Headache and visual disturbance

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Case 1

An 11-year-old boy presented with enteric fever (titres for *Salmonella typhi* positive as TH 640 and TO 320). He was prescribed pefloxacin 200 mg 12 hourly for 14 days. After regression of fever in five days, he complained of an occipitotemporal headache of increasing severity with vomiting and diplopia. No H/O ear discharge, visual symptoms or seizures.

Clinical examination revealed an alert young boy with normal vital signs. Bilateral papilloedema was observed, with left lateral rectus paralysis. There were no other focal neurologic deficits. Visual acuity was normal with bilateral concentric constriction of visual fields and enlargement of blind spots. Electroencephalogram (EEG) showed diffuse theta to delta slowing. A computed tomography (CT) scan of the head was normal. Spinal tap showed an opening pressure of 300 mm cerebrospinal fluid (CSF) with normal cytology, sugar and proteins.

Pefloxacin was withdrawn and the patient started on acetazolamide (250 mg eight hourly). He was symptom free in two weeks with regression of papilloedema in eight weeks.

Case 2

The patient was a 26-year-old woman who presented with an infection of the urinary tract (significant growth of *Escherichia coli* on culture). She was prescribed norfloxacin (400 mg bid) for 14 days with ibuprofen (400 mg) and paracetamol (325 mg) eight hourly for an initial four days, until fever and dysuria subsided. After one week of therapy she complained of severe occipitotemporal headache with vomiting and visual obscurations, along with restlessness and tremulousness. There was no history of ear discharge or intake of oral contraceptives.

Clinical examination revealed an anxious, thinly built woman with coarse action tremors. Vital signs were normal. The patient showed bilateral gross papilloedema with paradiscal haemorrhages and retinal edema. There were no focal neurologic deficits. Visual acuity was normal with peripheral constriction of fields and enlarged blind spots on perimetry. EEG was normal. CT scan of the head showed no mass lesion but lateral ventricles were small and chinked. Spinal tap revealed an opening pressure of 350 mm CSF with normal cytology, sugar and proteins.

Norfloxacin was discontinued. Acetazolamide (500 mg eight hourly) and alprazolam were prescribed. This led to relief of symptoms with regression of papilloedema in nine weeks. Mild tremors, claimed to be present since childhood, persisted.

Questions

- 1 What is the diagnosis in these cases?
- 2 How does the condition differ from idiopathic intracranial hypertension?
- 3 What other conditions may be associated with it?
- 4 Name the drugs known to be associated with this disorder.

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Answers

QUESTION 1

Symptomatic intracranial hypertension. The patients presented with features of intracranial hypertension and papilloedema with no focal localising neurologic signs together with a normal CSF composition and normal CT scan of the head. The intracranial hypertension was possibly associated with pefloxacin and norfloxacin therapy, respectively.

QUESTION 2

Patients with idiopathic intracranial hypertension have no clinical, laboratory or radiologic evidence of a space-occupying lesion or hydrocephalus, with no apparent cause for the intracranial hypertension. The typical patient is a young, obese, female who fulfills the modified Dandy’s criteria (box 1). Visual impairment of some degree is reported in over 50% of patients.

QUESTION 3

Symptomatic intracranial hypertension with no focal neurologic deficit has been associated with a vast array of medical conditions (box 2). However, conditions such as intracranial sino-

venous thrombosis and hyperviscosity syndrome must be excluded. Ideally, withdrawal of the putative causative agents should lead to resolution of intracranial hypertension and re-exposure to its recrudescence. Unfortunately, the cause and effect relationship has not been established in the majority of cases. It appears that in patients with symptomatic intracranial hypertension, an underlying obscure abnormality fails to manifest itself as intracranial hypertension without the addition of the precipitating factor.

QUESTION 4

A number of drugs (box 3) have been associated with development of intracranial hypertension, although compared to the frequency of their use, particularly antibiotics and steroids, provocation of intracranial hypertension seems to be rare. As with other causes of symptomatic intracranial hypertension, the exact pathogenesis remains obscure.

Discussion

Symptomatic intracranial hypertension with no focal neurologic deficit has been reported in association with diverse conditions (box 2),^{1,2} although a cause and effect relationship has not been confirmed with any of them. Conditions linked to causation of symptomatic intracranial hypertension must conform to the criteria described in box 4.

Modified Dandy’s criteria for the diagnosis of idiopathic intracranial hypertension

- signs and symptoms of increased intracranial pressure
- awake and alert patient
- no localising neurologic signs other than abducens nerve paresis
- normal neuroimaging studies except for small ventricles or empty sella
- documented increased pressure (> 200 mm of water in nonobese and > 250 mm of water in the obese patient), but a normal composition of CSF
- no other cause of intracranial hypertension present

Box 1

Conditions and diseases associated with intracranial hypertension

Endocrine

- adrenal insufficiency
- Cushing’s disease
- hypoparathyroidism
- hypothyroidism

Medication

Nutritional disorders

- hypervitaminosis A
- hypovitaminosis A
- hyperalimentation in deprivation dwarfism

Miscellaneous

- chronic renal failure
- systemic lupus erythematosus
- sarcoidosis

Box 2

Drugs reported to be associated with intracranial hypertension

- minocycline
- nalidixic acid
- isotretinoin
- tetracycline
- trimethoprim-sulfamethoxazole
- cimetidine
- tamoxifen
- corticosteroids
- lithium
- danazol
- nitrofurantoin
- levo-thyroxine
- amiodorone
- diphenylhydantoin
- quinolones (present cases)

Box 3

Criteria for causative factors of symptomatic intracranial hypertension

- at least two cases have been described
- the individual case satisfies the diagnostic criteria for idiopathic intracranial hypertension
- head trauma and conditions that result in intracranial sinovenous thrombosis and hyperviscosity syndrome have been excluded

Box 4

Drugs implicated in production of raised intracranial pressure (box 3) include oral contraceptives. However, oral contraceptive use is so common among women of child-bearing years that provocation of intracranial hypertension by them appears to be a chance association.⁴ Quinolones had not until now been identified as causative agents of intracranial hypertension. They are structural analogues of nalidixic acid with improved pharmacologic properties (increased potency, broad antibacterial spectrum, and ability to attain high concentration in most body tissues and fluids).⁵ The most active representatives of this group include ciprofloxacin, ofloxacin, pefloxacin, norfloxacin, and enoxacin. Although all the quinolones have a common basic structure of carboxylic acid, they belong chemically to different groups, which explains their different pharmacokinetics. A major proportion of pefloxacin is transformed metabolically to norfloxacin.⁶ The association of intracranial hypertension with quinolone therapy may well be related to their structural analogy with nalidixic acid.

The rise in intracranial pressure in patients on nalidixic acid therapy is mostly acute and has been reported in 1–3% of patients receiving it.^{7–9} Focal neurologic signs, drowsiness,

seizures, or abnormal EEG have been described in these patients and in this respect they differ from those with idiopathic intracranial hypertension which occurs predominantly in obese woman of reproductive age with a history of recent weight gain and menstrual irregularity.³

The exact pathophysiology of intracranial hypertension in patients on nalidixic acid is not clear. It appears to be an unpredictable and idiosyncratic response to the drug. Induction of cortical venous thrombosis, metabolic acidosis or altered CSF dynamics have been blamed but lack corroborative evidence.^{7,9} Whether the symptomatic intracranial hypertension found in our patients is an idiosyncratic reaction or a dose-related phenomenon is difficult to surmise. The elucidation of the cause and effect relationship of quinolones in such patients remains highly desirable.

Final diagnosis

Symptomatic intracranial hypertension, possibly associated with quinolones.

Keywords: quinolones, hypertension, headache, visual disturbances

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