Movement Disorders
CLINICAL PRACTICE
CLINICAL VIGNETTE

# Neuropathic Tremor in Chronic Inflammatory Demyelinating Polyneuropathy: The Acquired Equivalent of the Roussy-Levy Syndrome

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This 81-year-old woman with a previous history of chronic ischemic heart disease, on treatment with beta-blockers, diuretics, and aspirin, developed slowly progressive weakness and sensory impairment in all four limbs over 5 months at the age of 76 years. Her examination showed proximal-predominant weakness, areflexia, and tactile and proprioceptive impairment affecting all four limbs. Electrophysiology showed a diffuse and severe, primarily demyelinating polyneuropathy with absent sensory responses and F waves, multiple motor conduction blocks, markedly slowed conduction velocities (CVs), and chronodispersion of motor responses after proximal stimulation (see Table 1). Her cerebrospinal fluid (CSF) demonstrated albuminocytologic dissociation (1 cell/mm$^3$–135 mg/dL proteins titer). These findings met stringent criteria for chronic inflammatory demyelinating polyneuropathy (CIDP).[1] She was treated with full-dose prednisone leading to marked clinical improvement over time. She regained most strength and steroid treatment was gradually tapered and eventually discontinued in 2 years. After 3 years, at the age of 79, she had a relapse of ascending tetraparesis, with marked proprioceptive sensory loss and areflexia. She became unable to stand or walk a few steps without assistance. We documented similarly abnormal electrophysiological and CSF findings during this relapse. Brain and spine MRI, total body PET scan, and comprehensive screening for antineuronal, antigangliosides and anti-myelin-associated glycoprotein antibodies were negative; a monoclonal gammopathy was ruled out by electrophoresis and immunofixation on serum and urine.

Treatment with intravenous immunoglobulin (IVIG), used to prevent previously developed steroid-induced diabetes and hypertension, improved her weakness and, to a lesser extent, her areflexia and proprioceptive sensory loss. Though the patient was satisfied with the extent of strength and ambulatory improvements, she became disappointed by the insidious emergence of a disabling tremor within 4 months from initiation of IVIG, reaching a peak in severity at 6 months. This bilateral hand tremor was of similar magnitude at rest, on posture, and on action (see Video 1, Segment 1). The tremor was jerky, fluctuating in severity, frequency, burst duration, and pattern of muscle groups involved, exhibiting an alternating activation of antagonistic forearm muscles. Loading did not significantly modify its frequency, but stabilized the pattern of muscle involvement. Treatment with clonazepam and gabapentin did not yield any benefits. Treatment with intravenous cyclophosphamide at a dose of 1 g/m$^2$ was repeated four times at 3-month intervals because of recurrent urinary infections. This induced a slow, but measurable, improvement of the tremor, sustained over the past 14 months, with no further clinical CIDP relapses. The residual tremor has remained virtually absent at rest, with postural and kinetic components that no longer prevent the patient from feeding and washing herself (see Video 1).

Tremor is a well-known accompanying feature of both inherited and acquired peripheral neuropathies. Among demyelinating inherited neuropathies, a pattern of disabling tremor without major sensory loss is considered a feature of Roussy-Lèvy syndrome (RLS). This syndrome, a dominantly transmitted hereditary ataxia with tremor, was first described in 1926 by Gustave Roussy and Gabrielle Lévy. They reported a disorder characterized by unsteady gait during early childhood with pes cavus and generalized areflexia, distal amyotrophy and weakness, clumsiness, postural tremor with limb ataxia and usually preserved sensation. Molecular genetics later demonstrated RLS to represent a phenotypic variant of Charcot-Marie-Tooth syndrome type IA[2] or, occasionally, type IB.[3] The precise pathophysiology of the tremor and ataxia in this disorder remains insufficiently understood.[2]

Neuropathic tremor (NT) is often defined as "essential tremor (ET)-like." Both are generally postural and kinetic, distal-predominant, and may share similar amplitude and frequency. NT has often been described as more irregular or jerky than

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**TABLE 1** Summary of electroneurographic findings by the time of first investigation

| MCS | | | | | | |
|---|---|---|---|---|---|---|
| Nerve-rec. site<br>stim. site | M-lat. (ms) | M ampl. (mV) | M dur. (ms) | M Shape | CV (m/s) | F Wave |
| R ulnar-ADM | | | | | | |
| Wrist | 13.2 | 6.5 | 16.3 | P | 15.2 | NR |
| Elbow | 23.7 | 4.0 | 41.6 | MP | 34.6 | |
| Axilla | 26.9 | 1.3 | 47.9 | MP | 22.9 | |
| Erb | 37.4 | 1.1 | 62.3 | MP | | |
| L median-ABP | | | | | | |
| Wrist | 11.6 | 8.2 | 12.4 | P | 24.3 | NR |
| Elbow | 19.4 | 3.9 | 15.9 | P | 14.6 | |
| Axilla | 26.2 | 2.1 | 38.7 | MP | 32.1 | |
| Erb | 31.8 | 1.7 | 49.5 | MP | | |
| R peroneal-EDB | | | | | | |
| Ankle | 22.2 | 0.8 | 15.7 | P | 12.0 | NR |
| Fib-head | 45.0 | 0.6 | 18.9 | P | | |
| R peroneal-TA | | | | | | |
| Below Fib-head | 7.9 | 4.1 | 19.3 | P | 33.1 | NR |
| Above Fib-head | 10.9 | 3.9 | 26.5 | P | | |
| L femoral-VM | | | | | | |
| Ing-ligam | 41.3 | 2.9 | 47.4 | MP | — | — |
| L tibial-ABH | | | | | | |
| Ankle | 16.8 | 4.9 | 28.5 | MP | 19.0 | NR |
| Knee | 32.0 | 1.7 | 49.3 | MP | | |
| SCS | | | | | | |
| L & R sural, peroneal, median, ulnar and radial nerves: NR in all tested nerves | | | | | | |

Because of the polyphasic shape of most of the recorded potentials, M amplitude is calculated from maximal negative to maximal positive peak; M duration is calculated from onset of first negative peak to return to baseline of last negative peak.
R, right; L, left; MCS, motor conduction studies; stim, stimulation; M, compound muscle action potential; lat, latency; ampl, amplitude; dur, duration; ADM, abductor digiti minimi; ABP, abductor pollicis brevis; EDB, extensor digitorum brevis; TA, tibialis anterior; fib, fibular; VM, vastus medialis; ABH, abductor hallucis; P, polyphasic; MP, markedly polyphasic; NR, no response; SCS, sensory conduction studies.

ET. Both NT and atypical/severe ET cases may also exhibit a resting tremor, which, unlike our case, may be of lower amplitude than the postural and kinetic components. Moreover, pseudoathetotic/jerky movements and an abduction/adduction tremor pattern in the fingers, as observed in our case, are seldom observed in ET.

The pathophysiology of NT remains poorly understood. Available data suggest no clear relationship between tremor and severity of the accompanying neuropathy as assessed by proprioceptive loss, weakness, or fatigue.[4,5] CVs do not correlate with tremor emergence,[5] although this may influence its severity.[4]

Our case illustrates that severe acquired demyelinating polyneuropathies are capable of inducing a hand tremor reminiscent of RLS and with a severity unrelated to the extent of proprioceptive loss, consistent with previous observations.[4] Alternative mechanisms may be responsible for releasing central oscillatory generators in demyelinating neuropathic disorders. Indeed, experimental evidence strongly suggests a role for cerebellar dysfunction in these patients.[5] Finally, neurofascin immunoglobulin 4 antibodies, absent in our patient, may explain a subset of patients with CIDP and disabling tremor, particularly when the response to IVIG is insufficient.[6]

# Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

A.M.: 1A, 1B, 1C, 2B, 2C, 3A, 3B
M.C.M.: 1C, 2B, 2C, 3B
S.M.: 1C, 2B, 2C, 3B
A.J.E.: 2B, 2C, 3A, 3B

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# Supporting Information

A video accompanying this article is available in the supporting information here.

**Video 1.** Summary of patient's neurological exam; in the first part, the most remarkable finding is a severe and disabling either resting or action/intention tremor in both upper limbs, with atypical superimposed jerky-like and pseudoathetotic movements; the second part shows tremor improvement 2 years later, after treatment with cyclophosphamide.



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