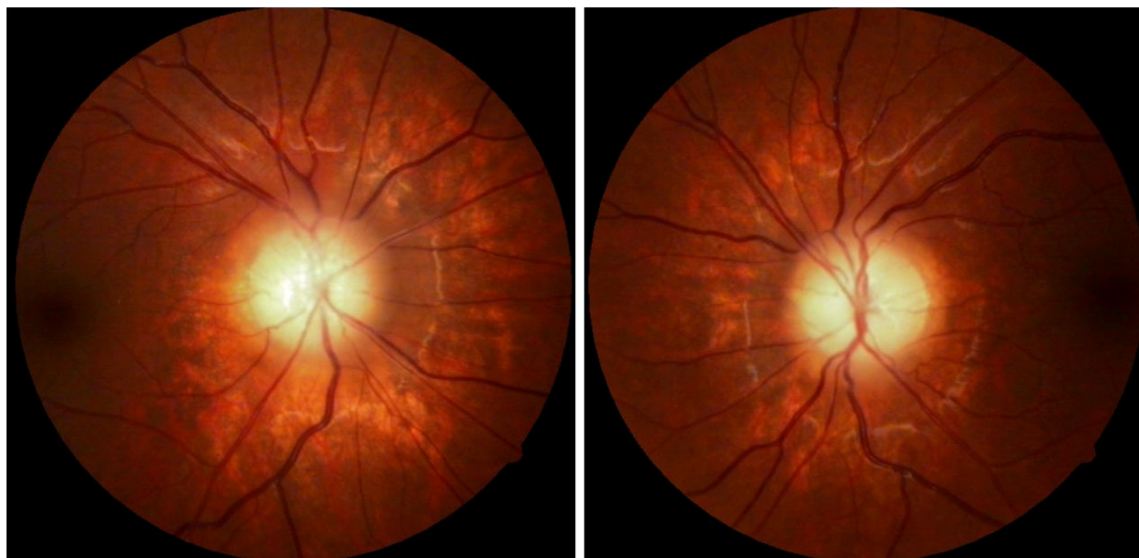
### Case Presentation

A 9 year old girl with no significant past medical history was referred because of rapidly progressive puberty. She presented with axillary odor, accelerated growth velocity and the larche onset at the age of 7 years, 6 months. On work-up, she showed advancement of bone age (bone age: 11 years, 6 months; chronological age: 9 years), gonadotropins at pubertal levels (basal LH levels: 2 U/L; FSH: 3.3 U/L-IFMA) and uterine volume of 12.3 cc. Because precocious pubertal development is associated with a loss of adult height and psychological immaturity, the patient started medical treatment at the age of 9 with a once-monthly dose of 3.75 leuprolide acetate. After three doses, she showed no symptoms or side effects.

In the 4th month of treatment, it was decided to increase the dosage of leuprolide acetate to 11.25 mg in once-quarterly doses. After four weeks of the first intramuscular injection of 11.25 mg leuprolide, she presented with moderate holocranial headache. Ten days after the onset of headache, she complained of transient visual obscuration followed by progressive visual loss. Despite the complaints, she received two further doses of 11.25 mg leuprolide as the cause of her headache was still being investigated.

After 6 months, she persisted with holocranial headache and progressive visual loss associated with ocular deviation. Neuro-ophthalmological examination revealed visual acuity of 20/200 in the right eye and 20/40 in the left eye, with relative afferent pupillary defect in the right eye and pale edema of the optic disc in both eyes (Figure 1). Extrinsic ocular motility examination showed

hypofunction of the lateral rectus muscle in both eyes consistent with bilateral involvement of the abducens nerve. Manual perimetry showed increased blind spot and generalized constriction of the isopters (more pronounced in the inferior nasal sector) in both eyes. Neurological examination revealed no significant deficit.



**Figure 1:** Bilateral atrophic papilledema.

CSF analysis showed opening pressure of 45 cm H<sub>2</sub>O (in a lateral decubitus position). No other alterations were found on CSF examination. Magnetic resonance imaging of the brain and orbit detected flattening of the posterior sclera (a suggestive sign of IH) and absence of mass or other alteration associated with IH or optic neuropathy (Figure 2). Magnetic resonance angiography showed no signs of cerebral venous thrombosis.

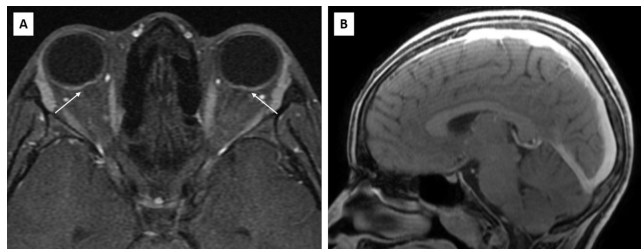
The patient's weight was within normal limits (body mass index of 17.1 kg/m<sup>2</sup>, 75 percentile) and no recent weight gain had been noted. No medication beyond leuprolide was used regularly before or at the time of the medical visit. There was no other pathological condition (besides the early puberty) associated with increased intracranial pressure in childhood, such as endocrine, rheumatologic or infectious diseases.

The most likely diagnosis was PTC associated with leuprolide acetate. Because of severe visual loss, treatment was started immediately with oral acetazolamide and leuprolide was discontinued. Headache and transient visual obscuration showed significant improvement (especially on the day of the lumbar puncture). After 1 month, CSF pressure was 17 cm H<sub>2</sub>O. Acetazolamide was discontinued for having induced metabolic acidosis. After 2 weeks, both headache and transient blurred vision recurred. On that occasion, CSF pressure was 22 cm H<sub>2</sub>O. A ventriculoperitoneal shunt was performed to control intracranial pressure as an alternative to acetazolamide treatment. The follow-up of 18 months showed CSF pressure of 14 cm H<sub>2</sub>O, stabilization of visual acuity and visual field and resolution of papilledema with persistent optic disc atrophy.

## Discussion

PTC associated to leuprolide acetate is an extremely rare event with only three cases reported in the literature [5-7]. Only one of those cases included visual loss [7], which was less severe than in our patient.

The association between a medication and PTC can be classified as possible, probable or certain cause depending on the pattern of presentation and temporal relationship [8]. Our patient presented with clinical manifestation of PTC (headache, strabismus, and papilledema) [3] in the first month of leuprolide acetate administration (11.25 mg) and lumbar puncture revealed increased CSF pressure. However, we could not observe a spontaneous decrease of CSF pressure after the suspension of 11.25 mg leuprolide because the ventriculoperitoneal shunt surgery was performed to control the progression of severe vision loss before the end of 11.25 mg leuprolide 3-month effect. These data suggest a possible association between leuprolide use and PTC.



**Figure 2:** Magnetic resonance imaging shows (A) flattening of the posterior sclera (arrows) and (B) absence of intracranial mass, ventriculomegaly and cerebral venous sinus obstruction.

Acute severe visual loss is an uncommon manifestation in idiopathic and medication-induced PTC; [9] however it may occur associated with secondary forms of PTC due disorders of cerebral venous outflow and cerebrospinal fluid composition [10]. In the present case report, the exclusion of idiopathic and secondary forms of PTC corroborates the association with leuprolide acetate.

The age of onset should classify the present case as childhood PTC. Classically, childhood PTC is a very rare condition with no sex predilection and no association with overweight. Currently, there is a growing suspicion that childhood PTC is different in younger children (true childhood PTC) than in older ones, and the line separating the younger and older groups is the onset of puberty (prepubertal and pubertal PTC) [11]. Some studies have analyzed the differences between prepubertal and pubertal PTC and found that in pubertal PTC there is a strong female preponderance and association with obesity similar to idiopathic PTC in adults [12,13]. The occurrence of precocious puberty in our patient (a female) suggests the diagnosis of idiopathic PTC; however, the absence of overweight is inconsistent with this diagnosis.

One limitation of the present case report is that no CSF pressure reduction was observed after discontinuing leuprolide acetate, which would corroborate the association. However, severe visual loss and metabolic acidosis caused by acetazolamide prompted ventriculoperitoneal shunt surgery.

Medication-induced PTC is an uncommon event that can occur with any medication, although tetracycline and vitamin A are the most frequent agents [3]. The onset of PTC manifestations such as headache, strabismus, transient visual obscurations and even visual loss after administration of a medication should be sufficient to warrant optic nerve examination, a visual field test and CSF pressure measurements, all of which are mandatory to prevent severe visual loss.

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