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Case Report

Pseudotumor Cerebri, the Elusive Diagnosis. A Case Report

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Abstract

Background: Pseudotumor cerebri (PTC) is a well-known syndrome, but sometimes difficult to diagnose; at the time of presentation, all typical symptoms and signs of this condition may not be present, leading to a delay in the diagnostic process and consequent possible permanent visual impairment.

Case Report: After multiple consultation and examination in different clinical practices, a 43-years-old Caucasian woman consulted spontaneously to our center because of persistent headache and unspecific daily transitory visual impairment for 2 months. Her general and ophthalmic examination were unremarkable except for elevated BMI and an extended blind spot in the left eye at the computerized visual field. Suspecting a possible central nervous system infection, a lumbar punction was performed; the cerebrospinal fluid analysis was normal; nevertheless, after the lumbar punction the patient described no more symptoms, therefore we suspected PTC syndrome. A five months' therapy of acetazolamide was initiated, and the patient was advised to lose weight; one year after the diagnosis, she had a lower BMI and no more symptoms.

Conclusion: The management of PTC is based on the concept of reducing intracranial hypertension to avoid optic nerve damages and relief headache. Diagnosis of PTC syndrome is an exclusion one and it is often delayed because the general knowledge of it is limited and multiple doctors from various specialties may have been consulted before patients are identified and treated.

Keywords: *Pseudotumor Cerebri; Intracranial Hypertension; Headache; Vision Loss*

Abbreviations

PTC: Pseudotumor Cerebri; CN: Cranial Nerve; BMI: Body Mass Index; BCVA: Best Corrected Visual Acuity; CSF: Cerebrospinal Fluid; IOP: Intraocular Pressure; OCT: Optical Coherence Tomography; VPS: Ventriculoperitoneal Shunt; LPS: Lumboperitoneal Shunt; VAS: Ventriculoatrial Shunt; ICP: Intracranial Pressure

Introduction

Pseudotumor cerebri syndrome (PTC) is a rare condition, characterized by an increased intracranial pressure of unclear aetiology [1], with a strong female predominance (female/male ratio 8:1). It is commonly described in overweight women of childbearing age (20 - 44

years old), with an annual incidence of 19.3/100.000 [2], and a clear increased risk related to high BMI (20-fold higher [3] than in normal-weight individuals). PTC may also occur in men, generally older and less likely to be obese, and very rarely in children. Quincke reported the first cases of intracranial hypertension of unknown cause in 1893 [4]. In 1914, Warrington coined the term "pseudotumor cerebri" [5], which remains the most popular name for this condition.

PTC classic symptoms are headache (in > 93% of patients [3]) and vision changes. Headache is frequently described as pressure-like, pulsatile, retro-ocular or occipital pain [6] (more likely than holocranial [2]), accompanied by nausea. It can occur daily and be more severe in the morning [2]. Vision loss is described in 70 - 80% of patients, but it is often transient (can lasts for a few seconds). It can be monocular or binocular, partial or complete [2] and precipitated by postural changes and Valsalva manoeuver [6]. Other common ophthalmic symptoms are photopsia (54%), eye pain (44%) and diplopia (38%). Unilateral positional tinnitus is also quite frequent (in 60% of patients [2]). In most cases, ophthalmic examination may reveal bilateral papilledema, visual field abnormalities and poor contrast sensitivity; visual acuity and colour perception are generally preserved in papilledema until it enters a chronic and atrophic stage [7]. Sometimes, cranial nerve palsies may be observed, especially CN VI (in 15% of patients).

Case Report

A 43-years-old Caucasian woman consulted spontaneously with our centre because of persistent headache for the previous 2 months. She described it as mild chronic tension-type headache without any pulsating elements; she reported only 2 episodes of acute headache, with pain mainly in her left eye, which lasted a few minutes. She also described daily transitory visual impairment, especially for near vision; she didn't report any transitory visual obscuration and pulsatile tinnitus was absent. Before coming to our practice, she already consulted with a university ophthalmic hospital, another private ophthalmic practice and a neurologist, who didn't find an origin for her headaches. Her past medical history was unremarkable except for uncorrected hyperopia; she had never suffered from headache and family history for migraine was negative. Her general clinical exam was normal, except for her elevated body mass index (BMI). Pupillary reaction was normal, as well as conjugate eye movements. Her BCVA was 1.25 bilaterally; ocular pressure was 10 mmHg measured by aplanometry in both eyes, slit lamp examination and fundoscopy was unremarkable, without any signs of papillary oedema; the absence of papillary oedema was confirmed by an optic coherence tomography. According to her symptoms, we first suspected a possible headache origin due to an accommodative spasm caused by her uncorrected hyperopia, therefore an optic correction was prescribed after performing a cycloplegic refraction. After a month, the patient came back to our practice describing only a mild improvement of her symptoms about the headache but no improvement in her visual impairment. Therefore, a computerised visual field was performed, which revealed an extension on the blind spot in her left eye (Figure 1). During her previous consultations with different ophthalmic practices the previous month, the patient already performed two computerised visual fields, which were both normal; she also had an MRI (Figure 2), which showed an arachnoid cyst of the posterior fossa in the midline, without mass effect.

In absence of a diagnosis explaining her symptoms and her visual field impairment, she was then referred to a neurosurgeon to have lumbar puncture made and have cerebrospinal fluid (CSF) analysed, to rule out a possible nervous system infection. Lumbar puncture was realised under CT scan because of the important adiposity of the patient. Four tubes of CFS were collected, each one containing 2 - 3 cc of CSF. CSF was directly sent to the laboratory, in order to have standard CSF chemical and physical analysis, cell count and cytology, bacterial and viral cultures and oligoclonal bands. All the CSF analysis were normal. One week after her lumbar puncture, the patient described a complete absence of headache and no more visual problem for near vision; another computerised visual field was performed, which showed no more visual impairment.

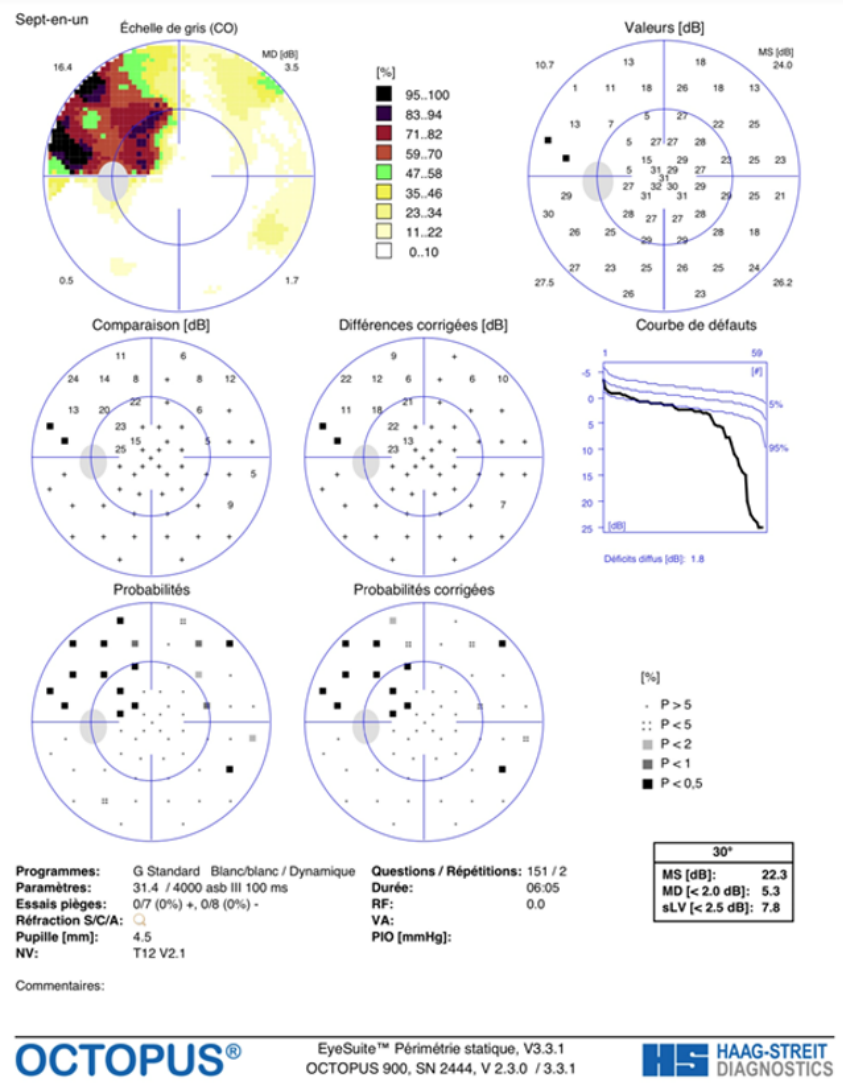

Figure 1: *The computerised visual field shows an extended blind spot in the left eye.*

One month and half after the lumbar puncture, she came back to our practice reporting again headaches and near vision transitory impairment. The hypothesis of a Pseudotumor cerebri syndrome was evocated. In order to confirm the diagnosis, a new lumbar puncture was performed. The opening pressure was 22 cmH20. During the procedure, 30 cc of CSF were subtracted. Some days after, the patient described again remission of headache and visual problems.

In this contest of possible diagnosis of pseudotumor cerebri, a five-month therapy of acetazolamide 250 mg daily was initiated, and the patient was advised to lose weight. One year after the diagnosis, her BMI had diminished, the patient was pain free, and her computerised visual field was normal.

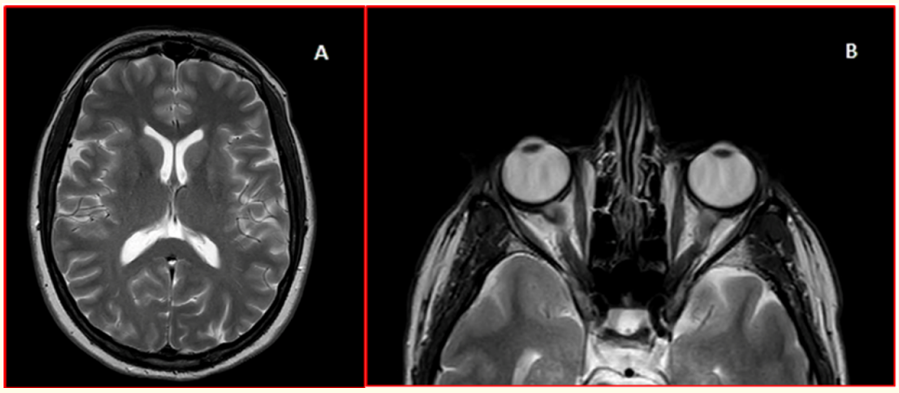

Figure 2: *T2-weight axial MRI, showing normal cerebral ventricles (A) and tortuous optic nerves (B).*

Discussion

PTC aetiology is still largely unknown, even if there are some individuals with the syndrome precipitated by an identifiable secondary cause [1]. Different mechanisms have been proposed to explain the elevated intracranial pressure in these patients. In 1893 Quincke speculated an impairment in the process of reabsorption/production of CSF [4]. Other authors suggest a venous outflow obstruction, e.g. in case of stenotic sinuses, as a possible mechanism. A stenotic transverse sinus was in fact identified in up to 90% of patients. There is controversy on this subject, because the sinus stenosis could be the consequence of the elevated intracranial pressure rather than the cause. As PTC is commonly observed in obese patients, some authors propose that obesity leads to elevated intrabdominal pressure, elevated intrathoracic pressure and finally elevated central venous pressure. Other studies observed endocrinologic dysregulation [8] (aldosterone excess affecting receptors of the choroid plexus, high levels of oestrogen or retinoic acid on epithelial cells [2]) and prothrombotic state as a possible cause of PTC, or iron-deficiency anaemia [6].

By definition, patients with PTC have brain imaging excluding other possible cause of intracranial hypertension. The gold standard brain imaging in these patients is a contrast-enhanced MRI, including orbital imaging and MR venography, as recommended by the American College of Radiologists [9]. Typical MR findings are the "empty sella", a transverse sinus stenosis, slit-like ventricles, the posterior globe flattening, the intraocular optic nerve head protrusion, the optic nerve sheath enlargement, the optic nerve tortuosity and its enhancement after the use of contrast. Lumbar puncture is mandatory to confirm the intracranial hypertension. An opening pressure ≥ 25 cm H_20, with normal CSF analysis is suggestive for PTC [2]. Ophthalmologic evaluation should include:

- Visual acuity with each eye tested separately with best correction: this is generally preserved until the disease enters an atrophic stage.
- Pupil examination.
- Anterior segment slit lamp examination, which is unremarkable in most cases.
- Aplanatory intraocular pressure (IOP), in order to exclude a possible glaucoma, which is one of the main differential diagnosis responsible for optic disc damage and consequent visual field defects [9]; moreover, visual loss is directly correlated to with the extent of disc oedema, which is thought to result from elevated IOP referred from elevated CFS pressure [10].
- Dilated fundal examination, to detect optic disc oedema which is present in 40% of patients [11]; however, papilledema is a nonspecific finding that can occur in other neurological and ophthalmic disease; other nonspecific sings include venous stasis, hyperaemia, haemorrhages, infarcts, choroidal and retinal folds [12].

- Peripheral vision assessment with computerised perimetry is essential, because central vision is impacted late in the disease and this test is fundamental for monitoring response to treatment.
- Optical coherence tomography (OCT) can provide longitudinal assessment of optic nerve swelling and can quantify the thickness of the retinal ganglion cell layers in the macula, a decrease in which is indicative of irreversible injury to the optic nerve [13].

In literature, there have been several articles discussing the diagnostic criteria for PTC. In 1985, Smith [14] proposed the modified Dandy criteria for diagnosis of PTC, which have been used for many years (Table 1).

1. Presence of symptoms and signs of increased intracranial pressure
2. No localizing neurologic signs
3. Cerebrospinal fluid studies demonstrating elevated opening pressure and normal CSF studies
4. Small or normal cerebral ventricles noted on neuroimaging

Table 1: *Modified Dandy criteria for pseudotumor cerebri [14].*

In 2013, Friedman revisited these diagnostic criteria [1]. She divided the criteria into "PTC with papilledema" and "PTC without papilledema" (Table 2). Nowadays, these are the most used criteria. Additionally, a patient with a high degree of suspicion for PTC, even in case of normal intracranial pressure, may still be diagnosed with "probable PTC" and managed based on clinical symptoms.

Diagnostic criteria of PTC with papilledema
1. Papilledema 2. Normal neurological examination except for cranial nerve abnormalities 3. Neuroimaging: normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI with gadolinium. If MRI is unavailable or contraindicated, contrast-enhanced CT may be used 4. Normal CSF composition 5. Elevated lumbar puncture opening pressure (≥ 250 mm CSF in adults and ≥ 280 mm CSF in children [250 mm CSF if the child is not sedated and not obese]) in a properly performed lumbar puncture A diagnosis of pseudotumor cerebri syndrome is definite if all criteria 1-5 are met. The diagnosis is considered probable if criteria 1 - 4 are fulfilled but the CSF pressure is lower than specified for a definite diagnosis.
Diagnostic criteria of PTC without papilledema
1. Criteria 2 to 5 and sixth nerve palsy (unilateral or bilateral) or 2. Criteria 2 to 5 and at least three of the following neuroimaging criteria: • Empty sella • Flattening of the posterior aspect of the globe • Distention of the perioptic subarachnoid space with or without a tortuous optic nerve • Transverse venous sinus stenosis.

Table 2: *Friedman's diagnostic criteria for pseudotumor cerebri [1].*

The management of PTC is based on the concept of reducing intracranial hypertension to avoid optic nerve damages and relief headache. If untreated, persistent visual loss can occur in 25 - 30% of patients [2]. Acetazolamide is the most used drug. It is a diuretic drug with a carbonic anhydrase inhibitor effect, which reduces CSF production (up to 50% [2]). So far, there are no guidelines on drug treatment duration. Jensen., *et al*. [3] suggest tapering the medication slowly down when the visual symptoms and papilledema are improved, the CSF-pressure is normalized, and 5 - 10% weight loss is achieved. Weight reduction plays an important role in the management of patients with PTC syndrome, as confirmed by several trials [3]. Weight loss of 5 - 10% of total body weight [2] results in a significant reduction in CSF pressure, headaches and papilledema and, in some selected cases, bariatric surgery can be proposed to reach the goal faster [9]. In patients who do not respond to the combination of conservative treatments and in case of severe and rapidly progressing visual field deficit, surgery should be considered [9]. The classical surgery is the implant of a CSF diversion system, like ventriculoperitoneal shunt (VPS), lumboperitoneal shunts (LPS) or ventriculoatrial shunt (VAS). Although effective in reducing ICP, complications include shunt blockage, infection and intracranial hypotension. Shunt revisions is required in up to 50% of patients [3]. Other surgical options are transverse sinus stenting (in case of radiological demonstrated stenosis) and the most recent technique of optic nerve sheath fenestration, which directly decreases pressure on the optic nerve by means of cuts in the optic nerve sheath behind the globe to allow CSF to leak from the subarachnoid space [9].

The prognosis depends on the rapidity of onset of symptoms and the severity of vision loss and papilledema at presentation [2]. Even in case of visual and pain improvement some weeks after treatment, the relapse rate is high at up to 40% [3], especially due to a poor compliance to treatment. Patient education and long-term follow-up are recommended, in order to avoid progression to optic atrophy and permanent visual loss.

Our clinical case was particularly challenging because the patient's symptoms at presentation were not specific and may lead to a wrong diagnosis. First, patient's headache description lacked specific features. She described only 2 episodes of acute focal pain in her left eye, without any pulsating elements and no aggravation by coughing, straining nor physical activity [3]. It is widely admitted that headache is undoubtedly one of the most frequent reasons for seeking medical help, which has a huge variety of differential diagnosis; being more specific, ocular causes of headaches include headache associated with refractive error, convergence insufficiency and accommodative spasm [15]. Secondly, our patient never reported transitory visual obscurations, as typically described for PTC syndrome; she related daily visual transient impairment for near vision, which was perfectly compatible with an early onset of presbyopia or uncorrected hyperopia, as she was 43-year-old and she had an hyperopic refractive error [16]. To note, the first two computerised visual field that she performed in different practices were normal. Finally, our patient didn't have papilledema. Absence of papilledema has been reported in many populations of patients with PTC, but its absence may be more suggestive of an alternative aetiology for headache and vision loss.

Our patient doesn't completely satisfy the diagnostic criteria proposed by Friedman, but she fulfils modified Dandy criteria. We decided to treat her as a patient with pseudotumor cerebri syndrome and she had a very good outcome regarding both visual problems and headache.

Conclusion

Pseudotumor cerebri is often a delayed diagnosis because its general knowledge is limited and multiple doctors from various specialties may have been consulted before patients are identified; moreover, at the time of presentation, all typical symptoms and signs of this condition may not be present, leading to a further delay in the diagnostic process. As this condition may cause permanent visual loss, it is important to bear it in mind in the differential diagnosis of patients with headache and visual impairment.

Conflict of Interest

The authors have no conflicts of interest to declare.

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