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Genetically confirmed Charcot–Marie–Tooth disease type 2A manifesting with postural tremor: a case report

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Abstract

Background Charcot–Marie–Tooth disease is a spectrum of inherited disorders characterized by both motor and sensory manifestations, which include prominent distal muscle weakness, foot deformities (pes cavus and hammer toes), and sensory deficits. Postural tremor as a manifestation of Charcot–Marie–Tooth is seldom present, except in a variant of Charcot–Marie–Tooth subtype 1 (Roussy–Levy syndrome), and its presence often results in a diagnostic dilemma.

Case presentation We present a 34-year-old Eritrean man who came to our hospital with a complaint of tremors of the hands of 6 months duration. Associated with this, he had difficulty walking and weakness of the distal extremities bilaterally, prominently involving the lower limbs. The patient denied a family history of such illness. Physical examination revealed distal muscle weakness (4+/5 on upper limbs, while 3/5 on lower limbs bilaterally), pes cavus deformity, absent ankle reflexes, and mild vibratory sensory loss. We noted a postural tremor that attenuated when the patient assumed an anatomic position. The tremor was limited to the hands. Nerve conduction study of upper and lower limbs showed moderate to severe motor axonal and demyelinating polyneuropathy (axonal > demyelinating), suggestive of mixed axonal and demyelinating hereditary polyneuropathy. Subsequently, genetic testing revealed copy number changes (heterozygous deletion) on the MPZ and MFN2, while the PMP22 gene showed ambiguous copy number changes (decrease) on exons 2 and 3. Tying the clinical, electrophysiologic, and genetic findings, consideration of Charcot–Marie–Tooth subtype 2A with postural tremor was made. Subsequently, the patient was managed with regular physiotherapy and an anxiolytic resulting in minimal symptom improvement.

Conclusion The present case describes a 34-year-old male patient with Charcot–Marie–Tooth subtype 2A presenting with neuropathic postural tremor, which is a rare presentation of a common hereditary polyneuropathy. This case highlights the fact that tremors can be associated with peripheral neuropathy syndromes, and a high index of suspicion is needed to rightly diagnose our patients.

Keywords Tremor, Hereditary polyneuropathy, CMT, Case report

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Introduction

Peripheral neuropathy is a pervasive term that describes conditions in which there is an affection of muscles and sensory organs as a result of damage to the nerves that supply them (the peripheral nervous system) [1]. Causes can be either acquired or inherited. Among hereditary neuropathies, Charcot–Marie–Tooth disease (CMT) is the most common type. Rather than one disease, CMT is a syndrome of many genetically distinct disorders characterized by both motor and sensory manifestations, which include prominent distal muscle weakness, foot deformities (pes cavus and hammer toes), and sensory deficits. The various subtypes of CMT are classified according to the nerve conduction velocities (NCVs) and predominant pathology (for example, demyelination or axonal degeneration), inheritance pattern (autosomal dominant, recessive, or X-linked), and the specific mutated genes [2]. Type 1 CMT (or CMT1) refers to inherited demyelinating sensorimotor neuropathies, whereas axonal sensory neuropathies are classified as CMT2. Both are inherited in an autosomal dominant fashion, with a few exceptions. There are no medical therapies for any of the CMTs, but physical and occupational therapy can be beneficial, as can bracing (for example, ankle–foot orthotics for foot-drop) and other orthotic devices [3].

A tremor that appears in a patient with peripheral neuropathy is referred to as a neuropathic tremor (NT) [1]. It is rarely a presenting feature in polyneuropathies, and its occurrence results in a diagnostic and therapeutic dilemma. In these cases, the tremor occurs because of exaggeration of the physiological or normal tremor as a result of the weakness [1]. The nerves to the peripheral muscles and sensory organs may be damaged by disease or injury, higher levels of nervous dysfunction, or systemic diseases. NT may be seen in certain areas only, typically the upper limb, or over the whole body [1]. From the CMT variants, Roussy–Levy syndrome (CMT1B), which prominently presents in childhood, is associated with tremors [4, 5].

Case presentation

Patient information

We present a 34-year-old right-handed married male patient from Asmara, Eritrea, who used to work as a goldsmith that was referred to our neurology clinic at Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia, after presenting with a progressive bilateral tremor of the hands of 6 months duration. Associated with this, he had difficulty walking and weakness in the distal extremities bilaterally. The lower limbs were prominently affected. Two weeks before his current presentation, the patient recalled that he was exposed to an expired chemical acid (ammonia solution). His manner of walking had been different for several years, as he was unable to fully lift his forefoot from the ground, with dragging of his toes and difficulty climbing stairs, but this was not a cause for concern as it did not alter his day-to-day activities. The patient had long-standing sniffles, since the age of seven, and at the time, he was diagnosed to have a nasal mass for which unspecified surgery was done, but the symptoms persisted. He had excessive snoring and associated difficulty breathing. Otherwise, the patient had no history of diabetes, hypertension, psychiatric, cardiac, renal, liver diseases, or cancers, and had no known family history of such illness. His father passed away 20 years ago, at age 56 years, and as per the patient's description, it was due to alcohol-related liver disease. His mother is alive and well. He had no history of illicit drug use and denied constitutional symptoms.

Clinical findings

His physical examination revealed a stable-looking young man, with a blood pressure of 110/70, pulse rate of 84, respiratory rate of 16, oxygen saturation of 94%, and a temperature of 36.7. His general medical exam revealed a left nasal polypoid mass and was otherwise unremarkable. The nervous system examination showed a well-groomed, tidy man, with no psychomotor agitation or impairment. The patient was cooperative, and his mood and affect were congruent. He had no active hallucinations or illusions, no flight of ideas or loose association, and no ideations and delusions. Judgment and insight were intact. His Glasgow coma scale (GCS) was 15/15. He scored 30/30 on the Mini-mental State Examination. Cranial nerves were grossly intact. His sensory examination revealed a mildly decreased vibratory sensation; otherwise, he had no sensory level. Sensation to light touch, crude touch, pain, and temperature, across aspects of the dermatome was intact. Proprioception across distal joint areas is intact and Romberg's sign was negative. On motor examination, he had comparable and symmetrical bulk, with no fasciculations. His power examination revealed bilateral foot drop (with high arched foot) but no wrist drops. The tone was normotonic and power across individual muscle groups (each graded out of 5 as per the MRC grading system) in the upper extremities is 5/5 bilaterally in proximal muscles, 4+/5 distal muscles, with no pronator's drift; while in the lower extremities, it is 5/5 bilaterally in proximal muscles and 3/5 distal muscles with pes cavus deformity (depicted in Fig. 1A and B). Muscle stretch reflexes were 2+ in the triceps, biceps, brachioradialis, and patellar areas, while ankle reflex was absent. Plantar response was down-going, and Hoffman's sign was not observed. Coordination, gait, and stance examination elucidated a stomping gait with slight limping. He had difficulty with tandem walking, tiptoeing,

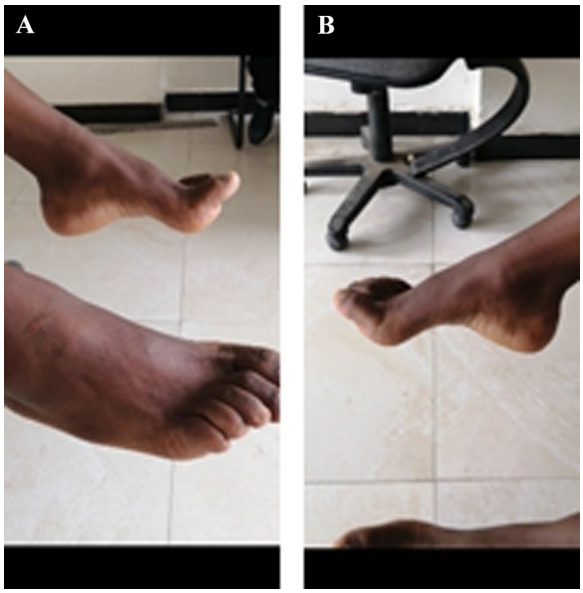

Fig. 1 **A** and **B** Pes cavus deformity (high arched feet), in a 34-year-old patient with hereditary polyneuropathy

and an obvious inability to walk on his heel. Rapid alternating movement, rapid supination and pronation over a surface, and finger tapping were done without difficulty. Finger to nose test was carried out easily. Meningeal signs were negative. Physical assessment of the tremor revealed a symmetrical tremor of 4–6 Hz in the hands with low amplitude noted whenever the patient extended his arms and assumed a certain posture, while the tremor attenuated with a neutral anatomic position. The tremor was limited to his hands. There were no noted bradykinesia or rigidity (cogwheeling or lead-pipe rigidity).

Diagnostic assessment

With this history and physical examination findings, consideration of hereditary motor-sensory polyneuropathy (CMT) was made; workups to confirm the diagnosis and to rule out possible differential diagnoses soon followed. Findings on the basic and metabolic work-ups [complete blood count (CBC) and organ function tests (OFTs), fasting blood sugar (FBS), vitamin B12 level, thyroid stimulating hormone (TSH), and erythrocyte sedimentation rate (ESR)] were unremarkable (Table 1). Testing for syphilis and HIV came back negative.

Imaging studies (from referring site) showed the following results:

- C-spine magnetic resonance imaging (MRI): bulge noted at all cervical disk levels.
- Brain MRI: remarkable for a nasopharyngeal polyp.
- Chest X-ray: unremarkable

Nasopharyngeal polyp biopsy demonstrated granulomatous inflammation (stratified columnar epithelium and goblet lined mucosa lined with intense inflammatory cellular response, few confluent and non-necrotizing

Table 1 Laboratory investigation summary of patient YM (patient's initials), done on 8 September 2021

8 September 21	Laboratory investigations	Results	Laboratory reference range
	WBC	5200	3600–10,200
	Neutrophil (%)	34.5	43.5–73.5
	Lymphocyte (%)	50.8	15.2–43.3
	Hemoglobin	16 g/dl	12.5–16.3 g/dl
	Hematocrit	46.3%	36.7–47.1
	MCV	87.5 fl	73–96.2 fl
	Platelets	315,000	152,000–348,000
	ESR	10 mm/hour	1–15 mm/hour
	UREA	17 mg/dl	7–18 mg/dl
	Creatinine	0.6 mg/dl	0.6–1.3 mg/dl
	Bilirubin (total)	0.4 mg/dl	–
	Bilirubin (direct)	0.06 mg/dl	–
	Albumin	4.2 g/dl	3.5–5.0 g/dl
	VDRL	Negative	Negative
	PICT	Negative	Negative
	TSH	1.357 µIU/ml	0.34–5.6 µIU/ml
	Vitamin B12 level	730 pg/ml	300–1000 pg/ml

dl, deciliter; ESR, erythrocyte sedimentation rate; MCV, mean cell volume; PICT, provider-initiated counseling and testing for HIV; TSH, thyroid stimulating hormone; VDRL, Venereal Disease Research Laboratory; WBC, white blood cell count

epitheloid granuloma) (a timeline of the patient visits provided in Table 2).

Electrodiagnostic study

- Nerve conduction study of upper and lower limbs show moderate-to-severe mixed sensorimotor axonal and demyelinating polyneuropathy (axonal > demyelinating), evidenced by reduced amplitudes and conduction velocities with prolonged distal latencies (Fig. 2A and B), and significantly prolonged F-wave latencies (Fig. 3A and B). A detailed description of the nerve conduction study findings are provided in Tables 3 and 4.

Genetic testing (slightly delayed due to financial issues and unavailability at our hospital).

- The copy number changes (heterozygous deletion) were observed on the MPZ and MFN2 genes and could be associated with CMT1B and CMT2A, respectively. This might be related to the clinical scenario; however, this investigation cannot confirm the relevance of the observed genetic alterations to the etiology. A more thorough investigation of this gene is necessary. The PMP22 gene showed ambiguous copy number changes (decrease) on exons 2 and 3. The other regions investigated also did not show significant copy number changes.

Considering our patient's age, clinical presentation, and electrophysiologic findings, a final diagnosis of CMT2A was made. As a differential diagnosis, an overlap of CMT1B and CMT2A was entertained.

Therapeutic interventions

After the diagnosis was made, genetic counseling was done. The patient was referred for possible rehabilitation and physiotherapy and counseled about possible aggravating factors (concomitant neuropathic conditions and medications). In addition, the patient was started on low-dose propranolol (20 mg PO TID). But, subsequently, the patient opted not to take the medication due to the little improvement obtained and merely continued his physiotherapy follow-up. The patient was later initiated on an anxiolytic (low-dose clonazepam), which better controlled the symptoms.

Follow-up and outcome

The patient continued his follow-up in our hospital for 1 year, until he left for his home country, Eritrea. No further follow-up diagnostic tests were done. He was adherent to his rehabilitation and physiotherapy program. For the postural tremor, low-dose clonazepam was started and better controlled the symptoms.

Discussion and conclusion

In this case report, we presented a 34-year-old male patient with distal extremity weakness and postural tremor, which is a rare combination of symptoms among patients with CMT. In approaching patients

Table 2 Timeline of the patient visits (34-year-old man) to Tikur Anbessa Specialized Hospital (TASH), September 2021–October 2022

List of notable patient visits	Date
Presented to our neurology clinic with a 6 months history of postural tremor and distal muscle weakness. History was taken and a complete neurologic examination was done	8 September 2021
Baseline investigations sent and appointed for a nerve conduction study (NCS)	8 September 2021
A nerve conduction study was done; findings were consistent with an axonal predominant hereditary motor and sensory polyneuropathy	15 September 2021
The need for genetic testing was discussed with the patient (linked to the physiotherapy unit)	16 September 2021
Catered physiotherapy was initiated	20 September 2021
CMT mutation panel collected	4 October 2021
CMT mutation panel results arrived: mutations (heterozygous deletions) were observed on the MPZ and MFN2 genes, which could be associated with CMT1B and CMT2A, respectively. The PMP22 gene has ambiguous copy number changes	30 October 2021
Genetic counseling was done; the risk of off-springs was discussed Initiated on propranolol 20 mg PO TID	1 November 2021
Follow-up visit; propranolol was not tolerated, and the patient had little to no improvement Since primidone is not available in our country, the patient was initiated on clonazepam 0.5 mg PO NOCT, which resulted in modest improvement	3 January 2022
Continued physiotherapy sessions • Orthotics and elbow crunch were provided	September 2021 to October 2022

CMT, Charcot–Marie–Tooth disease; MFN2, mitofusin 2; MPZ, myelin protein zero; NCS, nerve conduction studies; NOCT, night; PMP22, peripheral myelin protein 22; PO, per os; TASH, Tikur Anbessa Specialized Hospital; TID, three times daily

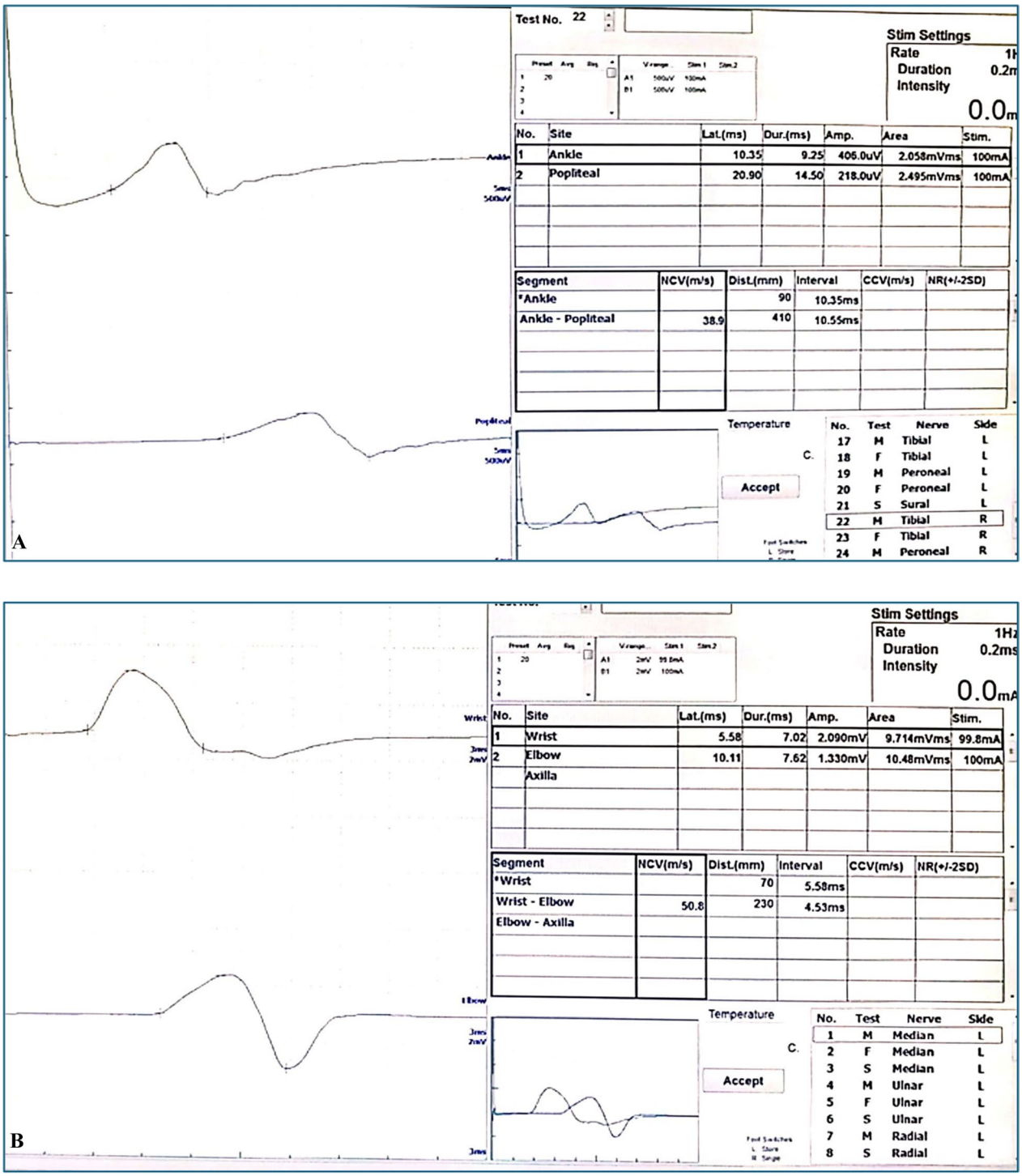

Fig. 2 **A** and **B** Motor nerve conduction study of the tibial and median nerves in a 34-year-old patient with hereditary polyneuropathy, depicting reduced amplitudes and conduction velocities with prolonged latencies

with hereditary neuropathies such as CMT, it is important to entertain key acquired conditions as differential diagnoses. Of these, the most important to recognize in the differential diagnosis of CMT are the immune-mediated neuropathies, particularly chronic immune mediated demyelinating polyneuropathy (CIDP) [6].

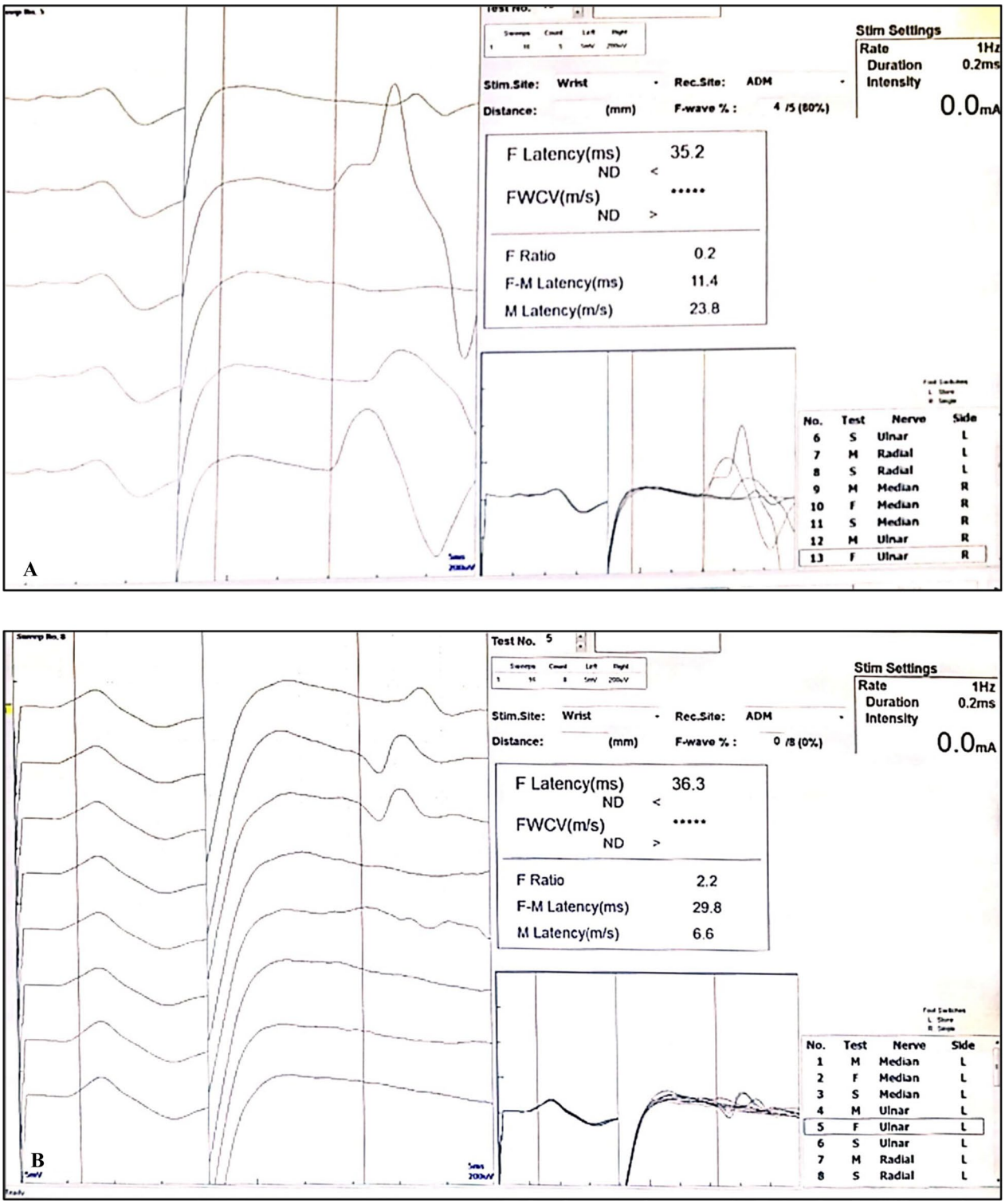

Fig. 3 **A** and **B** F wave study of the bilateral ulnar nerves, depicting significantly prolonged F wave latencies in a 34-year-old patient with hereditary polyneuropathy

Table 3 Motor nerve conduction study of patient YM done 8 September 2021

No.	Nerve	Latency		Amplitude		Duration		Distance	NCV	F Latency
		D(mS)	P(mS)	D(mV)	P(mV)	D(mS)	P(mS)	mm	m/s	mS
1	Median, left	5.58	10.11	2.09	1.33	7.02	7.62	230	50.8	34.9
2	Median, right	5.22	9.54	8.59	7.64	11.28	11.34	210	48.6	28.2
3	Ulnar, left	4.12	8.68	2.09	1.95	9.86	10.82	240	52.9	36.3
		8.68	11.68	1.95	1.82	10.82	5.4	100	33.3	
4	Ulnar, right	8.92	14.76	2.28	1.58	6.32	5.86	240	41.1	35.2
		14.76	18.00	1.58	1.01	5.86	5.76	100	30.9	
5	Peroneal, right	7.4	18.35	3.61	3.23	7.55	7.55	400	36.5	Absent
6	Tibial, right	10.35	20.9	0.406	0.218	9.25	14.5	410	38.9	69
7	Peroneal, left	9.35	20.55	3.66	3.12	12.55	11.85	380	34.5	67.3
8	Tibial, left	6.35	18.4	0.751	0.661	9.5	9.65	410	34.0	61.7

The study reveals a moderate to severe degree of amplitude reduction (axonal feature) and reduced conduction velocity and prolonged distal latency (demyelinating features)

D, distal; mS, millisecond; mm, millimeter; mV, millivolt; m/s, meter per second; NCV, nerve conduction velocity; P, proximal

Table 4 Sensory nerve conduction study of patient YM done 8 September 2021

No.	Nerve	Latency	Amplitude	Distance	Nerve conduction velocity (NCV)
		(mS)	(μV)	(mm)	(m/S)
1	Median, right	3.48	50.2	130	37.4
2	Median, left	2.52	57.0	130	51.6
3	Ulnar, right	2.72	52.8	110	40.4
4	Ulnar, left	2.32	47.9	110	47.4
5	Sural, right	3.50	10.5	140	40.0
6	Sural, left	2.9	24.8	120	41.4

The study reveals a varying degree of reduced conduction velocity and prolonged distal latency (demyelinating features), with preserved amplitude

mS, millisecond; mm, millimeter; mV, millivolt; m/s, meter per second; NCV, nerve conduction velocity; μV, microvolt

CIDP is a disorder of peripheral nerves and nerve roots with a number of variants. Both the cellular and humoral components of the immune system appear to be involved in the pathogenesis of CIDP and its variants. The classic form of CIDP is fairly symmetric, and motor involvement is greater than sensory. Weakness is present in both proximal and distal muscles. Most patients have globally diminished or absent reflexes. The course may be progressive or relapsing–remitting. In some cases, CIDP may mimic CMT [6]. Nerve conduction studies in CIDP typically show nonuniform, nonhomogeneous slowing with partial or complete conduction blocks, with no affection of amplitude. This finding can help differentiate CIDP from CMT, since nerve conduction slowing in the demyelinating forms of CMT is typically diffuse and homogeneous.

In the presence of tremor, another important differential diagnosis to entertain is essential tremor (ET). ET is the most common cause of action tremor, with an estimated prevalence worldwide of 1 percent overall and approximately 5 percent in adults over the age of 60 years [7, 8]. The incidence of ET increases with age, although childhood and early adulthood presentations do occur, especially when ET is familial [9].

Like that of neuropathic tremor, tremor frequency is typically moderate to high (6–12 Hz), although there is considerable variability [3, 10]. The type of tremor in ET may vary from a low-amplitude, high-frequency postural tremor of the hands to a much larger-amplitude tremor that is activated by particular postures and actions. We entertained neuropathic tremor in our patient, as there was an obvious feature of polyneuropathy, which could better explain the clinical presentation.

Furthermore, the genetic analysis of our patient was significant for heterozygous deletions of the MPZ and MFN2 genes; a peculiar symptom in our patient is the late presentation, as few of the reported cases with multiple mutations (concomitant MPZ and MFN2 mutations) depict a more severe and early (childhood) presentation [11].

The tremor in patients with CMT remains a source of diagnostic confusion for clinicians and a potential source of error in further genetic studies [3]. To our knowledge, cases of CMT with such a presentation are rarely reported [2–4], and no cases have been reported in our setting.

A tremor of minimal amplitude is a consistent clinical finding seen in patients with neuropathic tremors (NT). Tremor associated with peripheral neuropathy has the following characteristics: kinetic or postural tremor,

has a frequency of 3–6 Hz occurring primarily in the muscles of the upper limb, that is, the arm and hand; related signs and symptoms include weakness, hypoesthesia, absence of reflexes, impaired gait, and equilibrium with ataxia due to impaired proprioception, and it is associated with impaired conduction velocity within the nerve fibers [1].

Medical treatment of NT has focused on the use of a beta-blocker and an anticonvulsant. However, their use has not met expectations. Other more successful therapies include deep brain stimulation of the nucleus ventralis intermedius of the thalamus, with benefits being reported in the form of a 30–50% reduction in tremor intensity [1].

In our patient, the initial focus on the postural tremor, combined with the ataxia at the referring site, led to the entertainment of a central cause leading to a workup with brain and spinal MRI. After a thorough clinical evaluation (revealing pes cavus deformity, absent ankle reflexes, along with a postural tremor), we were able to entertain a peripheral cause (hereditary polyneuropathy), for which nerve conduction studies and genetic testing were made. Hence, a high index of suspicion is needed to clinch the diagnosis of CMT in patients presenting with postural tremors.

Abbreviations

CMT	Charcot–Marie–Tooth disease
ESR	Erythrocyte sedimentation rate
MCV	Mean cell volume
MFN2	Mitofusin 2
MPZ	Myelin protein zero
NCS	Nerve conduction studies
NT	Neuropathic tremor
PICT	Provider-initiated counseling and testing for HIV
PMP22	Peripheral myelin protein 22
TASH	Tikur Anbessa Specialized Hospital
TID	Three times daily
TSH	Thyroid stimulating hormone
VDRL	Venereal Disease Research Laboratory
WBC	White blood cell count

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13256-024-04945-x.

Supplementary Material 1: Video 1. Video depicts a prominent postural tremor of the hands that abates when patient assumes the neutral position.

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Author contributions
SM, SK, and FT contributed equally in compiling the data and summarizing the case report. EHG and ATH made the final edit and reviewed the report for the intellect. All authors have read and approved the manuscript.

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Availability of data and materials
All data sets on which the conclusions of the case report are based, are to be available as a medical record document and available from the corresponding author on reasonable request from the editors.

Declarations

Ethics approval and consent to participate
The authors' institution does not require ethical approval for the publication of a single case report.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Informed consent
Written informed consent was obtained from the patient and his next of kin for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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