

## LETTERS

### Use of prostacyclin (iloprost) in digital vasculitis secondary to meningococcaemia

Extracranial complications of meningococcal septicaemia occur in about 11–19% of cases, and include myocarditis, acute renal failure, arthritis, pneumonia, skin gangrene, conjunctivitis, endocarditis, pericarditis, endophthalmitis, urethritis, Waterhouse-Friderichsen syndrome, vasculitis, and digital ischaemia.<sup>1</sup>

We describe the use of a prostacyclin analogue in the treatment of cutaneous digital ischaemia in a patient with meningococcal meningococcal meningitis and meningococcaemia.

#### Case report

A 16 year old female developed progressive headache, photophobia and increasing neck stiffness over 3 days, with nausea and vomiting, and development of non-blanching purpuric rash over her trunk and right thigh. She became increasingly obtunded with depressed level of consciousness, resulting in cardiorespiratory embarrassment.

She was intubated, mechanically ventilated, and treated with volume expanders. Her initial investigations revealed leucocytosis, thrombocytopenia, anaemia, and coagulopathy. Computed tomography (CT) of the brain showed diffuse swelling of both cerebral hemispheres consistent with cerebral oedema. Meningococcal DNA polymerase chain reaction (PCR) was positive for group C serotype. She was treated with high doses of cefotaxime, benzylpenicillin, and steroids from the day of admission. Her condition improved after 48 hours of intensive care, and she was extubated. After 5 days, she developed pain and swelling in the thumb and middle finger of her left hand; within 24 hours these symptoms had worsened with marked swelling and pre-gangrenous changes of the acral regions of the involved thumb

and finger, and there was severe pain and tenderness (fig 1A, B).

A diagnosis of imminent digital gangrene due to digital vasculitis and/or septic embolisation secondary to endarteritis was made. In an empirical effort to improve digital perfusion high dose steroids were recommended and treatment with intravenous heparin, aspirin and clopidogrel was initiated; little improvement in the digital ischaemia occurred. In an attempt to save the digit she was then started on a prostacyclin (iloprost) infusion at a titrating dose of 0.5 ng/kg body weight/min with marked improvement in pain and coloration after 5 days of treatment. Four weeks following her discharge from hospital her fingers were nearly back to normal and she was pain free (fig 1C, D).

#### Comment

The pathophysiology of digital ischaemia in meningococcaemia is complex, and involves injury to the endothelium triggering the coagulation cascade, inhibition of the thrombomodulin protein C system, and lodgement of small emboli in digital capillaries. In this report we describe the use of a prostacyclin analogue, iloprost, in digital pre-gangrene due to digital ischaemia occurring as a complication of meningococcal septicaemia. Prostacyclin is a potent endogenous vasodilator that affects both the systemic and pulmonary circulations; it also inhibits platelet adhesion and aggregation and prevents smooth muscle proliferation. Iloprost, a stable synthetic prostacyclin analogue, has been used with varying success in the treatment of pulmonary hypertension, peripheral arterial occlusive disease,<sup>2,3</sup> thromboangiitis obliterans,<sup>6</sup> and digital vasculitis secondary to progressive systemic sclerosis,<sup>2</sup> Sjögren's syndrome and systemic lupus erythematosus.<sup>3,5,6</sup> In these situations, iloprost has been shown to improve perfusion, healing digital ulceration and reducing pain secondary to ischaemia in digital vasculitis, when given in a dose of 0.5–2.0 ng/kg body weight/min (according to individual tolerability) with incremental

increases in dose every 30 min. Side effects include headache, nausea, vomiting, and hypotension. Blood pressure and heart rate must be measured at the start of infusion and with each increase in dose.

The use of iloprost in digital ischaemia due to meningococcal septicaemia has not been reported previously. This report suggests that iloprost may be useful in preserving tissue integrity in the cutaneous manifestations of meningococcal septicaemia, and perhaps obviate the need for amputation in some patients. Although our report of a single case does not prove efficacy beyond doubt, the biological and pharmacological rationale behind the use of a prostacyclin analogue in this situation, and the apparent response to therapy in our patient, strongly support a direct therapeutic benefit. We believe that this is of sufficient importance to warrant therapeutic trials in patients with this potentially devastating condition.

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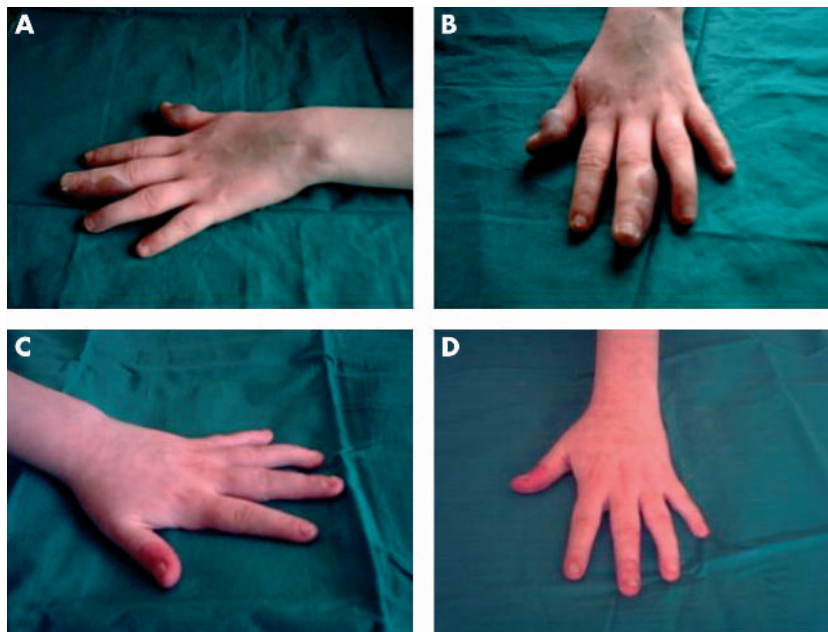
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#### Etizolam and benzodiazepine induced blepharospasm

Drug induced blepharospasm is an independent clinical entity, but it has not been established whether blepharospasms can be induced by benzodiazepine or by thienodiazepine derivatives, which are the most frequently used antipsychotic agents in Japan. To determine whether benzodiazepine or thienodiazepine derivatives can induce blepharospasm, the medication history of 254 consecutive patients (67 men, 157 women) with blepharospasm were examined retrospectively. There were 35 patients (13.8%) who had used etizolam before onset of blepharospasm, and this incidence was significantly higher than the two cases (3.3%) in the control group of 61 patients



**Figure 1** Pregangrenous changes (A, B) of thumb and middle digit of left hand, which resolved (C, D) following treatment with prostacyclin.

that had used etizolam ( $p < 0.05$ ) before onset of hemifacial spasms. Other psychotropics were used in 53 patients (20.9%) prior to development of blepharospasm, and this was significantly higher than those who had used other psychotropics (6.5%) in the control patients ( $p < 0.01$ ). The patients felt asymptomatic following termination of etizolam or benzodiazepines in five patients who had noted increased blinking and difficulty keeping eyes opened after a relatively short duration of the drug use. Significantly more women were seen in both groups pretreated with etizolam ( $p < 0.05$ ) or other psychotropics ( $p < 0.001$ ) when compared with the group with no drug history. We conclude that prolonged administration of etizolam or benzodiazepines can induce blepharospasms, especially in women.

Blepharospasms and Meige syndrome are local dystonias that can result in functional blindness and can develop in patients taking various neuroleptic agents.<sup>1-3</sup> In Japan, benzodiazepines, which are prescribed most frequently for patients with insomnia, psychosis, and depression have not been included in these neuroleptic agents. Ethizolam, a thienodiazepine derivative, is a popular anxiolytic with a high affinity for benzodiazepine receptors.

We have had several patients who used benzodiazepine derivatives before the onset of blepharospasms, and we have thus hypothesised that benzodiazepine usage will induce blepharospasms. To test this hypothesis of a causal relationship between the drug and disease, we conducted a detailed drug history for patients with blepharospasm.

We retrospectively examined the medication history of 254 consecutive patients (187 women and 67 men) before and after the onset of blepharospasm. These patients had two or more of the following characteristics; (1) could not generate rapid voluntary blinks but blinked frequently with spasmodic eyelid movements, (2) had high frequency or irregular, involuntary blinking, (3) had difficulty in maintaining their eyes open while walking or watching television, and (4) complained of photophobia or dry eyes. Exclusion criteria were; (1) exact medication history not available from the chart, (2) had irritated or painful ocular surface disease, and (3) dropped out before the six month follow up examination.

For control, the medication history of 61 age matched patients (17 men/44 women) with hemifacial spasm was examined. The spasm resulted from vascular compression

and was not related to any central nervous system disorder.

Etizolam was taken by 35 of the 254 patients (13.8%; 7 men, 28 women) before the blepharospasm developed, and only two of the 61 control patients (3.3%) before the hemifacial spasms. This difference in the incidence was statistically significant ( $p < 0.05$ , Yates' correction of  $\chi^2$  test).

Other psychotropic drugs had been used in 53 patients (20.9%; 6 men, 47 women) before development of blepharospasm. This incidence was significantly higher than that of the control group where three of 61 patients (5.1%) had taken other psychotropic drugs before the development of hemifacial spasm ( $p < 0.01$ , Yates' correction of  $\chi^2$  test).

The mean age of the group with a history of using etizolam was 51.6 (SD 14.0) years with a range of 27 to 75 years. These patients were slightly younger than the patients who had not used etizolam (55.2 (SD 11.2) years) but the difference was not statistically significant ( $p = 0.10$ , unpaired  $t$  test).

Thirteen patients had used only etizolam (table 1), and another 21 patients had also received other drugs; 11 received a benzodiazepine derivative, three had major tranquilizers, and seven had received both tranquilizers and etizolam.

The duration of etizolam use before the onset of blepharospasm was more than one year in 28 patients, and over five years in 13 of these 28 patients. The average dose of etizolam could be determined in 20 patients; 10 patients received 0.5 mg/day or less, five received 1.0-1.5 mg/day, and five received  $> 2.0$  mg/day.

Three patients noted an increase in the frequency of blinking and difficulty keeping eyes open within 6 months of etizolam use, and they stopped using the drug. Two of them felt a gradual improvement and became asymptomatic. In total, the drug was either stopped or the dosage was decreased in 16 patients including the two patients. Seven of the 16 patients reported that the symptoms of blepharospasm improved.

In the group that received psychotropics other than etizolam, the mean age was 56.3 (SD 15.8) years with a range of 23 to 79 years. This was not significantly different from the group with no drug history ( $p = 0.58$ , unpaired  $t$  test).

Except for two patients treated with major tranquilizers only, benzodiazepines were prescribed for 51 patients who developed blepharospasm, 16 of whom were taking benzodiazepines alone. The duration of use

of benzodiazepines before onset of blepharospasm was over one year in 44 patients, including 19 patients with over five years of usage. Two women given benzodiazepine for 1-2 months and one woman with a two year drug history became asymptomatic after termination of the drugs, without any further drug or botulinum toxin treatment.

The number of women was significantly higher in the group who had received etizolam (seven men, 28 women,  $p < 0.05$ ,  $\chi^2$  test) than in the group with no prior use of medication (54 men, 82 women). There were significantly more female benzodiazepine positive patients (six men, 47 women,  $p < 0.001$ ,  $\chi^2$  test).

Blepharospasm is a female dominated disease, and in the two groups, with no prior use of etizolam or usage of other psychotropics, there were significantly more women when compared with the group with no drug history.

Although the pathogenesis of blepharospasm is not known, abnormalities of cortical or subcortical neural pathways have been suggested.<sup>4</sup> A down regulation of GABAA receptors<sup>5</sup> involved in the neural circuits due to prolonged treatment with ethizolam or benzodiazepine may induce impairment of normal blinking. In any case, ophthalmologists and neurologists should remember that prolonged administration of ethizolam or benzodiazepines is a risk factor for blepharospasm especially in women. Thus, a careful medication history should be made before more expensive neurological tests are performed.

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**Pure motor stroke with major involvement of the index finger**

A selective weakness of a particular group of fingers due to cortical infarction has been reported by several authors.<sup>1-3</sup> This finding is related to the controversy over the somatotopic organization of the primary motor cortex (M1). Traditionally, a discrete somatotopic arrangement for individual fingers, with the radial fingers represented laterally and the ulnar fingers medially, has been assumed. However, recent theories have suggested functional overlapping of the cortical representation of the fingers. We describe here a case presenting with major weakness of the index finger due to a cortical infarction confirmed by MRI.

**Table 1** Patients taking etizolam alone prior to development of blepharospasm

Onset age (years)	Sex	Dose (mg/day)	Duration (years)	Drug use stopped	Outcome*
68	F	0.25/2 days	9	Yes	Improved 1
28	F	0.5/2 days	1 month	Yes	Improved 2
58	F	0.5/2 days	3	Yes	Improved 1
51	F	0.5	2 months	Yes	Improved 2
57	M	0.5	10 months	Yes	Improved 1
63	F	0.5	1	Changed drug	No change
62	F	0.5	17 months	Yes	No change
41	F	0.5	5	Yes	Improved 1
28	F	0.5	6	No	No change
52	F	0.5	7	Yes	No change
67	F	1.0	6	Reduced to 0.5 mg	No change
57	F	1.0	12	No	No change
42	F	1.5	10	Yes	Improved 1

\*Follow up period  $> 6$  months. Improved 1: patient reported improvement but still required botulinum toxin. Improved 2: patient became asymptomatic without any further treatment.

### Case report

A 71 year old right handed man noted difficulty in using his toothbrush one morning. He complained of weakness in his right index finger and was admitted to our hospital on the day of onset. He had no previous illnesses nor risk for stroke. Neurological examination revealed the following muscle weaknesses: extension, abduction, and adduction of the right index finger (2-/5 as scored by the Medical Research Council (MRC) grading system); radial abduction of the middle finger (3/5); and 4/5 for extension of the middle finger, abduction of the little finger, and flexor digitorum profundus of the index finger. Strength was normal for the other finger movements, including all directions of thumb movement, and wrist, elbow, and shoulder movements were also completely normal. He had no sensory deficits, including no deficit in combined sensations. There was no evidence of apraxia. Deep tendon reflexes were normal; the Babinski sign was negative on both sides. There were no significant laboratory abnormalities, and electrocardiography and echocardiography were normal. Carotid ultrasonography revealed a small plaque echo in the left common carotid artery. Needle EMG of the right first dorsal interosseus muscle, performed on the first day, showed a pattern consistent with central weakness. A brain MRI performed on the fifth day of admission revealed two hyperintense spots in the precentral knob and the subcortical white matter, by both diffusion-weighted and T2-weighted images, indicating an acute ischaemic stroke (fig 1). His symptoms began to improve within one week, and largely resolved in two weeks.

### Discussion

This case presented with a predominant weakness of the index finger; needle EMG revealed unequivocal central weakness. An MRI demonstrated two acute strokes, in the contralateral subcortical white matter and precentral knob, respectively. However, we

suggest that the latter was responsible for the symptoms, in that the precentral knob is associated with the motor hand area.<sup>4</sup> In addition, it is difficult to conceive of a mechanism whereby such selective weakness could be caused by a subcortical lesion.

Earlier studies proposed discrete M1 somatotopy for individual finger movements, arranged with the thumb most lateral and the little finger most medial, as illustrated by the renowned homunculus of Penfield.<sup>5</sup> However, more recent studies, using either cortical stimulation in monkeys or functional MRI in humans, have mostly demonstrated a dispersed and overlapping representation over a rather wide M1 area for finger and hand movements.

Patients with small cortical lesions can provide additional information on this issue. Several authors have reported examples presenting with predominant weakness of a particular finger or group of fingers; most presented with predominant weakness of either the thumb or the little finger.<sup>1,2</sup> Schieber emphasised that they had identified no cases, either in their own experience or in the literature, with the greatest weakness in the index, middle, or ring fingers, and with stronger fingers on either side.<sup>1</sup> He also stated that in no instance was a single digit more than one unit on the MRC scale weaker than the other four digits. The only exceptions hitherto may be the two cases reported by Kim<sup>2</sup> and Kim *et al*,<sup>3</sup> showing the greatest or isolated weakness in the index finger; but the strength of the index finger was only mildly affected (4/5) in both patients. Therefore, clear evidence for discrete somatotopy for individual fingers is lacking, although a lateromedial gradient in cortical representation for the fingers from the radial to the ulnar side has been suggested.<sup>1,2</sup>

The present case is unique in presenting with prominent weakness of the index finger (2-/5), sparing the thumb and largely sparing the fingers on the ulnar side. Another interesting feature is the clear dissociation between the weak extension and adduction/

abduction movements (2-/5) v the almost preserved flexion (4/5 or 5/5) of the index finger. The classical experiment by Penfield<sup>5</sup> indicated that certain cortical points did produce, although rarely, an isolated movement of a single finger. The present result suggests that there is a localised area predominantly responsible for the movement of a single finger, at least for the index finger, as well as for the specific direction of movement.

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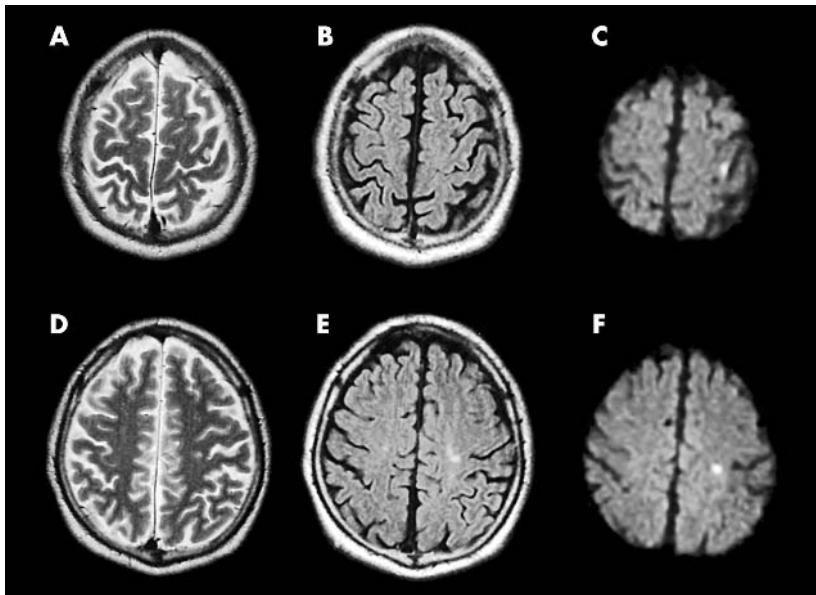
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### The effect of interferon beta-1a on spasticity in primary progressive multiple sclerosis

It has been suggested that spasticity may be increased in primary progressive multiple sclerosis (PPMS) following treatment with interferon beta.<sup>1</sup> In an open study using the Ashworth Scale and a reflex scale, Bramanti *et al* measured change in spasticity in 19 subjects treated with interferon beta-1b and in 19 untreated subjects. An increase in spasticity during treatment was seen in 68% of the treated participants compared with 11% of the untreated participants. To investigate this phenomenon further, we conducted a retrospective analysis of the spasticity studied in the recently published randomised controlled trial of interferon beta-1a in PPMS.<sup>2</sup>

We randomised 50 subjects to receive weekly for two years an intramuscular injection of either interferon beta-1a 30 µg (15 subjects); or interferon beta-1a 60 µg (15 subjects); or placebo (20 subjects). Following completion of the study, the clinical notes of all cases were reviewed and the occurrence of spasticity documented. Spasticity was not a predetermined outcome, but symptomatic spasticity had been recorded in the notes by the blinded treating physician, including both post-dose spasticity and any independent, sustained increase in the level of spasticity. Any increase in anti-spasticity medication was also documented. Statistical analysis was carried out on an intention to treat basis. Comparisons were made between the placebo and combined interferon group and the individual treatment groups using Fisher's exact test.

Two years of follow up were completed by 49 participants; 43 completed the study on treatment, with the dose having been halved in seven patients.<sup>2</sup> There were no significant



**Figure 1** T2-weighted (A) and (D), fluid attenuated inversion recovery (B) and (E), and diffusion weighted (D) and (F) MRI images are shown for the two axial slices. Two small high intensity spots were identified in the precentral knob (A-C) and at the subcortical white matter (D-F).

**Table 1** Number of subjects experiencing an increase in spasticity

Result	Placebo, n = 20	IFN, n = 30	IFN 30 µg, n = 15	IFN 60 µg, n = 15
Sustained increase in spasticity	13	11	9	2*
Post-dose spasticity	3	10	4	6
Increase in medication	6	4	3	1

n, number; IFN, interferon beta-1a. All statistical comparisons not significant (p>0.05) except \*p = 0.005.

differences in sustained increase in spasticity, post-dose spasticity, or anti-spasticity medication, when the combined interferon group was compared with the placebo group (table 1). No significant differences were seen between the individual treatment groups and the placebo group, except that a sustained increase in spasticity occurred less commonly in the group receiving interferon beta-1a 60 µg.

This study found no significant increase in spasticity in patients with PPMS treated with interferon beta-1a. There was a non-significant trend to an increase in post-dose spasticity in the interferon groups (33%) compared with the placebo group (15%). Transient increased spasticity following dosing with interferon beta has also been reported in secondary progressive and relapsing remitting MS.<sup>3, 4</sup> This phenomenon is not surprising, given that worsening of existing spasticity in association with intercurrent factors such as fever is a common experience in MS. However, there was no suggestion of a sustained increase in spasticity or increased requirements for anti-spasticity medication.

There are obvious limitations to this study, most notably the retrospective analysis. It is difficult to comment on the discrepancy between our findings and those of Bramanti *et al*, because of the different trial designs and the use of different types of interferon beta. Further investigation of the effect of interferon beta on spasticity would require a prospective randomised controlled study.

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**A breathtaking headache**

Thunderclap headache was the subject of a recent review in this journal, in which the pathophysiology was linked to segmental vasospasm.<sup>1</sup> Specifically, the abrupt onset of the headache was linked to vasospasm caused by neurogenic rather than biochemical mechanisms. Hyperventilation can probably induce generalised vasospasm through alkalosis of the cerebrospinal fluid.<sup>2</sup> We recently saw a patient where hyperventilation or exertion caused thunderclap-like headaches.

This previously healthy 15 year old boy was admitted to Leiden University Medical Centre because of acute (that is, maximum severity within one minute), severe left sided headache associated with, successively, a numb and tingling sensation in the right arm and leg, weakness of the right arm for 30 minutes, and difficulty in speaking. Four weeks earlier, after running for several minutes to catch a train, he suffered an acute, severe bifrontal, throbbing headache, which subsided within minutes after he stopped running. There were no associated symptoms. Three weeks before admission he experienced a similar headache for 30 minutes which started after 10 minutes of running. That evening a third episode occurred but this time the headache started spontaneously, lasted for two hours, and was accompanied by nausea and vomiting. In the subsequent three weeks until admission, these headache episodes occurred every one or two days, occasionally triggered by exertion, but often seemingly spontaneous.

On admission, physical examination was uneventful apart from non-fluent speech and decreased dexterity of the right hand. Brain magnetic resonance imaging scan, cerebrospinal fluid, and an electrocardiogram (ECG) were normal. The next day only a dull sensation in the head persisted and neurological examination was normal. Physical exertion (climbing stairs for 10 minutes) increased the dull sensation only slightly. However, forced hyperventilation while seated provoked a sudden severe headache that continued for 30 minutes after stopping hyperventilation and that was not accompanied by other symptoms. The patient recognised the headache as the same as those he had been suffering previously. Quantified hyperventilation was abnormal (positive on five of seven items). Spirometry was normal and no pulmonary cause for hyperventilation was found. He was discharged and relaxation exercises and physical therapy were initiated. He has since been able to exercise and run normally, and has had no more headaches. No re-challenge with forced hyperventilation was performed. Last follow up was six months after discharge.

This patient had three, apparently different types of severe, acute, alarming headaches: (1) exertion induced headaches, (2) sponta-

neous headaches, and (3) one episode of headache associated with nausea, vomiting, and transient focal neurological symptoms. Recurrent headaches following exertion may be caused by serious cerebral disorders such as subarachnoid haemorrhage, posterior fossa tumour, or Arnold-Chiari malformation, but these were all excluded.<sup>3</sup> Cardiac ischaemia is a rare cause of unilateral exertional headache. Although no ECG during exertion was performed, the normal ECG at the time of complaints and the ability to exercise normally after relaxation therapy make this an unlikely cause. Cerebral angiography was not performed.

Benign exertional headache typically presents as bilateral throbbing headaches for five minutes to 24 hours following physical exercise.<sup>3</sup> In the present patient, however, the headache was induced by hyperventilation following exercise, rather than by the exercise itself. His "spontaneous" headaches, most likely, were also caused by hyperventilation; this is supported by the complete disappearance of these headaches after initiation of relaxation therapy. Although hyperventilation can cause a dull and non-specific generalised headache in about 20% of patients, such an alarming, explosive type of headache has, to our knowledge, never been described.<sup>4</sup> The attack that prompted admission, most likely, was migraine with aura, as supported by the sequential rather than simultaneous development of neurological symptoms. Migraine seems to occur more frequently in patients with benign exertional headache.<sup>5</sup>

Our case illustrates that hyperventilation, both in rest and following physical exertion, may cause severe, acute, "explosive" headaches, and that adequate relaxation exercises and physical therapy can prevent these alarming headaches. The precise mechanism of the headache in our patient remains elusive. Additionally, although breathing exercises would not prevent physiological exercise induced hyperventilation, they may prevent excessive hyperventilation following exercise. Hyperventilation provocation tests can be diagnostic and should be considered in all patients with exertion induced headaches. In light of the recent review, magnetic resonance angiography could be considered in such cases to evaluate a possible involvement of cerebral vasospasm.<sup>1</sup>

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