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REVIEW ARTICLE

Nerve Excitability Changes in Chronic Inflammatory Demyelinating Polyneuropathy: A New Clinical Diagnostic Biomarker

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The diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) mainly relies on clinical presentation and traditional nerve conduction studies. However, diagnosing CIDP with an atypical presentation remains a challenge. Availability of an additional diagnostic utility, such as the nerve excitability test (NET), can improve clinicians' ability to diagnose CIDP. In this article, we present a review of published papers on the changes in nerve excitability parameters in CIDP. Among the nerve excitability parameters, a baseline increase of the threshold current in a stimulus–response curve, decreased strength–duration time constant, and "fanning-out" pattern of the threshold electrotonus are consistently noted. The recovery cycle might show increased superexcitability and the current–voltage relationship might show inward rectification, but these changes are less consistently noted. These parameters are compatible with membrane hyperpolarization in CIDP. On longitudinal follow-up, normalization of nerve excitability parameters is noted after intravenous immunoglobulin treatment. We also report a case of acute-onset focal CIDP with a longitudinal nerve excitability study, where nerve excitability changes consistent with previous studies have enabled early diagnosis. NET may be a useful tool for clinical neurophysiologists for early diagnosis and follow-up of CIDP.

1. Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a polyneuropathy mediated through autoimmune processes involving the myelin sheaths of peripheral nerves. Clinical manifestations of CIDP typically include symmetrical muscle weakness, various degrees of sensory deficit, and loss of tendon reflex, and its course is typically relapsing–remitting or progressive for more than 2 months.[1] Nevertheless, CIDP has many atypical clinical forms, including focal or multifocal sensorimotor symptoms, purely sensory symptoms, and even fatigue.[2–5] Up to 16% of CIDP patients present themselves with an acute disease (also known as acute-onset CIDP or A-CIDP).[5,6]

The diagnosis of CIDP largely relies on clinical presentation, disease course and duration, and conventional nerve conduction studies (NCS). The commonly used diagnostic criteria including the American Academy of Neurology (AAN),[7] modified AAN,[8] Koski,[9] and European Federation of Neurological Societies (EFNS) criteria,[10] all provide strict clinical and electro-diagnostic criteria in diagnosing CIDP. This approach can provide good specificity in diagnosing CIDP in patients with typical clinical symptoms when a demyelination pattern is seen in NCS after the disease has run its course; however, diagnosing CIDP with an atypical presentation remains a challenge, especially for the patients who develop symptoms within 2 months from the onset of the disease.[7,8,10] Availability of additional diagnostic utility, such as nerve excitability test (NET), could improve clinicians' ability to diagnose CIDP.

NET is a technique that uses threshold tracking to noninvasively measure several parameters of axonal excitability. This technique has been used to study various neuropathies in the past 15 years and is known to be clinically useful for evaluating internodal conductance in human axons.[11] Herein, we review the available literature on the application of NET for the diagnosis and follow-up of CIDP.

2. Pathophysiology of CIDP

2.1. Immunopathogenesis

The precise cause of CIDP is currently unknown. Much of our current understanding on the effects of humoral immune factors on the inflammatory demyelinating polyneuropathies is gained from

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the experimental allergic neuritis (EAN) model.[12] EAN has been induced successfully in rodents using immunization of Freund adjuvant,[12,13] P0,[14] P2,[15] or PMP22.[16] Both acute and chronic cellular infiltration and demyelination of the peripheral nerves have been observed in rodents with EAN, and the chronic EAN model supports the hypothesis that humoral immunity plays a role in CIDP.[17] However, none of the pathologic autoantibodies is consistently found in CIDP patients, suggesting that CIDP is immunologically heterogeneous.[18,19]

As in many other immune dysfunctions,[20] T-cells and macrophages also play a prominent role in the immunopathogenesis of CIDP, as evidenced by the infiltration of T-cells and macrophages observed in sural biopsy.[21,22] Macrophages are found to be more abundant than T-cells in biopsy specimens.[22] Schwann cells and macrophages present antigen to activate T-cells through the expression of the costimulatory molecules B7-1 and B7-2, showing B7-1 upregulation in CIDP.[23] Other studies have also demonstrated a T-cell-mediated attack against the peripheral nerve in CIDP.[24] The

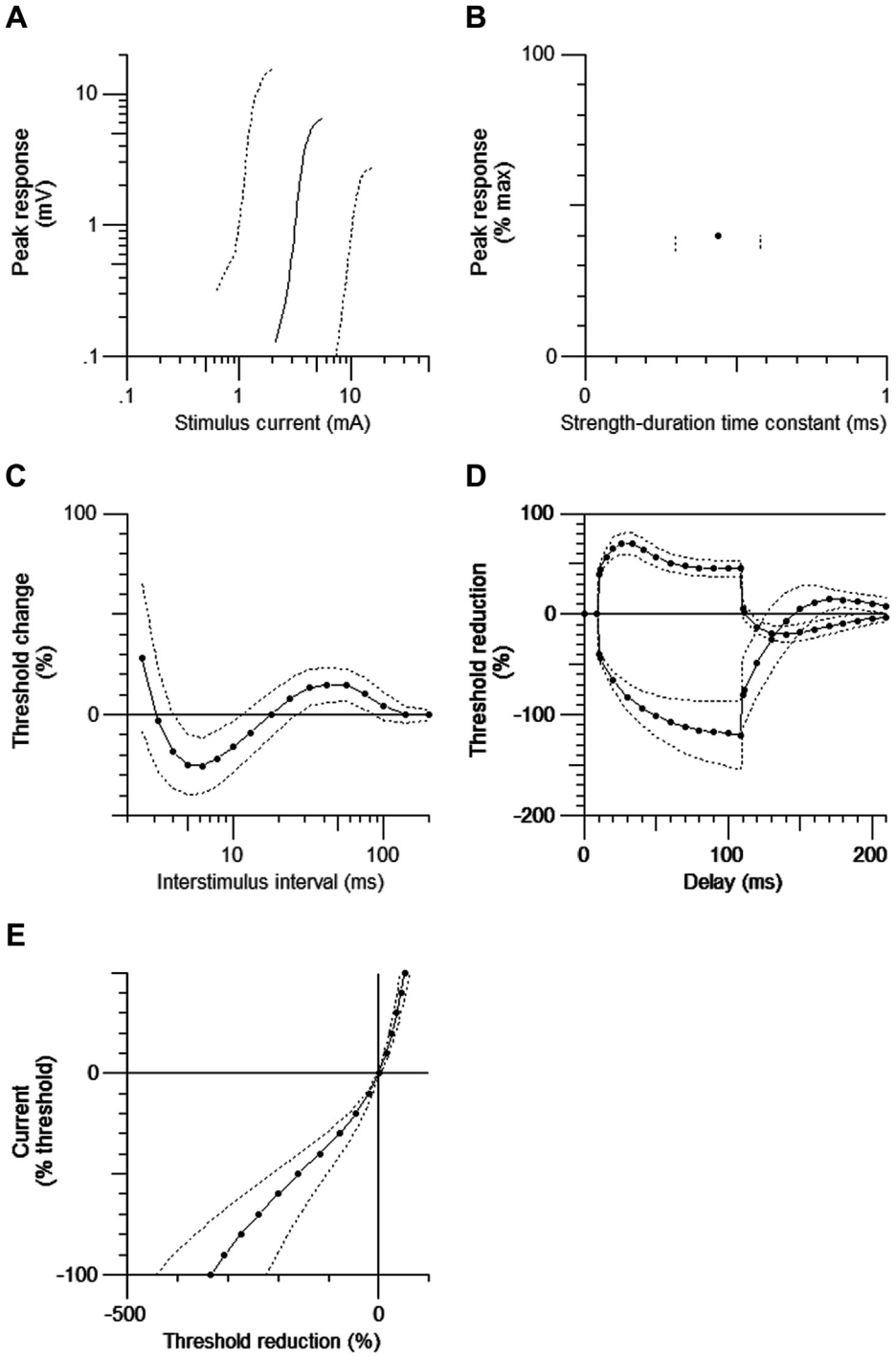

Figure 1 Nerve excitability parameters recorded from 84 control individuals. (A) S–R curve, (B) SDTC, (C) TE, (D) RC, and (E) *I*/*V* relationship are shown. Solid lines indicate the mean value of the patients, while the dotted lines indicate 95% confidence limit. *I*/*V* = current–voltage; RC = recovery cycle; SDTC = strength–duration time constant; S–R = stimulus–response; TE = threshold electrotonus.

demyelination in CIDP itself is thought to be caused by the direct action of macrophages. An ultrastructural examination of sural biopsies in CIDP revealed macrophage-associated demyelination, where macrophages invaded Schwann cell cytoplasm, split the myelin lamellae, and destroyed the myelin sheath.[25]

2.2. Conventional electrodiagnostic testing

As mentioned above, humoral and cellular immunities contributed to the demyelination in CIDP. The objective of the conventional electrophysiological study of CIDP is to detect the presence of peripheral nerve demyelination. As the disease progresses, demyelination in CIDP would eventually cause prolonged motor distal latencies, decreased nerve conduction velocity, motor conduction block or temporal dispersion, and prolongation or absence of F-waves on conventional NCS.[26] The main limitation of conventional NCS, as already mentioned, is its low sensitivity to diagnose early and/or atypical CIDP.

3. NET in CIDP

Although attempts to measure human nerve excitability have been made since 1933,[27] nerve excitability studies in peripheral nerve diseases have increased greatly after the development of QTRAC program by Bostock and associates.[28] The program provides a rapid record for different nerve excitability parameters. Shown in Figure 1A–E are nerve excitability parameters drawn based on data obtained from 84 control individuals. To date, seven published studies exist to describe NET findings in CIDP (Table 1).[29–35]

3.1. Stimulus–response curve

The stimulus–response (S–R) curve is drawn by plotting the peak response of compound action potential against increasing stimulus intensity (Figure 1A). Compound action potential of a stimulated nerve can increase with increasing stimulus intensity until a peak response is reached. Parameters that can be derived from the curve include supramaximal peak response (mV), stimulus required for 50% maximal response (mA), and the S–R slope. A hyperpolarized nerve would need a higher stimulus strength to produce a response, and its curve would be shifting to the right; on the contrary, a depolarized nerve would require a less stimulus strength and its curve would be shifting to the left.[36]

Meulstee et al[29] pioneered the study of nerve excitability in CIDP in 1997 by investigating the effect of CIDP on the S–R curve. The study showed that CIDP patients required higher currents for eliciting 90% maximum compound muscle action potential (CMAP) response on abductor digiti minimi muscle; in other words, the threshold current increased. Subsequent studies confirmed that an increased stimulus was required for eliciting 50% of the maximum response in the abductor pollicis brevis muscle by the stimulation of the median nerve.[30–33] Increased axonal threshold in CIDP could be related to the demyelinating process that decreases the diameters of axons.[32] Subperineural edema could also increase the threshold current.[32]

3.2. Strength–duration property

Increased stimulus duration can decrease the need of the stimulus current to produce a compound action potential of the same amplitude. Rheobase is the minimal current amplitude of infinite duration that can still produce an action potential. Chronaxie, another excitability parameter, is the stimulus duration needed to produce an action potential double the amplitude of rheobase. The strength–duration time constant (SDTC) of the nerve, as shown in Figure 1B, is the excitability property to indicate the increment rate of the threshold current, as the duration of the test stimulus is reduced to zero. The SDTC can be derived from Weiss's law. The law states that the stimulus charge (Q), which is the product of the stimulus current (I) and stimulus duration (t), is also the product of the rheobase current and 1 added to the SDTC. During depolarization, effects of subthreshold current pulses are prolonged, mainly due to the local response of low-threshold persistent Na^+ channels, resulting in a lower rheobase level and a higher SDTC. Hyperpolarization has the opposite effect.[37] A prior study in mice has shown that paranodal demyelination increases the SDTC and capacitance.[38]

In 2000, Cappelen-Smith et al[30] were the first investigators to detect changes in the strength–duration property in CIDP patients. The SDTC was decreased in CIDP patients, whereas their rheobase levels were increased. Those findings were unexpected at first for a demyelinating disease, because demyelination in mice has been

Table 1 Summary of published studies on nerve excitability changes in CIDP

Author (publication year)	Participant number	Initial nerve excitability parameter changes	Post-treatment nerve excitability parameter changes
Meulstee et al (1997)[29]	17	SR: ↑ threshold current	—
Cappelen-Smith et al (2000, 2002)[30,31]	7	SR: ↑ threshold current RC: ↓ superexcitability SD: ↓ SDTC	—
Cappelen-Smith et al (2001)[32]	11	SR: ↑ threshold current, ↓ slope of curve SD: ↓ SDTC RC: ↓ refactoriness, ↓ superexcitability, ↓ subexcitability TE: "fanning out" to hyperpolarizing current	—
Sung et al (2004)[33]	21	SR: ↑ threshold current RC: ↓ refactoriness, ↓ late superexcitability TE: "fanning out" to hyperpolarizing current *I*/*V*: ↑ inward rectification	—
Boerio et al (2010)[34]	10	SD: ↓ SDTC	SD: further ↓ SDTC
Lin et al (2011)[35]	27	SD: ↓ SDTC RC: ↑ superexcitability TE: "fanning out" to hyperpolarizing and depolarizing currents	SR: ↓ threshold current SD: further ↓ SDTC after single injection but ↑ on longitudinal follow-up RC: ↓ subexcitability, ↓ superexcitability TE: "fanning in" to hyperpolarizing and depolarizing currents

I/*V* = current–voltage relationship; RC = recovery cycle; SD = strength–duration properties; SDTC = strength–duration time constant; SR = stimulus–response curve; TE = threshold electrotonus.

found to have increased nodal capacitance and SDTC.[38] Nevertheless, this finding was confirmed by all subsequent studies. An decreased SDTC suggests that the axonal membrane in CIDP might be in a state of hyperpolarization. Another reason for the decreased SDTC is probably the decreased Na^+ channel density in the nodal area in CIDP patients due to destruction of the myelin sheath in CIDP patients. This could expose an area that was previously covered by the paranodal membrane.[32]

3.3. Recovery cycle

Following depolarization, a nerve undergoes a sequence of excitability changes prior to returning to its resting state. The state of excitability changes is known as the recovery cycle (RC), which is assessed by the double stimulation technique of using various conditioning-test intervals to detect changes in the current required to produce a compound action potential of a certain amplitude (Figure 1C). During the RC cycle, the absolute refractory period is followed sequentially by a relative refractory period (RRP), a superexcitable period, and finally a subexcitable period. The absolute refractory period is caused by the inactivation of transient, voltage-dependent Na^+ channel, and the RRP is the result of recovery of the channel. During depolarization of the neuron, Na^+ influx is greater than K^+ efflux, and current from the node charges the internode. Superexcitability following the RRP is the result of a negative after-potential due to the release of the current keeping the node depolarized. Subexcitability is caused by the action of slow K^+ channels activated during depolarization, causing membrane hyperpolarization. Background depolarization increases the RRP and decreases superexcitability. Hyperpolarization causes opposite changes.[36]

Earlier studies have found decreased refractoriness, superexcitability, and subexcitability in the neurons of CIDP patients.[30–33] With a larger sample number than each of the previous studies, Lin and coworkers[35] have observed increased superexcitability in CIDP patients. This increased superexcitability can be explained by axonal hyperpolarization in CIDP patients. Hyperpolarization may be related to the remyelinating process, which causes shortening of the internode and increases the number of Na^+ channels, resulting in a greater Na^+ influx during conduction and heightened neuronal Na^+/K^+ pump activity.[35,39]

3.4. Threshold electrotonus

The threshold electrotonus (TE) technique can be used to record the threshold changes produced by prolonged depolarizing or hyperpolarizing currents. As shown in Figure 1D, changes in the threshold are produced by a subthreshold, long-duration (100–200 milliseconds) polarizing current, and assessed using test pulses, to obtain the predetermined target compound action potential amplitudes (usually 20% and 40% of the maximum amplitude). After the initiation of the depolarizing pulse, an initial fast phase is found to correspond to the applied current (the F phase), followed by a further, but slower, decrease in the threshold current, which is known as the S1 phase. The S1 phase is followed by a S2 phase, in which nerve excitability is decreased. After the depolarizing current pulse is stopped, a slow overshoot phase of increased threshold occurs, and then the threshold gradually recovers to the control level.

After a hyperpolarizing current, the initial sudden increase in the threshold (F phase) is followed by a continuous increase in it. It then finally slows down near the end of the 100 milliseconds of hyperpolarizing current stimulation, and the waveform then turns toward the baseline. Increased threshold changes in either the depolarizing or the hyperpolarizing direction have been referred to as a "fanning-out" pattern due to its resemblance to the outward movement of the ribs of a Japanese fan.[40] This specific pattern is a typical finding in axons with demyelination or increased myelin resistance.[40]

"Fanning out" of TE under a hyperpolarization current has been observed consistently since the incorporation of TE into the standard NET protocol for CIDP patients.[32,33,35] Lin et al[35] have also observed "fanning out" of TE under depolarizing currents. Those findings are compatible with the increased myelin resistance due to demyelination. In their 2004 study, Sung et al[33] observed that an abnormal TE in CIDP was associated with a longer disease duration, more severe disability, and poorer response to immune treatment.

3.5. Current–voltage relationship and slope

The current–threshold plot of Figure 1E shows the threshold changes at the ends of a series of long current pulses of various amplitudes. Customarily, the threshold increment is plotted to the left, whereas the threshold decrement is plotted to the right. Depolarizing current is plotted toward the top and hyperpolarizing current is plotted toward the bottom. This current–threshold relationship reflects the rectifying properties of axons.[41]

Sung et al[33] found a threshold decrement toward the hyperpolarizing current, suggesting that an increased inward rectification exists in CIDP and that it is compatible with hyperpolarization.

3.6. Effects of contraction and ischemia on nerve excitability of CIDP patients

In studying the effect of maximal voluntary contraction and ischemia on nerve excitability of CIDP patients, Cappelen-Smith et al[30] found that after the maximal voluntary contraction, NET can reveal decreased maximal CMAP, increased threshold current to produce 70% CMAP, and decreased SDTC. These findings suggest that in CIDP, muscle contraction can induce hyperpolarization, resulting in a conduction block in the axons.

In a subsequent study, the same group of investigators studied nerve excitability changes in CIDP during and after ischemia. They found that during ischemia, CIDP patients show reduced (by 10%) maximal CMAP amplitude, decreased threshold current, increased SDTC, and decreased superexcitability.[31] These findings suggest that ischemic depolarization may induce a conduction block in CIDP. After ischemia is resolved, the CMAP amplitude attenuates by 19%, threshold current increases, SDTC decreases, and superexcitability decreases. These findings confirm that postischemia hyperpolarization is also associated with the conduction block in CIDP.[31] The nerve excitability experiment results show that both axonal depolarization and hyperpolarization can cause a conduction block in CIDP.[30,31]

3.7. Nerve excitability changes in CIDP after treatment

Currently, two published studies exist on the effect of intravenous immunoglobulin (IVIg) on nerve excitability changes in CIDP.[34,35] After single IVIg injection, the threshold current in the S–R curve decreases. The RC curve shows decreased subexcitability and superexcitability, whereas TE shows a reversal of the previous abnormal "fanning-out" pattern. Overall, these findings suggest that IVIg has a normalizing effect on membrane potential and can improve the axonal excitability of CIDP patients. The improvements have also been found to be sustained in longitudinal recordings.[35]

Of special interest are the changes in the strength–duration properties after IVIg treatment. In both studies, a short course of IVIg was found to further decrease the SDTC significantly.[34,35] A

decreased SDTC reflects a decreased persistent Na^+ current, and the observed change in SDTC is due to either the therapeutic effect of IVIg or the compensatory effect after IVIg administration.[34] Nonetheless, Lin et al[35] observed that, using longitudinal recordings, the SDTC values of CIDP patients were found to have increased, suggesting a longitudinal modulatory effect of IVIg on SDTC.[35]

4. Practical NET application in diagnosis and follow-up of CIDP: a case demonstration

The growing numbers of studies have provided a basis for using NET as a biomarker for supporting the diagnosis of CIDP and documenting the treatment effects on CIDP patients in clinical follow-up. NET can

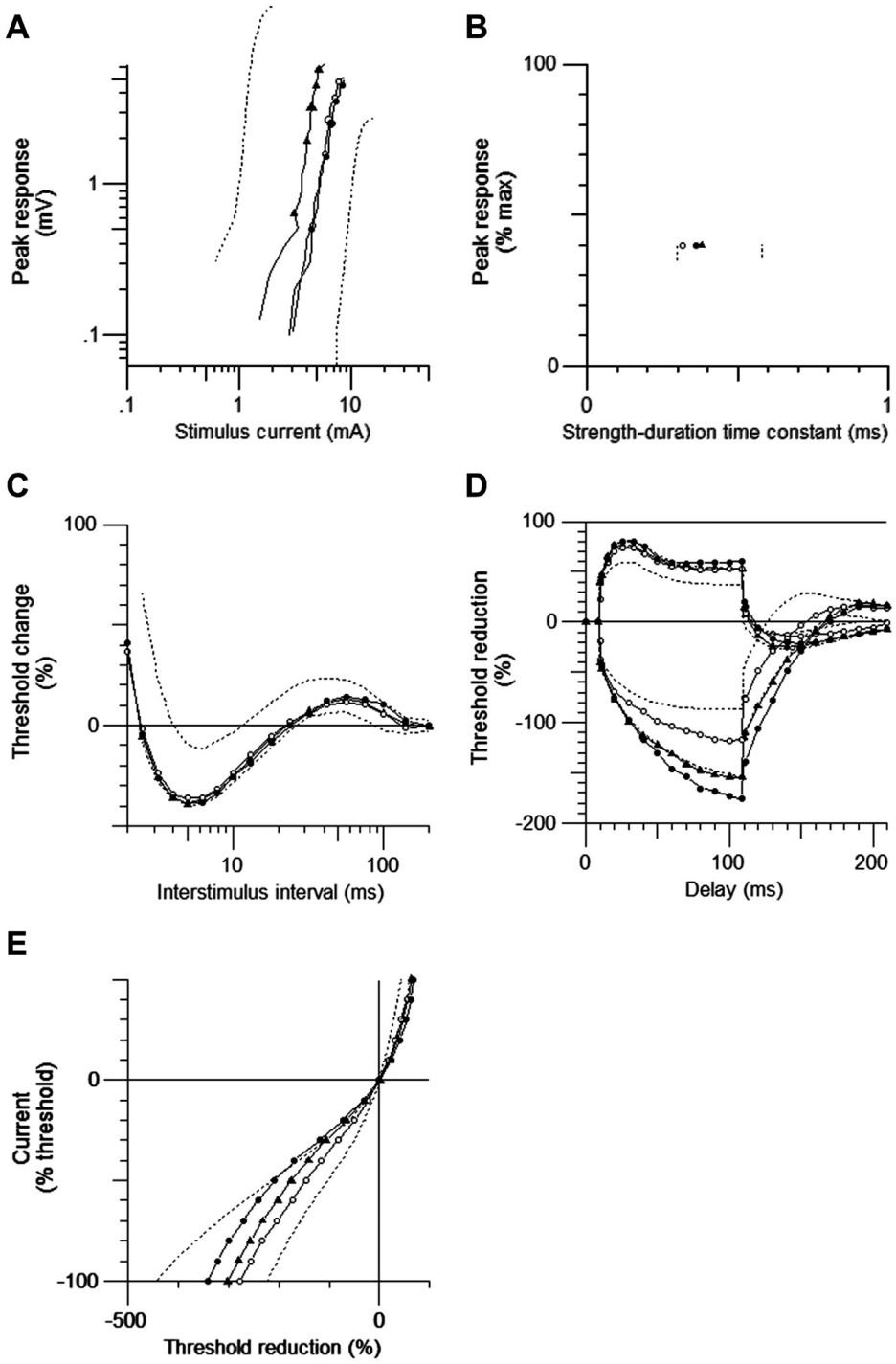

Figure 2 Nerve excitability parameters were recorded from a CIDP patient. Data were recorded prior to treatment (filled circles), 3 months after treatment (open circles), and 1 month after tapering off treatment (triangles). (A) The S–R curve showed increased threshold current initially, which decreased after treatment. (B) SDTC decreased initially, but increased after treatment. (C) Fanning out of TE was noted initially, followed by normalization after treatment. The abnormal excitability pattern was noted again during relapse following the tapering off of treatment. (D) Recovery cycle remained relatively constant throughout the disease course. (E) *I*/*V* relationship showed increased inward rectification initially, but normalized after treatment. Broken lines indicate 95% confidence limit from 84 normal control individuals. This case is selected from a recently completed study on the nerve excitability changes in CIDP (J. Tani, C.I. Chen, and J.Y. Sung, unpublished). CIDP = chronic inflammatory demyelinating polyneuropathy; *I*/*V* = current–voltage; SDTC = strength–duration time constant; S–R = stimulus–response; TE = threshold electrotonus.

potentially identify CIDP patients prior to when they fulfill the diagnostic criteria for CIDP, enabling early institution of specific treatment. Here, we describe a case of acute-onset CIDP in order to illustrate typical nerve excitability changes in CIDP (Figure 2A–E). This case is selected from a recent completed study on the nerve excitability changes in CIDP (J. Tani, C.I. Chen, and J.Y. Sung, unpublished).

A 24-year-old female patient presented herself with the chief complaints of weak left-hand pincer grip between the thumb and index finger and weak thumb and little finger adduction for 1 week. Her medical history was noncontributory, she did not smoke, and she had no history of drug abuse. She also had no family history of any neurological disorders. Results of the routine physical examination were normal, and those of cranial nerve examinations showed no abnormalities. She had Medical Research Council grade IV muscle strength in the left-hand pincer grip and adduction of the thumb and little finger. However, she did not have any muscle atrophy or fasciculation. The tendon reflex of her left knee was decreased, and a sensory examination showed normal results.

The results of complete blood count and biochemical profile were normal. An analysis of her cerebrospinal fluid showed a normal cell count and a protein level of 44 mg/dL. Initial NCS showed decreased amplitude of the left ulnar CMAPs, diffusely prolonged F-latency, sensory distal latency, and decreased conduction velocity in all the sampled nerves, but the EFNS CIDP criteria were not fulfilled yet.

The NET was performed on the median nerve, with stimulation over the left median nerve at the wrist, and CMAPs were recorded from the abductor pollicis brevis, according to previously described protocols.[41] Stimulation and recording were controlled by software (QTRAC version 9; Institute of Neurology, London, UK). The S–R curve showed an increased threshold (Figure 2A), and the SDTC was decreased (Figure 2B). TE showed significant changes, especially in the hyperpolarizing direction (Figure 2C). The "fanning-out" pattern is a typical finding in axons with demyelination or increased myelin resistance.[40] By contrast, the RC showed relatively increased superexcitability with normal subexcitability (Figure 2D). The *I*/*V* relationship showed increased inward rectification, consistent with hyperpolarization (Figure 2E). All the nerve excitability changes suggest axonal hyperpolarization typical of CIDP.

The patient received oral prednisolone 1 mg/kg/day, and the weakness in her left-hand pincer grip and the thumb and little finger adduction improved gradually. The results of NET 3 months later showed that TE returned to the normal range; however, no obvious changes were seen in the RC. Changes in TE suggested an improvement of axonal dysfunction, as the nerve became more excitable (Figure 1C). The results of NCS did not show any change, and the oral corticosteroid was then gradually tapered off and stopped.

Unfortunately, her symptoms progressed again after 1 month following the discontinuation of the steroid treatment. Her NET findings showed an increased threshold toward a hyperpolarizing current, as seen again on TE (Figure 1C), and increased inward rectification on the *I*/*V* relationship (Figure 1E), suggesting a return to pathologic axonal hyperpolarization. Nevertheless, her threshold current decreased (Figure 1A) and SDTC continued to increase (Figure 1B), perhaps suggesting a long-term modulatory effect on axonal excitability by corticosteroid. She continued follow-up clinic visits; during the following 2 years, her symptoms fluctuated, and her clinical and NCS presentations eventually fulfilled the EFNS and modified AAN criteria for CIDP.[8,10] Her TE fluctuated along with her clinical symptoms ("fanning out" has been found to be associated with symptomatic worsening, and normalization with symptomatic improvement), whereas her RC remained relatively constant. In this case, typical NET findings are consistent with CIDP, enabling us to make the diagnosis of CIDP early in the course of the disease, despite the focal presentation.

5. Conclusion

NET can be clinically useful in the diagnosis of CIDP for two reasons. First, being a noninvasive test, it has the potential to provide complementary data to support the diagnosis of CIDP. Second, it may be able to detect electrophysiological abnormalities of peripheral nerves earlier than traditional NCS, leading to an earlier diagnosis of CIDP. An earlier diagnosis of CIDP can enable clinicians to initiate specific treatments such as plasma exchange, intravenous globulin, or corticosteroids earlier, thus preventing potential complications associated with advanced disease, including irreversible axonal degeneration and permanent debilitating weakness.[42]

Among the nerve excitability parameters, a baseline increase of the threshold current in the S–R curve and a decreased SDTC are consistently noted in CIDP. "Fanning out" of TE under a hyperpolarizing current, another characteristic nerve excitability change in CIDP patients, is also correlated to worse clinical profile and outcome. Increased superexcitability and subexcitability also indicate axonal hyperpolarization. These changes are compatible with the diagnosis of CIDP. Moreover, normalization of the threshold current and TE are noted after IVIg treatment.

Stephanova and Bostock[43] have used mathematical models to study nerve membrane properties of peripheral neuropathies. In particular, a double-cable model[43] has been used to study the effects of mild focal demyelination,[44] severe focal demyelination, and systemic demyelination[45] on nerve membrane properties. Those investigators found that for mild focal demyelination, membrane properties did not change significantly. Severe focal demyelination also does not cause any significant changes in TE, and are found to increase superexcitability and subexcitability in the RC. By contrast, systemic demyelination causes significant "fanning out" of TE under both depolarizing and hyperpolarizing conditioning currents, and further increment of superexcitability and increased subexcitability in the RC compared to severe focal demyelination.[45] The findings could explain the variation in results of different NET studies in CIDP patients; it could be that CIDP patients with uniform demyelination of a segment of a nerve, measured by NET, are more likely to demonstrate significant "fanning out" of TE, and increased superexcitability and subexcitability changes in the RC. According to the model, NET shows increased superexcitability and subexcitability changes in patients with severe focal demyelination, but is less likely to detect significant changes in TE. Although available studies have identified characteristic nerve excitability changes in CIDP, clearly more nerve excitability studies using a larger number of patients with early manifestation is necessary to define a more precise role of NET in acute-onset CIDP patients.

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