ELSEVIER

Pseudotumor Cerebri Induced by Minocycline Therapy for Acne Vulgaris

Kiyofumi Mochizuki*, Tomoko Takahashi*,
Michihisa Kano†, Keiichi Terajima† and Nobuhide Hori‡

*Department of Ophthalmology, JA Gifu Koseiren, Chuno General Hospital, Gifu;
†Department of Neurosurgery, JA Gifu Koseiren, Chuno General Hospital, Gifu;
and ‡Department of Ophthalmology, Gifu University School of Medicine, Gifu, Japan

Background: We report a case of a young girl who developed pseudotumor cerebri while taking minocycline for acne vulgaris.

Case: A 16-year-old girl without a history of menstrual irregularity, weighing 60 kg (body mass index: 26.0%) presented with a history of 1 week of headache and sudden onset of a horizontal diplopia.

Observation: Examination revealed bilateral papilledema and an abduction deficit in her right eye. Her cerebrospinal fluid had an opening pressure of 400 mm H_2O and a normal composition. Following normal findings on computed tomography and magnetic resonance imaging, a diagnosis of pseudotumor cerebri was made. She reported receiving minocycline to treat acne vulgaris during the previous 3 weeks. The headache resolved with withdrawal of minocycline. The diplopia and papilledema resolved after two lumbar punctures, although the visual field defects persisted. The minocycline concentrations in the serum and cerebrospinal fluid taken after cessation of the drug were below the detectable level.

Conclusion: The role of minocycline should be considered and routine ophthalmologic examination during minocycline treatment should be performed when pseudotumor cerebri occurs in patients treated for acne vulgaris. **Jpn J Ophthalmol 2002;46:668–672** © 2002 Japanese Ophthalmological Society

Key Words: Minocycline, pseudotumor cerebri, sixth nerve palsy, visual field.

Introduction

Pseudotumor cerebri is uncommon in Japan. A recent study of 30 institutions reported 20 cases of pseudotumor cerebri in the past 5 years.[1] However, in Europe and the United States, the incidence of pseudotumor cerebri is 1 or 2 per 100,000 persons.[2] Pseudotumor cerebri is characterized by an elevated opening pressure on lumbar puncture examination with a normal cerebrospinal fluid composition, a normal brain scan, and papilledema.[2] Several medications have been implicated as causative agents of this condition, including systemic corticosteroids, vitamin A, nalidixic acid, tetracycline, and ciprofloxacin, among others.[2,3]

There have been several reports of minocycline-related pseudotumor cerebri since 1978;[4] however, to our knowledge, there have been no cases reported in Japan. We report the first case of minocycline-related pseudotumor cerebri in Japan, which developed in a young girl.

Case Report

A 16-year-old girl without a history of menstrual irregularity, weighing 60 kg (body mass index: 26.0%) had been treated with minocycline (200 mg per day) for acne vulgaris since December 30, 1999. After 3 weeks of this therapy, she presented with headache that had persisted for 1 week and a sudden

Received: October 20, 2001
Correspondence and reprint requests to: Kiyofumi MOCHIZUKI, MD, Department of Ophthalmology, JA Gifu Koseiren, Chuno General Hospital 5-1 Wakakusa-dori, Seki-shi, Gifu 501-3802, Japan

Published by Elsevier Science Inc.
0021-5155/02/$–see front matter
PII S0021-5155(02)00550-6

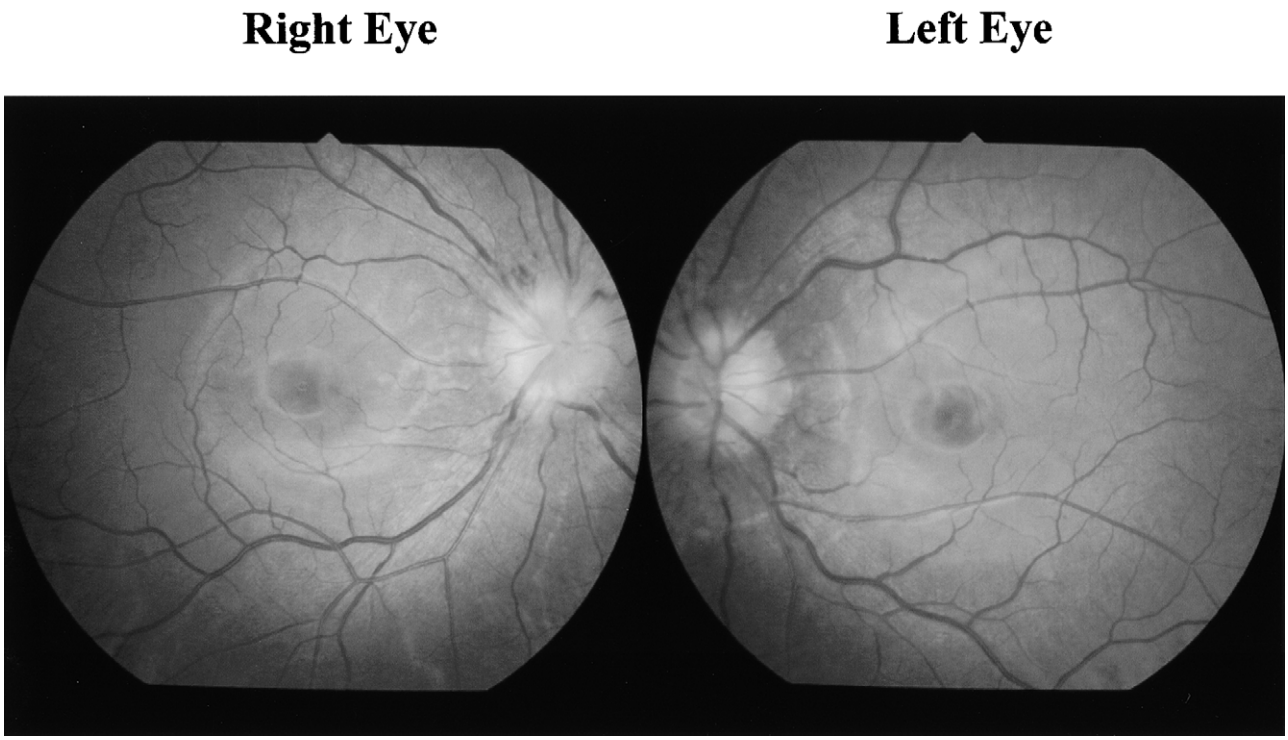

Figure 1. Fundus photographs taken during the first visit of a 16-year-old girl who developed pseudotumor cerebri while taking minocycline for acne vulgaris. Edema of the optic disc with adjacent hemorrhage was seen bilaterally.

onset of horizontal diplopia on the morning of February 4th, 2000. She denied visual loss, nausea, vomiting, and trauma. On examination in our hospital on February 7, her visual acuity was 1.0 in the right eye and 1.0 in the left eye. Her intraocular pressure was 20 mm Hg in the right eye and 19 mm Hg in the left eye. There was an abduction deficit of the right eye and full motility of the left eye. An afferent pupillary defect was not noted, and fundus examination showed bilateral papilledema with a single streak hemorrhage adjacent to the disc (Figure 1). The critical flicker fusion frequency was normal, as was her color vision according to a Panel D-15 test. Automated perimetry (Humphrey perimetry, central 30-2 threshold test) showed enlarged blind spots in both eyes, with mean deviations of −5.88 dB in the right eye and −6.57 dB in the left eye (Figure 2). No abnormal findings were seen by computed tomography and magnetic resonance imaging of the brain on February 9. Her cerebrospinal fluid had an opening pressure of 400 mm H_2O, was acellular, had a protein level of 17 mg/dL and a glucose level of 101 mg/dL. The culture was negative. The results of serologic studies for syphilis and endocrine disorders (Addison disease, Cushing disease, and hypoparathyroidism) were negative. Testing for antinuclear antibodies showed negative results. Minocycline intake was discontinued on February 9. Seven days after the first lumbar puncture, the sixth nerve palsy had disappeared and her headache resolved. Visual acuity was 1.0 in the right eye and 1.0 in the left eye, with mild resolution of the papilledema bilaterally. A second lumbar puncture was performed on the same day, and revealed an opening pressure of 230 mm H_2O. Her fundus oculi had returned to normal by March 11, and a third lumbar puncture revealed an opening pressure of 160 mm H_2O. On August 29, 2001, the final Humphrey mean deviations were −5.08 dB in the right eye and −5.76 dB in the left eye (Figure 3). After the last lumbar puncture, no recurrence has been documented for at least 1.5 years.

We found that the minocycline concentrations in the serum and cerebrospinal fluid on February 16 were below the detectable level (1.0 μg/mL).

Discussion

This case seems to fulfill the criteria for pseudotumor cerebri syndrome. Several conditions as well as medications have been associated with this syn-

Jpn J Ophthalmol
Vol 46: 668–672, 2002

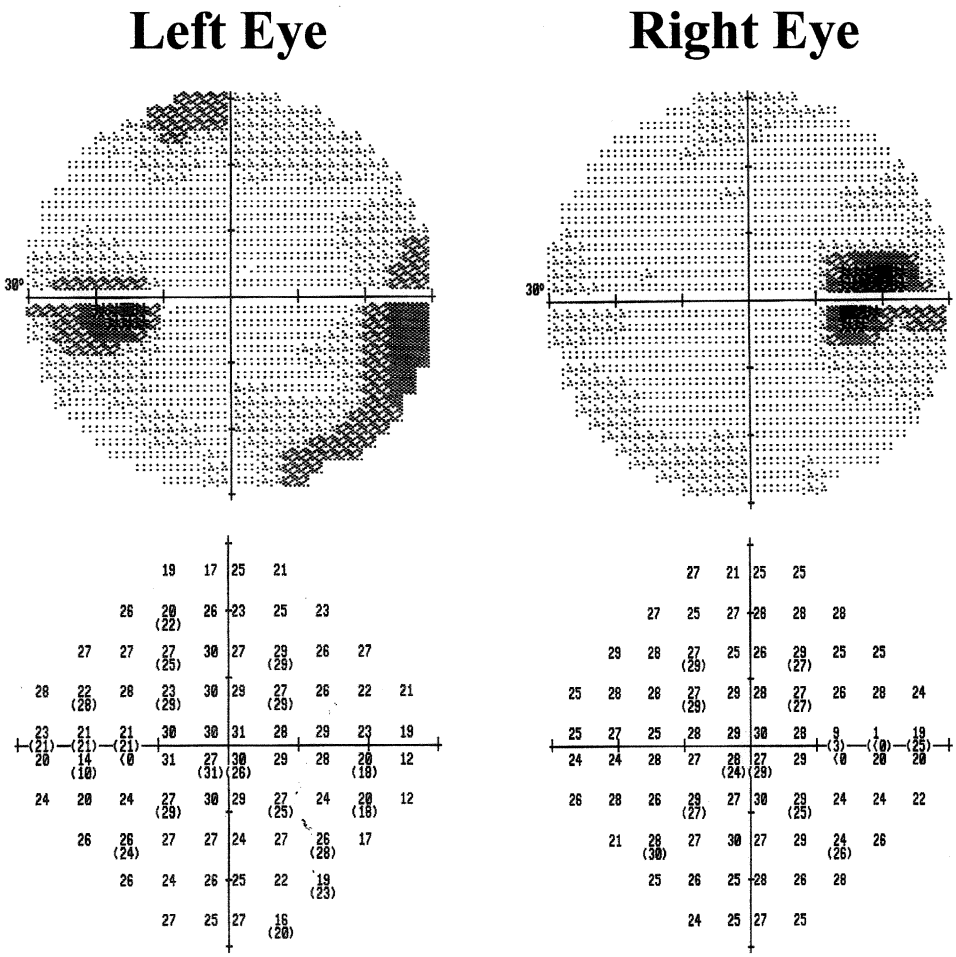

Figure 2. Perimetric results from the first visit. The Humphrey perimetry (central 30-2 threshold test) results showed bilateral enlargement of the blind spot and generalized depression bilaterally. Right eye: fixation losses, 0/24; false-positive errors, 0/17; false-negative errors, 0/13; fovea, 33 dB; mean deviation (MD), −5.88 dB; pattern standard deviation (PSD), 4.32 dB; short-term fluctuation (SF), 1.74 dB; corrected pattern standard deviation (CPSD), 3.84 dB. Left eye: fixation losses, 2/25; false-positive errors, 0/11; false-negative errors, 1/14; fovea, 33 dB; MD, −6.57 dB; PSD, 4.13 dB; SF, 2.25 dB; CPSD, 3.25 dB.

drome.[2] Systemic administration of vitamin A and minocycline are broadly used for treatment of acne vulgaris.[5] While both vitamin A and minocycline have been implicated as possible causes of pseudotumor cerebri,[5] our patient did not receive vitamin A. Minocycline has been shown to cause several side effects, including gastrointestinal disruption, vestibular dysfunction, headache, memory disturbance, cutaneous symptoms, vaginal candidiasis, and pigmentation.[6] A recent study of 700 patients treated with minocycline for acne vulgaris confirms that the frequency of pseudotumor cerebri may be as high as 1–1.4%.[6]

Epidemiologic studies have shown that pseudotumor cerebri tends to be a disease of early female adulthood (15–44 years) with obesity (overweight > 20% or body mass index > 26.0%).[2] Chiu et al[3] found that 8 of 12 patients with minocycline-related pseudotumor cerebri were not obese. The body mass index of our patient was 26.0%, so we cannot exclude the possibility that obesity was related to the development of pseudotumor cerebri in this case.

Chiu et al[3] reported that all patients with minocycline-related pseudotumor cerebri were females, and 75% developed symptoms of raised intracranial pressure within 8 weeks of starting minocycline therapy. None of the patients developed recurrences for at least 1 year. Visual field defects at final assessment were noted in 25% of cases based on Humphrey perimetry (at least 1 eye with a final mean deviation less than −5 dB). The most common symptoms were

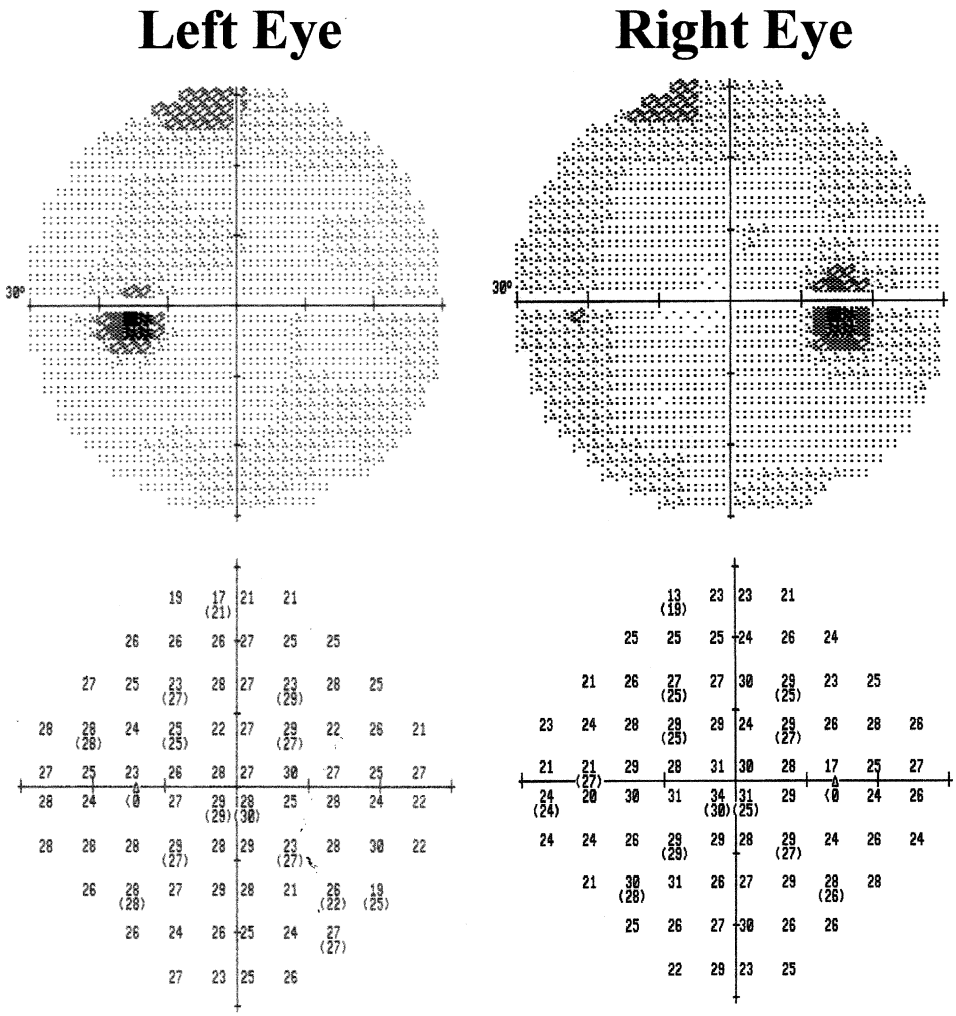

Figure 3. Perimetric results 19 months after the cessation of minocycline. The Humphrey perimetry (central 30-2 threshold test) results were near normal in spite of a remaining mean deviation of less than −5 dB. Right eye: fixation losses, 4/24; false-positive errors, 1/11; false-negative errors, 2/14; fovea, 33 dB; MD, −5.08 dB; PSD, 2.49 dB; SF, 1.32 dB; CPSD, 1.99 dB. Left eye: fixation losses, 5/26; false-positive errors, 0/21; false-negative errors, 2/15; fovea, 31 dB; MD, −5.76 dB; PSD, 2.27 dB; SF, 2.10 dB; CPSD, 0.00 dB.

headache (75%), transient visual obscurations (41%), diplopia (41%), pulsatile tinnitus (17%), and nausea and vomiting (25%). They also noted an abduction deficit that resolved with withdrawal of minocycline. However, in the present case, the headache appeared within 3 weeks after initiation of minocycline therapy, and horizontal diplopia with unilateral sixth nerve palsy persisted despite cessation of the minocycline treatment.

Because minocycline has greater lipid solubility than tetracycline and permeates the blood—brain barrier more rapidly, higher minocycline levels would be attained in the cerebrospinal fluid. However, in the present case, the minocycline level in the cerebrospinal fluid from the second puncture was below the detectable level (1.0 μg/mL). The mechanism of increased intracranial pressure in pseudotumor cerebri induced by minocycline has been attributed to decreased cerebrospinal fluid outflow at the arachnoid villi, leading to increased extracellular fluid volume and interstitial brain edema.[3] We suggest that minocycline might have a high affinity for the arachnoid villi and that its adverse effect there may cause the long-term elevated intracranial pressure.

Medical and surgical treatment, including repeated lumbar punctures, corticosteroids, acetazola-

Jpn J Ophthalmol
Vol 46: 668–672, 2002

mide, glycerol, optic nerve fenestration, and a lumboperitoneal shunt, have been tried in patients with pseudotumor cerebri.[7] We performed three lumbar punctures within 4 weeks in the present case and achieved rapid visual improvement and resolution of the papilledema and diplopia, which was not likely to have been due to the lumbar punctures alone.

According to a previous study,[3] the long-term outcome of minocycline-related pseudotumor cerebri may not be entirely benign. In the present study, the patient had a residual Humphrey mean deviation of less than −5 dB in both eyes. Significant visual field loss as a result of minocycline therapy has also been reported.[8,9] The possibility of drug-induced pseudotumor cerebri should be considered in any patient presenting with unexplained headache, especially if associated with visual symptoms.

We want to emphasize the possible role of minocycline when pseudotumor cerebri occurs in patients treated for acne vulgaris, and we recommend a periodic ophthalmologic examination during any minocycline treatment.

References

1. Mukuno K, Ishikawa S. Informal questionnaire on the incidence of pseudotumor cerebri in Japan. Neuroophthalmol Jpn 1994;11:52–54.
2. Radhakrishnan K, Ahlskog JE, Garrity JA, Kurland LT. Idiopathic intracranial hypertension. Mayo Clin Proc 1994;69:169–180.
3. Chiu AM, Chuenkongkaew WL, Cornblath WT, et al. Minocycline treatment and pseudotumor cerebri syndrome. Am J Ophthalmol 1998;126:116–121.
4. Monaco F, Agnetti V, Mutani R. Benign intracranial hypertension after minocycline therapy. Eur Neurol 1978;17:48–49.
5. Lascari AD, Bell WE. Pseudotumor cerebri due to hypervitaminosis A: toxic consequence of self-medication for acne in an adolescent girl. Clin Pediatr 1970;9:627–628.
6. Goulden V, Glass D, Cunliffe WJ. Safety of long-term high-dose minocycline in treatment of acne. Br J Dermatol 1996; 134:693–695.
7. Liu GT, Glaser JS, Schatz NJ. High-dose methylprednisolone and acetazolamide for visual loss in pseudotumor cerebri. Am J Ophthalmol 1994;118:88–96.
8. Lander CM. Minocycline-induced benign intracranial hypertension. Clin Exp Neurol 1989;26:161–167.
9. Donnet A, Dufour H, Graziani N, Grisoli F. Minocycline and benign intracranial hypertension. Biomed Pharmacother 1992; 46:171–172.