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

Extrameningeal complications of meningococcal septicemia occur in about 11–19% of cases, and include myocarditis, acute renal failure, arthritis, pneumonia, skin gangrene, conjunctivitis, endocarditis, pericarditis, endophthalmitis, urethritis. Waterhouse-Friederichsen syndrome, vasculitis, and digital ischaemia.

We describe the use of a prostacyclin analogue in the treatment of cutaneous digital ischaemia in a patient with meningococcal meningocenephhalitis 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 cyanosis over 3 days, with nausea and vomiting and increasing neck stiffness. Blood pressure and heart rate 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 septicemia has not been reported previously. This report suggests that iloprost may be useful in preserving tissue integrity in the cutaneous manifestations of meningococcal septicemia, 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.

References


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 benzodiazepine use in five women 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.1 2 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 thiendiazepine 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 while 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) stopped drug use or subcortical neural pathways have been suggested.3 A down regulation of GABAA receptors involved in the neural circuits due to prolonged treatment with etizolam or benzodiazepine may induce impairment of normal blinking. In any case, ophthalmologists and neurologists should remember that prolonged administration of etizolam 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.

Table 1

<table>
<thead>
<tr>
<th>Onset age (years)</th>
<th>Sex</th>
<th>Dose (mg/day)</th>
<th>Duration (years)</th>
<th>Drug use stopped</th>
<th>Outcome*</th>
</tr>
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<tbody>
<tr>
<td>68</td>
<td>F</td>
<td>0.25/2 days</td>
<td>9</td>
<td>Yes</td>
<td>Improved</td>
</tr>
<tr>
<td>28</td>
<td>F</td>
<td>0.5/2 days</td>
<td>7</td>
<td>Yes</td>
<td>Improved</td>
</tr>
<tr>
<td>58</td>
<td>F</td>
<td>0.5/2 days</td>
<td>2</td>
<td>Yes</td>
<td>Improved</td>
</tr>
<tr>
<td>51</td>
<td>F</td>
<td>0.5</td>
<td>12 months</td>
<td>Yes</td>
<td>Improved</td>
</tr>
<tr>
<td>57</td>
<td>M</td>
<td>0.5</td>
<td>10 months</td>
<td>Yes</td>
<td>Improved</td>
</tr>
<tr>
<td>63</td>
<td>F</td>
<td>0.5</td>
<td>1</td>
<td>Yes</td>
<td>Improved</td>
</tr>
<tr>
<td>62</td>
<td>F</td>
<td>0.5</td>
<td>17 months</td>
<td>No</td>
<td>No change</td>
</tr>
<tr>
<td>43</td>
<td>F</td>
<td>0.5</td>
<td>1</td>
<td>Yes</td>
<td>Improved</td>
</tr>
<tr>
<td>28</td>
<td>F</td>
<td>0.5</td>
<td>6</td>
<td>No</td>
<td>No change</td>
</tr>
<tr>
<td>52</td>
<td>F</td>
<td>0.5</td>
<td>7</td>
<td>Yes</td>
<td>No change</td>
</tr>
<tr>
<td>57</td>
<td>F</td>
<td>1.0</td>
<td>Reduced to 0.5 mg</td>
<td>No</td>
<td>Improved</td>
</tr>
<tr>
<td>42</td>
<td>F</td>
<td>1.5</td>
<td>10</td>
<td>Yes</td>
<td>Improved</td>
</tr>
</tbody>
</table>

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

References


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.4 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 of pure M1 stroke with major weakness of the index finger due to a cortical infarction confirmed by MRI.
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 interosseous 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.1 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.5 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.1,4 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. 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 Kim1 and Kim et al., 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.1,4

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 movements (2/5) v the almost preserved flexion (4/5 or 5/5) of the index finger. The classical experiment by Penfield 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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References


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.1 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.2 We randomised 50 subjects to receive 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 interferon beta-1a treatment, with the dose having been halved in seven patients.3 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).
A breathtaking headache

Thunderclap headache was the subject of a recent review in this journal, in which the pathophysiology was linked to segmental vasospasm. Specifically, the abrupt onset of a severe headache was caused by vasospasm caused by neurogenic rather than biochemical mechanisms. Hyperventilation can probably induce generalised vasospasm through alkalosis of the cerebrospinal fluid. 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 once or two days, occasionally triggered by exertion, but often seemingly spontaneous.

On admission, physical examination was uneventful apart from non-fluent speech and 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) provoking exertional headache was performed, the normal ECG and no pulmonary cause for hyperventilation was abnormal (positive on magnetic resonance imaging scan, cerebrospinal fluid, and transient focal neurological symptoms. Migraine seems to occur more frequently in patients with benign exertional headache.

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.

Table 1 Number of subjects experiencing an increase in spasticity

<table>
<thead>
<tr>
<th>Result</th>
<th>Placebo, n = 20</th>
<th>IFN, n = 30</th>
<th>IFN 30 μg, n = 15</th>
<th>IFN 60 μg, n = 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained increase in spasticity</td>
<td>13</td>
<td>11</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Post-dose spasticity</td>
<td>3</td>
<td>10</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Increase in medication</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

All statistical comparisons not significant (p > 0.05) except p = 0.005.

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