The outcome of pseudotumor cerebri induced by tetracycline therapy


Objective – To demonstrate the association between tetracycline treatment and pseudotumor cerebri (PTC). Methods – Consecutive patients from two neuro-ophthalmic referral centers, who developed PTC syndrome post-treatment with tetracycline, were enrolled and followed for a minimum of 2 years after cessation of tetracycline. Results – A total of 243 consecutive patients were diagnosed with PTC; 18 had concurrent history of tetracycline treatment; a third experienced a limited course of illness with no relapses; 12 had a variable course with a prolonged relapsing illness. Mean duration of tetracycline treatment prior to diagnosis was 2.73 months. Conclusions – Tetracycline, and especially minocycline, is currently considered a cause or a precipitating factor for PTC. Although there is little information on the natural course of tetracycline induced PTC, the present cases demonstrate that drug withdrawal is curative only in some patients.

Pseudotumor cerebri (PTC) or idiopathic intracranial hypertension (IIH) is a disorder associated with increased intracranial pressure (ICP) with no clinical, laboratory, or radiological evidence of an intracranial space-occupying lesion (1–4). Diagnosis of PTC/IIH is made according to the modified Dandy criteria (Table 1). The annual incidence of IIH in the general population is 0.9 per 100,000 (5). PTC/IIH in adults generally occurs in obese women of childbearing age.

To our knowledge, no medication has been proven by a case–controlled study to cause PTC/IIH; however, there have been many case reports linking intracranial hypertension to particular medications. Friedman et al. proposed that treatment with sulfon conjugated medications correlated with ICP in both humans and rodents (6). Many of the conditions previously thought to be associated with PTC/IIH such as mastoiditis, systemic lupus erythematosus or use of birth control pills result in increased cerebral pressure due to venous sinus thrombosis or related corticosteroids used (7).

Tetracycline and minocycline have been implicated to cause PTC/IIH in infants and adults (8–14). Gardner et al. (15) reported the use of tetracycline in twin sisters suggesting a possible genetic predilection. The small number of patients enrolled in case–controlled studies limited the possibility to correlate factors, e.g. medication, as a trigger/cause for PTC. The reason why tetracyclines would cause ICP is unclear. With the ubiquitous use of this drug in young adults for the treatment of acne, more cases should have been reported. In addition, vitamin A preparations are commonly combined with tetracycline in treating acne and may actually be the precipitating factor for ICP (9).

Several case studies have reported the resolution of ICP after the offending drug was withdrawn (11, 15). However, in several other cases, permanent visual loss has been reported even after cessation of the medication (13, 14).

Several reports of minocycline related PTC have been reported since 1978 (9). To our knowledge, there have been no case–controlled studies associating PTC/IIH with tetracycline use. However, the many case descriptions where withdrawal of the medication caused remission of the disease make this a likely association.

The aim of this study was to determine the frequency of tetracycline-related PTC.
Methods

The following inclusion criteria were used to select patients: tetracycline-minocycline treatment concurrent with a diagnosis of PTC, papilledema, absence of focal neurological deficits except VI nerve palsy, normal computerized tomography or magnetic resonance imaging of the brain, cerebrospinal fluid, opening pressure >250 mm of water and normal cerebrospinal fluid formula (3).

A review of patient records of those diagnosed with PTC at the Sheba Medical Center and Tel Aviv Sourasky Medical Center from 1985 to 2003 retrieved 243 patients with PTC—48 males, 195 females, of which 20 met the criteria.

Obesity was noted when prominent and in most cases according to body mass index (BMI) calculation. Visual parameters were compared with those at the last follow-up examination. Follow-up occurred at least 2 year after treatment for PTC had ceased.

Results

Of 243 consecutive patients diagnosed with PTC, 20 patients (8.23%) had a history of tetracycline treatment (minocycline or tetracycline) prior to PTC diagnosis. Two patients were rejected due to limited follow-up (<1 year). The remaining 18 patients were divided into two groups according to their clinical profile: 6 (group B) had a limited course of illness with no relapses (mean follow-up 84 months); 12 (group A) had a variable course with a prolonged relapsing illness (mean follow-up 81 months).

When comparing these two groups, no differences were noted in age, gender, presenting symptoms, obesity or relevant past history (such as contraceptive or steroid treatment) (Tables 1 and 2). Mean duration of tetracycline treatment prior to diagnosis was 2.73 months (0.75–12 months) in group A and 1.04 months (0.250–2.00 months) in group B ($P < 0.24$). Total duration of acetazolamide treatment was 18 months (range 6–38 months) in group A and 4.5 months (range 3–6 months) in group B.

Discussion

Cyclines are broad spectrum antibiotics often used in acne (in clinical use since the 1960s) (16). Although there are specific and useful differences between the tetracyclines currently available and the previous generations, they are generally very much alike. The tetracyclines possess a wide range of antimicrobial activity against gram positive and
gram negative bacteria. Most tetracyclines are adequately but incompletely absorbed from the gastrointestinal tract. The percentage of oral dose absorbed when the stomach is empty is lowest for oxytetracycline (30%); highest for doxycycline (95%) and minocycline (100%). The half-life of doxycycline and minocycline are long (17–20 h). Food does not interfere with the absorption of doxycycline and minocycline. Due to their enterohepatic circulation, they may be present in the blood for a long time after cessation of therapy.

Tetracyclines, especially minocycline, are widely used in treating acne. Although safe in most cases, these agents were found to be associated with PTC. Monaco et al. in 1975 (9) reported the first association. Whether tetracyclines are an independent risk factor or an added risk factor, is yet unknown.

We present 18 cases of tetracycline induced PTC with a minimum of 2 years follow-up after discontinuation of minocycline or tetracycline treatment. Our data supports the hypothesis that tetracycline may cause PTC, thus in some cases discontinuation of treatment ameliorates the disorder. However, in other cases tetracycline may serve as a trigger or an aggravating factor that induces the syndrome, thus discontinuation of treatment is insufficient and the patient faces a prolonged relapsing disease.

We suggest that in our two subgroups the trigger for PTC was induced by tetracycline: in group A, we suggest that tetracycline was the major offending agent while in group B other (yet unknown) risk factors contributed, thus tetracycline played a more minor role.

We propose that prior to tetracycline treatment, patients should be questioned and examined for visual disturbances; every patient treated with minocycline or doxycycline, especially childbearing patients need to be routinely checked for the papilledema, after the first month of treatment; to monitor the recurrence of PTC, a minimum of a 1 year follow-up is necessary.

**Table 2** Patients' data – group B

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age (year)</th>
<th>Gender</th>
<th>Presenting symptoms</th>
<th>Duration minocycline treatment (m)</th>
<th>Daily dose</th>
<th>Visual acuity at first attack</th>
<th>Weight height (BMI)</th>
<th>Visual fields at last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17 (F)</td>
<td>Headache</td>
<td>Headache</td>
<td>2 Weeks</td>
<td>100 mg</td>
<td>6/6 OD</td>
<td>H 157</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>27 (F)</td>
<td>Headache</td>
<td>Headache</td>
<td>1 Months</td>
<td>100 mg</td>
<td>6/6 OD</td>
<td>H 160</td>
<td>No data</td>
</tr>
<tr>
<td>3</td>
<td>36 (M)</td>
<td>TVO</td>
<td>TVO</td>
<td>1 Week</td>
<td>100 mg</td>
<td>6/6 OD</td>
<td>H 162</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>22 (F)</td>
<td>Headache</td>
<td>TVO</td>
<td>2 Months</td>
<td>100 mg</td>
<td>6/6 OD</td>
<td>W 70 (26.2)</td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>20 (F)</td>
<td>TVO</td>
<td>TVO</td>
<td>6 Months</td>
<td>100 mg</td>
<td>6/6 OD</td>
<td>W 80 (3.3)</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>39 (F)</td>
<td>TVO</td>
<td>TVO</td>
<td>2 Weeks</td>
<td>100 mg</td>
<td>6/6 OD</td>
<td>W 80 (3.3)</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**Conclusion**

Our study supports the notion of a linkage between tetracycline and especially minocycline treatment and PTC. This retrospective study did not examine the frequency of PTC in asymptomatic subjects treated with minocycline thus a definite causal link cannot be inferred.

The pathophysiology is presumed to be related to decreased cerebrospinal fluid absorption (17). Although the suspected risk in tetracycline treatment is low, the consequences may be serious. Dermatologists should be aware of the risk of PTC...
in patients receiving tetracycline for acne. Although most patients who develop PTC have prominent symptoms and are diagnosed promptly, others are asymptomatic and may have optic disc edema for a long period of time before diagnosis. It is recommended that after 1 month of tetracycline treatment patients undergo a complete ophthalmological examination (i.e. including optic disc evaluation). The development of headaches or transient visual obscurations in patients using tetracycline warrants prompt ophthalmologic evaluation to minimize potential visual complications.

References