TITLE

Neuropathic tremor in Guillain-Barrè Syndrome

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Word count (Text): 2841 (Abstract): 225

Running title: Neuropathic tremor in Guillain-Barrè Syndrome

Key words: Neuropathic tremor, Guillain-Barrè Syndrome, tremor analysis, dystonic tremor

ABSTRACT

Background: Neuropathic Tremor (NT) is a postural/ kinetic tremor of the upper extremity, often encountered in patients with chronic neuropathies such as paraprotein-associated and hereditary neuropathies.

Objectives: To describe the clinical and electrophysiological features of NT in a previously underrecognized setting- during recovery from Guillain-Barrè Syndrome (GBS).

Methods: Patients with a documented diagnosis of GBS in the past, presenting with tremor were identified from review of clinical records. Participants underwent structured, videotaped neurological examination, and electrophysiological analysis using tri-axial accelerometry-surface electromyography. Tremor severity was assessed using the Fahn-Tolosa-Marin Tremor Rating Scale.

Results: We describe the clinical and electrophysiological features of 5 patients with GBS associated NT. Our cohort had a fine, fast, and slightly jerky postural tremor of frequency ranging from 8-10 Hz. Dystonic posturing and overflow movements were noted in 4/5 patients. Tremor appeared 3 months- 5 years after the onset of GBS, when patients had regained near normal muscle strength and deep tendon jerks were well elicitable. Electrophysiological analysis of tremor strongly suggested the presence of a central oscillator in all patients.

Conclusion: NT is not limited to chronic inflammatory or hereditary neuropathies and may occur in the recovery phase of GBS. The tremor is characterized by a high frequency, jerky postural tremor with dystonic posturing. Electrophysiological evaluation suggests the presence of a central oscillator, hypothetically the cerebellum driven by impaired sensorimotor feedback.

Guillain-Barré syndrome (GBS) is a neurological autoimmune disorder of acute onset, inflammatory, polyradiculoneuropathy. Each year, an estimated 100,000 patients worldwide contract GBS.[1] GBS can range from very mild symptoms with brief weakness to severe devastating paralysis.[2] Tremor is not usually encountered in GBS, except for intention tremor that may be associated with ataxia in specific variants of GBS, such as the Miller-Fischer Syndrome. While it has rarely been reported in the context of GBS, tremor is known to be a manifestation of chronic inflammatory demyelinating neuropathy (CIDP) or paraproteinemic neuropathies.[3,4] Neuropathic tremor (NT) is a movement disorder consisting of postural and/or kinetic tremor affecting the distal upper extremities that occurs in the context of a peripheral neuropathy[5]. NT is more common in demyelinating neuropathies, compared to axonal neuropathies; it usually occurs late in the course of an inflammatory or hereditary demyelinating polyneuropathy. Presence of tremor has no known correlation with the severity of neuropathy.[6] The pathogenesis of NT is not fully known. Electrophysiological studies in NT associated with paraproteinemia or hereditary neuropathies suggest that the tremor is of central origin and the accelerometric tremor peaks do not shift on loading weight. The central tremor originator is postulated to be the cerebellum in inflammatory neuropathies, whereas tests of cerebellar function were normal in patients with hereditary neuropathy and NT. The phenomenology and pathogenesis of tremor in patients with GBS remains unexplored. Here we describe the clinical and electrophysiological features of tremor in five patients with NT after recovery from GBS.

METHODS

This study was conducted at the All India Institute of Medical Sciences, New Delhi, between Mar 2021 to Mar 2022. Patients were identified by a retrospective review of the following sources: out-patient registers of the movement disorder clinic (2016-2022; 2067 patients), neuromuscular disorders clinic (2019-2022; 1311 patients) and an existing tremor video database (2019-2022; 165 patients). We included patients who had a documented diagnosis of GBS at any time in the past and now presented with complaints of limb tremor. We also included patients who were noted to have tremor during follow-up visits, although this was not a presenting complaint of the patient. Potentially eligible participants were contacted over telephone or in person and invited to participate in this study. We collected demographic data, details regarding GBS diagnosis (clinical evaluation, nerve conduction studies (NCS), cerebrospinal fluid examination, if available), course of illness including need for mechanical ventilation, treatment offered and response to treatment from the patient and medical records. We assumed the patient has recovered from GBS if they have no symptoms or only minor ones, and can walk unassisted for 10 meters or more, which corresponds to a GBS disability score of 0-2.[7] Data regarding medications for tremor and response were recorded wherever available. All participants underwent a structured videotaped neurological examination including an assessment of tremor at several positions (rest- arms on the lap fully supported against gravity; posture 1- arms outstretched forwards, elbows extended; posture 2- arms abducted at shoulder, flexed at elbow and fingers pointing towards each other; finger nose testing, writing, and pouring tasks). Tremor severity was assessed using the Fahn Tolosa Marin tremor rating scale (FTM-TRS)[8]. Three raters reviewed the tremor videotapes to characterize the phenomenology of tremor and classify it according to Axis 1 definitions of the 2018 MDS consensus classification of tremor[9]. We performed combined tri-axial accelerometry-

surface electromyography (EMG) tremor analysis in all participants (Biopac, USA). Tremor was recorded at rest, posture 1, posture 2 and after loading the limb with 500g weight in posture 1. Tremor epochs were recorded for 30 seconds in each position with the accelerometer placed on the middle phalanx of the middle finger. EMG was recorded from the wrist flexors and extensors with a sampling rate of 2000Hz and low-pass filter 500Hz, high-pass filter 5Hz. We derived the Peak Frequency (PF), Total Power (TP, between 1-30Hz) and Peak Power (PP) of the accelerometer spectrum using Power Spectral Density transformation individually for the 3 axes and computed the resultant ($\sqrt{(x^2+y^2+z^2)}$). EMG data were smoothened and rectified prior to PSD transformation and visually inspected for peaks corresponding to tremor frequency.

RESULTS

Review of records identified 7 patients with tremor after GBS. Two were lost to follow up and could not be included in this study. Results of the remaining five patients are presented below and summarized in Table 1

Case 1 (NT1):

55-year-old male presented with descending flaccid quadriparesis of 4 days duration. At admission, muscle strength was MRC grade 1/5 in the proximal upper and lower limbs and grade 2/5 distally. Vibration and joint position sense were impaired at both great toes and deep tendon jerks were in-elicitable. NCS revealed an asymmetric motor demyelinating polyneuropathy affecting all four limbs consistent with GBS, Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP) variant. He received 25 g of

Intravenous Immunoglobulin (IVIG) daily for 5 days following which he had gradual improvement in weakness. At 9 months after onset of symptoms, patient reported bilateral upper limb postural tremors. At this time, muscle strength was 5/5 in all 4 limbs and deep tendon reflexes were elicitable. On examination, he had bilateral symmetrical rest, postural and action tremor with dystonic posturing of bilateral fifth digits and overflow movements in the right hand on writing with the left hand (Video 1). He had no bradykinesia, rigidity, or other features suggestive of parkinsonism. There was no family history of tremor or other movement disorders. The FTM-TRS total score was 22. Thyroid function tests were normal. He was offered Propranolol 40mg for tremor to which there was no significant response subjectively.

Case 2 (NT2):

25-year-old-female presented with bilateral upper limb postural tremor for 5 years. She had a history of GBS 10 years back, resulting in severe flaccid quadriparesis requiring mechanical ventilatory support for 3 months. She recovered gradually over the next 2 years and had a residual left foot drop. Details regarding NCS and treatment were not available. Examination revealed asymmetric, jerky, rest, postural and action tremor with subtle finger dystonia. Dystonia was prominent while writing with overflow dystonia (extension of the index finger) in the right hand while writing with the left hand (Video 2). Muscle strength was 5/5 in all 4 limbs (except left foot dorsiflexion 2/5) and deep tendon jerks were elicitable. The FTM-TRS total score was 19. Thyroid function tests revealed subclinical hypothyroidism. There was no family history of tremor or other movement disorders.

Case 3 (NT3):

43-year-male presented with ascending quadriparesis, numbness in the feet and diplopia for 10 days. At admission, muscle strength was 3/5 in the proximal lower limbs and 5/5 in all other muscle groups; left lateral rectus palsy was noted leading to a suspicion of Miler-Fischer variant of GBS. Sensations were intact and bilateral knee and ankle jerks were absent. Other deep tendon jerks were elicited normally. NCS revealed sensorimotor predominantly demyelinating neuropathy consistent with AIDP variant of GBS. CSF studies showed albumino-cytological dissociation. He received IVIG 2g/kg of body weight over 5 days and was discharged with improvement in muscle strength (MRC grade 4/5 in proximal limbs) and diplopia. Six months later, postural tremors in bilateral upper limbs were noted by the treating physician (Video 3). Examination at the time revealed grade 5/5 power in all 4 limbs with intact reflexes and sensations. FTM-TRS total score was 15. There was no progression in tremor at six months and he did not require any medications for the same.

Case 4 (NT4):

22-year-old male presented with tremors of both upper and lower limbs of 1 ½ years duration. He had a documented history of areflexic quadriparesis, diagnosed as GBS and treated with 5 days of IVIg at an outside hospital, 2 years back. Tremors were noted about 3 months after recovery from this illness. Examination revealed slightly asymmetrical bilateral upper limb jerky postural tremor, with occasional rest tremor. Postural tremors

were also noted in bilateral lower limbs. He had dystonic posturing of fingers (extension at the distal interphalangeal joints of digits 2, 3 and 4) while writing with the dominant right hand, and overflow movements on attempting to write with the left hand (Video 4). Muscle strength, sensations and deep tendon reflexes were intact. The FTM-TRS total score was 30. Thyroid function tests were normal. He reported good benefit on tremor with Propranolol 40mg.

Case 5 (NT5):

18-year-old male presented with descending areflexic quadriparesis of 2 days duration. At admission, muscle strength was MRC grade 2/5 in the upper limbs and 1/5 in the lower limbs, symmetrical. NCS revealed pure motor axonal neuropathy consistent with AMAN (acute motor axonal neuropathy). He received 4 cycles of therapeutic plasma exchange and was discharged with improved muscle strength of grade 3-4/5 in all groups (except ankle 1-2/5). Eight months later he presented with bilateral upper limb tremors. At this time, muscle strength was normal (except mild right lower limb distal weakness) and deep tendon jerks were all elicitable. Examination revealed bilateral upper limb, jerky, rest, and postural tremor with dystonic posturing of the fingers on writing (Video 5). Overflow dystonia in the dominant right hand was noted on writing with the left hand. FTM-TRS total score was 30.

Tremor analysis

Results of accelerometric tremor analysis are shown in Table 2 and Figure 1. Representative tremor spectra from tri-axial accelerometer and EMG are shown in Figure 2.

DISCUSSION

We report the phenomenology and electrophysiological features of NT in five patients with GBS. Tremor was seen during the recovery from acute phase of GBS, becoming apparent at 3 months – 5 years after recovery. Tremor was noted in patients with both demyelinating (n=3) and axonal (n=1) variants of GBS. Clinically, the tremor was remarkably similar in all patients being a fast and slightly jerky, postural tremor of frequency ranging from 8-10 Hz. Dystonic posturing and/or overflow dystonia were noted in 4/5 patients. The tremor seemed to appear late in the recovery phase of GBS, when patients had regained near normal muscle strength and deep tendon jerks were well elicitable. Electrophysiological analysis of tremor strongly suggested the presence of a central oscillator in all patients.

Prior studies on NT in GBS are limited to reports of single cases.[6] Coltamai et al reported a patient who developed 8-10Hz postural tremor during recovery from AMAN variant of GBS; tremor was responsive to pregabalin.[10] Rossi et al reported 4 children with GBS, who were noted to have mild intention tremor on recovery; all had ataxia during the acute phase.[11] Patients with CIDP associated with anti-neurofascin-155 antibodies may have an acute onset of illness, with tremor and/or ataxia being a prominent symptom.[12] However, these patients typically respond poorly to treatment and progress to develop

CIDP, unlike our cohort who showed distinct clinical improvement in motor weakness. NT is well described in hereditary neuropathies and chronic inflammatory neuropathies, including CIDP and paraprotein associated neuropathy.[4] Over 50% of patients with these conditions may have NT contributing to their overall disability. The tremor was described as a mild–moderate tremor of mean frequency 6Hz (3.3-10Hz) with a central oscillator, similar to that seen in our patients.[4] Dystonic posturing of the hands was a novel phenomenology seen in our patients, and is previously unreported in NT. The tremor was fine with mild kinetic component in some patients, indicating that the symptom maybe underreported. However, low frequency, high amplitude tremor may also occur after GBS.

The pathophysiology of NT is not well established. Current understanding implicates an abnormal sensorimotor feedback to the cerebellum owing to impaired peripheral conduction, resulting in cerebellar dysfunction and tremor.[13] This hypothesis is supported by abnormal cerebellar activation and modulation of tremor by peripheral nerve stimulation, documented in patients with paraprotein associated neuropathy.[14] Eyeblink classical conditioning and paired associative stimulation, tests of cerebellar learning and spike-time dependent plasticity, were impaired in patients with NT.[15] Indeed, response to paired associative stimulation in NT suggested lack of topographic specificity and an abnormal sensorimotor plasticity- a typical feature electrophysiological feature of dystonia, rather than tremor.[16] Alternate hypotheses regarding the origin of tremor in GBS include an exaggerated physiological reflex tremor, triggered by neuronal regeneration in the recovery phase. However, electrophysiological analysis and the lack of tremor frequency changes with mechanical loading excluded a mechanical-reflex tremor in our

patients and suggested a central origin of the tremor. Although the tremor appears jerky, rising suspicion of a fasciculatory tremor, EMG did not reveal fasciculations in any of the patients; the tremor was clearly rhythmic with well-defined peaks on accelerometry (Figure 1), distinguishable from the dispersed and variable peaks of a fasciculatory tremor. Given the jerky character of the tremor, peripheral myoclonus superimposed on tremor may be considered, akin to hemifacial spasms arising on recovery from seventh cranial neuropathy. However, the jerks were rhythmic and had burst durations >50ms. There was no clinical evidence of direct cerebellar involvement or central demyelination in any of the patients during the acute stage. Co-existence of a tremor condition such as essential tremor or dystonic tremor is a possibility, however all patients were previously healthy and the relatively acute appearance of tremor alongside the history of neuropathy, makes these conditions less likely. Taken together, our results are consistent with a central oscillator generating tremor in these patients, consistent with the prevailing hypothesis of etiology of NT. In addition to expanding the syndrome of NT to the setting of acute inflammatory polyradiculoneuropathies, our series also highlights the presence of dystonia in these patients. This has not been reported previously in NT. One possibility is that dystonia was not formally assessed or underreported in prior studies of NT; on the other hand, whether the relatively rapid resolution of nerve damage in GBS prompts a dystonic phenotype compared to the long-term degeneration in chronic neuropathies merits further study. It is interesting to note that while the neuropathy in GBS is often ascending with severe involvement of the lower limb nerves, tremor and dystonia were prominent in the upper limb. Abnormal sensory processing such as impaired temporal discrimination thresholds are characteristically seen in dystonia; development of dystonia

and tremor in patients with GBS supports the crucial role of peripheral feedback in these disorders.[13] Indeed, follow up studies of patients with GBS have demonstrated that long-term sensory deficits (light touch, vibration, cold perception) may persist, despite minimal disturbance to functional abilities[18,19]. Severe loss of proprioception can result in pseudodystonia- however, sensations including joint position testing were intact in our patients. Additionally, pseudodystonia is often apparent or worse with eyes closed, this was not the case in our patients, in whom dystonia persisted despite visual cues. Subtle sensory impairment and subsequent impaired sensorimotor integration at the cerebellar level is more likely to be the cause of dystonia in GBS associated NT.

There are several interesting questions that remain unanswered. Why only some patients with GBS develop tremor and dystonia is not known. We did not study a comparator cohort of patients with GBS without tremor- it would be important to compare both nerve conduction parameters as well as cortical electrophysiology in age, sex, and severity matched patients to understand risk factors and physiological features that may lead to tremor. Use of surface EMG without needle EMG to assess fasciculations and myoclonus is a limitation of this study. In the absence of objective markers, there is often poor agreement among raters regarding the presence or absence of dystonia.[20,21] We attempted to minimize the diagnostic uncertainty by review of videotapes by three movement disorder expert raters and described dystonia only where a consensus could be reached among the raters. While mirroring and overflow are often used interchangeably in the setting of dystonia, current understanding suggests that these movements in the contralateral limb represent an overflow phenomenon rather than true

mirroring. For the sake of conformity, we have used the term overflow to describe these movements throughout the manuscript. We acknowledge that all mirroring/overflow does not imply dystonia, and therefore patients with only overflow without any overt abnormal posturing at rest/posture/ action of the ipsilateral limb were not considered to have dystonia. Although none of our patients reported a family history of tremor, whether genetic predisposition plays a role needs to be investigated. Comparison of GBS associated NT with other types of NT- such as chronic inflammatory and hereditary neuropathies may provide further insights into the pathophysiology. It would also be interesting to see how tremor characteristics evolve in these patients. Finally, the spectrum of tremor and dystonia in our cohort ranged from mild to moderate- the effect of these symptoms on the patient's disability and quality of life needs to be determined.

CONCLUSION

NT is not limited to chronic inflammatory or hereditary neuropathies and may occur in the recovery phase of GBS. The tremor is characterized by a high frequency, jerky postural tremor with dystonic posturing. Electrophysiological evaluation suggests the presence of a central oscillator rather than a peripheral cause; we assume that the cerebellum driven by impaired sensorimotor feedback might be the cause of the tremor, but this should be confirmed in other studies. Longitudinal follow up studies are warranted in larger cohorts of GBS to probe cerebellar function, cortical plasticity and somatosensory inputs modulating the same.

video is part of ms 16

AUTHOR ROLES

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FUNDING SOURCES AND CONFLICT OF INTEREST

This study was funded by a UCL-AIIMS collaborative grant to Roopa Rajan and Kailash P Bhatia. The authors declare that there are no conflicts of interest relevant to this work.

FINANCIAL DISCLOSURES FOR THE PREVIOUS 12 MONTHS

The authors report that there are no additional disclosures to report.

ETHICAL COMPLIANCE STATEMENT

This study was approved by the Institute Ethics Committee, AIIMS New Delhi (IEC-85/05.02.21, RP-13/2021). Written informed consent was obtained from all participants. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Table 1. Demographic and clinical characteristics of GBS patients with tremor

	Case 1 (NT1)	**Case 2 (NT 2)**	**Case 3 (NT 3)**	**Case 4 (NT 4)**	**Case 5 (NT 5)**
Age (years)	55	25	43	22	18
Gender	M	F	M	M	M
Clinical presentation at time of GBS	Flaccid quadriparesis, Impaired proprioception in LL, generalised areflexia	Flaccid quadriparesis, generalised areflexia, requirement of mechanical ventilation	Flaccid quadriparesis, absent LL reflexes, left LR palsy	Flaccid quadriparesis, generalised areflexia	Flaccid quadriparesis, generalised areflexia
GBS type as per NCS	AIDP	NA	AIDP	AIDP	AMAN
Latency to develop tremor after GBS (in months)	9	60	6	3	8
Muscle strength at recruitment (in MRC scale)	5/5 in all 4 limbs	5/5 in all 4 limbs, except left foot dorsiflexors (2/5)	5/5 in all 4 limbs	5/5 in all 4 limbs	5/5 in all 4 limbs, except right foot dorsiflexors (4/5)

Tremor characteristics	Bilateral symmetrical rest, postural and action tremor of both ULs with dystonic posturing of bilateral fifth digits	Asymmetric, jerky, rest, postural and action tremor of left UL with subtle finger dystonia	Bilateral postural tremor of the ULs	Asymmetrical bilateral jerky postural tremor of ULs with occasional rest tremor. Postural tremors in bilateral LLs. Dystonic posturing of fingers (extension at the distal interphalangeal joints of digits 2, 3 and 4) while writing	Bilateral jerky, rest, and postural tremor of ULs with dystonic posturing of the fingers on writing
FTM -TRS score	22	19	15	30	30

GBS- Guillain-Barrè Syndrome, NT-neuropathic tremor, M-male, F-female, UL-upper limb, LL-lower limb, NCS- nerve conduction study, AIDP-acute inflammatory demyelinating polyradiculoneuropathy, AMAN- acute motor axonal neuropathy, NA-not available, MRC- Medical Research Scale, FTM-TRS- Fahn Tolosa Marin tremor rating scale

Table 2. Tri-axial accelerometry in neuropathic tremor associated with GBS.

ID	Rest, TP (g^2/Hz-Hz)	Rest, PP (g^2/Hz-Hz)	Rest, PF (Hz)	P1, TP (g^2/Hz-Hz)	P1, PP (g^2/Hz-Hz)	P1, PF (Hz)	P2, TP (g^2/Hz-Hz)	P2, PP (g^2/Hz-Hz)	P2, PF	Load, PP (g^2/Hz-Hz)	Load, TP (g^2/Hz-Hz)	Load, PF (Hz)	Frequency change on loading (Hz)
NT1	2.07E-06	1.91E-06	9.4	2.13E-06	1.56799E-06	9.6	1.12E-06	3.30E-07	9.8	2.67E-06	2.13E-06	9.4	-0.2
NT2	1.51E-05	6.53E-07	9.5	2.02E-05	6.09E-06	5.4	4.15E-06	4.31E-06	9.5	2.53E-05	3.32E-05	6.6	1.2
NT3	1.78E-08	6.39E-09	6.9	3.19E-07	4.34E-08	8.4	4.15E-07	1.29E-07	7.6	1.25E-07	3.40E-07	9.0	0.6
NT4	3.33E-07	2.71E-05	6.1	4.00E-03	1.00E-03	8.4	3.20E-02	5.60E-02	9.1	2.63E-02	7.00E-02	8.7	0.3
NT5	3.30E-07	1.05E-07	10.0	1.72E-06	1.02E-06	8.9	2.55E-05	1.04E-05	9.3	1.89E-05	2.83E-05	7.9	-1.0

TP: Total Power, PP: Peak Power, PF: Peak Frequency, P1: posture 1, P2: posture 2.

FIGURE LEGEND

Figure 1. Bar diagram showing Total Power, Peak Power and frequency of tremor from accelerometer spectra at rest, posture 1, posture 2 and load weight. See Table 2 for data.

Figure 2. Representative Power Spectral Density spectra from patient NT4. Accelerometry at rest (A) showing tremor peak at 6.1Hz, Posture 1 (B) with 8.4Hz tremor, Posture 2 (C) with 9.1 Hz tremor and after loading weight at posture 1 (D) showing 8.7Hz tremor. Lowest panel shows corresponding EMG peaks in the wrist extensors at posture 1 (E) and after loading weight (F). Overall features are consistent with a central oscillator.

VIDEO LEGENDS

Video 1: NT 1, video shows bilateral symmetrical rest, postural and action tremor with dystonic posturing of bilateral fifth digits during posture 1, 2 and overflow movements in the right hand while writing with the left hand.

Video 2: NT2, video shows asymmetric, jerky, rest, postural and action tremor with finger dystonia. Note the dystonic posturing while writing with right hand and prominent overflow dystonia in the right hand (extension of first and second digits), while writing with the left hand.

Video 3: NT3, video shows bilateral postural tremors in the upper limbs.

Video 4: NT4, video shows asymmetrical, bilateral upper limb jerky postural tremor, with occasional rest tremor. Note the dystonic posturing of fingers (extension at the distal interphalangeal joints of digits 2, 3 and 4) while writing with the dominant right hand, and overflow movements on attempting to write with the left hand.

Video 5: NT5, video shows bilateral upper limb, jerky, rest, and postural tremor with dystonic posturing of the fingers on writing. Note the prominent overflow dystonia of the dominant right hand when writing with the left hand.