A Comparison Between the Clinical Features of Pseudotumor Cerebri Secondary to Tetracyclines and Idiopathic Intracranial Hypertension

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• PURPOSE: Comparisons between clinical features of tetracycline-induced pseudotumor cerebri (PTC-T) and those of idiopathic intracranial hypertension (IIH) are absent in the literature. We hypothesized that significant clinical differences between these etiologies exist and could be better understood by retrospective analysis.

• DESIGN: Retrospective cohort study.

• METHODS: We reviewed patients diagnosed with pseudotumor cerebri syndrome (PTCS) at our center and identified those who developed PTC-T after treatment with a tetracycline-class antibiotic and those with IIH. Groups were compared by demographics, body mass index, ophthalmic examination, treatment, clinical course, and visual outcomes.

• RESULTS: We identified 52 cases of PTC-T and 302 cases of IIH. Obesity rates were significantly different (43.8% for PTC-T vs 79.2% for IIH, $P < .001$). The mean age at diagnosis was younger for PTC-T (19.8 years vs 28.1 years for IIH, $P < .001$). Diplopia was more common with PTC-T (40.4% vs 20.1% for IIH, $P = .001$). The mean illness duration was shorter for PTC-T (18.3 weeks vs 62.9 weeks for IIH, $P < .0001$). Recurrence rates were significantly different (4.0% for PTC-T vs 16.5% for IIH, $P < .001$). The frequency of surgical intervention was similar. Vision loss was uncommon but occurred with similar frequency.

• CONCLUSION: We identified significant clinical differences but also identified important similarities between the 2 groups. There appear to be nonobese patients who develop PTC-T, discontinue the antibiotic, and never develop PTCS again. There are other patients who develop PTC-T, discontinue the antibiotic, and later develop IIH. We conclude that PTC-T represents a spectrum of disease in susceptible individuals. (Am J Ophthalmol 2020;220:177–182. © 2020 Elsevier Inc. All rights reserved.)

PSEUDOTUMOR CEREBRI SYNDROME (PTCS) IS CHARacterized by increased intracranial pressure with normal brain parenchyma, including absence of hydrocephalus, mass lesion, or underlying infection or malignancy.[1] PTCS can be classified as primary—ie, idiopathic intracranial hypertension (IIH)—or secondary.[2,3] Secondary causes of PTCS include, but are not limited to, venous sinus thrombosis, central nervous system infections, and medications such as vitamin A and the tetracycline class of antibiotics.[3] Tetracyclines are commonly prescribed in the treatment of acne vulgaris and have long been associated with PTCS, though a causative relationship has not been established.[4]

The association between these antibiotics and elevated intracranial pressure was first noticed in infants in the 1960s. It was fairly well known among pediatricians that tetracyclines could lead to bulging of the anterior fontanelle, typically 12 hours to 4 days after initiation of therapy.[5] Of note, this response was not associated with cerebrospinal fluid abnormalities or an abnormal neurologic examination. Since then, >100 cases of tetracycline-induced PTCS (PTC-T) have been described in the literature. Many of these patients have improvement in their signs and symptoms without any treatment other than discontinuation of the antibiotic.[4,6]

At first glance, IIH and PTC-T would appear to manifest similar symptoms and signs. Indeed, PTC-T patients commonly present with headache, papilledema, and diplopia.[2,4] However, there are no reports in the literature of a systematic comparison between the 2 diseases.

We hypothesized that there may be important clinical differences between PTC-T and IIH. We focused our efforts on comparing differences in patient demographics, body mass index (BMI), presenting symptoms, family history,

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duration of illness, recurrence rates, visual outcomes, and the incidence of surgical treatments. We reasoned that a better understanding of the clinical differences between these 2 diseases potentially could help guide research related to the pathogenesis of both PTC-T and IIH. These data also could help physicians who prescribe tetracycline antibiotics to better inform their patients about the symptoms of PTC-T, and to help these physicians more rapidly identify symptoms of PTC-T in patients using these antibiotics.

METHODS

THIS STUDY AND DATA COLLECTION WERE CARRIED OUT with approval from the University of Utah Institutional Review Board. Because this study was retrospective and no identifiable protected health information was used, informed consent was not obtained from study subjects. The study was conducted in accordance with Health Insurance Portability and Accountability Act regulations.

The authors retrospectively reviewed charts of patients who were evaluated for PTCS at the John A. Moran Eye Center at the University of Utah between June 1993 and June 2013. We began by identifying all patients who were assigned *International Classification of Diseases, 9th revision* codes 348.2 (benign intracranial hypertension/pseudotumor cerebri) or 377.01 (papilledema associated with increased intracranial pressure). Study data were collected and managed using the REDCap electronic data capture tool.

The research team identified all patients who were suspected of having tetracycline-induced disease and those who were diagnosed with IIH. The investigators verified that patients met the revised diagnostic criteria for PTCS, which include a normal neurologic examination except for cranial nerve abnormalities, normal neuroimaging, elevated lumbar puncture (LP) opening pressure (≥250 mm of water), and normal cerebrospinal fluid composition.[7]

Patients were diagnosed with PTC-T if they met these criteria and had taken a tetracycline antibiotic within 3 months of the onset of symptoms. Patients were diagnosed with IIH if they met these criteria and no other secondary cause for increased intracranial pressure could be identified.

The authors compared differences in patient demographics, BMI, presenting symptoms, family history, duration of illness, recurrence rates, visual outcomes, and the incidence of surgical treatments.

• **STATISTICAL METHODS:** Differences in proportions were tested using the χ^2 test. For variables where there were sparse cells, the Fisher exact test was used. Differences in means were tested using a Student *t* test for normal data. Non-normal data were analyzed using a Wilcoxon rank sum test. An alpha level of 0.05 was used for statistical significance. Analyses were performed using SAS/STAT software (version 9.4; SAS Institute Inc, Cary, North Carolina, USA).

• **PREVIOUS REPORTS OF PSEUDOTUMOR CEREBRI SECONDARY TO TETRACYCLINE:** To compare the findings presented here with previous case reports of PTC-T, the authors conducted a literature search in PubMed combining the search terms "pseudotumor cerebri" or "intracranial hypertension" with "tetracycline," "minocycline," or "doxycycline." The investigators then recorded the number of patients in the series, the ages and sexes of the patients, the antibiotics involved, BMI, presenting symptoms, duration of antibiotic therapy before presentation, LP opening pressure, treatments prescribed, and visual outcome. The investigative team excluded articles that were unavailable electronically, articles for which an English translation was not available, and articles in which ≥3 data points (antibiotics used, BMI, presenting symptoms, duration of antibiotic therapy, LP opening pressure, treatment, and visual outcome) were not reported.

RESULTS

THE AUTHORS IDENTIFIED 460 CASES OF PTCS BETWEEN JUNE 1993 and June 2013. Among these, the investigators identified 52 cases of PTC-T and 302 cases of IIH. The other 106 cases of PTCS were caused by other, secondary causes. Minocycline was the antibiotic most commonly associated with PTC-T, accounting for 41 of 52 cases (78.8%). Tetracycline (the specific agent, as opposed to the antibiotic class) accounted for 7 cases (13.5%) and doxycycline accounted for the remaining 4 cases (7.7%). In 37 of 52 PTC-T cases (71.2%), the indication for tetracycline antibiotic therapy was documented in the patient's chart. Acne vulgaris was the indication in 35 cases (94.6%), with the other 2 being rosacea and hidradenitis suppurativa.

• **PATIENT DEMOGRAPHICS AND BMI:** The demographics and BMI of the subjects are summarized in Table 1. There was a statistically significant difference in age at presentation between the 2 groups, with PTC-T patients initially presenting at a mean age of 19.8 years (SD 6.2 years) compared with 28.0 years (SD 9.9 years) in the IIH group ($P < .001$). Obesity, defined as BMI ≥30 kg/m^2, was less common among patients with PTC-T than those with IIH (43.7% vs 79.3%, $P < .001$). No significant difference in gender distribution was noted between the PTC-T and IIH groups; most patients in both groups were female (92.3% PTC-T vs 92.5% IIH). A family history of PTCS was not present in any of the PTC-T cases and was only present in 6 cases of IIH (2.0%).

TABLE 1. Comparison of the Age and Sex Distributions in a Group of 52 Patients With Tetracycline Antibiotic-Induced Pseudotumor Cerebri and 302 Patients With Idiopathic Intracranial Hypertension

	PTC-T (n =52)	IIH (n = 302)	P Value
Sex, n (%)			
Male	4 (7.7)	22 (7.5)	1.000
Female	48 (92.3)	271 (92.5)	1.000
Age (y), n (%)			
Overall, mean ± SD (median)	19.8 ± 6.2 (18.0)	28.0 ± 9.9 (27.0)	<.001[a]
<10	0 (0)	3 (1.0)	1.000[a]
10-19	34 (65.4)	52 (17.7)	<.001
20-29	13 (25)	119 (40.6)	.044
30-39	4 (7.7)	79 (27)	.009
40-49	1 (1.9)	34 (11.6)	.097[a]
≥50	0 (0)	6 (2.0)	1.000[a]
Data missing	0	9	
BMI (kg/m^2)			
Overall, mean ± SD (median)	29.4 ± 7.2 (27.9)	36.1 ± 8.1 (35.0)	<.001
<18.5	1 (2.1)	1 (0.4)	1.000[a]
18.5-24.9	8 (16.7)	12 (4.5)	<.001
25-29.9	18 (37.5)	42 (15.8)	<.001
30-34.9	15 (31.3)	76 (28.7)	.718
35-39.9	3 (6.3)	61 (23)	.010[a]
≥40	3 (6.3)	73 (27.5)	.002[a]
Data missing	4	37	

BMI = body mass index; IIH = idiopathic intracranial hypertension; PTC-T = tetracycline-induced pseudotumor cerebri; SD = standard deviation.

On average, patients with PTC-T tended to be younger and were less likely to be obese, compared with their IIH counterparts.

[a]Either a Fisher exact or a Wilcoxon rank sum test was used (see Methods).

• **CLINICAL PRESENTATION AND EXAMINATION FINDINGS:** The mean duration of symptoms before presentation was 7.5 weeks (SD 7.0 weeks) for the PTC-T group vs 20.0 weeks (SD 38.0 weeks) for the IIH group (range 1.0-37.0 weeks PTC-T vs 0.4-260 weeks IIH, $P = .343$). A comparison of the presenting symptoms reported by the 2 groups is shown in Table 2. Some of the most commonly reported presenting symptoms in both groups were headache (90.4% PTC-T vs 85.7% IIH), pulsatile tinnitus (48.1% PTC-T vs 46.4% IIH), and transient visual obscurations (32.7% PTC-T vs 43.3% IIH). Diplopia was reported twice as frequently among PTC-T patients compared with IIH patients (40.4% PTC-T vs 20.1% IIH, $P = .001$).

At initial examination, a relative afferent pupillary defect was detected in 13.5% of PTC-T subjects vs 9.9% of IIH subjects ($P = .002$). Cranial nerve VI palsy was documented in 11.6% of PTC-T subjects vs 6.8% of IIH subjects ($P = .253$). The mean LP opening pressure at presentation was 414 mm H_2O (SD 130 mm H_2O) in the PTC-T group vs 369 mm H_2O (SD 96 mm H_2O) in the IIH group ($P = .07$). Differences in baseline best-corrected visual acuity in the worse-seeing eye, papilledema grade, and Humphrey visual field mean deviation were not statistically significant.

• **CLINICAL COURSE AND VISUAL OUTCOME:** The frequency of surgical treatments was similar in the 2 groups; shunting procedures were performed in 3.8% of cases in both groups and optic nerve sheath fenestrations were performed in 7.7% of PTC-T patients vs 9.2% of IIH patients. At the last recorded visit, a relative afferent pupillary defect was documented in 12.0% of the PTC-T patients vs 8.3% of the IIH patients ($P = .509$). Disease recurrence was documented in 4.0% of the PTC-T patients vs 16.5% of the IIH patients ($P < .001$). No significant differences were noted in the last recorded visual acuity or Humphrey visual field mean defect.

• **PREVIOUS REPORTS OF PTC-T:** The literature search for reports of PTC-T resulted in the identification of 42 English articles with complete data (<4 data points missing) describing 96 cases (Supplemental Table). The mean age of presentation in these studies was 18.6 years (compared with 19.8 years in the present study). Females made up 85.4% of patients compared with 92.3% in the present series. Minocycline was determined to be the inciting agent in 62 cases (64.6% of all cases, compared with 78.8% in this series), tetracycline in 21 cases (21.9% of all cases, compared with 13.5% in this series), and doxycycline in 13 cases (13.5% of all cases, compared with 7.7% in this

TABLE 2. A Comparison of Presenting Symptoms Reported by Patients With Tetracycline-Induced Pseudotumor Cerebri and Idiopathic Intracranial Hypertension

Symptom(s) at Presentation, *n* (%)	PTC-T (*n* =52)	IIH (*n* = 302)	*P* Value
Headache	47 (90.4)	251 (85.7)	.361
Pulsatile tinnitus	25 (48.1)	136 (46.4)	.825
Transient visual obscurations	17 (32.7)	127 (43.3)	.151
Blurred vision	20 (38.5)	89 (30.4)	.248
Nausea/vomiting	12 (23.1)	74 (25.3)	.738
Diplopia	21 (40.4)	59 (20.1)	.001
Photophobia	7 (13.5)	58 (19.8)	.282
Neck pain	2 (3.8)	21 (7.2)	.550
Dizziness	2 (3.8)	18 (6.1)	.750
Photopsia	2 (3.8)	17 (5.8)	.750
Retrobulbar pain	2 (3.8)	10 (3.4)	.699
Paresthesia	2 (3.8)	9 (3.1)	.674
Positive visual phenomena	0 (0)	7 (2.4)	.600
Asymptomatic	0 (0)	6 (2)	.597
Confusion	1 (1.9)	1 (0.3)	.279

IIH = idiopathic intracranial hypertension; PTC-T = tetracycline-induced pseudotumor cerebri.

The prevalence of various symptoms at presentation was similar in both groups except for double vision, which was much more prevalent in the PTC-T group than in the IIH group. Data for every symptom were not available for every IIH patient; data are presented as a percent of patients for whom data were available.

series). The mean duration of antibiotic use before symptom onset from 91 cases was 18.9 weeks (compared with 14.4 weeks in this study). Headache, nausea, and blurred vision were the most common reported symptoms at presentation. In the present study, headache, pulsatile tinnitus, and diplopia were the most common symptoms. LP opening pressure was documented in 86 cases, with a mean of 339 mm H_2O (compared with 414 mm H_2O in this study). The most common disease treatments documented in the literature search were antibiotic withdrawal and acetazolamide.

DISCUSSION

THE RESULTS PRESENTED HERE SUPPORT THE HYPOTHESIS that significant clinical differences exist between patients diagnosed with PTC-T and those diagnosed with IIH. Most notably, the findings presented here suggest that patients with PTC-T tend to be younger, are less likely to be obese, and are more likely to experience diplopia. Patients with PTC-T are also less likely to experience disease recurrence than their IIH counterparts. At the same time, it is important to note that many similarities exist between the 2 groups, including gender distribution, presenting symptoms, frequency of surgical treatments, and visual outcomes.

Tetracycline antibiotics, particularly minocycline, are commonly used in the treatment of acne, so it is not surprising that the patients with PTC-T tended to be younger than patients with IIH.

In this series, minocycline was the antibiotic that was most commonly associated with PTC-T. The authors suspect that this association with minocycline reflects its preferred use in the treatment of acne vulgaris[8] and not an increased propensity for this antibiotic to cause PTC-T compared with other tetracyclines.

The BMI of patients with PTC-T varied widely, with fewer than half being classified as obese. By contrast, nearly 80% of patients with IIH were classified as obese. Friedman and associates[9] reported that 5 of 7 patients with PTC-T were obese (71.4/%), while Chiu and associates[4] reported that 4 of 12 cases of PTC-T were obese (33.3%). Paley and associates[10] identified 11 pediatric patients with PTCS caused by tetracycline-class antibiotics as part of a larger study of pediatric patients with secondary PTCS. Of the 9 patients for whom data were available, all were either overweight or obese. Because the present series is significantly larger than these previous studies, and because the PTC-T cohort was directly compared with an IIH cohort, the authors conclude that the rate of obesity in patients with PTC-T is likely less than that in patients with IIH.

An association between obesity and acne could be a confounding factor. However, the research regarding obesity and acne is conflicting, with some authors finding an increased risk of acne with increased BMI (eg, Heng and Chew[11]) and other authors finding an inverse relationship between acne and BMI (eg, Snast and associates[12]).

As with previously reported cases, symptoms of increased intracranial pressure generally improved among the patients in this study after discontinuation of tetracycline antibiotics. Symptoms and signs of PTCS recurred in 2 of 52 patients with PTC-T. In both cases, the recurrence was associated with weight gain and not re-exposure to a tetracycline, and the recurrence was less severe than the original presentation. Kesler and associates[6] also reported disease recurrence after antibiotic withdrawal, suggesting that tetracyclines, at least in some instances, may serve only as an aggravating factor in patients who are already predisposed to PTCS. In an analysis of the prevalence of PTCS among patients prescribed a tetracycline antibiotic, the unadjusted model suggested a 70%-91% increased hazard of PTCS among tetracycline users.[13] However, after adjustment for confounders, the increased hazard was no longer statistically significant. In this series, the proportion of patients with IIH with disease recurrence was approximately 4 times the proportion observed in patients with PTC-T. The authors conclude that while tetracyclines may be just an aggravating factor in some cases, there appear to be several cases in which tetracyclines are the sole factor.

• **ARE PTC-T AND IIH THE SAME DISEASE?:** Experts continue to question the role of tetracycline antibiotics in the development of PTCS, and it is unlikely that this question will be definitively answered in the near future. For instance, in this article, the rate of obesity was much lower in the PTC-T group compared with the IIH group. Obesity and weight gain are considered to be causative factors in the development of IIH,[14] and the signs and symptoms of IIH often improve with weight loss.[15] The observation that weight gain and obesity are associated with IIH, and yet many of the patients with PTC-T studied were not obese, supports the contention that tetracyclines can cause PTCS. On the other hand, in this article, there was a distinct preponderance of females in both the PTC-T group and the IIH group, suggesting that PTC-T and IIH are the same disease and that tetracyclines merely aggravate or trigger IIH in susceptible individuals.

These 2 possibilities may not be mutually exclusive; there appear to be nonobese patients who develop PTC-T, discontinue the antibiotic, and never develop PTCS or IIH again. Then there are other patients who develop PTC-T, discontinue the antibiotic, and later develop IIH (such was the case with 2 of the patients described herein who had a recurrence of PTCS after the antibiotic had been discontinued). The authors conclude that PTC-T likely represents a spectrum of disease in susceptible individuals.

• **PATHOPHYSIOLOGY OF PTC-T:** To date, there have been no case-control studies proving a causative link between tetracycline antibiotics and PTCS. While it is hypothesized that these agents may lead to intracranial hypertension by inhibiting the formation of cyclic adenosine monophosphate at the arachnoid villi, the mechanism by which tetracyclines contribute to PTCS is not fully understood.[3,4] Quinn and associates[16] pointed out that demeclocycline, a member of the tetracycline drug class, can induce nephrogenic diabetes insipidus. They hypothesized that the tetracycline class of antibiotics, because they cross the blood-brain barrier, could, by a similar mechanism, block absorption of cerebrospinal fluid into the venous sinuses.[16] Regen and associates[17] suggested that minocycline directly interferes with metabolism of endogenous retinoic acid, another substance commonly linked to the development of PTCS. While our study cannot prove causation, it further substantiates the widely recognized association between tetracycline antibiotics and PTCS. Future research into the mechanism by which tetracycline may cause PTCS in susceptible individuals may help us better understand not only PTC-T but also better understand the pathophysiology of IIH.

• **COMPARING RESULTS WITH PREVIOUSLY PUBLISHED DATA:** The clinical characteristics of the PTC-T cohort are similar to those reported in previous retrospective case series. Treatment prescribed in these previous reports was similar to that observed in the cohort presented here, primarily antibiotic withdrawal and acetazolamide. The authors conclude that the PTC-T patients presented here are likely representative of the PTC-T patients encountered in most centers.

Generally, the use of tetracycline antibiotics is considered safe, but because of the uncommon but serious potential for vision loss, it is the recommendation of the authors that patients taking these medications be warned about the symptoms of increased intracranial pressure. Specifically, based on these observations, it is recommended that physicians who prescribe these antibiotics consider asking their patients to report symptoms of headache, pulsatile tinnitus, vision changes, or diplopia. Patients who report these symptoms while taking these medications should promptly be evaluated by an ophthalmologist who can determine if patients have ophthalmic manifestations of increased intracranial pressure.

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