Mononeuritis multiplex in diabetes mellitus: evidence for underlying immune pathogenesis

P Kelkar, G J Parry

Four patients with type 2 diabetes mellitus developed mononeuritis multiplex subacutely. Sural nerve biopsies showed multifocal axonal loss in all patients, with epineurial perivascular inflammation affecting small calibre vessels in three. Three patients improved with immunotherapy. These observations suggest that mononeuritis multiplex in diabetes may be caused by an immune mediated vasculopathy and that it is pathogenetically akin to the more common and better recognised diabetic amyotrophy.

Mononeuritis multiplex is defined as a disorder involving two or more named peripheral nerve trunks and most often occurs in collagen vascular disorders or as a manifestation of non-systemic vasculitis restricted to peripheral nerves.1 Although diabetes mellitus is commonly mentioned as a cause of mononeuritis multiplex,1 very few cases have been clearly documented in published reports. Furthermore, the mechanism of the nerve injury is uncertain. We previously reported preliminary findings in two diabetic patients with mononeuritis multiplex suggesting an inflammatory basis.2 We now report clinical, electrophysiological, and sural nerve biopsy findings and the treatment outcome in four diabetic patients with mononeuritis multiplex.

CASE REPORTS

Four patients with type 2 diabetes who developed mononeuritis multiplex were evaluated in the neuromuscular clinics at the Universities of Minnesota and Iowa between 1995 and 2001. All patients had undergone detailed medical and neurological examination. None had any systemic autoimmune disorder, malignancy, toxic exposure, or HIV risk factors. Laboratory studies included haemoglobin A1C, erythrocyte sedimentation rate (ESR), anti-nuclear and Sjogren’s syndrome antibodies, rheumatoid factor, and serum immune fixation electrophoresis.

Investigations

Nerve conduction and needle electromyographic studies (EMG) were done using conventional techniques. Sural nerve biopsies were undertaken using a standard approach. The specimen was divided into two 2 cm sections. One piece was stretched and fixed in glutaraldehyde/paraformaldehyde and used for plastic embedded sections stained with MAB (methylene blue, azure II, basic fuschin). The unstretched sample was fixed in 10% formalin and stained with haematoyxlin and eosin, and in two cases with immunohistochemical monoclonal stains for T and B lymphocytes.

Treatment

Patients were treated with immunosuppressive agents including intravenous immune globulin, oral prednisone, intravenous pulsed methylprednisolone, and oral chlorambucil.

Description of case 1

A 47 year old man with a four year history of type 2 diabetes, treated with an oral hypoglycaemic agent, had had mild symmetrical numbness in the feet for four years. Eighteen months before our initial evaluation he noted left foot drop with painful onset, which progressed over six months, requiring a brace and the use of a cane. Four months later he developed pain of sudden onset in the right wrist, numbness, and weakness progressing to wasting of the interosseous muscles. Two months later he developed numbness over the dorsum of the left hand and increased weakness in the right hand. After another two months he developed pain and numbness in the left T8 dermatome. He had lost 13.6 kg (30 pounds) over the 18 months but had no other constitutional symptoms.

Examination showed severe weakness and atrophy in the right interossei with normal strength in the abductor digitii minimi, and left foot drop. Sensory examination revealed decreased cutaneous sensation in the distribution of right ulnar, left dorsal ulnar cutaneous, and lef superficial peroneal nerves along with mild distal symmetrical loss in the lower extremities. Tendon reflexes were normal including the ankle jerks.

Laboratory evaluation was normal or negative, including antinuclear antibodies, rheumatoid factor, serum immune fixation, ESR, and C reactive protein. HbA1C was 7.0%.

Electrodiagnostic studies

Bilateral sural and left ulnar sensory nerve action potential amplitudes were reduced. Right ulnar motor study recorded from the abductor digitii minimi was normal. With recording over the first dorsal interosseus muscle, however, there was marked reduction in the compound muscle action potential (CMAP) amplitude, suggesting fascicular involvement of the ulnar nerve. Left peroneal CMAP amplitude was markedly reduced, while right peroneal and bilateral tibial CMAP amplitudes were normal. Needle EMG showed diffuse fibrillation in the right first dorsal interosseus muscle with absent motor unit potentials (MUP). Fibrillations were also seen in left tibialis anterior with large amplitude polyphasic MUP and moderately reduced recruitment.

Left sural nerve biopsy (fig 1, panels A to C) showed moderate loss of large myelinated fibres with inhomogeneous distribution suggesting multifocal ischaemic nerve injury. There were several areas with perivascular collections of > 50 mononuclear cells (T lymphocytes) surrounding small epineurial blood vessels. There was no fibrinoid necrosis or transmural inflammation.

The patient was treated with oral prednisone 60 mg/day for six weeks, followed by gradual taper over one year. Pain improved within one month of treatment and weakness started improving within six weeks, with nearly complete recovery of motor and sensory deficits and independent ambulation within six months. Prednisone has been discontinued for over two years and the patient remains well.
Overview of clinical features and investigations in the four cases

Three of our four patients were women. Patients were 47 to 72 years of age, and the duration of diabetes was one to four years. All patients had type 2 diabetes mellitus; three were treated with oral hypoglycaemic agents and one (patient 2) with insulin. All presented with mononeuropathy multiplex evolving in a stepwise manner over 16 to 18 months (table 1). All patients reported moderate to severe pain in the region of the affected nerves. They all had motor and sensory deficits in the distribution of the affected nerves in addition to mild distal symmetrical sensory loss in the feet. Ulnar and peroneal nerves were affected in all the patients. Three patients had weight loss of 6.8 to 13.6 kg (15 to 30 pounds). Two patients had a raised ESR (54 and 70 mm/h) with no other clinical or serological evidence of a systemic autoimmune disorder. HbA1C was mildly raised in all patients (6.4% to 7.0%).

Electrodiagnostic studies

Electrodiagnostic studies showed reduced or absent sensory and motor responses in the distribution of the affected nerves, indicating axonal degeneration in all patients. No patient showed focal slowing of conduction velocity or segmental temporal dispersion of responses across potential sites of compression. One patient had a more than 50% amplitude decrement in the ulnar nerve in the mid-forearm at the time of the initial study. A repeat study 10 days later showed that the distal amplitude had fallen, indicating that this was noncontinuity conduction block, probably caused by an acute ischaemic lesion. Sural sensory potentials were absent in two and reduced in two (to 1.8 and 3 µV).

Sural nerve biopsies showed multifocal loss of axons in all four patients (fig 1). Three had perivascular collections of mononuclear inflammatory cells (T lymphocytes) surrounding small calibre epineurial blood vessels, consisting of > 50 lymphocytes (fig 1C) in one, and smaller collections of 20 to 50 lymphocytes in two (fig 1F). None showed fibrinoid necrosis or transmural inflammation.

One patient had complete resolution of weakness and sensory loss within six months of treatment with prednisone. One continued to deteriorate in spite of prednisone and intravenous immune globulin, though her condition eventually improved spontaneously two years after presentation. One patient improved with intravenous pulsed methylprednisolone, 500 mg weekly for 12 weeks; she relapsed with increasing pain and weakness four weeks later, with subsequent improvement with a second course, along with oral chlorambucil. One patient improved over three months...
with intravenous pulsed methylprednisolone followed by oral chlorambucil. Pain improved remarkably in these three patients within one to two months of the treatment. There was no change in the distal symmetrical sensory neuropathy in the feet following treatment in any of the four patients.

**DISCUSSION**

The clinical spectrum of multifocal neuropathies in diabetes includes diabetic amyotrophy, truncal neuropathies, cranial neuropathies, mononeuropathies, and mononeuritis multiplex. Mononeuritis multiplex differs from diabetic amyotrophy in that it has slower stepwise progression, distal extremity involvement, and sensory-motor multifocal abnormalities, whereas diabetic amyotrophy progresses more rapidly and has predominantly proximal, almost exclusively motor, involvement. Peroneal and ulnar nerves were involved in all our patients as well as in most of the previously reported cases and these nerves seem to be particularly susceptible. Pain and weight loss are common in both disorders.

We do not believe that these were compressive neuropathies as the characteristic features of focal nerve compression—namely, conduction slowing and temporal dispersion—were lacking. Rather, these patients had multifocal axon loss presumably secondary to nerve ischaemia. This may explain the presence of severe pain which is common with ischaemic nerve injuries.

Mononeuritis multiplex most often occurs in collagen vascular disorders or as a manifestation of non-systemic vasculitis restricted to peripheral nerves. Although diabetes is often included among the causes of this disorder, we have found only five clearly documented cases affecting the extremity nerves in diabetic patients in English language reports. The prevalence of true mononeuritis multiplex in diabetes is unknown and it is possible that the condition is underrecognised. There have been no large series of cases, and some that have been reported as having mononeuropathy multiplex in fact had diabetic amyotrophy. Biopsy findings were reported in three of the above five patients with mononeuritis multiplex and showed multifocal axon loss and perineuritis. Immunotherapy (plasma exchange and prednisone in one, intravenous immunoglobulin in one, and prednisone in one) were given in these three patients and two improved.

All four of our patients showed inhomogeneous fibre loss and three had perivascular inflammatory infiltrates consisting of > 50 or > 20 T lymphocytes, suggesting that an immune mediated vasculopathy was the underlying cause of their neuropathy. Scattered mononuclear cells are a non-specific finding and can be seen in diabetes; however, perivascular collections of lymphocytes, especially of more than 10 to 20 cells, are usually interpreted as evidence of an inflammatory condition. We therefore treated our patients with immunosuppressive agents and one made a nearly complete recovery, while two improved to a lesser extent. We also noted marked improvement in pain in these patients with treatment. One patient failed to respond to treatment initially, but had eventual improvement over a two year period. The natural history of mononeuritis multiplex in diabetes is unknown and our numbers are small, but we feel there was probably a true therapeutic response in the three patients, as in each of them the disease had continued to progress until the treatment was started. Likewise marked improvement in pain suggests a therapeutic response. These patients also had mild distal symmetrical sensory loss in the feet, which probably reflected the more common length dependent, predominantly sensory polyneuropathy in diabetes, which remained unchanged following the immune treatment.

There is increasing evidence that diabetic amyotrophy is caused by ischaemic nerve injury secondary to microvasculitis rather than diabetic microangiopathy. Furthermore it appears that diabetic amyotrophy may be amenable to immuno-therapy. Our findings suggest that mononeuritis multiplex occurring in diabetes may have a similar pathogenesis and that these patients can show a favourable response to immunosuppressive treatment. We recommend that patients with diabetes who develop mononeuritis multiplex should undergo nerve biopsy to look for inflammatory changes. Immune modulating treatments should be considered even in the absence of inflammatory changes, especially in patients who have progressive neuropathy. A larger study is required to explore the pathophysiology, natural history, and possible treatment options for patients with mononeuritis multiplex in diabetes.

**ACKNOWLEDGEMENTS**

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**Table 1 Clinical features and treatment outcome**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>Duration of DM (months)</th>
<th>Progression of MM (months)</th>
<th>Weight loss (kg)</th>
<th>Involved nerves</th>
<th>Functional limitations</th>
<th>Pain</th>
<th>Treatment</th>
<th>Follow up (months)</th>
<th>Pain</th>
<th>Functional status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47/M</td>
<td>4 years</td>
<td>18</td>
<td>13.6</td>
<td>R, L peroneal, L, dorsal ulnar cutaneous, L T8</td>
<td>Brachial and back</td>
<td>Severe</td>
<td>Prednisone</td>
<td>24</td>
<td>1</td>
<td>Normal, independent walking</td>
</tr>
<tr>
<td>2</td>
<td>55/F</td>
<td>4 years</td>
<td>18</td>
<td>11.4</td>
<td>L&gt;R peroneal, L, L ulnar</td>
<td>Wheelchair</td>
<td>Severe</td>
<td>Prednisone, IVIG</td>
<td>12</td>
<td>1</td>
<td>No change: wheelchair</td>
</tr>
<tr>
<td>3</td>
<td>72/F</td>
<td>1 year</td>
<td>16</td>
<td>6.8</td>
<td>L&gt;R peroneal</td>
<td>Walker</td>
<td>Moderate</td>
<td>IVM, chlorambucil</td>
<td>Improved in two months</td>
<td>6</td>
<td>Improved: ambulation, cane</td>
</tr>
<tr>
<td>4</td>
<td>61/F</td>
<td>3 years</td>
<td>16</td>
<td>None</td>
<td>R, L peroneal, L femoral</td>
<td>Brachial and back</td>
<td>Moderate</td>
<td>IVM, chlorambucil</td>
<td>Improved in two months</td>
<td>6</td>
<td>Improved: ambulation, brace, and cane</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; F, female; IVIG, intravenous immunoglobulin; IVM, intravenous pulse methylprednisolone 500 mg weekly for 12 weeks; L, left; M, male; MM, mononeuritis multiplex; R, right.
A 38 year old woman, originally from the Pacific Islands with a history of residence in south western United States, presented with new onset severe headaches. Past medical history included disseminated coccidioidomycosis involving cervical lymph nodes two years earlier, which was incompletely treated with oral fluconazole because of non-compliance. Serum complement fixation coccidioides titres had risen from 1:8 to 1:32. MRI demonstrated multiple isointense, dural based lesions that uniformly enhanced upon contrast administration. These were located over the right parieto-occipital convexity (fig 1a) as well as on the tentorium at the left occipital pole (fig 1b). These lesions were consistent in appearance with en plaque meningiomas. Given the patient’s history, however, the possibility of chronic dural inflammation from coccidioidomycosis of the CNS was also considered. The patient was started on high dose fluconazole (800 mg) therapy and followed with serial MRIs. Despite improvement in the patient’s headaches, follow up MRI showed minimal change in lesion size. The patient underwent a left occipital craniotomy and biopsy for definitive diagnosis three months after reinitiating fluconazole. Intraoperatively, numerous bosselated, firm, dural based lesions were noted pushing into the surface of the brain. Pathological evaluation of the biopsy revealed granulomatous inflammation consistent with smoldering coccidioidomycosis (fig 1c).

Coccidioidomycosis is an endemic fungus of south western United States. Infection results from inhalation of windborne arthropores and characteristically manifests with pulmonary symptoms. An infrequent complication of coccidioidomycosis is dissemination beyond the lung and hilar lymph nodes to bone, skin, subcutaneous tissue, and joints. In addition, infection may spread to the CNS, typically causing chronic meningitis. Our case illustrates an exceedingly rare example of CNS coccidioidomycosis resulting in dural based mass lesions resembling meningiomas. The treatment for this condition remains controversial. Patients who fail oral fluconazole therapy may be candidates for intravenous amphotericin B and surgical debulking. The roles of experimental therapies such as caspofungin or varicocycle remain undefined in the treatment of coccidioidomycosis CNS mass lesions.

Figure 1 [A] Gadolinium enhanced MRI demonstrating an enhancing dural lesion over the right parieto-occipital convexity. [B] Gadolinium enhanced MRI demonstrating an enhancing dural lesion along the left tentorium near the transverse sinus. [C] Microscopic appearance of the dural biopsy. The specimen shows confluent granulomata of various sizes, some of which demonstrate centrally necrotic foci, and multinucleated giant cells. The larger granulomata display hyalineisation (haematoxylin and eosin stain; original magnification >50).

References


Coccidioidomycosis of the brain, mimicking en plaque meningioma

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Neutralising antibodies to interferon β during the treatment of multiple sclerosis

Giovannoni and colleagues are to be commended for their detailed analysis of the impact of neutralising antibodies (NAB) to interferon β (IFNβ) during the treatment of multiple sclerosis. We are in general agreement with many of their statements and conclusions, but a few points should be discussed in a wider context.

With respect to the clinical significance of neutralising antibodies to IFNβ, the authors state that “IFNβ has little if any clinical and MRI efficacy in the presence of neutralising antibodies.” We think it is appropriate to be more circumspect, as most published studies suggest that in NAB positive patients, clinical and MRI efficacy of interferon treatment is present when compared to placebo, and that there is some evidence that more immunogenic higher dose treatment can be more effective than less immunogenic lower dose treatment. Giovannoni et al appear to base their statement on the increase in T2 burden of disease in the NAB positive group in the PRISMS extension study, but they do not mention similar comparisons which, if interpreted in the same way, would indicate that the NAB positive group does better than the placebo group. For example, the relapse in placebo patients was 1.3/year in years one to two, whereas it was 0.81 and 0.50 in NAB positive and negative high dose patients in years three to four. We recognise that this specific comparison is fraught with difficulties owing to time trends in the relapse data, but these potential difficulties are present in all such comparisons. In a recent paper we report—in probably the largest study of neutralising antibodies in multiple sclerosis—describing 100 NAB positive patients in the European SPMS study—that high titres of neutralising antibodies do have a clinical impact, but that this impact is rather limited, and that on both clinical and MRI measures patients on active treatment who develop neutralising antibodies continue to do consistently better than those on placebo. The main conclusions of this paper are based on longitudinal analyses of the data on those patients who switched from NAB negative to NAB positive status; this is the only statistical approach that allows a direct assessment of whether the change from NAB negative to NAB positive status is associated with diminished efficacy of a treatment. Cross sectional comparisons are not fully reliable for establishing the impact of neutralising antibody positivity, as NAB positive and negative subgroups may differ on baseline variables (maybe unobserved) that are predictive of both neutralising antibody formation and diminished clinical response.

Giovannoni et al also state that during continued treatment “in the case of IFNβ-1b some NAB positive patients revert to NAB negative status over two to five years of follow up” and that “patients with high titres of neutralising antibodies seldom revert to being negative.” In the European study of IFNβ-1b in secondary progressive multiple sclerosis the proportion of treated patients who have been NAB positive and subsequently revert back to being NAB negative is about 40% after a treatment duration up to three years (without convincing evidence that patients with higher titres revert less frequently), whereas in the study by Rice et al this percentage is close to 80% after a mean treatment duration of more than eight years.

In our opinion, these data suggest that the clinical impact of neutralising antibodies to IFNβ during the treatment of multiple sclerosis may be more limited and more transient than suggested in the editorial, and that the development of neutralising antibodies in itself does not provide justification for switch treatments or for considering (aggressive) strategies to reduce or reverse the development of neutralising antibodies. Given the current rather uncertain state of knowledge concerning the impact of neutralising antibodies, we advocate that treatment decisions should be based on clinical grounds rather than on neutralising antibody titres.

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References

Neutralising antibodies to interferon β

I read the editorial by Dr G Giovannoni and colleagues' with great interest. I have, however, to report a minor error concerning the list of the excipients of the Rebif® in table 1. In the table the authors reported the following excipients: mannitol, HSA, sodium acetate, acetic acid, sodium chloride. Actually, as you can check in the summary of product characteristics published from EMEA (www.emea.eu.int) on 29 March 1999, in the list of excipients sodium chloride is absent, whereas sodium hydroxide is present.

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Authors' reply

We would like to thank Dr Ortenzi for pointing out our transcription error in relation to the excipients of Rebif® in table 1 of our editorial.

We agree with Polman and colleagues that recent comparisons show that the more immunogenic higher dose interferon β (IFNβ) preparations are more efficacious than the lower dose less immunogenic preparations over 24 months and six month periods of observation. However, as discussed in our editorial, the development of neutralising antibodies and their effects on the clinical efficacy of IFNβ are delayed. In the PRISMS study the effect of neutralising antibodies on clinical efficacy only became apparent at years 3–4.

In the pivotal IFNβ-1b study an effect on relapse rate was only observed in the 19–24 and 25–30 month epochs. Hence we would argue that these comparative studies are simply too short, and in the case of the INCOMIN trial underpowered (n = 188), to demonstrate an effect of neutralising antibodies on clinical efficacy. It is therefore impossible to extrapolate the significant short term difference in relapse rate to the periods of observation reported.

Because of regression to mean and the well documented tendency for the relapse rate to decrease with disease duration, it is not possible to draw any meaningful conclusions from a comparison of the relapse rate in years 1–2 and years 3–4 from the PRISMS extension study. In addition to the impact of neutralising antibodies on relapse rate, the PRISMS extension study clearly shows—using the more objective T2 lesion volume or burden of disease—that the average annualised increase in lesion volume over four years in the neutralising antibody positive (NAB+) patients is similar to the increase in the annualised lesion volume in the placebo treated patients in the first two years of the study (NAB+ 4.4% vs placebo 5.4%). Similarly, in the IFNβ-1b study the relapse rate of NAB+ patients is identical to patients on placebo (1.08 vs 1.06). In the IFNβ-1a (Avonex®) trial, the impact of neutralising antibodies was limited to MRI outcomes. The failure of neutralising antibodies to have an effect on disease progression and relapse rate in this study probably reflects the size and duration of follow up, as the study was terminated prematurely. It is these data from the pivotal relapsing multiple sclerosis clinical
trials, and other studies on in vivo markers of IFNβ activity discussed in our editorial, that we use to support our statement that “interferon β has little if any clinical and MRI efficacy in the presence of neutralising antibodies.”

Data on the impact of neutralising antibodies in secondary progressive multiple sclerosis (SPMS) trials is less clear. This is to be expected, however, as the efficacy of IFNβ on disease progression—the primary outcome measure in SPMS trials—is limited and hence it would be difficult to demonstrate a significant impact on neutralising antibodies on the primary outcome measure when the actual therapeutic intervention itself is only marginally effective. It would be very surprising if neutralising antibodies had a significant impact on disease progression, as none of the trials is powered to detect an effect of neutralising antibodies on this outcome. For example, in the European SPMS study, 100/360 (28%) of IFNβ-1b treated patients became NAB+ (titre > 20) over the course of the trial if we apply a conservative approach by applying the results from the trial, and assuming that NAB+ patients behave like the original IFNβ-1b treated cohort, one would expect 49.8% of the 100 NAB+ patients to progress over three years, compared with 38.9% of the 260 NAB− patients. At the same level of significance (0.029) from the original study, it would only have a 35% chance of detecting a significant difference between NAB+ and NAB− patients (Fishers exact test). Compare this to a power of 80% used in the design of the original study. This poor power calculation is an overestimate as it ignores the therapeutic effect observed before the development of neutralising antibodies, as evidenced in this study, which if taken into account would seem reasonable if there are no carryover therapeutic effects of IFNβ-1b treatment from the NAB− to NAB+ phase and if the follow up in the NAB+ phase is of sufficient duration to account for the delayed effects (24 to 48 months) of neutralising antibodies on clinical efficacy. In this study the mean follow up in the NAB+ phase would be on average too short (less than 24 months) for one to be confident of excluding a delayed effect of neutralising antibodies on disease progression. Despite the lack of power of these subanalyses, they produce some surprising results. In the cross sectional study there was a trend towards greater disease activity in the NAB+ group in the third year, and a significant percentage 12 volume change from baseline to year 1, year 2, and the last visit; in the underpowered and potentially flawed longitudinal analysis there was no indication of an attenuation of treatment effects on disability progression but, surprisingly considering the lower relapse rate in secondary progressive multiple sclerosis, there was a robust effect on relapse rate.

Another way of interpreting the European SPMS NAB data as presented by Polman and colleagues is that the much higher dose of IFNβ-1b (875 µg/week) given in that study, in comparison with the lower licensed doses of IFNβ-1a (30–132 µg/week), acted to quench some of the neutralising activity of the antibodies. Similarly, the higher doses may be responsible for inducing high dose tolerance in a subset of the patients. These phenomena are well observed with other biologicals in which the read-outs are more objective than in multiple sclerosis—for example, coagulation in anti-factor VIII and glucose levels in anti-insulin antibody positive patients.

Polman and colleagues have misinterpreted our recommendations. We do not recommend routine screening of neutralising antibodies at present, nor the switching of treatments in NAB+ patients unless clinically justified, nor aggressive strategies to reduce or reverse the development of neutralising antibodies. We simply state that further research is necessary to assess whether these strategies are appropriate. Polman and colleagues’ concluding statement that treatment decisions should be based on clinical grounds rather than on neutralising antibody titres is entirely in keeping with our recommendations.

We disagree with Polman and colleagues’ statement that “the clinical impact of neutralising antibodies to interferon β during treatment of multiple sclerosis may be more limited and more transient than suggested in the editorial.” Short to intermediate term data (<4 years) from the relapsing multiple sclerosis studies discussed above do not support this claim, and long term clinical data (>4 years) on the effects of transient neutralising antibodies on the therapeutic efficacy of IFNβ-1b do not exist to support the latter half of their claim. In addition, evidence in the literature so far suggests that NAB+ patients behave as if they are on placebo and NAB− patients behave like the original IFNβ-1b treated cohort, one would expect 49.8% of the 100 NAB+ patients to progress over three years, compared with 38.9% of the 260 NAB− patients. At the same level of significance (0.029) from the original study, it would only have a 35% chance of detecting a significant difference between NAB+ and NAB− patients (Fishers exact test). Compare this to a power of 80% used in the design of the original study. This poor power calculation is an overestimate as it ignores the therapeutic effect observed before the development of neutralising antibodies, as evidenced in this study, which if taken into account would seem reasonable if there are no carryover therapeutic effects of IFNβ-1b treatment from the NAB− to NAB+ phase and if the follow up in the NAB+ phase is of sufficient duration to account for the delayed effects (24 to 48 months) of neutralising antibodies on clinical efficacy. In this study the mean follow up in the NAB+ phase would be on average too short (less than 24 months) for one to be confident of excluding a delayed effect of neutralising antibodies on disease progression. Despite the lack of power of these subanalyses, they produce some surprising results. In the cross sectional study there was a trend towards greater disease activity in the NAB+ group in the third year, and a significant percentage 12 volume change from baseline to year 1, year 2, and the last visit; in the underpowered and potentially flawed longitudinal analysis there was no indication of an attenuation of treatment effects on disability progression but, surprisingly considering the lower relapse rate in secondary progressive multiple sclerosis, there was a robust effect on relapse rate.

A 1908 systematic review of the laterality of hysterical hemiplegia

Since the publication of our systematic review of the laterality of functional or medically unexplained weakness and sensory disturbance (1965–2000) we have come across a study from 1908 with a similar focus. Ernest Jones, later an eminent figure in the psychoanalytic movement, published his paper in French while working as an assistant physician at the London School of Medicine. He reported on the cumulative analysis of 277 cases of hysterical hemiplegia described by 146 authors in 164 articles published between 1880 and 1908. Most of this material is in French and German and includes cases mentioned in doctoral theses and books. There was no excess of left sided hemiplegia compared with right in hysteria in his analysis—54% had paralysis on the right side and 46% on the left. This was contrary to the prevailing opinion of the time and also disagrees with another less systematic review of older studies (covering 100 subjects, 13 publications and 6 authors between 1885–1937). Jones’ conclusions—that the laterality of hysterical hemiplegia has no diagnostic value—were the same as ours. His study has not been cited for at least 40 years (and probably much longer even than that). It has been neglected, like many other negative studies before and since, but it deserves recognition on this subject.

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References
Resolution of psychiatric symptoms secondary to herpes simplex encephalitis

We read with interest the editorial by Kennedy et al.,1 detailing the short-term treatment of herpes simplex encephalitis (HSE). We agree with the authors that we cannot overemphasise the seriousness of the neuropsychiatric symptoms that a number of these patients display in the long term.

We report a 55 year old woman who was diagnosed with HSE; diagnosis was confirmed with a positive PCR test for herpes simplex in the CSF and acyclovir was started the following day after presentation. After a few weeks the patient’s recovery was almost complete and she was discharged home. Six months later, there was an abrupt change when the patient developed insomnia and would sit up all night watching children’s videos; she also became hostile and confused. She was admitted to a psychiatric unit where she continued to be confused and agitated with episodes of extreme behaviour such as undressing or trying to attack staff.

MRI showed appearances consistent with severe hemispheric atrophy of the right temporoparietal lobe with evidence of gliosis in the frontal and temporal lobes consistent with previous HSE. It was surprising that the EEG tracing was normal with no focal or epileptiform features.

The patient remained in the psychiatric unit for seven months during which time she failed to respond to different antipsychotic medications and she was heavily sedated. The nursing staff reported that the patient was generally confused but there were distinctive episodes when the patient would stare and then display abusive and disruptive behaviour for periods of up to an hour or twice a day. This was started and when the patient reached a dose of 400 mg twice daily these episodes ceased completely and the patient’s behaviour showed dramatic improvement. She continued to have mild cognitive impairment affecting mainly short-term memory.

Psychiatric problems after HSE are not uncommon; Hokkanen et al.2 found that psychiatric problems are the main cause of long-term disability in these patients. Despite the fact that clinical relapse of HSE is well documented,3 cognitive and psychiatric problems are usually already in place in the acute stage and further deterioration or relapse is uncommon.4 In our case the comparatively long period between recovery and onset of behavioural and psychiatric symptoms seemed to cast doubt about the association with the HSE and uncertainty regarding the appropriate treatment.

Vallini et al.5 reported successful treatment of a HSE patient presenting with severe emotional liability and explosive emotional outbursts. The patient responded to carbamazepine, which was started after his EEG showed seizure activity detected in temporal structures. Despite the absence of any EEG abnormalities in our case, it showed a similar favourable response to carbamazepine. We feel that any patient with persistent behavioural or psychiatric symptoms after HSE should have a therapeutic trial of carbamazepine, even in the absence of any clinical or neurophysiological evidence of seizure activity.

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References

Authors’ reply
Gaber and Eshiett report an interesting case of carbamazepine responsive neuropsychiatric syndrome after herpes simplex encephalitis (HSE). Neuropsychiatric symptoms after HSE are well recognised.6 The frontal and temporoparietal lesions in HSE are particularly likely to cause behavioural and psychiatric symptoms. Retrospective studies have previously implicated HSE in the delayed syndromes of violent psychoses7 and major depression.8 However, psychiatric disorders are also common after non-herpes virus encephalitis. Hunter and others had emphasised the importance of considering encephalitic antecedents, even if clinically unapparent, in the differential diagnosis of psychiatric patients.9 Long term follow up data from the National Childhood Encephalopathy study have shown more recently that 20% of the affected children developed epilepsy and a similar proportion had behavioural problems, hyperactivity or unsociable behaviour.10

Besides being a first line antiepileptic, carbamazepine is also recognised to possess considerable therapeutic value in certain psychoses and is an effective long term treatment for bipolar disorder in some cases.11 Carbamazepine responsive in this particular case may not, therefore, imply that the psychiatric symptoms were epileptic in origin. However, EEG signatures of epilepsy are often absent interictally, and the presence of psychoses is known to normalise EEG changes (‘‘forced normalisation’’) in epilepsy patients.12 In this particular case, we certainly concur with the authors’ use of carbamazepine and were delighted to learn of the favourable response.

Radiofrequency neurotomy

In reading the study by Govind and colleagues,1 in which they report the findings of an unblinded, uncontrolled, non-randomised trial of radiofrequency neurotomy for the treatment of third occipital headache, we are surprised that the authors advocate this therapy.

The last statement of the abstract is: “No other form of treatment has been validated for this common form of headache”. This implies that Govind et al believe they have validated radiofrequency neurotomy for the treatment of third occipital headache. Presumably they are prepared, given the apparently impressive numbers of responders, to forego the usual practice of placebo controlled trial.

We do not understand how the authors can expect this treatment to be realistically adopted in clinical practice with no attempt to validate it the way treatments are meant to be validated, through randomised, placebo controlled trials. The statement in their final paragraph that “some practitioners may be averse to implementing a treatment that requires repetition” could perhaps more appropriately state that “some practitioners may be averse to implementing a treatment that remains unvalidated”.

The authors state that one reason they did not do a placebo controlled study is that a previous study has already validated this technique in other patients.13 That a single trial of radiofrequency neurotomy in 24 so-called “whiplash patients” is sufficient basis for the current authors to abandon validation with double blinding methodology seems absurd, especially when closer inspection of that trial lays it in a less positive light.14 We do not accept an argument that it was impossible to blind these subjects. It would be entirely reasonable to see just how often a placebo procedure does indeed work.

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References
“fool” the patient. Govind et al seem to have already decided that this is not possible, a convenient assumption.

Further, we are concerned that Govind et al state categorically that “among patients with whiplash injuries, third occipital headache is common”. The study group from which they determine this prevalence has been reviewed elsewhere, and is wholly inappropriate for a prevalence estimate, being best described as an unusual, highly select, and heterogeneous group of subjects. It is of note that, in regard to validated therapies for whiplash patients, the current study would have been rejected by the criteria of the Quebec Task Force on Whiplash Associated Disorders. We suggest that an invasive procedure should not be advocated until it has been subjected to proper study. Fortunately, we are aware that others are undertaking a properly controlled trial of this form of therapy.

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References


Authors’ reply

Our study reported an audit of outcomes for a treatment of a condition for which there is no other treatment available. It showed what proportion of patients obtained complete relief of pain, and for how long. Readers who wish to adopt this treatment for their patients can do so. If not, they should explain to their patients that they, personally, cannot offer them any treatment that is known to work; but they should not claim that there is no treatment. Our study shows that there is an option. A placebo controlled trial would not prove that this treatment does not work. The outcomes should be the same as the benchmark established by our study, unless the operators perform the procedure poorly. A placebo controlled study could only show that all or part of the outcome is attributable to non-specific effects.

We consider this to be an unlikely outcome for we have never encountered in any of our own studies, nor in the literature, results showing that 86% of patients obtain complete relief of spinal pain following a sham procedure. Radiofrequency neurotomy has been shown to be associated with placebo responses in only a small proportion of patients, and for a limited duration. They claim that responses to third occipital neurotomy is only a conjecture. In principle it is worthy of testing, but in practice it cannot be tested.

The precepts of informed consent require that participants in a randomised controlled be informed of all the consequences and potential complications of a procedure. Numberness in the territory of the third occipital is an unavoidable side effect of third occipital neurotomy. It is a sign that the target nerve has been coagulated. It is an essential requirement for the procedure to work. The numbness lasts as long as the pain relief lasts. In a double blind trial this side effect cannot be masked. Therefore, patients who underwent a sham procedure would automatically know that they did not have the real treatment. Thereby the patients would be unblinded. Any placebo controlled trial which suffered unblinding would be fatally flawed and, therefore, unacceptable.

Any study that used a control short of a sham procedure would also be flawed, and would not escape criticism. Pundits would argue that patients would recognise that simply blocking the nerve, or simply inserting the electrode without mimicking the two hour procedure assiduously, is an obvious sham, and that any patient so treated would exhibit a nocebo effect.

For these reasons we did not venture to conduct a placebo controlled trial. If Dr Kwan and Dr Friell can show that a sham procedure on the third occipital nerve succeeds in achieving complete relief of pain in 86% of their patients we will gladly convert to their sham procedure.

We recognise it as a pity that our study would not be accepted by systematic reviews; but that is a problem for those who rely on reviews as the only source of evidence. In that regard we stand in good company: Were we to rely only on a priori systematic reviews, radiofrequency neurotomy for trigeminal neuralgia would not be an accepted treatment; nor would we be allowed to perform appendicectomies.

While others are satisfied to deny care to patients while they engage in purist debates about levels of evidence, we are rewarded with patients grateful for the relief that they obtain, and who report: “you must repeat the procedure because I am never going back to suffering headaches again”. If someone devises a better treatment for third occipital headache, we will adopt it. In the meantime we feel it would be dishonest of us to tell our patients there is nothing we can do for you.

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Reference


CORRECTIONS

In the neurological picture of the June issue (Komotor JR, Clatterbuck RE. Cocidiodymyositis of the brain, mimicking en plaque meningeoma. J Neurol Neurosurg Psychiatry 2003; 74:806) the initials of the first author were reversed; his name should read as Komotor BJ.

The ordering of the authors in the letter by Soragna D, Tulpur R, Ratti et al in the June issue (An Italian family affected by Nasu-Hakola disease with a novel genetic mutation in the TREM2 gene. J Neurol Neurosurg Psychiatry 2003; 74:825-6) is incorrect, it should be as follows: D Soragna, L Papi, MT Ratti, R Sestini, R Tulpur, L Montalbetti.

The ordering of the authors in the letter by De Tiège, Laureys, Goldman, et al in the July issue (Regional cerebral glucose metabolism in akinesis catatonia and after remission. J Neurol Neurosurg Psychiatry 1998; 63:172) is incorrect, it should read as follows: X De Tiège, JC Bier, I Massat, S Laureys, F Lotstra, J Berré, JM Mendlewicz, S Goldman.

In the June issue of JNPP fig 1 of the paper by Cagli S, Oktar N, Dalbasti T, et al (Failure to detect Chlamydia pneumoniae DNA in cerebral aneurysmal sac tissue with two different polymerase chain reaction methods. J Neurol Neurosurg Psychiatry 2003; 74:756-9) was incorrect. The following figure is the correct image that should have been published.

Figure 1. C pneumoniae TETR PCR of clinical samples. Lanes 1 to 3, 5 to 7 clinical samples. Lanes 4 and 8 negative control (water). Lanes 9 and 11 positive control (C pneumoniae 4×10^4 and 4×10^7 CFU). Lane 10 water. Lane 12 DNA molecular weight marker (XIV, 100 bp ladder, Roche Diagnostics). (Correction to J Neurol Neurosurg Psychiatry 2003; 74:756-9.)