OLGU SUNUMU / CASE REPORT

Gülhane Tıp Derg 2015;57: 456-459

doi: 10.5455/gulhane. 160604

Primary pseudotumor cerebri syndrome without headache: A report of 3 cases and review of the literature

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SUMMARY

Background: Pseudotumor cerebri syndrome (PTCS) encompasses a variable combination of signs and symptoms of raised intracranial pressure without a brain tumor or space occupying lesion. The lack of continuous pancephalic/retro-orbital headache or pulsating tinnitus is a well-documented observation.
Cases' presentation: We report on 3 non-obese women who presented with progressive visual loss. All of them stated that their headache was mild, non-significant, intermittent, or migraine-like which did resolve spontaneously or after the use of oral paracetamol. Nausea and/or vomiting were present. Variable degrees of reduction in the visual acuity, enlargement of the physiological blond spot, peripheral visual field constriction, papilloedema, and secondary optic atrophy were found. Their CSF opening pressure was 42, 37, and 39 cm H2O respectively; other CSF parameters were normal. Their diagnosis was primary PTCS.
Conclusion: PTCS remains a diagnostic challenge. The lack of significant headache (and obesity) contributed to the delayed diagnosis with resultant visual loss.

Key words: *pseudotumor cerebri; idiopathic intracranial hypertension; headache*

Introduction:

Pseudotumor cerebri syndrome is a variable combination of symptoms and signs of raised intracranial pressure without brain tumors or space occupying lesions. The pathogenesis of the elevated intracranial pressure is still poorly understood. Headache is the commonest presenting symptoms and it is one of the core features of this syndrome.[1-5]

Cases' presentation:

Patient number one was a 29-year-old married woman who presented to us with gradual visual deterioration over a period of 6 months. The visual impairment started on the right side and was followed by the left one after a few weeks. The patient had infrequent nausea and vomiting but she declined the presence of seizures, weakness, tinnitus, or double vision. Careful questioning revealed mild infrequent bi-frontal headache which had responded very well to on-needed oral paracetamol tablets. She was on no regular medications and her past histories were unremarkable.

Her vital signs were unremarkable and the patient's body mass index (BMI) was 23 Kg/m2. Neurological examination revealed decreased visual acuity to finger counting (right eye) and 6/12 (left eye). Left-sided enlargement of the physiological blond spot and with mild constriction of the peripheral field was detected. Right-sided secondary optic atrophy and left-sided grade 4 papilleodema were seen on fundoscopic examination.

An extensive battery of investigations was run; the results turned out to be normal. Lumbar puncture revealed normal cerebrospinal fluid (CSF) parameters apart from opening pressure of 42 cm H2O.

A diagnosis of primary pseudotumor cerebri syndrome (idiopathic intracranial hypertension) was made. The patient was given oral acetazolamide 500 mg twice a day with oral prednisolone 60 mg a day. After 2 weeks, we re-measured the CSF's opening pressure; it was 17 cm H2O. The patient did report some improvement in her left vision; the right eye vision did not show any improvement. The oral prednisolone therapy was tapered gradually and then stopped after 1 month. Two neurosurgeons declined doing any form of surgical intervention. The patient was put on a scheduled follow-up visit at a 1-month interval. Her vision was static after a period of 1 year. Her treatment was acetazolamide 750 mg per day.

Patient number two was a 31-year-old married woman who sought a medical advice for her "multiple sclerosis treatment." She had been receiving subcutaneous beta interferon injections since 8 months for her relapsing-remitting multiple sclerosis (RRMS) but she had noticed no improvement in her left eye vision. In fact, she stated that her right-sided vision started to

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Makalenin Geliş Tarihi: Oct 04, 2012 • Kabul Tarihi: Jan 29, 2013 • Çevrim İçi Basım Tarihi: 30 Haziran 2015

decrease few months ago, in addition. To start with, she said that her left vision was becoming gradually foggy (about a year ago). Afterwards, she had noticed gradual deterioration over 3 months to a severe degree. Her right-eye was entirely normal as she said until the last 3 months when she had noticed sudden dimming in vision upon standing from a low position. Since then, her right vision had become blurred. The patient's past histories were unremarkable. We reviewed her past investigations (which included two brain MRIs and one cervical cord MRI) and we did not find "anything abnormal." She underwent CSF examination as part of her RRMS work-up at that time; all CSF parameters were normal but no opening pressure was measured.

The woman's vital signs were normal and her body mass index (BMI) was 25 Kg/m2. Neurological examination revealed decreased visual acuity to light perception (in the left eye) and 6/15 (in the right eye). Constriction of the right-sided peripheral field and a large physiological blind spot were seen. Left-sided florid secondary optic atrophy was present while grade 4 papilloedema was detected on the right side. Both planter reflexes were flexors and no cranial nerve palsies were found. All modalities of sensation were intact.

The same battery of investigations (as in patient number one) was ordered for this patient; all (including her brain and cervical cord MRI with gadolinium) were unremarkable. Her CSF parameters were normal apart from opening pressure of 37 cm H2O.

The patient was given a diagnosis of primary pseudotumor cerebri syndrome. She was prescribed oral acetazolamide 1000 mg per day and prednisolone 60 mg per day. After few days, the patient noticed an improvement in her right-sided vision (visual acuity of 6/12) while the left-sided vision improved minimally (she said that the can see the light now better than before). Over a matter of one moth, her prednisolone was tapered to 10 every other day (and was stopped after 2 months) and her acetazolamide daily dose was decreased to 750 mg. We have been seeing and examining the patient every month for the past 6 months; her vision had been static since then. No neurosurgical intervention was suggested by a neurosurgeon.

Patient number 3 was a 34-year-old housewife. The patient had noticed progressive and bilateral (somewhat symmetrical) deterioration in her vision over 2 months. The patient stated that her vision was mildly blurred as if there was a transparent curtain in front of her eyes but it had become more dimly recently. Her past histories were unremarkable and she was on no regular medications. Several episodes of transient visual obscuration each day had developed; she thought that these were insignificant.

The patient's vital signs were unremarkable and her body mass index (BMI) was 22 Kg/m2. Neurological examination revealed visual acuity of 6/9.5 in both eyes with bilateral enlargement of the physiological blind spot; no peripheral visual field constriction was noted. Bilateral grade 4 papilloedema was found.

She underwent an extensive work-up (similar to the other 2 patients); the results turned out to be unremarkable. Lumbar puncture and CSF analysis revealed an opening pressure of 39 cm H2O while the other CSF parameters were normal.

We diagnosed primary pseudotumor cerebri syndrome and oral acetazolamide and furosemide, 1000 mg and 40 mg per day respectively, were prescribed together with oral potassium 1200 µg per day. At the end of the first week of treatment, the patient noticed an improvement in her vision; the visual acuity was the same. Her vision had become plateaued over the past 4 months. Her last CSF opening pressure, which was done 20 days after the start of therapy, was 14 cm H2O. A neurosurgical opinion was sought; no need for any intervention was the answer.

Discussion:

Taylor was the first one who described the syndrome of signs and symptoms of raised intracranial pressure and no intracranial tumor in the year 1880.[1] In 1893, the German physician Heinrich Quincke reported on cases of intracranial hypertension of unknown cause and labeled them as "meningitis serosa."[2] He thought that inadequate CSF absorption was the culprit behind the development of such cases. In the year 1904, the constellation of signs and symptoms of raised intracranial pressure of unknown etiology was named pseudotumor cerebri (PTC) by Nonne.[3] Folly suggested the use of the term "benign intracranial hypertension" in 1955.[4]However, Bucchein and colleagues strongly questioned the adjective "benign;" simply, because of the patients' evolution of symptoms and visual loss.[4]

The American neurosurgeon Dandy E. Walker published a landmark paper in the year 1937. He reported on 22 patients with symptoms and signs of raised intracranial pressure but none of them got an intracranial tumor or a space-occupying lesion.[5] All (n=22, 100%) of his patients had headache but most of them had loss of vision. He also found an unexplainable fluctuation in the intracranial pressure; at times, this waxing and waning occurred rapidly and from one extreme to another. Therefore, he noticed that the elevation in the intracranial pressure was rarely constant. He labeled the condition as "intracranial pressure without brain tumor." The very first case he saw was 21-year-old normal-looking woman who complained of headache and failing vision.[5] Thanks to this report, the original Dandy criteria for the diagnosis of benign intracranial hypertension arose. However, Lawton Smith modified these criteria in 1985.[6]

Friedman and Jacobson revised these criteria in the year 2002 and proposed some changes. They favored and used the term idiopathic intracranial hypertension to describe the primary/idiopathic variety only, which is typically seen in obese women of child-bearing age; the atypical patients were identified as men, slim women, prepubescent children, and patients older than 44 years of age. [7,8]

Their criteria were:

1. Symptoms, if present, represent increased intracranial pressure or papilledema.

2. Signs represent increased intracranial pressure or papilledema.

3. Documented elevated intracranial pressure during lumbar puncture measured in the lateral decubitus position.

4. Normal cerebrospinal fluid composition.

5. No evidence of ventriculomegaly, mass, structural, or vascular lesion on magnetic resonance imaging or contrast-enhanced computed tomography for typical patients, and magnetic resonance imaging and magnetic resonance venography for all others.

6. No other cause (including medication) of intracranial

hypertension identified.

In late 2013, Friedman and coworkers updated these criteria and provided more clarification.[9] They used term "pseudotumor cerebri syndrome" (PTCS) rather than "benign intracranial hypertension" or "idiopathic intracranial hypertension." They subdivided the syndrome into primary (idiopathic) and secondary (to an identifiable etiology, ranging from medication-induced to cerebral venous sinus thrombosis).

Friedman and coworkers identified three clinical scenarios and they provided diagnostic criteria for each one of them:[9]

1. Pseudotumor cerebri syndrome with papilledema:

Neurological examination is normal except for cranial nerve abnormalities; neuroimaging is normal except for findings suggestive of high pressure; cerebrospinal fluid (CSF) composition is normal; and the opening pressure of a properly performed lumbar puncture is elevated (≥250 mm CSF in adults and unsedated children and ≥280 mm CSF in sedated children).

2. Pseudotumor cerebri syndrome without papilledema:

Criteria are the same as above, along with unilateral or bilateral sixth nerve palsies.

3. Suggested pseudotumor cerebri syndrome:

Criteria for this scenario are fulfilled if there is no papilledema or sixth nerve palsy, but the other criteria are met and neuroimaging findings suggest high pressure.

Two striking points should be noted; headache was not part of the criteria and chronic daily headache is not (in itself) a strong indication for doing lumbar puncture in order to investigate for a suspected elevated intracranial pressure.

According to González-Hernández and colleagues,[10] headache was present in 85.4% of their 55 patients; the headache was continuous in 63.8% of patients and diffuse in 51% of them. They concluded that this headache may easily mimic primary headache syndromes and so a high level of suspicion is needed to avoid diagnostic delay and its catastrophic consequences of visual loss. Patients one and three got a delayed diagnosis while patient number two was misdiagnosed as RRMS.

Huna-Baron and Kupersmith retrospectively analyzed 240 pregnant women with headache; they diagnosed PTCS in 12 (5%) of the patients. However, two (16.6%) cases were entirely "headache-free;" surprisingly, this finding was not discussed further.[11] De Simone et al[12] reported on two PTCS patients without headache. They concluded that the lack of headache in one patient may reflect an inherited condition of protection against neurovascular headache development, since neither the patient nor her first-degree relatives reported headache in their lives. In the other patient, the headache remitted during pregnancy, which is considered a strong migraine protective factor.

Headache was the presenting symptom of PTCS in 95%, 75%, and 81% of studied patients according to Johnston et al,[13] Rush et al,[14] and Corbett et all[15] respectively. Therefore, it's absent in 5% to 19% of patients.

The cornerstone of morbidity and most fearful complication of PTCS is papilloedema-associated visual loss. Wall and George analyzed 50 patients with PTCS prospectively and found visual field defects (at the time of presentation) in at least one eye were present in 96% of patients assessed with the Gold-mann perimeter, and in 92% of patients assessed with the Humphrey perimeter. After starting medical treatment, 60% of patients got a variable degree of improvement while 30% of patients remained stable and a further 10% got worsening, as assessed with Goldmann perimetry. Assessed with the Humphrey perimeter, 50% of patients improved, 28% remained stable, and 22% worsened. [8,16]

Johnston et al[13] found that 65% of their patients displayed some form of visual impairment at the time of presentation, a figure which was consistent with that of Rush et al (i.e., 68%). [14] Diplopia was found in approximately one third of patients. [13-15]

According to Wall, the visual acuity usually remains normal in patients with papilledema except when the condition is longstanding and severe or if there is a serous retinal detachment present and optic disc edema extends to the macula.[17] He also noticed that in about one third of this visual loss is mild and unlikely to be noticed by the patient. However, the loss of visual field may be progressive and severe, leading to blindness in about 5% of cases. The time course of visual loss is usually gradual; however acute severe visual loss can occur. [17]

Freidman and Jacobson suggested that the following are the potential culprits behind the development of visual acuity loss in patients with PTCS: chronic (atrophic) papilledema, chorioretinal folds, macular edema or exudates, infarction of the optic disc, subretinal peripapillary hemorrhage extending through the fovea, and subretinal peripapillary neovascular membrane.[8]

Wall and coworkers[18] analyzed 12 female patients with PTCS using computerized visual analysis. They found that in seven out of their 12 patients, the visual field loss was permanent and that the follow-up period was too short for the final outcome to be determined in two other women. They also found that the most common visual field defects were blind spot enlargement (n=1 2, 100%), isopter constriction (n=9), and loss on the nasal side of the visual field (n=7), especially in the inferonasal quadrant. Four patients (25%) had diminished visual acuities as well. One of their conclusions was that the reversibility of the visual field defects was correlated well with the presence (nonreversible) or absence (reversible) of ophthalmoscopic signs of chronic papilledema.

Carta et al suggested that it is possible that poor visual outcome reported in several studies is related to the delay in the diagnosis and in the therapeutic intervention (as in our patients). In respect to the visual outcome after treatment, the visual acuity was better than 20/32 (6/9.5) in all patients when last seen, but peripheral visual field was moderately restricted in two cases, whereas diffuse reduction of sensitivity was observed in two other cases.[19]

Krogsaa and colleagues studied 20 PTCS patients. They found that initially at the time of presentation all patients showed marked papilledema, normal visual acuity, considerable enlargement of the blind spot area, and significantly delayed pattern reversal visual evoked potentials. During the course of medical treatment, eleven patients demonstrated a rapidly regression and normalization of papilledema, blind spot area, and visual evoked potentials within 3-6 months. On the other hand, eight patients (40%) continued in showing papilledema including disc gliosis, enlargement of blind spot area, and pathological visual evoked potentials. One patient (5%) developed secondary and permanent optic nerve atrophy.[20]

The headache pattern in our patients was non-specific to a migraine-like one. Neither the patients nor their physicians paid a considerable attention to it. The first patient lived in a mountainous area which lacks specialized medical/neurological services. Although patient number three was told (by her ophthalmologist) to visit a neurologist, we don't know what he was thinking of.

The visual loss in patient number three prompted her neurologist to think of and diagnose multiple sclerosis in spite of the presence of several inconstancies with this diagnosis; the no continuous holocephalic headache misguided the diagnostic plan. All of those patients demonstrated a BMI of <30 Kg/m2, i.e., no obesity.

In conclusion, in spite of more than one century of continuous researches and advances in the medical literature, PTCS remains a diagnostic and therapeutic challenge and the pathogenesis of the primary (idiopathic) variety remains to be clarified. Although headache is one of the core features of PTCS, but it may be absent, or it may be intermittent non-specific or migraine-like in nature. Together with lack of obesity, the whole symptomatology may prompt physicians to think of an alternative diagnosis (other than PTCS) with resultant diagnostic delay and inevitable visual loss.[21,22]

Acknowledgment:

Special thanks go to our patients and their families; without their kind help and "patience," this paper would have not been published.

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