Inflammation and neuropathic attacks in hereditary brachial plexus neuropathy

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Objective: To study the role of mechanical, infectious, and inflammatory factors inducing neuropathic attacks in hereditary brachial plexus neuropathy (HBPN), an autosomal dominant disorder characterised by attacks of pain and weakness, atrophy, and sensory alterations of the shoulder girdle and upper limb muscles.

Methods: Four patients from separate kindreds with HBPN were evaluated. Upper extremity nerve biopsies were obtained during attacks from a person of each kindred. In situ hybridisation for common viruses in nerve tissue and genetic testing for a hereditary tendency to pressure palsies (HNPP; tomaculous neuropathy) were undertaken. Two patients treated with intravenous methyl prednisolone had serial clinical and electrophysiological examinations. One patient was followed prospectively through pregnancy and during the development of a stereotypic attack after elective caesarean delivery.

Results: Upper extremity nerve biopsies in two patients showed prominent perivascular inflammatory infiltrates with vessel wall disruption. Nerve in situ hybridisation for viruses was negative. There were no tomaculous nerve changes in two patients intravenous methyl prednisolone ameliorated symptoms (largely pain), but with tapering of steroid dose, signs and symptoms worsened. Elective caesarean delivery did not prevent a typical postpartum attack.

Conclusions: Inflammation, probably immune, appears pathogenic for some if not all attacks of HBPN. Immune modulation may be useful in preventing or reducing the neuropathic attacks, although controlled trials are needed to establish efficacy, as correction of the mutant gene is still not possible. The genes involved in immune regulation may be candidates for causing HBPN disorders.

RESULTS

Clinical features and response to treatment

The four patients from whom nerve biopsies were obtained were unrelated (fig 1), and had no known viral illnesses before their attacks in hereditary brachial plexus neuropathy (HBPN), an autosomal dominant disorder characterised by attacks of pain and weakness, atrophy, and sensory alterations of the shoulder girdle and upper limb muscles.

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present neuropathic attacks. Patients 2 and 4 were unaware that they had a family history of the disorder until other family members were evaluated. Patients 1 and 3 had postpartum attacks and close-set eyes. The clinical findings are summarised in Table 1.

**Patient 1**

Patient 1 had previous attacks of brachial plexus neuropathy including postpartum attacks. Such postpartum attacks had occurred in 10 of 12 affected women in her family. Her first postpartum attack, six years earlier, resulted in painful left hand and arm paresis. In her most recent pregnancy we studied her prospectively at 16, 26, and 35 weeks of gestation and postpartum attack, six years earlier, resulted in painful left hand weakness. She again had intravenous methyl prednisolone 500 mg for two days with pain resolution. Five days after completing the second course of prednisolone, painful symptoms returned along with acute (within hours) right wrist weakness.

At two weeks postpartum her NIS score was 18 points, and one week later 36 points, with worsened symptoms on NSC testing. The changed subscore of the NSC (comparing symptoms at interview with those at discharge after initial intravenous methyl prednisolone) showed worsening (≥20 points). Given her clinical decline, a superficial radial nerve biopsy was obtained to characterise the pathological alterations and to justify treatment choices. After reviewing the biopsy, intravenous methyl prednisolone 500 mg per treatment was initiated twice a week for two weeks (four weeks postpartum). She again had improvement in pain and no new symptoms.

Twenty weeks after onset of the neuropathic attack she had hyperesthesia of the hands and forearms. Her repeat NIS was unchanged at 36.5 points. At 40 weeks after attack onset her NIS score was 19 points and the NSC was normalised for symptoms of pain, with the sensory and motor deficit remaining as the primary abnormality. At the time of her previous postpartum attack, she had had difficulty in caring for her infant, typing, and opening doors at one year postpartum; followed her previous parturition. On the fifth day she was discharged from hospital without symptoms.

### Table 1 Clinical features, course, and treatment in four cases of hereditary brachial plexus neuropathy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y) at 1st attack/sex</th>
<th>Age (y) at biopsy</th>
<th>No of episodes</th>
<th>Clinical features of current attack</th>
<th>CSF</th>
<th>HNPP gene testing</th>
<th>CT/MRI</th>
<th>NIS score</th>
<th>NSC</th>
<th>Treatment of biopsied attack</th>
<th>Treatment response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19/F</td>
<td>28</td>
<td>3</td>
<td>Painful weakness bilaterally; BPN postpartum</td>
<td>N</td>
<td>Neg</td>
<td>Neg</td>
<td>17</td>
<td></td>
<td>IV MP tapered over 1.5 months</td>
<td>Dramatic pain reduction; worsened pain with steroid taper</td>
</tr>
<tr>
<td>2</td>
<td>10/M</td>
<td>46</td>
<td>4</td>
<td>Painful weakness L&gt;R; BPN</td>
<td>Protein↑ (60 mg/dl)</td>
<td>Neg</td>
<td>ND</td>
<td>7</td>
<td></td>
<td>1 g IV MP ×3d; then 60 mg prednisolone ×1m; then 50 mg ×1m; then tapered off</td>
<td>Dramatic pain reduction; worsened pain and possible weakness with steroid taper</td>
</tr>
<tr>
<td>3</td>
<td>18/F</td>
<td>21</td>
<td>2</td>
<td>Painful weakness bilaterally; BPN postpartum</td>
<td>N</td>
<td>ND</td>
<td>ND</td>
<td>11</td>
<td></td>
<td>Prednisolone 60 mg/d tapered over 3 weeks</td>
<td>Uncertain</td>
</tr>
<tr>
<td>4</td>
<td>9M</td>
<td>28</td>
<td>3</td>
<td>Painful weakness R; BPN</td>
<td>N</td>
<td>Neg</td>
<td>Neg</td>
<td>1*</td>
<td></td>
<td>Prednisolone 80 mg/d tapered over 4 weeks</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

*Patient's father’s history, examination, and nerve conduction/EMG studies (performed by us) consistent with recurrent brachial plexopathy. BPN, brachial plexus neuropathy; CSF, cerebrospinal fluid; CT, computed tomography; d, day; HNPP, hereditary brachial plexus neuropathy; IV, intravenous; L, left; m, month; MP, methyl prednisolone; MRI, magnetic resonance imaging; N, normal; ND, not done; R, right; y, year.

### Table 2 Nerve biopsy results in hereditary brachial plexus neuropathy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Nerve</th>
<th>Inflammation*</th>
<th>Distribution</th>
<th>Axonal degeneration</th>
<th>In situ hybridisation†</th>
<th>Density of myelinated fibres</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Radial sensory</td>
<td>Mononuclear multiple infiltrates (moderate)</td>
<td>Epineurial (perivascular); vessel wall involvement/ destruction</td>
<td>Marked (17%); multifocal</td>
<td>No hybridisation</td>
<td>Slightly reduced</td>
<td>Rare early onion bulbs; frequent regenerating clusters; thin myelin</td>
</tr>
<tr>
<td>2</td>
<td>Radial sensory</td>
<td>Mononuclear multiple infiltrates (small)</td>
<td>Epineurial (perivascular); subperineurial (perivascular); vessel wall involvement/ destruction</td>
<td>Severe (95%)</td>
<td>No hybridisation</td>
<td>Moderately reduced</td>
<td>Diffuse axonal degeneration; regenerating clusters; thin myelin</td>
</tr>
<tr>
<td>3</td>
<td>Median motor (single fascicle)</td>
<td>None</td>
<td>Not applicable</td>
<td>None</td>
<td>No hybridisation</td>
<td>Normal</td>
<td>Frequent intervascular neuropathis; probably preparatory</td>
</tr>
<tr>
<td>4</td>
<td>Radial sensory</td>
<td>Mononuclear infiltrate (individual)</td>
<td>Epineurial; perivascular</td>
<td>None</td>
<td>No hybridisation</td>
<td>Normal</td>
<td>Thin myelin; regenerating clusters</td>
</tr>
</tbody>
</table>

*Collections of mononuclear inflammatory cells: individual, <10 cells; small, 10–49 cells; moderate, 50–99 cells; large, ≥100 cells.
†For cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, and herpes simplex virus.
did not show inflammatory infiltrates.

Attacks. Steroid treatment was not retried when the biopsies were obtained at two and three months, respectively, after worsening symptoms of pain and sensory loss, nerve biopsies were obtained. Patients 3 and 4 had been treated with oral prednisone with uncertain benefit before being referred to us (table 1). Because of worsening symptoms of pain and sensory loss, nerve biopsies were obtained at two and three months, respectively, after attacks. Steroid treatment was not retried when the biopsies did not show inflammatory infiltrates.

Figure 1 Pedigrees of the four affected individuals studied. The arrow identifies the proband and biopsied person. Patients 2 and 4 were initially not aware that other family members were also affected. Patient 4’s father had previous attacks of arm paralysis related to rotator cuff injury and complicated carpal tunnel syndrome. His electromyogram showed bilateral chronic diffuse denervation of multiple muscles innervated by the brachial plexus and distal nerves.

He was given intravenous methyl prednisolone (1 g) on three successive days. He reported dramatic improvement in pain, so that he could sleep through the night for the first time in months, and developed no new symptoms. He was placed on tapering oral prednisone beginning at 60 mg/day. His NIS was 27 points two weeks before treatment and remained unchanged two weeks later. His symptoms, as graded by the NSC scores, improved during treatment. The change in NSC subscore showed worsening before treatment (−35 points) and two weeks after the prednisolone treatment there was improvement (+13 points). The previous symptoms of jabbing, tingling, burning, and aching pain had abated. Four months later (on prednisone 10 mg/day) his pain worsened (NSC change subscore +35) and he reported new weakness in hands and wrists, but the overall NIS score was essentially unchanged at 31 points.

Electrophysiological and quantitative sensory studies

Patient 1
Patient 1 had serial nerve conduction studies, electromyography (EMG), and quantitative sensation testing before and after parturition. The nerve conduction and quantitative sensation results in the upper limbs were normal throughout pregnancy. Initial needle EMG (at 16 weeks of gestation) showed evidence of an old left brachial plexopathy (diffuse large motor unit potentials and no fibrillation potentials). At two weeks postpartum, quantitative sensation testing became abnormal, with increased vibration thresholds (hyposensitivity) in the hands. Nerve conductions and EMG were unchanged from the prepartum studies. Twenty weeks after the beginning of the attack, bilateral median and ulnar summed motor and sensory compound action potentials were reduced by 50% compared with earlier values. Cooling thresholds were raised (hypoparesthesià) and heat pain thresholds decreased (hyperalgesia). At 40 weeks, median and ulnar motor and sensory responses improved and were normal in some cases; needle examination showed multifocal fibrillation potentials with neurogenic potentials. On quantitative sensation testing she remained hypoparesthesià to vibration but was no longer hyperalgesic on heat pain testing.

Patient 2
Patient 2 had limited nerve conductions with EMG nine weeks before and 12 weeks after initiation of intravenous methyl prednisolone. The nerve conduction studies were normal throughout and an EMG showed unchanging chronic neurogenic potentials with fibrillations in serratus anterior and trapezius muscles.

Patients 3 and 4
At the height of their attacks, patients 3 and 4 were also found to have nerve conduction and EMG abnormalities consistent with an active multifocal process in the brachial
plexus or proximal upper limb nerves. Quantitative sensation testing was not done.

Pathology findings
The biopsy findings are summarised in table 2 and shown in figs 2 and 3 (patients 1 and 2). Biopsied nerves from both these patients showed multiple microvessels with epineurial perivascular inflammatory cell infiltrates and active axonal degeneration. The inflammation involved vessel walls and appeared disruptive. Fibrinoid necrosis was not seen. In patient 4 the neuropathic abnormalities were limited to small myelinated fibres with increased regenerating clusters and limited inflammation. Patient 3 was the only one not showing neuropathic or definite interstitial abnormalities, but the sample size of a single fascicle was small. In situ hybridisation of nerve at and away from sites of inflammation was negative for all viruses examined, while positive controls showed robust staining. Teased fibres did not show reduplicated myelin (tomaculi), and genetic testing for HNPP was negative in all three patients examined (table 1).

DISCUSSION
Some of the patients with HBPN studied here provide pathological evidence that inflammation, probably reflecting immune alterations, underlies at least some and perhaps all of their neuropathic attacks. The evidence for immune mechanism as the basis for attacks is as follows:

- there were prominent mononuclear cell infiltrates in nerve taken at the time of neuropathic attacks in two patients—one beginning three hours after parturition at a time when the immune status is changing to be less tolerant of foreign proteins;
- in situ hybridisation studies did not suggest viral infection;
- mechanical forces, as the basis for the neuropathy, were ruled out in one case by avoidance of labour and the act of parturition;
- intravenous methyl prednisolone appeared to ameliorate the symptoms.

There is limited information on the underlying pathological alterations in HBPN. Upper extremity nerve biopsies are not
reported. Bradley et al, studying recurrent brachial plexus neuropathy, found focal sausage shaped thickenings of reduplicated myelin (tomaculi) in sural nerve biopsies from two patients with lower extremity involvement and a family history. Our patients did not have tomaculi or deletion of 17p11.2, the genetic alteration seen in HNPP (tomaculous neuropathy) (tables 1 and 2). The prominent perivascular epineurial inflammatory infiltrate observed in two of our four patients has also been described in non-inherited immune brachial plexus neuropathy. The severity and the epineural, perivascular, and vascular wall localisation of the inflammation makes it unlikely that the inflammation is a reaction to fibre degeneration. Two of our patients with HBPN had prominent axonal degeneration, while those without inflammation had minimal or no neuropathic changes. The absence of neuropathic or interstitial changes in one of the patients may simply reflect the patchy nature of the illness, inadequate sampling, or a different cause—for example, genetic heterogeneity. Linkage analysis of our families will be important in identifying the specific chromosomal localisation of these pathological findings.

The fact that altered immunity may contribute to the pathogenesis of hereditary neuropathic injury was proposed earlier. In some patients with hereditary motor and sensory neuropathy (HMSN), worsening neuropathy has improved with immunotherapy. In addition, Schmid et al have shown that immune factors play a role in the progression of an animal model of P0 mutated neuropathy. The results of our present study imply that immune mechanisms play a prominent role in the expression of HBPN, so genes involved in immune regulation may be the candidate genes.

Pathological studies of biopsied nerves from our four patients enabled us to draw several other important conclusions: first, the inflammatory infiltrates were usually associated with epineurial microvessels; second, axonal degeneration appears to be typical of the fibre alterations; and third, mononuclear cell infiltrates occurred in distal nerves, thus providing evidence of multifocal lesions extending to peripheral nerves beyond the brachial plexus (a brachial plexus neuropathy). The pathological findings are consistent with the clinical response. Two of our patients appeared to respond to intravenous methyl prednisolone, at least as judged by improvement of symptoms (NSC), and acutely by stabilisation of signs (NIS). Pain relief appeared to be the greatest benefit of treatment. High dose intravenous methyl prednisolone seemed to be more beneficial than low dose prednisone.

The significance of the negative in situ nerve hybridisation studies for common viruses is unclear, but suggests that these viruses are unlikely to be the cause of the local inflammation. On the other hand occult or proximal plexus or nerve viral activation cannot be excluded as a trigger for an attack of immune inflammation, as has been suggested in Bell’s palsy. Why distal upper extremity nerves and the brachial plexus are preferentially affected in this condition is unknown. Predominant upper or lower extremity involvement, however, has been observed in immune brachial plexus neuropathy and in diabetic and non-diabetic lumbosacral radiculoplexopathy. In the latter illnesses, microvessel wall disruption has also been observed. Speculation about this anatomical selectivity might include impairment of the blood–nerve barrier at complex branching points within plexuses, or selective antigenic determinants within these regions. The former explanation seems less likely as the inflammation was also observed in distal nerves.

Conclusions
In at least some cases of HBPN, the mutant gene abnormality is expressed, resulting in an inflammatory response that is pathogenic for nerve attacks and axonal degeneration. This inflammation is multifocal (probably immune) in the brachial plexus and upper limb nerves. Intravenous methyl prednisolone appears to ameliorate the symptoms, especially the severe pain that characterises this disorder. In the sporadic form, oral and intramuscular steroids also provide relief from pain, but there is no evidence that early treatment alters the course of the disease. The results presented here suggest the

Figure 3  Top: Semithin transverse epoxy section of superficial radial nerve from patient 2 stained with methylene blue, showing severe axonal degeneration especially in large fibres, and empty nerve tubes with degenerating myelin. Bottom: Closely applied teased fibre preparations of the superficial radial nerve from patient 2 showing severe axonal degeneration at various stages.
need for formal clinical trials. Immune modulation may be useful in preventing or reducing the neuropathic expression of HBPN, though correction of the mutant gene abnormality is still not possible.

ACKNOWLEDGEMENTS
We gratefully acknowledge the help of Darlene Peterson and Mary Lou Hunziker in the preparation of the manuscript, and JaNean Engelstad for assistance in the preparation of the figures. We acknowledge the help of Ricardo V Lloyd MD for the in situ hybridisation studies, and Dr Christopher Lynch for proofing the manuscript. This work was supported in part from grants received from the National Institute of Neurologic Disorders and Stroke (NS36797).

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