Chronic Cryptogenic Sensory Polyneuropathy

Clinical and Laboratory Characteristics

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Background: Chronic sensory-predominant polyneuropathy (PN) is a common clinical problem confronting neurologists. Even with modern diagnostic approaches, many of these PNs remain unclassified.

Objective: To better define the clinical and laboratory characteristics of a large group of patients with cryptogenic sensory polyneuropathy (CSPN) evaluated in 2 university-based neuromuscular clinics.

Design: Medical record review of patients evaluated for PN during a 2-year period. We defined CSPN on the basis of pain, numbness, and tingling in the distal extremities without symptoms of weakness. Sensory symptoms and signs had to evolve for at least 3 months in a roughly symmetrical pattern. Identifiable causes of PN were excluded by history, physical examination findings, and results of laboratory studies. We analyzed clinical and laboratory data from patients with CSPN and compared findings in patients with and without pain.

Results: Of 402 patients with PN, 93 (23.1%) had CSPN and stable to slowly progressive PN syndrome. These patients presented with a mean age of 63.2 years and a mean duration of symptoms of 62.9 months. Symptoms almost always started in the feet and included distal numbness or tingling in 86% of patients and pain in 72% of patients. Despite the absence of motor symptoms at presentation, results of motor nerve conduction studies were abnormal in 60% of patients, and electromyographic evidence of denervation was observed in 70% of patients. Results of laboratory studies were consistent with axonal degeneration. Patients with and without pain were similar regarding physical findings and laboratory test abnormalities. Only a few patients (<5%) had no evidence of large-fiber dysfunction on physical examination or electrophysiologic studies. All 66 patients who had follow-up examinations (mean, 12.5 months) remained ambulatory.

Conclusions: Cryptogenic sensory polyneuropathy is a common, slowly progressive neuropathy that begins in late adulthood and causes limited motor impairment. Isolated small-fiber involvement is uncommon in this group of patients. Management should focus on rational pharmacotherapy of neuropathic pain combined with reassurance of CSPN's benign clinical course.

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A CQUIRED chronic sensory-predominant polyneuropathies (PNs) are common in middle and late adulthood, with an estimated prevalence of more than 3%.1 Most are secondary to readily identifiable causes, such as diabetes. However, once known causes are excluded, a sizable minority remain idiopathic. The cryptogenic group was thought to compose as much as 50% to 70% of PN cases in early series2,3 and even in 1 recent report.4 Recent studies5-8 have revised this number down to 10% to 35%. Likely reasons for the declining percentage include better recognition of hereditary neuropathies,9 recognition of immune-mediated neuropathies,9 causes becoming apparent over time,3 and the development of more sophisticated diagnostic approaches.

There are few detailed reports of electrophysiologic findings in the literature, but available data suggest that most idiopathic PN is axonal.9,10 There is less consensus on the clinical course for this group of patients. In 1 report,7 most patients (81%) were unchanged or improved after median follow-up of 3 years. Another study10 reported some progression in all 71 patients followed up for 4 to 7 years.

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This article is also available on our Web site: www.ama-assn.org/neuro.
PATIENTS AND METHODS

Medical records were reviewed on all patients evaluated for PN during a 2-year period in our university-based neuromuscular clinics. We defined patients with CSPN on the basis of pain, numbness, or tingling in the distal extremities without symptoms of weakness. Sensory symptoms had to occur in a roughly symmetrical pattern in the distal lower extremities or upper extremities or both and evolve for at least 3 months. On neurologic examination, patients had to demonstrate distal sensory deficits to either light touch, vibration, position, or pinprick that were not confined to the distribution of an individual peripheral nerve. Slight distal weakness in foot or hand intrinsic muscles was permitted as long as motor symptoms were not a presenting complaint.

Routine laboratory tests consisted of a complete chemistry battery and blood cell count, erythrocyte sedimentation rate, antinuclear antibodies, rheumatoid factor, vitamin B12 level, thyroid function tests, syphilis serologic test, and antibodies to hepatitis B. Serum protein electrophoresis and immunoelectrophoresis were done in all patients. Routine testing for antineuropathy antibodies (anti-SIgA, anti-SIgG, anti-SIgM, anti-myeloma Ig) was also done.

Clinical and laboratory data from patients with CSPN with pain were compared with results in the smaller group of patients who did not report pain. The chi-square test was used for most comparisons. When appropriate, the Fisher exact test or Student t test was substituted.

Symptomatic therapy for painful sensory symptoms was attempted using a variety of standard pharmacologic agents. A favorable clinical response was considered present if patients reported a significant decrease in or resolution of their symptoms.

This study’s intent was to better define the clinical and laboratory characteristics of a large group of patients with chronic cryptogenic sensory polyneuropathy (CSPN) evaluated in 2 university-based neuromuscular clinics. In addition to routine electrophysiologic studies, we analyzed data from quantitative sensory testing (QST) and immunologic studies. We determined the frequency of CSPN among our referral population and collected data on the clinical course, prognosis, and response to pharmacological therapy. We also compared clinical and laboratory data from patients with CSPN with pain vs those without.

RESULTS

A total of 402 patients were evaluated for PN in the 2 clinics during a 2-year period, 93 (23%) of whom (44 women and 49 men) met entry criteria for CSPN. At presentation, mean age was 63.2 years (range, 37.0-94.0 years), and mean duration of symptoms was 62.9 months (range, 3.0-240.0 months).

PRESENTING SYMPTOMS

Pain with numbness or tingling was the most common presentation (reported in 58 patients), followed by numbness or tingling without pain (22 patients) and pain alone (9 patients) (Figure 1). Gait unsteadiness and tremor were uncommon presentations, accounting for only 4 patients. In all, 67 patients presented with pain and 26 patients presented without pain. Symptoms were confined to the distal lower extremities in 41 patients (44%). In another 39 patients (42%), initial symptoms were restricted to the lower extremities for at least several months but later spread to the hands. Symptoms confined to the upper extremities were rare, being reported in only 2 patients (2%). In 1 patient, symptoms first appeared in the hands and later spread to the feet. Simultaneous development of upper and lower extremity symptoms occurred in 6 patients (6%). Four patients could not recall the initial distribution of their symptoms.

Of the 93 patients, 74 (80%) reported progression of their symptoms before our evaluation. The remaining patients (20%) believed their symptoms had improved or reached a plateau.

EXAMINATION FINDINGS

Sensory examination demonstrated abnormal results for proprioception in 28 patients (30%), light touch in 50 (54%), pinprick in 69 (74%), and vibration in 79 (85%). Pinprick was the most sensitive modality in assessing the proximal extent of sensory loss, with 58 patients demonstrating impairment at the calf, 25 at the knee, 30 in the hands, and 11 in the forearms (Figure 2). On mo-
tor examination, mild distal weakness was observed in 38 patients (41%) and distal muscle atrophy was observed in 14 (15%). Intrinsic foot muscle weakness was present in 35 patients (38%), hand weakness in 17 (18%), and foot and hand weakness in 14 (15%). Therefore, it was rare to see hand weakness without foot weakness. Deep tendon reflexes were absent in the ankles of 47 patients (50%), the knees of 14 (15%), the biceps of 7 (8%), and the triceps of 6 (6%).

Follow-up examinations were performed on 66 patients. Mean follow-up in this group was 12.5 months (range, 1.0-42.0 months). All 66 patients remained ambulatory. Ten patients (15%) had progression on either sensory or motor examination. Only 4 patients (6%) demonstrated increased weakness. Progression was more common in those followed up longer than 18 months (7 [33%] of 21 patients), two of whom had motor progression.

ELECTROPHYSIOLOGIC STUDIES

Results of NCSs are summarized in Table 1. An abnormal sural sensory amplitude was the most common abnormality, seen in 69% of patients. The most common motor NCS abnormalities were reduced peroneal amplitudes and reduced tibial conduction velocities. Overall, abnormal sensory NCS results were seen in 77% of patients and abnormal motor NCS results were seen in 60% of patients. Except for 3 patients, those with abnormal motor NCS results in the upper extremities also had abnormal motor responses in the lower extremities. When absent responses were excluded from analysis, the mean values of all NCS variables were within the reference ranges for our laboratories. No patient had NCS results that satisfied electrophysiologic criteria for demyelinating neuropathy.

Because sural sensory responses are often reduced or absent in healthy people older than 60 years, we analyzed NCS results in this age group separately. Of the 56 abnormal sural study results, 39 (70%) occurred in patients 60 years or older, with 29 being absent. Thirty-seven of these 39 patients had other abnormal findings on NCSs. The 2 remaining patients had additional laboratory evidence for PN: 1 patient had abnormal vibration and cold thresholds on QST and the other had chronic neurogenic motor unit potentials in the tibialis anterior on EMG.

Needle EMG abnormalities were present in 45 (70%) of 64 patients, only 1 of whom had EMG abnormalities restricted to intrinsic foot muscles. The other 44 patients demonstrated abnormalities in the tibialis anterior, medial gastrocnemius, or intrinsic hand muscles. Fibrillation potentials were recorded in 27 studies (42%), which

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**Table 1. Electrophysiologic Findings in Patients With CSPN**

<table>
<thead>
<tr>
<th>Nerve†</th>
<th>Distal Latency (DL)</th>
<th>Amplitude (amp)</th>
<th>Conduction Velocity (CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD, ms</td>
<td>No. Abnl % Abnl</td>
<td>Mean ± SD, mV</td>
</tr>
<tr>
<td>Median motor (n = 74)</td>
<td>3.98 ± 0.75</td>
<td>13 (0) 17.6</td>
<td>17.2 ± 3.04</td>
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<tr>
<td>Ulnar motor (n = 72)</td>
<td>3.07 ± 0.46</td>
<td>15 (0) 20.8</td>
<td>8.49 ± 2.73</td>
</tr>
<tr>
<td>Peroneal motor (n = 82)</td>
<td>5.39 ± 1.60</td>
<td>14 (8) 26.8</td>
<td>2.83 ± 2.51</td>
</tr>
<tr>
<td>Tibial motor (n = 82)</td>
<td>4.93 ± 1.53</td>
<td>8 (7) 18.3</td>
<td>6.81 ± 5.62</td>
</tr>
<tr>
<td>Median sensory (n = 78)</td>
<td>ND</td>
<td>27 (3) 38.5</td>
<td>ND</td>
</tr>
<tr>
<td>Ulnar sensory (n = 76)</td>
<td>ND</td>
<td>17 (7) 31.6</td>
<td>ND</td>
</tr>
<tr>
<td>Sural sensory (n = 81)</td>
<td>4.10 ± 0.52</td>
<td>8 (38) 56.8</td>
<td>8.17 ± 6.20 µV</td>
</tr>
</tbody>
</table>

†Not all nerves were studied in each patient, hence the different n values.

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and chronic neurogenic motor unit potentials or reduced recruitment or both were recorded in 41 (64%). Table 2 compares the yields of various laboratory tests in the population with CSPN.

**QUANTITATIVE SENSORY TESTING**

Quantitative sensory testing was performed on 39 patients. Abnormal cold and vibration thresholds were seen in 22 patients, abnormal cold but normal vibration thresholds in 9 patients, and abnormal vibration but normal cold thresholds in 2. Results of 6 studies (15%) were normal, 4 of which were in patients with pain. In 15 studies with abnormal results, elevated thresholds were restricted to the feet in accordance with a length-dependent process. Only 1 patient had QST abnormalities in the hands but not the feet. Of 33 patients with abnormal QST results, 3 had normal NCS results and presented with painful feet but had abnormal vibration, light touch, and pinprick thresholds on examination. Two patients had abnormal thresholds for cold only and 1 patient had abnormal thresholds for cold and vibration.

**COMPARISON OF PATIENTS WITH CSPN WITH OR WITHOUT PAIN**

Of 93 patients, 67 (72%) presented with pain and 26 presented without pain. Clinical and laboratory data for these 2 groups are compared in Table 3. A longer duration of symptoms in patients presenting with pain (mean ± SD, 70.7 ± 56.3 months) vs those without pain (mean ± SD, 42.9 ± 43.7 months) reached statistical significance. However, no physical or laboratory abnormality was more common to either clinical group at \( P < .05 \). Lower extremity motor NCS results were more often abnormal in patients presenting without pain but at \( P = .08 \). Abnormal sensory NCS results, EMG findings, and vibratory thresholds on examination and QST were seen at similar frequency in both groups. Only 8 (12%) of 67 patients with pain had intact reflexes and normal sensation for light touch, vibration, and proprioception. This compared with 1 (4%) of 26 patients without pain. Of the 8 patients presenting with pain who had normal large-fiber modalities on examination, only 2 patients had normal NCS findings. Five of the patients with CSPN with pain had completely normal NCS and EMG findings, and another 6 patients had normal NCS results, but EMG was not performed. Among the 27 patients with CSPN with pain who underwent electrophysiologic testing and QST, only 2 (7%) had no abnormalities on either study. No patients presenting without pain had normal electrophysiologic study and QST results. Two patients without pain had normal NCS results, but they did not undergo EMG and QST.

**OTHER LABORATORY STUDIES**

Monoclonal proteins were present in 4 of 83 patients who underwent serum protein and immunofixation electrophoresis. The paraprotein was IgA-k in 2 patients, IgG-k in 1 patient, and IgG-\( \lambda \) in 1 patient. All 4 patients were diagnosed as having MGUS. Antisulfatide antibodies were negative in all 41 patients tested. Cerebrospinal fluid (CSF) was examined in 5 patients, and results were normal in 4 patients. One patient had an elevated CSF protein level of 89 mg/dL. He was diagnosed with a small-fiber sensory-predominant PN and had normal motor examination findings, normal serum protein and immunofixation electrophoresis results, and no evidence of demyelination on NCSs.

Of the 14 patients who underwent sural nerve biopsy, histological findings showed axonal degeneration in 13 (93%). One biopsy sample showed prominent evidence of demyelination with lesser features of axonal degeneration.

**THERAPEUTIC RESPONSE**

Empiric treatment for painful paresthesia or dysesthesia was attempted with a variety of agents, including tri-
cyclical antidepressant agents, carbamazepine, phenytoin, and gabapentin. Nineteen (49%) of 39 patients reported a clinical benefit from cyclical antidepressant drug use, and 10 (50%) of 20 patients reported a benefit from carbamazepine therapy. Mexiletine hydrochloride treatment improved sensory symptoms in 2 of 4 patients, and gabapentin treatment improved sensory symptoms in 5 of 15 patients. Topical capsaicin application was effective in 3 (21%) of 14 patients. Only 1 (9%) of 11 patients taking nonsteroidal anti-inflammatory agents and none of 9 patients taking phenytoin sodium noted clinical improvement.

Chronic PN accounts for a frequent problem referred to neurologists and neuromuscular clinics. Although results of early series suggested that 50% or more of chronic PN was idiopathic, these studies were based on younger hospitalized patients, many of whom presented with severe weakness resembling acute or chronic inflammatory demyelinating PNs. More recent studies of chronic PN estimate that 10% to 33% are idiopathic, still a considerable number of patients. In our large population of PN referrals, 23% were classified as CSPN. Results of previous studies found that men are overrepresented in unclassified PN by as much as 3:1 to 4:1. Our CSPN population was more evenly divided between the sexes. There was no male predominance in 2 studies of painful idiopathic sensory PN.

Because cryptogenic PN is essentially a diagnosis of exclusion that can be established only after performing a careful history, thorough neurologic examination, and directed laboratory testing, the possibility of overlooking an underlying cause always exists. For instance, re-evaluation of cryptogenic PN ultimately uncovered a cause in 5% to 76% of previously unclassified patients. Neuropathies related to hereditary factors, diabetes, and alcohol abuse are particularly prone to being missed on initial evaluation. Review of family history and medical records alone may miss 30% of hereditary PN. By excluding patients with prominent motor involvement from the analysis and performing chemistry batteries, liver function tests, and serologic screening on all patients, we believe it is unlikely that neuropathies related to diabetes, alcohol abuse, connective tissue disorders, and heredity were included in our CSPN population. One could argue that further investigative studies are required before labeling a neuropathy cryptogenic. For example, Grant et al recently advised that patients with unclassified sensory-predominant PN undergo ophthalmologic testing for keratoconjunctivitis sicca to exclude the possibility of sicca complex or Sjögren syndrome as a cause. Because sicca symptoms are often mild and are not volunteered by patients without direct questioning, this cause may be overlooked. How far one should proceed with diagnostic testing in unclassified PN is a difficult question. In the case of sicca complex, our practice is to directly inquire about dry eye and mouth symptoms and to obtain an erythrocyte sedimentation rate, rheumatoid factor, and antinuclear antibodies on all patients. If xerophthalmia or xerostomia is present, we check anti-Sicca syndrome A and B, although we realize that occasionally seronegative patients with PN related to sicca complex are incorrectly labeled as cryptogenic using this approach. For this reason, it is important to inquire about new symptoms on follow-up visits and to remain open to other diagnostic possibilities.

In our study, patients with CSPN had a relatively homogeneous PN syndrome beginning in the sixth decade of life with long-term stable to slowly progressive symptoms and axonal features on electrophysiologic and histological studies. Typical patients had symptoms for several years before evaluation in a neuromuscular clinic. Patients with pain had a longer duration of symptoms. We do not have an obvious explanation for this finding, although the onset of positive symptoms such as pain may be easier for patients to recall than negative symptoms. Other possibilities are that the patients with CSPN with pain had less impressive physical findings in early stages or had responded adequately to pain management, thereby delaying referral to a specialty clinic. In patients with CSPN for whom follow-up examination results were available, approximately 15% demonstrated progression, but all have remained ambulatory. This pattern is consistent with previous reports. More than 80% of patients with cryptogenic PN in the series by McLeod et al were unchanged or improved at mean follow-up of 3 years. Half of the patients with idiopathic “small-fiber” neuropathy did not progress during mean follow-up of 2 years. A plateau phase seems to be particularly common in patients with pure sensory PN. In the follow-up report by Notermans et al, only 1 of 21 patients with sensory neuropathy required an assistive device for walking after 5 years. Our study suggests, however, that progression on examination will become evident in at least one third of patients as follow-up is extended. Still, debilitating motor impairment seems uncommon in our patients with CSPN and in other series. In the study by Prineas, in which mean follow-up extended to nearly 9 years, no patients became bedridden and most could walk without assistance. Discomfort or pain was a common symptom, present in 69% of patients in the series by Grahn and et al, 65% of patients with sensory PN in the series by Notermans et al, 80% of patients with idiopathic small-fiber PN in the series by Gorson and Ropper, and just more than 70% in our patient group.

Results of electrophysiologic and pathologic studies in CSPN indicate an axonal neuropathy. No patients in our series had primarily demyelinating findings on NCSs or satisfied demyelinating criteria. We found abnormalities on EMG in most patients (70%) who underwent needle examination despite the absence of motor symptoms. Therefore, subclinical motor involvement is often detected on electrophysiologic studies in patients with cryptogenic PN who have only sensory signs. Of the sural nerve biopsy samples obtained, 13 demonstrated typical features of axonal degeneration, including 1 patient with MGUS.

In previous series of idiopathic PN, most patients demonstrated axonal features on electrophysiologic and pathologic studies. Approximately 95% of patients in 2 large series had axonal features on NCSs. In the series
OF THE 83 PATIENTS WITH CSPN TESTED, ONLY 4 (5%) HAD A MONOCLONAL PROTEIN, 2 OF WHOM HAD SLIGHT WEAKNESS IN THE DISTAL UPPER AND LOWER EXTREMITIES. HAND WEAKNESS WAS PRESENT IN ONLY 17% OF PATIENTS WITHOUT A MONOCLONAL PROTEIN. IN A RECENT SERIES, 25 PATIENTS WITH IDIOPATHIC PN AND MGUS TENDED TO HAVE MORE UPPER EXTREMITY INVOLVEMENT. OTHERWISE, AS IN OUR SERIES, PATIENTS WITH MGUS WERE DIFFICULT TO DISTINGUISH ON CLINICAL AND ELECTROPHYSIOLOGIC GROUNDS FROM THOSE WITHOUT A PARAPROTEIN. THE DETECTION OF MONOCLONAL PROTEINS IN OUR MOSTLY ELDERLY POPULATION MAY BE INCIDENTAL BECAUSE PARAPROTEINS ARE FOUND IN UP TO 3% OF HEALTHY ADULTS IN LATER LIFE. 22 IN THE SERIES BY NOTERMANS ET AL., 21 18% OF PATIENTS HAD A MONOCLONAL PROTEIN, BUT PATIENTS WITH SENSORY AND MOTOR SYMPTOMS WERE INCLUDED. RESULTS OF FURTHER ANALYSIS SUGGEST THAT PATIENTS WITH AN IG M PARAPROTEIN PROGRESSED FASTER, WITH MORE WEAKNESS AND SENSORY SIGNS THAN THOSE WITH AN IG A OR IG G MONOCLONAL PROTEIN. 23 NONE OF OUR PATIENTS HAD AN IG M PARAPROTEIN.

WE DID NOT DETECT ELEVATED IG M OR IG G ANTISULFATID EP ABST NEWS LEVELS IN ANY OF THE 41 TESTED PATIENTS. THIS CONTRASTS WITH RESULTS OF PREVIOUS REPORTS IN WHICH APPROXIMATELY ONE QUARTER OF PATIENTS WITH IDIOPATHIC SENSORY-PREDOMINANT NEUROPATHY SELECTED FROM CASE RECORDS OR A CLINIC POPULATION HAD ANTISULFATID EP ANTIBODIES. 24, 25 NOTERMANS ET AL., 8 HOWEVER, ALSO FAILED TO DETECT SUCH ANTIBODIES IN 70 PATIENTS WITH CHRONIC IDIOPATHIC SENSORY OR SENSORIMOTOR NEUROPATHY, AND RESULTS OF OTHER REPORTS 10, 26 CONFIRM THEIR LOW FREQUENCY. FURTHERMORE, THE FREQUENCY OF IG M ANTISULFATID EP ANTIBODIES IN THIS POPULATION WAS RECENTLY REVISED DOWNWARD TO 0.7%. 27 THEREFORE, OUR EXPERIENCE AND THAT OF OTHERS DO NOT SUPPORT THE CONCEPT THAT ANTISULFATID EP ANTIBODIES ARE A COMMON FINDING IN IDIOPATHIC SENSORY-PREDOMINANT PN.

WE DID NOT FIND THAT CSF STUDIES CONTRIBUTED TO THE EVALUATION OF THE 5 PATIENTS WITH CSPN WHO UNDERWENT LUMBAR PUNCTURE. RESULTS OF CSF STUDIES WERE NORMAL IN 4 PATIENTS AND SHOWED AN ELEVATED PROTEIN LEVEL IN 1 PATIENT WHO HAD NO CLINICAL OR ELECTROPHYSIOLOGIC EVIDENCE OF AN INFLAMMATORY OR DEMYELINATING PN. SIMILARLY, RESULTS OF CSF ANALYSIS WERE LARGELY UNREMARKABLE IN RECENT STUDIES OF CRYPTOGENIC PN THAT EXCLUDED INFLAMMATORY NEUROPATHIES. THE MEAN CSF PROTEIN CONCENTRATION FROM 73 UNCLASSIFIED PATIENTS IN THE STUDY BY NOTERMANS ET AL. 28 WAS 43 MG/DL. SIX (14%) OF 44 PATIENTS IN THE SERIES BY MCLEOD ET AL. 29 HAD A CSF PROTEIN LEVEL GREATER THAN 100 MG/DL. HOWEVER, 4 OF THESE 6 PATIENTS WERE FOUND TO HAVE A MALIGNANT NEUROPLASM. IN OUR OPINION, CSF EXAMINATION IS OF LOW YIELD IN PATIENTS WITH CHRONIC PN WHO REMAIN UNCLASSIFIED AFTER ROUTINE LABORATORY STUDIES, HAVE MINIMAL MOTOR INVOLVEMENT, AND DO NOT DEMONSTRATE DEMYELINATING FEATURES ON NCSs.

Electrophysiologic test results were abnormal in most patients with CSPN. Overall, 87% had either abnormal motor or sensory NCS results. In the few patients with normal NCS results, EMG findings were usually normal as well. Patients with pain were more likely to have normal NCS results. Still, 75% of the NCSs in this population were abnormal. Our findings differ somewhat from those of the study by Gorson and Ropper, 17 in which 45% of patients with idiopathic distal small-fiber neuropathy had normal electrophysiologic study results. This raises the question, “How common an entity is idiopathic pure small-fiber sensory neuropathy?” One might predict that a pure small-fiber neuropathy would occur more often in patients with CSPN with pain. However, most of our population had clinical or laboratory evidence of large-fiber involvement, regardless of whether pain was present. No physical or laboratory variable of large-fiber dysfunction was significantly more common in patients with or without pain. Only 8 (12%) of 67 patients with CSPN with pain had normal light touch, vibration, proprioception, and reflex examination results. Of these 8 patients, 6 had abnormalities on NCSs. To establish a diagnosis of small-fiber PN in the remaining patients, additional tests such as autonomic studies and QST can be pursued. Measuring intraepidermal nerve fiber density on punch skin biopsy samples is also advocated for this purpose because it provides objective evidence of small-fiber loss and is less invasive than sural nerve biopsy examination. 16, 28-30 However, this novel technique is available only through a few peripheral nerve laboratories and is primarily a research tool.

The usefulness of NCSs in the evaluation of idiopathic PN, especially in patients with a painful, small-fiber neuropathy, is limited by several factors. First, as mentioned earlier, patients with idiopathic painful PN often have normal electrophysiologic study findings. 17 Second, the sural sensory response may be absent in healthy subjects older than 60 years, complicating the interpretation of such a finding in this elderly group of patients. 15 In our population, however, 37 (95%) of 39 patients older than 60 years with normal sural sensory responses had more extensive abnormalities on NCSs. Therefore, we rarely encountered the ambiguous scenario in which a reduced sural response was the only abnormality on NCSs in an elderly patient. Furthermore, the 2 patients with isolated sural abnormalities had additional laboratory evidence for PN on either QST or EMG studies.

Using standardized controls, QST results for vibration and cold thresholds were abnormal in approximately 85% of patients tested, a figure similar to a preliminary report. 30 Vibration and cold thresholds were abnormal in two thirds of the studies. Cold threshold abnormalities alone were present in 24% of patients with CSPN with pain and in 30% of patients with CSPN without pain. Quantitative sensory testing for cold thresholds may not be an ideal small-fiber measurement because it presumably assesses both A δ and C fibers. 31 Quantitative sensory testing of warm or heat pain thresholds theoretically provides a better measure of C fibers. We do not routinely perform heat pain thresholds in our laboratory, and CASE IV equipment does not include normative values for warm thresholds. However, it should be emphasized that more than 90% of the population with
CSPN had evidence of large-fiber dysfunction, and, therefore, the addition of warm and heat pain QST would have been of diagnostic value in only a few patients. Because many of our patients with CSPN had impaired vibration or proprioception responses or both on examination and abnormal electrophysiologic study findings, the demonstration of abnormal QST results was adjunctive evidence for a PN. Although QST has been shown to have some use as a diagnostic, staging, and outcome measure in large peripheral neuropathy studies,32,33 its role in routine practice is not established. Furthermore, as a subjective test dependent on patient attention and cooperation, QST is not an ideal measure of small-fiber function.

In theory, an impaired thermal threshold on QST may represent the only laboratory abnormality in small-fiber PN. However, our experience suggests that this is an uncommon occurrence. Only 2 (9%) of 23 patients with CSPN with pain and abnormal cooling thresholds on QST had normal NCS results. Therefore, thorough clinical and electrophysiologic examinations detected evidence of large-fiber involvement in all but a few patients with painful PN. Thermal threshold testing can detect small-fiber dysfunction in most of the remaining patients with PN.30,34,35

Our findings contrast with those from other studies of painful small-fiber PN. However, these investigators35,30,34 excluded patients with large-fiber involvement by requiring normal electrophysiologic study results and intact strength, proprioception, and deep tendon reflexes.30 Because these patients with “pure” small-fiber involvement represent only a fraction of all painful neuropathies,30 our experience is likely to be more reflective of routine clinical practice.

Although by definition the cause of CSPN is unknown, our experience suggests that general diagnostic criteria can be developed for these patients. Such criteria should broadly define the symptoms, signs, and laboratory abnormalities that are expected and sufficient to arrive at a diagnosis of CSPN. Table 4 outlines clinical criteria for CSPN that we recommend based on our experience and that of other investigators. We chose a minimum of 3 months of sensory symptoms to classify patients as having CSPN. This excludes patients with an acute sensory neuropathy caused by a toxic, iatrogenic, or immune-mediated process that potentially is self-limiting. In our opinion, sensory symptoms alone are not sufficient to diagnose CSPN. It is at times difficult to ascertain whether a patient with sensory symptoms and normal neurologic examination results actually has neuropathy. Therefore, in this clinical setting, we believe that abnormalities on NCSs, EMG, QST, or other studies, including nerve biopsy or punch skin biopsy examinations, are required to diagnose CSPN. By our definition, CSPN is chronic in nature, and whether acute, self-limited forms exist awaits further study. We suspect that, as investigators devote more attention to this previously underemphasized patient group, diagnostic criteria will evolve. Although patients with CSPN share many clinical features, further work will almost certainly elucidate a variety of causes.

We found tricyclic antidepressant drug use and carbamazepine therapy to have roughly equivalent efficacy in relieving symptoms of painful paresthesias and dysesthesias. Approximately 50% of patients responded to treatment with either agent. Similar success was found with mexiletine hydrochloride treatment in a few patients. Each of these agents has demonstrated efficacy in the treatment of neuropathic pain in double-blinded, crossover studies of painful diabetic neuropathy.30,37 Gabapentin, a newer antiepileptic drug with a favorable adverse effects profile, has been effective in a variety of neuropathic pain syndromes, including radiculopathies, postherpetic neuralgia, human immunodeficiency virus neuropathy, and trigeminal neuralgia,30,42 and has shown promise in preliminary controlled trials of painful diabetic neuropathy.31,42 One third of our patients taking gabapentin had symptomatic improvement. Topical capsaicin use benefits a few patients. Use of phenytoin and nonsteroidal anti-inflammatory drugs, in contrast, was largely of no benefit. In a double-blind, crossover study, Saudek et al43 also did not demonstrate efficacy for phenytoin therapy in painful diabetic neuropathy.

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Table 4. Diagnostic Criteria for CSPN*

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tr>
<td>Symptoms</td>
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<tr>
<td>Loss of sensation (numbness) or altered sensation (tingling/paresthesia/dysesthesia) or pain beginning in the distal extremities (usually with onset in feet before hands)</td>
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<tr>
<td>Symptoms present for at least 3 mo</td>
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<tr>
<td>No symptoms of weakness</td>
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<tr>
<td>Symptoms of gait unsteadiness and autonomic dysfunction are allowable</td>
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<tr>
<td>Signs</td>
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<tr>
<td>Sensory signs are present in a symmetrical fashion in distal limbs and may include any of the following: loss of vibration, proprioception, light touch, pain (pinprick), or temperature</td>
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<tr>
<td>Hyperreflexia or areflexia may be present but is not required, even at the ankles</td>
</tr>
<tr>
<td>Minimal weakness or atrophy is allowable in muscles supplying movement to the finger and toes</td>
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<tr>
<td>Laboratory studies</td>
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<tr>
<td>Electrophysiology: sensory and motor NCS and needle EMG are often, but not invariably, abnormal; when abnormal, findings indicate a primarily axonal PN</td>
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<tr>
<td>Quantitative sensory tests: vibration and temperature thresholds are often, but not invariably, abnormal</td>
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<td>Other studies: if NCS/EMG and QST are normal, other studies including skin punch biopsy to measure epidermal nerve fiber density and autonomic studies including sudomotor tests (quantitative sudomotor axon reflex test, Silastic imprint testing, sympathetic skin response) and vasomotor tests (heart rate variability to deep breathing, Valsalva ratio) may provide evidence of peripheral nerve dysfunction</td>
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<td>Blood and urine tests: these should be normal or negative; a monoclonal protein by serum protein electrophoresis and/or immunofixation electrophoresis is allowable in patients with MGUS</td>
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<th>Exclusion Criteria</th>
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<tr>
<td>Any identifiable metabolic, toxic, infectious, systemic, or hereditary disorder known to cause PN</td>
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<tr>
<td>NCS abnormalities consistent with demyelination</td>
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<tr>
<td>If a monoclonal gammopathy is present, the presence of an underlying lymphoproliferative disorder, malignancy, or amyloidosis</td>
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<td>Weakness on examination other than mild toe and/or finger weakness</td>
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*CSPN indicates cryptogenic sensory polyneuropathy; NCS, nerve conduction studies; EMG, electromyography; PN, polyneuropathy; QST, quantitative sensory testing; and MGUS, monoclonal gammopathy of uncertain significance.
We did not use immunosuppressive therapy in our patients with CSPN. Although literature exists describing benefits of using corticosteroids, intravenous gammaglobulin, and other immunosuppressive agents in idiopathic axonal PN, we do not subscribe to their widespread use. The potential for serious adverse events, the significant monetary expense of some agents, the lack of concrete evidence for an autoimmune or inflammatory cause for the PN, and the relatively favorable long-term prognosis all argue against administering immunosuppressive agents to patients with cryptogenic sensory-predominant PN.

In our experience, patients with CSPN follow a stable course and rarely develop disabling motor deficits despite the presence of motor nerve involvement on electroneurophysiologic studies. Although the mean duration of follow-up is limited, 35 of our patients had symptoms of neuropathy for 5 years or longer before our evaluation. All patients with follow-up examination results have remained ambulatory. We found that these patients are often anxious about their future, with many having been told previously by other physicians that their prognosis is bleak and they will become physically incapacitated over time, requiring a wheelchair or becoming bedridden. Perhaps the most useful intervention is reassuring these individuals that they are unlikely to develop disabling motor impairment and that continued physical independence is almost certain. Although such reassurance provides a degree of mental, and possibly physical comfort for patients, further studies are needed to elucidate the underlying pathogenesis of CSPN and to develop rational therapeutic strategies for this common form of PN.

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REFERENCES