Multifocal axonal polyneuropathy in celiac disease
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Neurology 2006;66;1923-1925
DOI: 10.1212/01.wnl.0000208413.40583.6c

This information is current as of June 28, 2006

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Acquired multifocal neuropathies are generally classified as demyelinating or axonal. The acquired demyelinating multifocal neuropathies are considered to be immune mediated, as in multifocal motor neuropathy or multifocal acquired demyelinating sensorimotor polyneuropathy, also referred to as the Lewis-Summer syndrome. Mononeuropathy multiplex can be associated with diabetes, vasculitis, or other inflammatory, infective, or neoplastic conditions and is typically a multifocal axonal polyneuropathy.  

Celiac disease (CD) is an inflammatory enteropathy caused by the loss of tolerance to gluten in wheat and similar proteins in barley and rye. In this article, we report the occurrence of multifocal axonal neuropathy in six patients with biopsy-proven CD.

Methods. We reviewed charts of patients with multifocal neuropathy and biopsy-proven CD. Patients were diagnosed with a multifocal neuropathy if they fulfilled two of the following three criteria: 1) clinical history consistent with multifocal motor or sensory involvement, 2) objective findings of multifocal motor or sensory involvement by neurologic examination, and 3) electrophysiologic findings of multifocal motor or sensory involvement. Clinical motor or sensory asymmetry and electrophysiologic asymmetry were defined according to published criteria. Six to eight motor nerves and four to eight sensory nerves were routinely tested. The diagnosis of CD was made based on elevated gliadin or transglutaminase antibodies, with confirmatory duodenal biopsy testing. The three patients with mild gastrointestinal symptoms (Patients 1, 3, and 6) noted resolution of these gastrointestinal symptoms following adherence to the gluten-free diet.

Results. Six patients (three men, three women) with CD and multifocal neuropathy were identified. The age at onset of neuropathic symptoms ranged from 37 to 79 years. The age at diagnosis of CD ranged from 39 to 79 years. In five of six patients, neurologic symptoms antedated the diagnosis of CD by as much as 4 years. In Patient 3, the neurologic symptoms progressed insidiously, punctuated by periods of relapses and remissions between ages 37 and 79, when the diagnosis of CD was finally made. All patients had a stepwise progression of neurologic deficits. In four of six patients (Patients 1, 2, 3, and 5), neuropathic symptoms began with a unilateral foot drop, followed by involvement of the contralateral leg and then the hands. Patient 4 developed excruciating left arm pain that migrated to the right hand, right leg, and finally to the left leg. In Patient 6, symptoms began with a left foot drop and left leg weakness followed by recovery and a period of remission. Four years later, she developed left hand weakness (wrist drop) with later involvement of the right hand and then left leg.

In all cases, neurologic, rather than gastrointestinal, symptoms were the presenting symptoms. In five of six patients, multifocal neuropathy symptoms were the presenting complaints that prompted medical attention and the subsequent diagnosis of CD. Patient 1 was discovered to have CD during the workup of anemia; however, 2 years before this diagnosis, she had experienced leg numbness and weakness that resolved spontaneously. Three patients had no gastrointestinal symptoms, and three patients (Patients 1, 3, and 6) had only mild gastrointestinal disturbances (gas, abdominal bloating, and mild diarrhea).

None of the patients had evidence for other causes of neuropathy, such as diabetes, malignancy, systemic vasculitis, diabetes, nutritional deficiencies, infectious diseases, drug toxicity, GM1 antibodies, and monoclonal gammopathy. Patient 4 had a remote history of thyroiditis.

Clinical and electrophysiologic studies (table) revealed a sensorimotor neuropathy in five patients and a sensory neuropathy in one patient (Patient 4). No demyelinating range electrophysiologic abnormalities were seen in any of the tested nerves. An asymmetric pattern of involvement was noted in five of six patients by electrophysiologic testing. In Patient 2, severe axonal involvement (with absent motor and sensory responses) precluded electrophysiologic detection of asymmetry.

Sural nerve biopsies, obtained in four patients (Patients 1, 2, 3, and 4), revealed no evidence of vasculitis or demyelination. No transmural mononuclear inflammatory cells, vessel wall necrosis, onion bulbs, or inflammatory infiltrates were detected. All showed axonal loss of large myelinated fibers, severe in three patients (Patients 1, 2, and 3). Patient 4 had mild to moderate endoneurial fibrosis and a reduction in the number of large myelinated fibers.

CSF studies in Patient 2 revealed normal cell counts, and glucose and protein levels. MRIs in Patients 1 (cervi-
### Table Clinical data in patients with biopsy-proven celiac disease* and multifocal axonal polyneuropathy

<table>
<thead>
<tr>
<th>Patient/sex/age†</th>
<th>Clinical history</th>
<th>Physical examination</th>
<th>Electrodiagnostic features/sensory findings</th>
<th>Motor findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/38</td>
<td>Foot drop and numbness (R then L), followed by bilateral arm numbness and weakness</td>
<td>Distal upper and lower (R &gt; L) extremity atrophy, weakness and mildly decreased vib/pin; DTRs absent at ankles and knees</td>
<td>Absent R median, ulnar and sural SNAPs; low amp R radial SNAP</td>
<td>Low amp R peroneal CMAP; active denervation R TA</td>
</tr>
<tr>
<td>2/M/52</td>
<td>Foot drop and numbness (R then L), followed by B upper extremity numbness and weakness</td>
<td>Dorsiflexor weakness (severe on the R and mild on the L); absent DTRs</td>
<td>Absent B median, ulnar and sural SNAPs</td>
<td>Absent B peroneal CMAPs; active/chronic denervation bilateral TA</td>
</tr>
<tr>
<td>3/M/37</td>
<td>Foot drop and numbness (R then L), followed by B extremity weakness</td>
<td>Dorsiflexor weakness (severe on the R and mild on the L) and moderately decreased pin/vib; atrophy of B thighs/calves</td>
<td>Absent R sural SNAP</td>
<td>Peroneal CMAP amplitude asymmetry (&gt; 50% difference, R &gt; L); absent R and prolonged L peroneal F-wave responses; active denervation R TA</td>
</tr>
<tr>
<td>4/F/52</td>
<td>Numbness and paresthesias affecting hands (L then R) and later the legs (R then L)</td>
<td>Vib absent at B toes, ankles, knees, L fingers and wrist; positive Romberg; absent DTRs</td>
<td>Absent L median, bilateral ulnar and R sural SNAPs; low amp R median SNAP; mild L sural conduction velocity slowing</td>
<td></td>
</tr>
<tr>
<td>5/M/47</td>
<td>R foot pain and weakness, followed by L foot numbness, and hand pain and weakness (L then R)</td>
<td>Atrophy of shoulder girdle, FDIs, thighs; B shoulder abductor weakness; moderate R dorsiflexor weakness; mildly decreased pin/vib in R foot and absent vib in L large toe; absent DTRs</td>
<td>B sural conduction velocity slowing; low amp R ulnar SNAP; later progressed to: absent B sural, ulnar and median SNAPs</td>
<td>Absent R tibial and severely low amp L ulnar CMAPs; absent B peroneal &amp; ulnar CMAPs, severely low amp B median CMAPs, and a decreased R FDI interference pattern</td>
</tr>
<tr>
<td>6/F/37</td>
<td>Transient L leg weakness, followed by L wrist drop, R hand weakness, and L leg weakness</td>
<td>Atrophy of B forearms and L intrinsic hand muscles; B wrist extensor weakness (paretic on L, mild on R); mild L extensor hallucis longus weakness</td>
<td>Absent L tibial H-reflex; chronic denervation L TA</td>
<td></td>
</tr>
</tbody>
</table>

* All six patients had histologic findings consistent with celiac disease (e.g., villous atrophy, “scalloping” of duodenal folds, or inflammatory changes such as intraepithelial lymphocytosis).
† Age (in years) at onset of neuropathic symptoms.

B = bilateral; DTR = deep tendon reflexes; Pin/vib = pinprick/vibration; Amp = amplitude; SNAP = sensory nerve action potential; CMAP = compound muscle action potential; TA = tibialis anterior; FDI = first dorsal interosseous.

cal, lumbar, and thoracic spine), 3 (brain), and 6 (brain, cervical spine, and brachial plexus) were unremarkable.

All patients received counseling regarding a gluten-free diet. None of the six patients noted any improvement of their neuropathic symptoms following adherence to the GFD alone. All six patients received IVIg treatment with only two noting any improvement. Patient 6, whose condition was deteriorating despite adherence to the GFD, had complete resolution of her weakness following IVIg therapy (40 g per treatment for a total of 10 treatments). However, 8 weeks after IVIg was discontinued, her right hand weakness recurred. This again resolved following resumption of IVIg therapy. Patient 2 had modest improvement of balance and distal leg strength after concomitant IVIg therapy and adherence to a GFD. The following immunomodulatory treatments were administered and considered ineffective: plasmapheresis (Patients 1, 3, and 5), mycophenolate mofetil (Patient 1), azathioprine (Patients 2 and 4), or steroids (Patients 1, 4, and 5).

### Discussion.

CD is estimated to occur in 1% of the population. Most patients currently present due to nongastrointestinal manifestations, such as deficiency anemia, dermatitis herpetiformis, osteoporosis, infertility, autoimmune diseases, and neurologic disorders.4

Neurologic manifestations are estimated to occur in 6 to 10% of adults with CD, with peripheral neuropathy and ataxia the most frequently reported.5,6 Predominantly sensory symmetric neuropathies and neuropathies associated with ataxia, extrapyramidal signs, or myoclonus are the most frequently reported types of neuropathy.5,7

Mononeuropathy multiplex, specifically a multifocal axonal polyneuropathy as seen in our six patients, has rarely been reported in patients with CD. In one case, a 45-year-old man developed patchy numbness initially in his right leg, then in his right arm, followed by gradual weakness of intrinsic muscles of both hands.8 A second case involved a 47-year-old woman with acute left wrist drop and right hand symptoms who had complete resolution of the neuropathy with oral prednisone. Biopsy of the left anco...
neus muscle showed epimysial, endomysial, perineural, and perivascular lymphocytic infiltrates and necrotic and regenerating fibers. The nerve biopsy revealed significant loss of myelinated fibers.\textsuperscript{9}

The recent finding of non-length-dependent patterns of skin biopsy abnormalities in patients with small fiber neuropathy and CD also supports a multifocal process.\textsuperscript{10}

No evidence of vasculitis was detected in the four patients in this study who underwent sural nerve biopsy, although it is possible that active focal lesions could have been missed due to sampling error or timing.

Although elimination of gluten reverses the histologic lesion in the gastrointestinal tract and ameliorates the gastrointestinal symptoms of CD, none of our six patients' neurologic symptoms improved in response to the gluten-free diet. This could be due to continued exposure to small amounts of gluten, irreversible axonal or neuronal degeneration, or induction of autoreactive memory T cells that no longer require exposure to gluten. A role for persistent autoimmunity in some patients was suggested by the dramatic response to immunomodulatory treatment in the one patient (Patient 6) who had marked weakness and mild electrodiagnostic findings.

\textbf{References}

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