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Chronic immune sensory polyradiculopathy
A possibly treatable sensory ataxia

M. Sinnreich, MD, PhD; C.J. Klein, MD; J.R. Daube, MD; J. Engelstad, HT; R.J. Spinner, MD; and P.J.B. Dyck, MD

Abstract—Background: Chronic inflammatory neuropathies can present with a sensory ataxia due to involvement of dorsal root ganglia (DRG) or sensory nerves. Selective inflammatory involvement of sensory nerve roots proximal to the DRG has been postulated. Methods: The authors identified 15 patients with a sensory syndrome and normal nerve conduction studies. Sensory nerve root involvement was suggested by either somatosensory evoked potential (SSEP) or imaging abnormalities. CNS disease was excluded. Results: All patients had gait ataxia, large fiber sensory loss, and paresthesias, and nine had frequent falls. The disease course was chronic and progressive (median duration 5 years, range 3 months to 18 years). Sural sensory nerve action potential amplitudes were preserved and SSEP abnormalities were consistent with sensory nerve root involvement. Five patients had enlargement of lumbar nerve roots on MRI with enhancement in three. The CSF protein was elevated in 13 of 14 patients tested. Three patients had lumbar sensory rootlet biopsies that showed thickened rootlets, decreased density of large myelinated fibers, segmental demyelination, onion-bulb formation, and endoneurial inflammation. Six patients who required aids to walk were treated with immune modulating therapy and all had marked improvement with four returning to normal ambulation. Conclusion: Based on the described clinical features, normal nerve conduction studies, characteristic somatosensory evoked potential (SSEP) abnormality, enlarged nerve roots, elevated CSF protein, and inflammatory hypertrophic changes of sensory nerve rootlet tissue, we suggest the term chronic immune sensory polyradiculopathy (CISP) for this syndrome. This condition preferentially affects large myelinated fibers of the posterior roots, may respond favorably to treatment, and may be a restricted form of chronic inflammatory demyelinating polyradiculoneuropathy.

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A number of disorders can present with chronic sensory ataxia: vitamin deficiencies or excesses, inherited conditions (including spinocerebellar ataxias), infectious diseases (syphilis), lympho- and myeloproliferative disorders, toxic exposures, paraneoplastic diseases, metabolic conditions, and inflammatory demyelinating neuropathies (acute inflammatory demyelinating polyradiculoneuropathy [AIDP] and chronic inflammatory demyelinating polyradiculoneuropathy [CIDP]) as well as other immune disorders (sensory polyganglionopathy or Sjögren’s syndrome). Sensory ataxia theoretically may be due to involvement of dorsal columns, dorsal root entry zone, dorsal root, dorsal root ganglia (DRG), and sensory nerves. Inflammatory neuropathy with predominant involvement of the dorsal roots has been hypothesized in isolated cases as the cause of sensory ataxia. Here we provide clinical, electrophysiologic, radiologic, and pathologic description in a series of patients, suggesting that chronic immune sensory polyradiculopathy (CISP) is a definable, under-recognized, and possibly treatable clinical entity.

Methods. We identified patients with a sensory polyradiculopathy by conducting a retrospective chart review from 1990 to 2002 of the Mayo Clinic, Rochester, MN, database. Medical records of 981 patients coded as having CIDP, polyganglionopathy, or ataxia were reviewed. Also reviewed were electrophysiologic studies with normal nerve conductions and EMG and abnormal somatosensory evoked potential (SSEP). Patients gave consent to have their records reviewed as monitored by our Institutional Review Board. We selected patients with localized neuropathy of the posterior roots based on the following criteria: 1) presence of a sensory syndrome without weakness; 2) essentially normal nerve conduction and EMG studies; 3) imaging studies that excluded brain, cerebellum, spinal cord, or compressive nerve root lesions; and 4) either SSEP or imaging abnormalities consistent with nerve root involvement.

Electrophysiologic and quantitative sensory testing methods. Nerve conduction studies, EMG, and SSEP tests were performed using Nicolet Viking IV or Viking Select systems. Quantitative sensory testing was performed on the dorsal great toe or foot using CASE IV.

Histologic methods. Three dorsal nerve rootlet biopsies were performed at Mayo Clinic, Rochester, MN. The pathologic alterations of three biopsied dorsal lumbar rootlets and of three age-range matched postmortem control specimens were evaluated in our laboratory, one of the control cases having been published previously. Standard histologic stains and immunohistochemistry (CD45, CD68) were prepared on paraffin sections. Semithin epoxy sections were stained with methylene blue and p-phenylenediamine. Electron microscopy was performed to better demonstrate ultrastructural changes. Tissue sections were prepared...
Table 1 Clinical examination and laboratory features of patients with chronic immune sensory polyradiculopathy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Presenting age, y</th>
<th>Sex</th>
<th>Duration, y</th>
<th>Gait aids</th>
<th>Frequent falls</th>
<th>Reflexes</th>
<th>NIS, points</th>
<th>CSF protein, mg/dL</th>
<th>Thickened lumbar nerve roots on MRI</th>
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<tr>
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<td>Normal</td>
<td>18</td>
<td>138</td>
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</table>

Large fiber = vibration and joint position and motion; small fiber = pinprick; UE = upper extremity; LE = lower extremity; NIS = Neuropathy Impairment Score; ↓ = reduced; ↓↓ = absent; NA = not available.

and graded by previously defined pathologic criteria. Morphometric analysis was performed using our Imaging System for Nerve Morphometry.

Results. Case presentation. A 66-year-old previously healthy woman with corrected hypothyroidism presented with marked sensory ataxia (Patient 1, tables 1 and 2). Ten years earlier, she noted onset of paresthesias in both lower extremities and loss of feeling in the left foot. The symptoms gradually worsened and spread proximally to become symmetric below the hips, and she progressively had difficulty walking. At presentation, she was using a wheelchair for long distances and two canes at home. She had started to experience pricking in her hands, and she had lack of feeling in her lower limbs without pain. Clinical examination revealed normal strength throughout. She had lack of feeling in her lower limbs without pain. The sensory ataxia was so extended to involve upper extremities leading to clumsiness in use of their hands. The sensory ataxia was so

cauda equina showed hypertrophic nerve roots with enhancement post gadolinium (figure 1).

A dorsal lumbar rootlet nerve biopsy was obtained. The myelinated fiber density was normal, but the fiber size distribution was altered with a marked reduction of large myelinated fibers (figure 2). There were scattered endoneurial lymphocytes (CD45), and endoneurial macrophages (CD68) were prominent despite absence of visible degenerating fiber profiles. Electron micrographs showed features of myelin remodeling with frequent onion-bulbs and thin myelin.

The patient was treated with IV immunoglobulin (IVIg) (0.4 g/kg body weight) twice weekly for 8 weeks and then weekly for another 8 weeks. A rapid and large functional improvement was observed, and she regained her ability to walk, run, and even hike mountain trails. There was improvement in muscle stretch reflexes and joint position and motion sense. Currently, the patient receives IVIg treatment every 3 weeks and develops acral paresthesias at the end of the inter-treatment interval.

Clinical features. We identified 15 patients (including the patient presented), 5 women and 10 men, with a median age at disease onset of 63 years (range 30 to 78 years) who have a similar syndrome of sensory polyradiculopathy (see table 1). Eight patients were personally cared for by the authors and seven were identified retrospectively. Gait ataxia was a symptom in all patients causing frequent falls in nine (see table 1). Three required wheelchair assistance because of their severe sensory ataxia and five more required canes for ambulation. In seven patients, the ataxia extended to involve upper extremities leading to clumsiness in use of their hands. The sensory ataxia was so
severe in one patient (Patient 11) that he was unable to sit unassisted, he had to be tied in his wheelchair, and he could not use his hands. All 15 patients had paresthesias in their lower limbs and 12 had paresthesias in their upper limbs. All patients also had dead-type numbness (lack of feeling with an asleep quality) in their lower extremities and four had dead-type numbness in their upper extremities. Although pain was not a severe problem, it was common and nine patients had mild pain, mostly of their feet. In six, it had a burning quality.

The sensory symptoms often began unilaterally or asymmetrically (7 of 15 patients) but over time they became more widespread and symmetric (12 of 15). Four patients remembered a specific onset date, whereas for others the disorder began insidiously. The course was chronic and progressive in all and none had spontaneous improvement. The median duration of the symptoms was 5 years (range 3 months to 18 years) from onset of symptoms until most recent evaluation at our institution.

On neurologic examination, all patients had gait ataxia and large fiber sensory abnormalities of lower extremities, including altered joint position and motion sense or vibration sense (see table 1). Ten had additional small fiber modality abnormalities but these were less severe than the large fiber abnormalities. Fourteen of the 15 patients had absent or reduced deep tendon reflexes. No patient had weakness.

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**Table 2** Nerve conduction studies, somatosensory evoked potentials, and quantitative sensory testing in patients with chronic immune sensory polyradiculopathy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sural sensory</th>
<th>Tibial motor</th>
<th>Median SSEP</th>
<th>Tibial SSEP</th>
<th>Quantitative sensory testing</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>A (µV) CV (m/s) DL (ms)</td>
<td>A (µV) CV (m/s) DL (ms)</td>
<td>Long N13 or N9-N13 latencies</td>
<td>Nonlocalized slowing</td>
<td>VDT, %</td>
</tr>
<tr>
<td>1</td>
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<td>11.3 40 3.2</td>
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<td>&gt;99 30 50</td>
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<td>2</td>
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<td>7.6 43 4.6</td>
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<td>NA</td>
<td>&gt;99 &gt;99 40</td>
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<tr>
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<tr>
<td>4</td>
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<td>16.7 46 4.0</td>
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<td>&gt;99 92 25</td>
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<tr>
<td>5</td>
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<td>4.4 49 4.3</td>
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<td>NA</td>
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<td>4.9 41 4.7</td>
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<td>No‡</td>
<td>&gt;97 30 50</td>
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<td>6.1 49 3.8</td>
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<td>No§</td>
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<tr>
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<td>14.6 43 4.5</td>
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<td>6.5 40 5.2</td>
<td>Yes</td>
<td>Yes</td>
<td>&gt;99 50 98</td>
</tr>
</tbody>
</table>

* N13 = cervical response; N9-N13 = clavical to cervical interpeak latency.
† Normal upper extremity nerve conduction studies.
‡ Absent tibial SSEP responses.
§ Nonlocalized slowing on median SSEP.

SSEP = somatosensory evoked potential; A = amplitude; CV = conduction velocity; DL = distal latency; nl = normal; VDT = vibration detection threshold; CDT = cooling detection threshold; HP 5 = heat pain 5; NA = not available.

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Figure 1. Sagittal and transverse (inserts) MR images of the cauda equina from two patients with chronic immune sensory polyradiculopathy (CISP). Both patients had enlarged nerve roots (arrows) and subsequently underwent dorsal root biopsies. The image on the left (Patient 1, T1 post-gadolinium image) shows nerve root enhancement, whereas the image on the right (Patient 13, T2 image) shows thickened lumbar nerve roots.
Laboratory results. CSF examination was performed in 14 patients: 13 had elevated CSF protein; the median protein was 83 mg/dL (range 31 to 161 mg/dL, see table 1). None of the CSF specimens had elevated white blood cell counts or oligoclonal bands. All patients had negative syphilis serologies and normal thyroid stimulating hormone and vitamin B<sub>12</sub> levels. Spinocerebellar ataxia panels were negative and ACE levels were normal. ENA and ANA antibodies were not detected and the sedimentation rate was elevated in only 1 of 14 patients tested (Patient 11, 62 mm/hour). All 12 patients who had a paraneoplastic antibody screen had negative test results, GM1 and GD1b antibodies were negative in the seven patients tested, and GQ1b antibodies were negative in the four patients tested.

Electrophysiology. Sensory and motor nerve conduction studies of limb nerves were preserved in all patients for amplitude, conduction velocity, and distal latency (see table 2). The median sural sensory nerve action potential (SNAP) was 11 μV (range 6 to 20), whereas the median tibial compound muscle action potential was 7.6 mV (range 4.2 to 16.7). The needle examinations of limb muscles were normal, except for Patient 6, who had evidence of an old L<sub>1</sub> radiculopathy. Paraspinal muscles were normal except for two patients (11 and 14) who had occasional thoracic or lumbosacral fibrillation potentials. Twelve patients had median and tibial SSEPs performed, and abnormal studies were found in all. On median SSEPs, seven patients had prolonged N<sub>13</sub> (cervical) latencies or N<sub>9</sub>-N<sub>13</sub> interpeak latencies (from the clavicle to the cervical spine, which includes the nerve root segment) (figure 3) and another one had non-localized slowing (see table 2). On tibial SSEPs, nine patients had delayed scalp responses with absent cervical and lumbar responses (non-localized slowing) and in two others all of the tibial SSEP responses were absent. Abnormality of both median and tibial SSEPs was seen in seven patients (see table 2). Three patients did not have SSEP testing performed (Patients 2, 10, and 13) but their MRI showed thickening of the lumbar nerve roots. Quantitative sensory testing was available in 11 patients and large myelinated fiber sensory abnormality predominated. Ten patients had elevated (>97th percentile) vibration detection thresholds (mediated by large myelinated fibers)
elinated fibers (mean 14,300/mm²), two had elevated cooling detection thresholds (mediated by small myelinated Aβ fibers), and two had elevated and two had reduced (<3rd percentile) heat pain 5 levels (mediated by unmyelinated C fibers) (see table 2).

Radiologic findings. MRI of brain, cerebellum, and spinal cord were normal in all patients. Five patients had enlargement of lumbar nerve roots with enhancement in three after contrast administration (see table 1, figure 1).

Pathologic results. Histologic sections of two sural nerve specimens obtained from outside institutions were normal. Three patients (Patients 1, 12, and 13) underwent lumbar sensory rootlet biopsies. On surgical inspection, the lumbar roots appeared thickened in two and normal in one patient. All three biopsies showed a normal density of myelinated fibers but a marked alteration in size distribution, with decreased numbers of large myelinated fibers (see figure 2). No degenerating profiles were seen in any of the biopsies. In the biopsies of Patients 1 and 13, the endoneurium was edematous and prominent onion-bulb formations were seen. Demyelinated axons were also observed in the biopsy of Patient 13 (see figure 2).

The three patients’ lumbar root specimens were compared to three postmortem dorsal lumbar nerve roots from persons matched for the same age range. Morphometric analysis was performed. The density of the patients’ myelinated fibers (mean 14,300/mm², SD ± 1,850) was comparable to the control group (mean 16,700/mm², SD ± 1,200/mm²). The density of myelinated fibers of the rootlets of Patient 1 was 15,000/mm², of Patient 12 was 15,700/mm², and of Patient 13 was 12,200/mm². Although the density of myelinated fibers was normal for all patients’ biopsies, the size distribution was not. In all control roots, the myelinated fiber size distribution was bimodal: the small myelinated fiber diameter peak was at 3.1 μm (control 1), 3.1 μm (control 2), and 2.8 μm (control 3), whereas the large myelinated fiber diameter peak was at 8.5 μm (control 1), 8.0 μm (control 2), and 8.5 μm (control 3). By contrast, the rootlet biopsies of all three patients showed only one peak in the small myelinated fiber range (Patient 1 at 3.0 μm, Patient 12 at 3.2 μm, and Patient 13 at 2.8 μm) (see figure 2).

Teased fiber preparations were only available for one biopsy (Patient 13) and showed a high rate of segmental demyelination (38% normal, 37% segmental demyelination, 23% segmental remyelination, and 2% axonal degeneration) (figure 4). Immunohistochemistry showed rare scattered lymphocytes (CD45) in the endoneurium in all three patients’ rootlet biopsies. Prominent diffuse endoneurial macrophage staining (CD68) was seen in the rootlet biopsies of Patients 1 and 13 (figure 5). Neither lymphocyte nor macrophage reactivity was seen in the control specimens. Electron microscopy was performed on the biopsy specimens of Patients 1 and 13 and showed evidence of chronic demyelination and remyelination with naked axons, frequent onion bulbs, and thinly myelinated fibers (figure 6).

Response to treatment. Six severely affected patients, who required aids to walk and who were personally treated by the authors, were given immune modulating therapy. All had rapid and marked improvement of their sensory ataxia and ambulation in spite of their prolonged disease courses and four returned to normal ambulation.

Four patients (Patients 1, 2, 9, and 12) were treated with IVIg and two (Patients 11 and 14) were treated with IV steroids. Patient 1 is presented in detail in the case report above. Patient 2 (5 year history of ataxia) was treated with biweekly IVIg (0.4 g/kg), and returned to normal ambulation within several months. On discontinuation of treatment, the ataxia and lower extremity numbness returned, but with re-administration of IVIg, his gait normalized. Patient 9 (18 year history of ataxia) was treated with biweekly IVIg (0.4 g/kg), and had improvement of her sensory ataxia so that by 12 weeks she could walk with canes instead of being wheelchair dependent. She regained vibration and joint position sense in her feet. Patient 11 had a subacute onset (over 3 months) of such severe ataxia that he was unable to use his hands, could not sit independently, or walk. He was treated with 1.0 g IV methylprednisolone daily for 5 doses initially, then biweekly for 2 months and then weekly. Within days, he was able to sit independently and use his hands; within several weeks, he could walk with a walker; and by 12 weeks, he had returned to normal ambulation. His deep tendon reflexes, joint position sense, and vibration sense (all of which had previously been absent) had returned to normal. Patient 12 (12 years of ataxia) was treated with biweekly IVIg (0.4 g/kg) for 12 weeks, and returned to normal ambulation. He was able to sit independently and use his hands; within several weeks, he could walk with a walker; and by 12 weeks, he had returned to normal ambulation.
g/kg) for 6 weeks and then weekly for another 6 weeks. By 12 weeks, his sensory examination and his gait were much improved, and he no longer needed a cane to ambulate. Several months after discontinuation of treatment, his ataxia became much worse and he began using a wheelchair. Patient 14 (7 months of ataxia) was treated with 187 mg of IV dexamethasone weekly for 5 weeks and then once every other week. By 13 weeks, he had recovered and his gait, reflexes, and proprioception and vibration senses returned to normal. Patients 13 and 15 were recently diagnosed with CISP and are currently receiving immune-modulating treatment. The other seven patients in the study were identified by a retrospective chart review and were not treated.

**Discussion.** Involvement of nerve roots is common in varieties of both acute (AIDP) and chronic (CIDP) inflammatory demyelinating polyradiculoneuropathies but generally the distal nerve is also affected by these diseases. Isolated inflammatory or immune involvement affecting the sensory roots proximal to the DRG has been hypothesized in isolated cases but there has not been pathologic confirmation. We describe a syndrome likely due to an immune mediated demyelination predominantly involving the dorsal roots proximal to the DRG. Supporting evidence for this is the constellation of large fiber sensory loss (confirmed pathologically and documented on quantitative sensory testing), gait ataxia, reflex loss, normal nerve conduction and EMG studies, characteristic SSEP abnormalities, elevated CSF protein levels, thickened lumbar nerve roots on MRI scans, inflammatory demyelinating changes on lumbar rootlet biopsies, and favorable response to immune-modulating treatment.

Isolated involvement of the sensory root is difficult to prove and partial involvement of the dorsal root entry zone, the dorsal root ganglia, or proximal nerve segments cannot be categorically excluded. Since the magnitude of the premorbid sural SNAPs is unknown, it is theoretically possible that the sural SNAPs measured at the time of evaluation are relatively reduced from their premorbid baseline, which would reflect partial DRG cell loss. However, this possibility seems unlikely since patients who present with a similar degree of ataxia due to neuronopathy or peripheral neuropathy usually have absent sural SNAPs, in marked contrast to the preserved sural amplitudes in our patients (see table 2). Moreover, the return to normal function with immunotherapy argues for a reversible pathology, which would be inconsistent with loss of DRG neurons. It is theoretically possible that the peripheral sensory nerve is affected at sites proximal or distal to those studied electrophysiologically. If the involvement of proximal sites were primarily demyelinating without significant axon loss, the SNAP amplitudes still might be preserved. Similarly, involvement of the very terminal nerve fibers distal to the segment of the sural nerve studied electrophysiologically could also be hypothesized. Although near nerve needle conduction studies and other techniques may better assess terminal sensory nerve function than do traditional sural studies, they were not performed.

The differential diagnosis for proximal sensory neuropathies is large, and discussed above. Patients with the Miller Fisher syndrome present with...
sensory ataxia and areflexia but differ from our patients in that their illness is acute and monophasic and usually accompanied by cranial nerve involvement. Anti-GQ1b antibodies were absent in the patients tested. The sensory neuropathy of Sjögren’s syndrome characteristically affects the DRG and therefore isolated involvement of the adjacent sensory root is an appealing hypothesis. However, none of our patients had ENA antibodies, sicca symptoms were rare, and the pathologic findings did not suggest a microvasculitis (as is typically seen in Sjögren’s neuropathy). In tabes dorsalis, the disease locus is thought to involve the dorsal root entry zone, but none of our patients had a positive syphilis serology or chronic meningitis. The chronic ataxia seen in our patients would be in keeping with spinocerebellar ataxias but the lack of cerebellar abnormalities on examination and imaging, the asymmetric disease onset, and the improvement with immunotherapy would not. The possibility of a CNS demyelinating disease causing selective involvement of dorsal root entry zones without involvement of adjacent fiber tracts is unlikely. This possibility is even further diminished since no associated signal abnormalities on MRI of brain and spinal cord were found and typical CSF abnormalities of MS were not seen.

The histologic findings described here are those of chronic immune demyelination and are similar to changes observed in the peripheral nerves of patients with CIDP. The presence of endoneurial macrophages in the absence of degenerating profiles, usually associated with secondary macrophage infiltration, argues for a primary demyelinating event.

Chronic inflammatory demyelinating polyneuropathies may affect varied components and segments of the peripheral nervous system. Such patterns include motor predominant, proximal and distal, symmetric, as seen in classic CIDP; motor only, multifocal, as seen in multifocal motor neuropathy (MMN); predominant distal sensory, as seen in paraprotein associated CIDP or distal acquired demyelinating symmetric neuropathy (DADS); multifocal sensorimotor, as seen in the Lewis-Sumner syndrome, and purely sensory, as in chronic sensory demyelinating neuropathy. This latter entity is of particular interest here, since it represents an end of the CIDP spectrum with isolated sensory symptoms. However, these patients differ from ours in that their distal sensory nerves usually show evidence of demyelination, whereas in our patients, the pathologic process appears to be localized to the sensory roots. Similar to the above-mentioned varieties, the syndrome of sensory polyradiculopathy presented here may well be an additional phenotype in the spectrum of CIDP.

Based on the described clinical features, normal nerve conduction studies, characteristic SSEP abnormalities, enlarged nerve roots, elevated CSF protein, inflammatory hypertrophic changes of sensory nerve rootlet tissue, and response to immunotherapy, we suggest the term chronic immune sensory polyradiculopathy (CISP) for this syndrome. This condition preferentially affects large myelinated fibers of posterior roots leading to gait ataxia and may evade routine diagnostic testing, since nerve conduction studies and CNS imaging are normal. Because of this difficulty in diagnosis, patients may be labeled with a hysterical gait disorder, as was the case in four of our patients on their initial evaluation. All patients treated with immunotherapy had improvement of their ataxia, although we believe it is premature to make specific treatment recommendations at this time. Nevertheless, we believe that therapeutic trials of immunotherapy in patients with chronic sensory polyradiculopathies seem reasonable. CISP should be included in the differential diagnosis of sensory ataxia, especially because it may be treatable.

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