SHORT REPORT

Cyclosporin associated headache

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Abstract

Despite successful orthoptic liver transplantation some patients develop a recurrent headache that interferes with their quality of life. To estimate the frequency of this symptom 34 patients who had undergone orthoptic liver transplantation were questioned about the history and character of any headache. Six patients described a recurrent headache typical of migraine only since transplantation. In two patients the pain improved after reduction of cyclosporin dosage and thereby plasma cyclosporin concentration.

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Although cyclosporin is said to cross the blood brain barrier poorly, neurological side effects are well recognised, and include seizures, tremor, encephalopathy, ataxia, and cortical blindness.^{1,2} Headache after starting cyclosporin has been described after bone marrow transplant,³ in treating disorders of the skin,⁴ and after renal transplantation in 15 of 467 patients.⁵ In some patients a severe headache has been reported to relate to drug dosage and plasma concentration^{2,6,7} and in others severe headache has resulted in its discontinuation.⁶ The character of headache associated with cyclosporin has been poorly documented.

Following referral of three patients who developed severe recurrent headache after successful liver transplantation, we questioned 31 other patients under regular review by the liver transplant unit as to the occurrence, frequency, and character of headache both before and after their transplant. All patients were taking immunosuppressant medication that included cyclosporin.

Case reports**CASE 1**

Five months after successful liver transplantation for primary biliary cirrhosis, a 48 year old woman developed recurrent headache. The pain was preceded by a visual disturbance in which her central vision was blurred "like looking through fish scales". Within minutes this was followed by a severe unilateral (left

or right) frontotemporal headache, throbbing in nature and associated with photophobia, nausea, and occasional vomiting. Occasionally with the onset of headache there was an accompanying numb sensation of the limbs. She would have to lie down. The attacks occurred on average once every six weeks, tending to start in the morning and last all day. The patient remembers a similar episodic headache some 20 to 30 years previously. There has been no benefit from propranolol, amitriptyline, or pizotifen, but more recently the patient has found effective relief of her headache one hour after self injection with sumatriptan. Her cyclosporin dosage at 400 mg per day has not been adjusted since transplantation, as the plasma level is consistently within the normal range (last value 59 ng/ml).

CASE 2

A 59 year old lady underwent liver transplantation for primary biliary cirrhosis five years ago. Eight months later she developed recurrent headache initially once every two weeks but more recently once a month. The headache was right or left temporal, aching in nature, and with associated nausea and occasional vomiting. Preceding the pain she often experienced a tingling sensation in her limbs. She does not recall a similar headache before transplantation. Two years ago at the time of an episode of rejection, cyclosporin was increased from 250 mg per day to 400 mg per day with associated increase in severity of headache. The dosage has subsequently been reduced to 350 mg per day with a plasma cyclosporin concentration of 45 ng/ml. Dividing up the daily dose of cyclosporin had no effect on the headache. The pain failed to respond to simple analgesia or ergotamine but is successfully relieved by sumatriptan.

CASE 3

About three months after liver transplantation for primary biliary cirrhosis, a 59 year old man developed episodic bifrontal, aching, throbbing, headache. The pain is preceded by a visual disturbance described as difficulty in focusing. This tends to persist while the headache is severe. During the attack he describes an acute sensitivity to noise and light, with nausea and vomiting later in the course of the headache. There may be

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accompanying diarrhoea. After progressive reduction in cyclosporin dosage the frequency and severity of headaches have decreased to three per month. Furthermore, at a lower dose the patient states he feels more alert. The last cyclosporin concentration was 45 ng/ml at a dose of 125 mg per day. There was slight relief of headache with paracodeine and he has not tried sumatriptan.

Of 31 other patients with successful orthoptic liver transplants, a further three patients described a recurrent headache since transplantation with the characteristics of migraine, two of whom have associated aura. The mean latency to onset of headache in all six patients with migraine after transplant was four months (SD two months; range two to eight months). Two patients in total have noted a reduction in frequency of headache with decrease in cyclosporin dose. Of the remaining 28 patients, one with migraine present before transplantation has not noted any change since transplantation. Six others describe an intermittent mild diffuse headache since transplantation. Twenty one patients are either free of headache or have not noted any change in their headache since transplantation.

Discussion

In at least three patients the frequency and severity of headache was clearly interfering with the quality of life. The character of their headache is that of migraine. Although one patient described a similar headache 20 to 30 years ago there was no history of a similar headache before transplantation in the other five patients with migraine.

The mechanism of migraine remains mysterious; therefore, attempts to explain the association in our patients is speculative. An acute parenteral dose of cyclosporin is said to reduce cerebral blood flow,⁸ perhaps by its

effects on thromboxane A2 release, and production of prostacyclin,⁹ or by its sympathetically mediated contractile effects on vascular smooth muscle.¹⁰ This may be of relevance in an older patient with an already compromised cerebral circulation. A suggestion that the neurological effects of cyclosporin may relate to hypocholesterolaemia, and hypomagnesaemia has not been substantiated by others.²

In treating the headache the use of non-steroidal anti-inflammatory agents should be avoided due to the potential nephrotoxic effects of cyclosporin in combination with these.¹¹

Cyclosporin is an important major chronic treatment in liver transplantation. Although any explanation for an associated recurrent headache is inadequate, the frequency and severity in some patients deserves recognition and appropriate treatment.

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