

Pseudotumor Cerebri Secondary to Minocycline Intake

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Background: Pseudotumor cerebri, or idiopathic intracranial hypertension, is a condition most commonly affecting women of childbearing age who are obese or who have experienced recent weight gain. Frequently the patient complains of headache accompanied by dizziness, nausea, or visual defects, and it is characterized by elevated intracranial pressure in the absence of a space-occupying lesion or infection

Methods: A patient had been prescribed minocycline and subsequently developed symptoms 6 weeks after an increase in the original dosage. She was initially examined by an ophthalmologist, then was sent to the Emergency Department, and finally admitted under the family practice service. Articles were searched through MEDLINE, MD Consult, and Google. Key words included "pseudotumor cerebri," "benign intracranial hypertension," "idiopathic intracranial hypertension," and "minocycline."

Results and Conclusion: Although the pathogenesis of pseudotumor cerebri is not completely understood, an association has been observed with minocycline use. This report describes a 16-year-old girl who developed idiopathic intracranial hypertension while taking minocycline for acne. Symptoms of blurred vision and severe headache unrelated to position or activity; an absence of fever, bilateral disk edema, and focalizing neurologic signs; negative neuroradiographic findings; increased cerebrospinal fluid pressure with a normal cell count; and exclusion of systemic or structural cause of increased intracranial pressure satisfy the criteria for the diagnosis of idiopathic intracranial hypertension. Minocycline is often used by family physicians for the treatment of acne, and this complication requires vigilance to protect against potential vision loss. (J Am Board Fam Pract 2002;15:229–33.)

Idiopathic intracranial hypertension is a distinct syndrome in which patients have intracranial hypertension, papilledema, an absence of focal neurologic signs, and essentially normal cerebrospinal fluid. Benign intracranial hypertension, as it is also known, is usually a self-limited condition, although in some instances it can be a chronic condition. Annual incidence varies from 1 to 2 cases per 100,000 persons; however, among obese women in the reproductive age-group, the incidence jumps to 19 to 21 cases per 100,000.¹ The pathogenesis and natural course remains unclear.

Methods

A case is reported of a patient admitted through the Emergency Department after being seen by an ophthalmologist for headaches and blurred vision. Information regarding her case was obtained by chart reviews, interviews with the patient and her family, the attending family physician, and the con-

sulting ophthalmologist, and the recommendations of the consulting neurologist were reviewed. A MEDLINE and MD Consult literature review was undertaken using the key words "pseudotumor cerebri," "benign intracranial hypertension," "idiopathic intracranial hypertension," and "minocycline."

Case Report

A 16-year-old girl complained of a 3-day history of severe headache, described as dull, nonradiating, and continuous, associated with blurred vision localized to the occipital region. There was no relation between the symptoms and position or activity. She had no history of fever, nausea, or vomiting, nor was there a history of trauma. Acetaminophen and ibuprofen brought little relief of the symptoms. With the persistence of the symptoms, as well as development of a slightly stiff neck, the patient was brought to an ophthalmologist. On examination, she was found to have bilateral disk edema consistent with increased intracranial pressure and was subsequently sent to the emergency department for further evaluation and treatment.

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The patient's medical, surgical, and family history were all unremarkable. She did not smoke and denied alcohol and illicit drug use. She had been taking minocycline, 50 mg orally twice daily, for her acne as prescribed by her family physician for more than a year. Recently, under the guidance of her physician, she doubled the dose to 100 mg orally twice daily 6 weeks before the onset of her symptoms.

When examined, she was a well-developed girl of normal weight, who was alert, oriented, and in no acute distress. Her temperature was 97.6°F, pulse was 67 beats per minute, respirations were 16/min, and blood pressure was 149/82 mm Hg. Her face had scattered erythematous papules and pustules, especially on the cheeks and forehead. Her pupils were bilaterally dilated as a result of the topical cycloplegic medication given earlier. Mild papilledema was seen bilaterally on funduscopic examination. Extraocular movements were intact, and there was no ptosis or nystagmus. Her uncorrected visual acuity was 20/25 in the right eye, and 20/100 in the left eye. No gross deficit in the visual fields was observed using confrontation testing. The patient did not wear eyeglasses or contacts. Both of her tympanic membranes were intact, and there was no evidence of bulging or discharge. Her neck was supple and was negative for Kernig and Brudzinski signs. There was no lymphadenopathy. There was some neck pain when the patient flexed her neck, but motion was not limited. Findings of an examination of the lungs, heart, and abdomen were benign. Neurologically her cranial nerves II to XII were intact, manual muscle testing in all extremities was 5/5, and deep-tendon reflexes were all 2/4. Cerebellar function was intact, as was gait, and Babinski reflexes were downward bilaterally. Sensation was intact to pain and soft touch.

A complete blood count and basic metabolic panel returned the following values: white cell count $7.23 \times 10^3/\mu\text{L}$, hemoglobin 15.0 g/dL, hematocrit 43.8%, and platelet count $226 \times 10^3/\mu\text{L}$, and her sodium, potassium, magnesium, and chloride levels were all within normal limits. A computerized tomographic (CT) scan of the brain showed normal findings. Lumbar puncture was performed, and the opening pressure was 55 cm H₂O. Findings from cerebral spinal fluid analysis were essentially normal, and a diagnosis of pseudotumor cerebri was made.

The patient was given 500 mg of oral acetazolamide in the emergency department, and she was

admitted to the hospital under the care of the family physician who originally prescribed the minocycline. Acetazolamide, 500 mg twice daily, was continued, and minocycline was discontinued. A neurological consultant suggested magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) to exclude the possibility of a sinovenous thrombosis. Findings of both MRI and MRA were normal. The patient's headache began to improve, but it was now dependent more on position. The blurred vision persisted, however. The patient was released from the hospital the next day with a prescription for acetazolamide.

One week after discharge, when the patient was seen for a follow-up examination in the outpatient clinic, she stated that the headaches, which remained postural, had improved. She still had papilledema. She had stopped taking the acetazolamide because of nausea, so caffeine was recommended for her postural headaches. The patient and her parents were told to telephone if her symptoms got worse or failed to resolve, and she was advised to continue follow-up visits with the ophthalmologist to ensure there was no deterioration of her visual acuity.

Discussion

The syndrome of intracranial hypertension with papilledema, no focal neurologic deficit, normal cerebrospinal fluid, and normal to small ventricles was described nearly a century ago by Quinke² as serous meningitis. Other names include otitis hydrocephalus, toxic hydrocephalus, sinus thrombosis causing intracranial hypertension, hypertensive meningeal hydrops, pseudoabscess, intracranial pressure without brain tumor, brain swelling of unknown cause, and pseudotumor cerebri.

Modified Dandy criteria¹ for the diagnosis of idiopathic intracranial hypertension include signs and symptoms of increased intracranial hypertension² and no localizing neurologic signs (other than abducens nerve paralysis³) in an awake and alert patient, normal imaging studies except for small ventricles or empty sella,⁴ increased lumbar pressure (≥ 25 cm of water) with normal cerebral spinal fluid,⁵ and no primary structural or systemic causes of intracranial hypertension.³

In a retrospective review of 120 patients by Weisberg,⁴ 99% of patients had headaches, and 35% had visual changes. In a study of cases of idiopathic intracranial hypertension in an emer-

gency department, Jones et al⁵ found that the mean patient age was 27 ± 8.9 years, 83% were women, and 67% were obese. Ninety-two percent complained of headache, 75% had nausea and vomiting, 71% reported dizziness, and 65% had disturbances of visual acuity. Other symptoms included photosensitivity, diplopia, stiff neck, paresthesias, myalgias, tinnitus, and vertigo. Bilateral papilledema was observed in 67%, 54% had a visual field defect, and 29% had sixth cranial nerve palsy. Four percent had seventh cranial nerve palsy. If ocular motility defects other than from the sixth cranial nerve are encountered, the diagnosis of idiopathic intracranial hypertension is less likely. Unilateral papilledema is also possible, although less common, and is not associated with the duration of disease or severity of symptoms. It should also be noted that idiopathic intracranial hypertension can occur in the absence of headache or papilledema.

CT and MRI findings are typically normal, although there might be nonspecific findings, such as empty sella, prominent cisterna magna, and dilated optic nerve sheaths. In a study of 29 male patients with idiopathic intracranial hypertension by Digre and Corbett,⁶ an empty sella was noted in 55% of the CT scans.

Cerebrospinal fluid pressure should be elevated, and the protein levels should be low or normal, glucose levels normal, and cell counts normal. A diagnosis of idiopathic intracranial hypertension should not be made without performing a lumbar puncture. An opening pressure of greater than 250 cm H₂O is diagnostic. When clinical and radiologic evidence is highly indicative of idiopathic intracranial hypertension, and the opening pressure is normal, a second lumbar puncture or continuous intracranial pressure monitoring might be necessary.

Intracranial sinus thrombosis, which is associated with head injury, otitis media, and hypercoagulable and hyperviscosity syndromes, most often causes intracranial hypertension without focal neurologic defect. Findings of a CT scan and cerebrospinal fluid are normal, although an MRI might show an abnormality, especially in the transverse sinus. MRA and digital subtraction confirm the diagnosis.

Epidemiologic studies have confirmed an association between female sex, reproductive age-group, menstrual irregularity, obesity, and recent weight gain. Other associated conditions, although unconfirmed by case-control studies, include adre-

nal insufficiency, Cushing disease, hypoparathyroidism, hypothyroidism, chronic renal failure, and systemic lupus erythematosus.

Of particular interest, especially in this case, is the association of intracranial hypertension with medication intake. Minocycline-related pseudotumor cerebri was first reported in 1978.⁷ Since then 16 additional cases have been reported. Chiu et al,⁸ in a retrospective study, reviewed 12 cases of minocycline-induced pseudotumor cerebri syndrome. Seventy-five percent of the patients developed pseudotumor cerebri within 8 weeks of starting minocycline. Six (50%) of the patients were not obese. Two patients developed symptoms after 1 year of minocycline use. Pseudotumor cerebri was diagnosed by finding papilledema on routine examination in 1 patient who was asymptomatic after taking minocycline for 1 year. After discontinuing minocycline, all patients recovered from pseudotumor cerebri syndrome, and after at least 1 year of follow-up, there were no recurrences.

Four cases of minocycline-induced intracranial hypertension were documented in Australia by Lander.⁹ Durations of therapy ranged from 25 days to 18 months. All had severe headaches and papilledema, and visual disturbance was reported in two cases. Cessation of minocycline reversed the intracranial hypertension, although 1 patient had persistent lower nasal quadrantic field-of-vision loss 6 months later. In all cases, the diagnosis was missed by the primary care physician. The ability of minocycline to decrease cerebrospinal fluid absorption is the postulated mechanism for minocycline-induced pseudotumor cerebri. Isotretinoin, tetracycline, trimethoprim-sulfamethoxazole, cimetidine, corticosteroids, tamoxifen, lithium, nitrofurantoin, and levothyroxine have been implicated in addition to minocycline.

The only serious complication of idiopathic intracranial hypertension is vision loss, which can be sudden or gradual and can occur at any time during the course of the disease. Appropriate treatment can prevent vision loss, however. Risk factors for vision loss include duration of related symptoms before diagnosis, systemic hypertension, anemia, older age, and high degrees of myopia. African American men also appear to be at higher risk. Studies have shown that perimetry, using either the Goldman manual perimeter or a computed automated perimeter, is the best test to detect and

monitor vision loss associated with idiopathic intracranial hypertension.

Treatment is directed at preventing vision loss and treating the cephalgia. Initially, predisposing factors should be corrected, such as stopping possible inciting medications and or treating any underlying medical condition. Lumbar puncture, aside from being diagnostic, is therapeutic. If the symptoms resolve after the initial lumbar puncture, no further action is warranted. If the symptoms are unresolved, repeated lumbar punctures, up to four in the first 2 to 4 weeks, are recommended. Beyond the first 4 weeks, repeated lumbar punctures are unlikely to be of benefit.

Acetazolamide (Diamox), a carbonic-anhydrase inhibitor, is frequently used for idiopathic intracranial hypertension. Treatment is started at a dosage of 250 mg/d and gradually increased until target doses of 500 mg four times a day is reached or until side effects are encountered. Adverse reactions include paresthesias, drowsiness, nausea, malaise, metabolic acidosis, altered taste, and renal calculi. For those who are intolerant or unresponsive to acetazolamide, a short course of oral corticosteroids might be of benefit. Prednisone, 40 to 60 mg/d, should resolve symptoms in 10 to 14 days, at which point the medication is tapered for the next 2 weeks.

Surgery should be considered when vision loss does not respond to medical treatment, when initial vision loss is severe, or when the patient response is unreliable at visual field testing and there is an increased delay in the major positive peak of visual evoked response. Surgical options include lumbo-peritoneal shunt or optic nerve decompression. Fenestration of the optic nerve sheaths is becoming the treatment of choice. It provides immediate decompression of the optic nerve, as well as long-term filtration of cerebrospinal fluid. Complications include papillary dysfunction, peripapillary hemorrhage, chemosis, and chorioretinal scarring. Although lumboperitoneal shunting has been shown to fail to prevent the progression of vision loss,¹⁰ this procedure is appropriate in those who do not respond to optic nerve fenestration.

In summary, pseudotumor cerebri, or idiopathic intracranial hypertension, is a syndrome in which patients most commonly complain of headache and visual disturbance and have signs and symptoms typical of increased intracranial pressure, no focal neurologic signs, normal neuroimaging studies, in-

creased opening pressure on a lumbar puncture with a normal cerebrospinal fluid findings, and no structural or systemic cause for intracranial hypertension. It is most often seen in reproductive-age women who are obese, who have recently gained weight, and who have irregular menses. Although an abducens nerve palsy might be observed, any other ocular motility disorder makes the diagnosis of idiopathic intracranial hypertension unlikely. Idiopathic intracranial hypertension can be associated with endocrine dysfunction, systemic lupus erythematosus, chronic renal failure, and with some medications.

A history of minocycline use should be determined in cases of pseudotumor cerebri, especially when the patient is not obese. Minocycline is among the top four oral antibiotics most commonly prescribed for the treatment of acne, with more than 374,000 prescriptions written a year.¹¹ Family physicians who prescribe minocycline should be vigilant, as this potential complication is not entirely benign. Patients must be aware of the symptoms and seek medical attention should they arise. Additionally, physicians should be knowledgeable of this complication, screen their patients with questions regarding the symptoms of intracranial hypertension, and routinely perform ophthalmologic examinations of their patients who are taking this medication. Treatment, which is directed toward the prevention of visual loss by correcting predisposing factors, includes lumbar puncture, serial if necessary, acetazolamide, corticosteroids if there is no response to acetazolamide, or surgery when visual loss is severe or unresponsive to medical therapy.

References

1. Duncan FJ, Corbett JJ, Wall M. The incidence of pseudotumor cerebri. Population studies in Iowa and Louisiana. *Arch Neurol* 1988;45:875-7.
2. Quinke H. Ueber Meningitis serosa und verwandte Zustände. *Dtsch Z Nervenheilk* 1897;9:149-68.
3. Radhakrishnan K, Ahlskog JE, Garrity JA, Kurland LT. Idiopathic intracranial hypertension. *Mayo Clin Proc* 1994;69:169-80.
4. Weisberg LA. Benign intracranial hypertension. *Medicine (Baltimore)* 1975;54:197-207.
5. Jones JS, Nevai J, Freeman M, McNinch DE. Emergency department presentation of idiopathic intracranial hypertension. *Am J Emerg Med* 1999;17: 517-21.

6. Digre KB, Corbett JJ. Pseudotumor cerebri in men. *Arch Neurol* 1988;45:866–72.
7. Monaco F, Agnetti V, Mutani R. Benign intracranial hypertension after minocycline therapy. *Eur Neurol (Paris)* 1988;144:218–20.
8. Chiu A, Chuenkongkaew WL, Cornblath WT, et al. Minocycline treatment and pseudotumor cerebri syndrome. *Am J Ophthalmol* 1998;126:116–21.
9. Lander CM. Minocycline-induced benign intracranial hypertension. *Clin Exp Neurol* 1989;26:161–7.
10. Rosenberg M, Smith C, Beck R, Corbett J, et al. The efficacy of shunting procedures in pseudotumor cerebri. *Neurology* 1989;39(Suppl 1):209.
11. Stern RS. Medication and medical service utilization for acne 1995–1998. *J Am Acad Dermatol* 2000;43:1042–8.