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

Extrameningeal 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-Friederichsen syndrome, vasculitis, and digital ischaemia.1

We describe the use of a prostacyclin analogue in the treatment of cutaneous digital ischaemia in a patient with meningococcal meningoencephalitis 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 rash over her trunk and right thigh. She became increasingly obtunded with purpuric rash over her trunk and right thigh. Her initial investigations revealed leucocytosis, thrombocytopenia, anaemia, and coagulation cascades; 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,4,5 thromboangiitis obliterans, and digital vasculitis secondary to progressive systemic sclerosis.6 Sjögren's syndrome and systemic lupus erythematosus.7,8 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 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 tiensodiazepine 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.
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 women who had noted increased blinking and difficulty keeping eyes open 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 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, (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.

Ethizolam was taken by 38 of the 254 patients (13.8%; 7 men, 31 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 χ² 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 χ² 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 tranquillizers, and seven received both tranquillizers 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 = 0.38, unpaired t test).

Except for two patients treated with major tranquillizers 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 who had used etizolam (seven men, 28 women, p<0.05, χ² 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, χ² 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.4 A down regulation of GABAA receptors 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 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  Patients taking etizolam alone prior to development of blepharospasm

<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>
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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 1</td>
</tr>
<tr>
<td>28</td>
<td>F</td>
<td>0.5/2 days</td>
<td>1 month</td>
<td>Yes</td>
<td>Improved 2</td>
</tr>
<tr>
<td>58</td>
<td>F</td>
<td>0.5/2 days</td>
<td>5</td>
<td>Yes</td>
<td>Improved 1</td>
</tr>
<tr>
<td>51</td>
<td>F</td>
<td>0.5</td>
<td>2 months</td>
<td>Yes</td>
<td>Improved 1</td>
</tr>
<tr>
<td>57</td>
<td>M</td>
<td>0.5</td>
<td>10 months</td>
<td>Changed drug</td>
<td>No change</td>
</tr>
<tr>
<td>63</td>
<td>F</td>
<td>0.5</td>
<td>1</td>
<td>Changed drug</td>
<td>No change</td>
</tr>
<tr>
<td>62</td>
<td>F</td>
<td>0.5</td>
<td>17 months</td>
<td>Yes</td>
<td>No change</td>
</tr>
<tr>
<td>41</td>
<td>F</td>
<td>0.5</td>
<td>1</td>
<td>Yes</td>
<td>No change</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>No change</td>
</tr>
<tr>
<td>61</td>
<td>F</td>
<td>1.5</td>
<td>10</td>
<td>Yes</td>
<td>Improved 1</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. 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 more 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.
Case report

A 71 year old right handed man noted difficulty in using his toothbrush one morn-
ning. 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 direc-
tions of thumb movement, and wrist, elbow, and shoulder movements were also comple-
tely 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, per-
formed 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 pre-
central knob and the subcortical white matter, by both diffusion-weighted and T2-
weighted images, indicating an acute ischae-
mic 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.3 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 soma-
totopy 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.6 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.6 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,4 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 representa-
tion 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/
abduction movements (2–5) v the almost
preserved flexion (4/5 or 5/5) of the index
finger. The classical experiment by Penfield6
indicated that certain cortical points did pro-
duce, 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

1 Schieber MH. Somatotopic gradients in the
distributed organization of the human primary
motor cortex hand area: evidence from small
2 Kim JS. Predominant involvement of a particu-
lar group of fingers due to small cortical infarction.
Neurology 2001;56:1677–82.
3 Kim JS, Chung JP, Hla SW. Isolated weakness of
index finger due to small cortical infarction.
Localization of the motor hand area to a knob on
the precentral gyrus. A new landmark. Brain
1997;120:141–57.
5 Penfield W, Boldrey E. Somatic motor and
sensory representation in the cerebral cortex of
man as studied by electrical stimulation. Brain
1937;60:389–443.

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 spas-
ticity 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 con-
trolled trial of interferon beta-1a in PPMS.2

We randomised 50 subjects to receive weekly
for two years an intramuscular injec-
tion 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, sus-
tained increase in the level of spasticity.
Any increase in anti-spasticity medication was
also documented. Statistical analysis was
conducted with 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 and
were on 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).
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.14 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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References


A breathtaking headache

Thunderclap headache was the subject of a recent review in this journal, in which the pathophysiology was linked to segmental vasospasm.1 Specifically, the abrupt onset of the headache was forced to vasospasm caused by neurogenic rather than biochemical mechanisms. Hyperventilation can probably induce generalised vasospasm through alkalosis of the cerebrospinal fluid.2 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 bilateral, 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 headache 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 one or two days, occasionally triggered by exertion, but often seemingly spontaneous.

On admission, physical examination was uneventful apart from non-fluent speech and right leg weakness of the right arm for 30 minutes. Spirometry 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). Spimetry 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’s history apparently different types of severe, acute, alarming headaches: (1) exertion induced headaches, (2) spontaneous 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.1 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 makes 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.1 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.2 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.1

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 test 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.1

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References

1 Dodick DW. Thunderclap headache. J Neurol Neurosurg Psychiatry 2002;72:6–11

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>
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<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>

n, number; IFN, interferon beta-1a. All statistical comparisons not significant (p>0.05) except *p = 0.005.
Pure motor stroke with major involvement of the index finger

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