DIAGNOSTIC UTILITY OF SOMATOSENSORY EVOKED POTENTIALS IN CHRONIC POLYRADICULOPATHY WITHOUT ELECTRODIAGNOSTIC SIGNS OF PERIPHERAL DEMYELINATION

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ABSTRACT: Introduction: Diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) remains uncertain when nerve conduction studies (NCS) fail to show demyelination. Methods: We conducted a retrospective study of patients who presented with clinical criteria of CIDP in whom electrodagnostic (EDx) criteria of definite or probable CIDP were missing [axonal sensorimotor neuropathy (n = 23), normal EDx with pure sensory presentation (n = 3)]. All patients received immunomodulatory treatment. Twenty-six patients were evaluated with somatosensory evoked potentials (SSEPs), MRI of spinal roots, cerebrospinal fluid analysis, and/or nerve biopsy. Diagnosis of CIDP was considered to be confirmed in patients who responded to immunotherapy. Results: Twenty-two of 26 patients (85%) had SSEPs reflecting abnormal proximal conduction in sensory fibers, including 14 who had only clinical and SSEP data in favor of CIDP. SSEPs were abnormal in 16 of 20 responders (80%) to immunotherapy. Conclusion: SSEP recording contributes to the diagnosis of CIDP when nerve conduction studies fail to detect peripheral demyelination.


The diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) is crucial, because effective immunotherapies are available.1–4 The diagnosis is based on clinical, biological, and electrodagnostic features.1–6 However, electrodagnostic (EDx) criteria rely on motor conduction velocities assessed by nerve conduction studies (NCS) and may fail to show demyelination, either because of secondary axonal degeneration or when motor nerve conduction is normal in pure sensory forms of polyradiculopathy. In these atypical forms, other diagnostic tools are available. Cerebrospinal fluid (CSF) analysis shows an elevated protein level in 40–95% of CIDP patients.7–10 Cervical and lumbar magnetic resonance imaging (MRI) can reveal gadolinium enhancement and/or hypertrophy of nerve roots, but diagnostic sensitivity has not been determined.11–15 Histopathology on sural nerve biopsy can provide evidence suggestive of demyelination,16–18 but these abnormalities can be missing due to axonal degeneration and/or preferential involvement of proximal nerve segments.19 In this context, somatosensory evoked potentials (SSEPs) that explore conduction in sensory fibers from the periphery to the somatosensory cortex20–22 represent an alternative tool for CIDP diagnosis.23–25 In this study we assessed the diagnostic yield of SSEPs in patients with a clinical presentation suggestive of CIDP but in whom NCS criteria for CIDP were not fulfilled.

METHODS

Inclusion Criteria. This study was a retrospective cross-sectional study based on the cohort of patients referred to the Neurological University Hospital of Lyon between 2004 and 2013 for assessment of CIDP (n = 139). Patients were included based on the clinical criteria proposed by the French CIDP Study Group1 and the Peripheral Nerve Society (PNS),2,3 namely: (1) a sensorimotor neuropathy with EDx signs of axonal loss in motor and sensory peripheral fibers (23 of 26) or a pure sensory polyradiculopathy with normal EDx findings (3 of 26); (2) findings unexplained by any other known etiology; and (3) a progressive course over at least 2 months. NCS were performed in the same laboratory by the second author (P.P.) using Kpnet 2011 equipment (Natus Medical, Inc.) and interpreted on the basis of normative data acquired in this laboratory with the same equipment. Nerve conduction studies (NCS) to Erb point stimulation were not performed before SSEP testing. All patients fulfilled at least 1 of the following criteria: (1) proximal weakness; (2) motor and sensory loss in all 4 limbs or the upper limbs; (3) gait ataxia; (4) diffuse areflexia; (5) relapsing course; or (6) cranial nerve involvement. All patients had undergone the following serum investigations: blood count; glucose; liver and renal tests; vitamin B12 and folic acid levels; hepatitis; HIV and Lyme serologies; and search for
monoclonal immunoglobulin by serum electrophoresis and immunofixation and antiganglioside antibodies.

We excluded patients: (1) with NCS criteria of definite or probable demyelination, as proposed in the 2010 PNS guidelines2; (2) with lumbar or cervical spondylody sion that could affect spinal responses; (3) in whom response to treatment could not be evaluated retrospectively; (4) with a known cause of neuropathy; and (5) with any disease of the central nervous system that might cause weakness and/or numbness.

Diagnosis of CIDP was considered to be confirmed in patients who responded to immunotherapy with a follow-up of at least 3 months. Response to treatment by steroids or intravenous immunoglobulin (IVIg) was defined as an improvement by at least 2 Medical Research Council (MRC) grades in any muscle and/or by a 1-point improvement on the modified Rankin scale. Patients with no improvement after 3 courses of IVIg, 2 months of corticosteroids, or 6 sessions of plasma exchange (PE) were classified as non-responders.

Complementary criteria included: (1) elevated CSF protein level (over 0.5 g/L); (2) enlarged nerve roots or nerve root signal enhancement after gadolinium injection on MRI; and (3) evidence of demyelination on nerve biopsy.

To ensure that the SSEP normative data used in our department, gathered from a 25–60-year-old population20–22 did not introduce a risk of false positive results, we obtained peripheral and spinal SSEP data in 28 age-matched patients without any abnormalities affecting the peripheral nervous system or spinal tracts.

Normative Data and SSEP Interpretation. We used the data obtained from our population of 28 age-matched subjects to interpret SSEP latencies and amplitudes of peripheral and segmental spinal responses in patients (Supplementary Files S2 and S3 online). Compared with our normative data obtained in a 25–60-year-old population20–22 mean latencies of spinal N13 and N22 tended to be longer and N22 amplitude lower in the age-matched population, and only 3 subjects if this group had latencies or amplitudes outside the normal ranges calculated in the younger control group. Latencies were considered abnormal when they exceeded the mean value + 2.5 SD in the age-matched control population. The N9 potential was considered to be decreased when the N6/N9 ratio was greater than the mean + 2.5 SD of the age-matched control population. The N13 potential was considered to be decreased when it was <0.5 μV or had an N13/P9 voltage ratio <1.220–22 (Supplementary File S1 online). N22 was considered to be abnormal when it was absent. The normal latency limit was adjusted for height only for the N8 and N22 components of tibial nerve SSEPs (+0.15 ms/cm for body height >175 cm for N9, and +0.18 ms/cm for body height >175 cm for N22).

Classification of SSEP Diagnostic Impact. Peripheral and spinal SSEP data were used to classify results into 3 groups according to their diagnostic impact:

Normal SSEPs: SSEPs with preserved peripheral potentials at elbow, Erb point, and popliteal fossa; normal spinal N13 or N22 latencies and amplitudes and normal N9–N13 interval were considered normal in the context of a CIDP diagnosis, as they reflect normal peripheral and dorsal root conduction.

Confirmative SSEPs: We classified as confirmative of CIDP diagnosis: (1) median nerve SSEPs with a normal peripheral potential at the elbow and delayed or decreased brachial plexus responses with a reduced or delayed N13 spinal potential reflecting conduction slowing and/or dispersion of the afferent volley in brachial plexus trunks and/or dorsal roots; and (2) tibial nerve SSEPs with a preserved N8 potential and an absent N22 spinal potential reflecting a conduction abnormality in proximal segments of the tibial nerve, lumbar-sacral plexus trunks, and/or dorsal roots.

Non-applicable SSEPs: We classified SSEPs as non-applicable when there was bilateral absence of peripheral potentials at the elbow and in the popliteal fossa, which precluded evaluation of conduction

**SSEP Recordings.** All SSEP studies were carried out and interpreted according to the guidelines of the International Federation of Clinical Neurophysiology (IFCN)20,22 (refer to Supplementary File S1 in Supplementary Material, available online). SSEPs were recorded after stimulation of median nerves at the wrist and tibial nerves at the ankle.

We evaluated the peak latencies and voltages of the following SSEP components:

For *median nerve SSEPs*: N6 responses at elbow, Erb point N9, cervical P9 and N13, scalp P9, P14, and cortical N20 potentials.

For *tibial nerve SSEPs*: N8 responses at popliteal fossa, segmental spinal N22, cervicomedullary P30, and cortical P99 potentials.
abnormality in proximal nerves, plexus trunks, or dorsal roots.

RESULTS

Patients. As shown in Figure 1, 15 of the 41 patients fulfilling the inclusion criteria were excluded because of severe lumbar and/or cervical spondylosis \((n=5)\), no treatment being undertaken \((n=6)\), or discovery of a cause of neuropathy during follow up \((n=4)\). The 6 untreated patients had mild symptoms that did not warrant the risks of immunotherapy; all had confirmatory SSEPs.

Of the 26 patients included, 20 were considered as definite CIDP, because they responded to immunotherapy. Fourteen were men, and the mean age was 68 years \((\text{range } 36–88 \text{ years})\). The mean disease duration was 8 years \((\text{range } 1–17 \text{ years})\). The most frequent clinical symptom was ataxia \((85\%)\), followed by diffuse areflexia \((50\%)\), non–length-dependent sensory or motor loss \((35\%)\), relapsing course \((35\%)\), and proximal motor weakness \((30\%)\). No patient presented with cranial nerve involvement. In responders to immunotherapy the median value of the modified Ran-kin scores was 3 \((\text{range } 2–4)\) pretreatment and 1 \((\text{range } 1–3)\) posttreatment \((P=0.00008; \text{Wilcoxon test})\); individual values are given in Supplementary File S4 online.

Before treatment, NCS showed an axonal sensorimotor neuropathy in 23 patients, of whom 10 had an abnormality suggesting demyelination in a single nerve \((\text{Supplementary File S5 online})\). According to PNS guidelines,\(^2\) NCS data were not confirmatory of CIDP in these patients, who could only be classified as possible CIDP. NCS were normal in 3 patients with pure sensory and ataxic clinical presentations.

CSF analysis was performed in 25 of 26 patients. An elevated protein level was found in 10 \((40\%)\) patients \((\text{range } 0.52–1.13 \text{ g/L}, \text{median } 0.80 \text{ g/L})\), all in the definite CIDP group. Of the 17 patients who underwent lumbar MRI, 2 had lumbar nerve root signal enhancement after gadolinium injection. Sural nerve biopsy was performed in 7 patients. Histopathology suggested demyelination in 2 patients, showing onion-bulb formations, naked fibers, and thin myelin sheaths, but no lymphocytic infiltration. All patients were treated with 3 series of IVIg 2 g/kg over 5 days every 4 weeks followed by, in responders, additional series at longer intervals in case of relapse. Prednisone \((1 \text{ mg/kg/day for 6 weeks}, \text{then slowly tapered})\) or plasma exchange \((6 \text{ PEs during the first month followed by a progressive increase in the interval between exchanges})\) were used as second-line therapy in 5 and 6 patients, respectively, after they had insufficient or no response to IVIg. The overall response rate to treatment was 77\% \((20 \text{ of } 26 \text{ patients})\).
SSEP data are summarized in Supplementary File S4 and detailed in Supplementary File S6 (both online). Tibial nerve SSEP data were not available in 1 patient. No response to tibial nerve stimulation could be obtained at any recording site on either side in 7 patients. Peripheral response (N8) in the popliteal fossa was absent in 17 of 25 patients, bilaterally in 16. The lumbar N22 was absent or delayed in 23 of 25 patients. Tibial nerve SSEPs showed abnormal spinal responses with preserved peripheral responses, confirmatory for CIDP, in only 7 of 25 patients (28%); abnormalities were unilateral in 2 patients and bilateral in 5. Tibial nerve SSEPs were normal in 2 patients and were non-applicable because of absent peripheral N8 responses on both sides in 16 patients. The cervicomedullary P30 or cortical P39 responses were recordable on 1 side in 4 patients and on both sides in 12 patients with prolonged latencies in most cases (15 of 16; 93%). Only 2 patients with missing N22 had a BMI >30 kg/cm² (Supplementary File S7 online).

After median nerve stimulation, elbow and Erb point responses were recordable on both sides in all patients except 1, in whom the spinal cervical N13 was also missing on both sides, but SSEPs were normal in 3 patients. The N6 was present at the elbow in 25 of 26 patients, and there was a slight delay (≤1.2 ms) in 5 patients (unilaterally in 4). The Erb point N9 was delayed in 13 of 26 patients (bilaterally in 9), and 5 of them also had a reduced N9 amplitude (increased N6/N9 ratio). The cervical N13 was delayed, reduced, or absent in 22 of 26 (85%) patients (see Fig. 2). N13 abnormalities were bilateral in all patients except 1. Thus, median nerve SSEPs were confirmatory for CIDP by showing abnormal N9 and/or N13 responses with preserved responses at the elbow in 22 patients (85%). The N20 potential was present on both sides in all patients but 2, with prolonged latencies in 10 patients.

Globally, SSEP abnormalities affected only 1 limb in 1 patient, 2 limbs in 14 patients (upper limbs in 13, lower limbs in 1), 3 limbs in 3 patients, and all 4 limbs in 4 patients. Upper or lower limbs were affected regardless of the clinical presentation. Thirteen of the 22 patients with contributory SSEPs had non-recordable peripheral potentials in the lower limbs, so that only upper limb SSEPs contributed to the diagnosis. Cervicomedullary and cortical responses added no contributory information.

**Diagnostic Impact of SSEPs.** Combining median and tibial nerve responses, SSEPs confirmed CIDP in 22 of 26 patients, of whom 16 of 22 (73%) responded to immunotherapy. SSEPs were the only contributing data in favor of a CIDP diagnosis in 14 patients, of whom 10 responded to immunotherapy. The group of 20 responders to immunotherapy consisted of 16 patients with confirmatory SSEPs and of all the 4 patients whose SSEPs were classified as non-applicable (n = 3), or normal (n = 1). There was no significant correlation between SSEP data and response to immunotherapy (chi-square test, P = 0.54). One of the 6 patients with confirmatory SSEPs and no response to treatment showed demyelination on sural nerve biopsy.

The only patient with definite CIDP and normal SSEPs presented with distal hypesthesia and painful paresthesiae in all 4 limbs and had a relapsing course, abnormally high CSF protein level, normal NCS, normal CO₂ laser–evoked potential findings, normal small-fiber density on skin biopsy, and a response to IVIg treatment, so that SSEPs were falsely negative.

The 6 patients who did not respond to immunotherapy showed SSEP abnormalities, considered confirmatory of a CIDP diagnosis. All of these patients presented with ataxia and/or diffuse areflexia and a progressive course compatible with the diagnosis of probable CIDP, including a patient with scoliosis and deafness but no family history suggestive of inherited neuropathy. Except for 1 patient whose CSF protein level was abnormally high and whose nerve biopsy was in favor of demyelination (see above), none of these 6 patients had MRI abnormalities, increased CSF protein levels,
or demyelination features on nerve biopsy. In 5 of them the NCS showed severe axonal involvement with non-recordable responses in the lower limbs.

**DISCUSSION**

Several CIDP criteria, based on clinical presentation and NCS evidence of peripheral demyelination, have been proposed. CIDP is defined as a sensorimotor symmetric non–length-dependent neuropathy with a progressive course over 2 months, unexplained by known causes of neuropathy, with NCS findings indicative of demyelination on motor NCS. However, some patients, as all of those included in this study, have a clinical presentation of CIDP but do not fulfill EDx criteria for demyelination. They show only signs of axonal sensorimotor neuropathy (23 of 26) or have normal NCS (3 of 26). Consequently, the prevalence of CIDP is probably underestimated, and patients who would benefit from immunotherapy are thus left untreated in spite of progression of their disease. This situation is illustrated by the mean disease duration of 8 years before immunotherapy was undertaken in our patients. Contrary to what is observed in classical forms of CIDP, ataxia was more frequent than proximal motor weakness in our patients, which suggests that “axonal” forms of CIDP may represent a variant of the disease, with a clinical presentation resembling that seen in chronic immune sensory polyradiculopathies. In most of our patients (23 of 26) the EDx presentation was that of an axonal neuropathy of unknown etiology, and the finding of suggestive SSEP abnormalities represents a strong argument in support of an indication for immunotherapy.

The PNS guidelines include SSEP abnormalities reflecting impaired conduction in the proximal segments of ganglion cells as a supportive criterion for CIDP. SSEPs offer the possibility of investigating conduction in proximal segments of peripheral nerves and/or dorsal root fibers. The segmental spinal N13 and N22 potentials reflect the response of dorsal horn neurons to the afferent volley in dorsal roots. When peripheral SSEPs are obtained at the elbow or popliteal fossa, even with reduced amplitudes, spinal potential abnormalities reflect conduction slowing or dispersion of the afferent volley at the plexus and/or dorsal root levels.

Only a few studies have evaluated the diagnostic utility of SSEPs in CIDP. They have demonstrated proximal sensory nerve dysfunction in 83–100% of patients with typical CIDP, but none focused on patients with clinically probable CIDP in whom NCS fail to demonstrate peripheral nerve demyelination. When NCS criteria are not met, root hypertrophy on MRI and elevated CSF protein with normal cell count are considered to favor a CIDP diagnosis, but these criteria were missing in 11 (55%) of our patients who responded to immunotherapy.

Our data show that, in 22 of 26 patients (85%) who met clinical but not electrophysiological criteria for CIDP, SSEPs reinforced the diagnosis by showing abnormal conduction in peripheral sensory fibers at the plexus or dorsal root levels. In 16 of the 22 patients with confirmatory SSEPs, the CIDP diagnosis was supported by a response to immunotherapy at a rate of 73%, which is in line with that reported in CIDP with NCS signs of peripheral demyelination. SSEPs also proved helpful in 2 of 3 our patients who had pure sensory–ataxic CIDP and normal NCS findings, including sural sensory nerve action potentials; they all responded to immunotherapy, including the third patient who had false negative SSEPs. Moreover, all diagnostic tools except SSEPs were non-contributory to the diagnosis of CIDP in 14 patients, of whom 10 benefited from immunotherapy.

This high proportion of contributory SSEPs was reached because both upper and lower limb nerves were explored. In 9 of the patients who responded to immunotherapy, only upper limb SSEPs were contributory. Thus, it appears crucial to test both upper and lower limb nerves regardless of the clinical presentation, because peripheral responses in lower limbs were missing in the majority of patients (16 of 25). Moreover, the mean age of our patients was higher than that of subjects included in most available SSEP normative data banks, so adjusting normal values to those obtained in an age-matched control group is mandatory to avoid overestimation of SSEP abnormalities.

The diagnostic utility of SSEPs is hampered by lumbar or cervical spondylosis. Twelve percent (5 of 41) of patients who fulfilled our inclusion criteria were excluded from the analysis for this reason. Moreover, in patients suspected of CIDP, but with an EDx presentation of axonal neuropathy, peripheral responses can be missing in all limbs. SSEPs in these patients cannot contribute to diagnosis, because proximal conduction cannot be determined, as was observed in 3 of our 4 patients with non-contributory SSEPs. Another limitation of lower limb SSEPs is that the lumbar N22 was absent in 9% of normal subjects in our normative data bank, particularly in overweight patients. Only 2 of our patients had a BMI 

<sup>30</sup> kg/m<sup>2</sup> (Supplementary File S7 online), and N22 was present in all of our age-matched controls. It is noteworthy that in none of our patients were SSEPs classified as confirmatory of CIDP on the sole basis of missing N22, so that no patient could have been misclassified as having confirmatory SSEPs. Our findings are also limited by the retrospective nature of the study, which was not set up as a trial to evaluate the sensitivity and specificity of
SSEPs. Because of the absence of any definite “gold standard” for CIDP diagnosis, a drawback common to all existing studies of EDx in CIDP, diagnosis was considered as confirmed in patients who responded to immunotherapy. According to this criterion, 3 patients in whom SSEPs were not applicable for CIDP diagnosis due to absent distal peripheral responses and 1 patient with normal SSEPs responded to immunotherapy (see Fig. 1). This latter patient may have had an axonal autoimmune neuropathy. In the other 3 patients, this interpretation would be speculative, because a proximal conduction abnormality could not be ruled out on the basis of SSEP findings. Sixteen of 22 of patients with suggestive SSEP abnormalities responded to immunotherapy. This difference in response rates to immunotherapy between patients with confirmatory SSEPs and those with non-confirmatory SSEPs was not statistically significant because of the small number in the latter group (n = 4), but mostly because this group included the 3 patients in whom SSEPs were not usable to assess proximal conduction slowing. The question of whether SSEPs could be helpful in identifying potentially immunotherapy-responsive patients among those with an atypical EDx presentation deserves to be addressed prospectively.

Finally, this study suggests that SSEPs are helpful in confirming CIDP diagnosis in patients with a clinical presentation of CIDP but an EDx presentation of axonal neuropathy or normal NCS. In these patients whose NCS bring no firm argument in favor of demyelination but whose SSEPs detect abnormal proximal conduction in sensory fibers, immunotherapy has a high response rate of 75%. Last, it appears crucial to test both upper and lower limb nerves regardless of the clinical presentation, because tibial nerve SSEPs may be non-contributory in patients in whom peripheral responses are missing due to axonal damage.

The authors are grateful to Dr. Sylvain Rheims for useful comments on study design and for participation in the clinical evaluation of patients.

REFERENCES


