NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

CASE REPORT

Arch Neuropsychiatry 2024;61:184–188
https://doi.org/10.29399/npa.28430

Generalized Peripheric Nerve Hyperexcitability with Neuropathy: Case Series with Long-Term Outcome

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ABSTRACT

Introduction: Peripheric nerve hyperexcitability (PNH) syndromes are a rare, heterogenous group of diseases characterized by continuous muscle overactivity due to spontaneous discharges of the lower motor neurons.

Case Series: Here we report four patients presented with painful cramps, generalized muscle twitches and lower extremity weakness. All patients had evidence of neuropathy and neuromyotonic discharges on electrodiagnostic studies. Screening for a broad panel of anti-neuronal antibodies proved uncharacterized neuropil antibodies in one patient. Despite extensive serologic and genetic investigations, no definitive etiology was found in our cohort. One out of three patients responded well to immunotherapy. No other diseases including malignancy appeared for 1.5–3 years follow-up duration.

Conclusion: Our case series indicate a putatively high prevalence of neuropathy in PNH and emphasize anti-neuronal antibody positivity and early diagnosis as potential favorable prognostic factors.

Keywords: Isaacs syndrome, neuromyotonia, peripheric nerve hyperexcitability

Cite this article as: Akan O, Baysal L, Aksu Uzunhan T, Tüzün E. Generalized Peripheric Nerve Hyperexcitability with Neuropathy: Case Series with Long-Term Outcome. Arch Neuropsychiatry 2024;61:184–188.

INTRODUCTION

Peripheric nerve hyperexcitability (PNH) syndromes are defined as a heterogeneous group of diseases characterized clinically by muscle overactivity associated with the presence of spontaneous fasciculation potentials, myokymic and neuromyotonic discharges on the needle electromyography (EMG). This rare disorder is mostly autoimmune mediated (also referred to as Isaacs syndrome) and responds to immunosuppression and antiepileptic drugs (AEDs) (1–3). Here we report clinical, electrophysiological findings and the long-term prognosis of 4 patients with generalized PNH and their genetic and serological findings.

Highlights

- **Immunomodulatory agents should be a treatment option for Neuromyotonia.**
- **Anti-neuronal antibody positivity may indicate a good prognosis.**
- **Hereditary etiology should be considered in young-onset cases.**

CASE SERIES

All of the patients were diagnosed with generalized PNH on the basis of clinical symptoms and electrophysiological tests. None of them had a family history of a neurological disease (Table 1).

All the patients underwent neurological examination and electrodiagnostic testing including motor and sensory nerve conduction studies (NCS), repetitive nerve stimulation (RNS), F waves, and concentric needle electromyography (EMG) (Figure 1, Table 2). Concentric needle EMG of the upper and lower extremity muscles revealed spontaneous repetitive discharges firing between 30 and 130 Hz in doublets, triplets, and quadruplets in all patients. There were no fibrillation potentials, positive sharp waves, or myotonic discharges. Voluntary motor unit potentials were of normal duration and amplitude. The recruitment of motor unit potentials (MUPs) and the interference pattern during maximum voluntary effort were slightly reduced in the distal muscles of the patients 3 and 4. Afterdischarges following initial compound muscle action potentials (CMAPs) were assessed.

Comprehensive laboratory tests and a detailed screening for malignancy were unremarkable in all four patients. During the patients' follow-up, no other diseases, including malignancy, were discovered. Table 1 summarizes the results of genetic tests.

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Received: 08.02.2023, **Accepted:** 29.04.2023, **Available Online Date:** 06.07.2023

Table 1. Clinical and laboratory features of patients with peripheric nerve hyperexcitability

		Patient 1	Patient 2	Patient 3	Patient 4
Clinical findings	Age (years), Gender	18, F	37, F	54, M	15, M
	Disease duration	1 year	5 months	2 years	1 year
	Past medical history	Unremarkable	Lumber disc operation 3 months ago	Alcohol dependency	Thalassemia minor
	Family history	None	None	None	None. Consanguineous parents (first degree cousins)
	Clinical pattern PNH features Polyneuropathy features Additional symptoms	Face, distal limbs Lower limbs Exercise intolerance	Generalized Lower limbs	Lower limbs Lower limbs Gait impairment	Generalized Lower limbs Gait impairment
	Somatic/autonomic symptoms	None	Hyperhidrosis, Weight loss	Hyperhidrosis, Weight loss	None
	CNS symptoms	None	Insomnia	Insomnia	None
	Neurological examination	Distal upper and lower limb weakness (MRC 4/5), DTR absent in the lower extremities, continuous twitching of the facial and distal extremity muscles	Normal muscle strength, DTR reduced in the lower extremities, fasciculations on lower limbs	Distal lower extremity weakness (MRC 3/5-left predominant), DTR reduced in the lower extremities, fasciculations on lower limbs	Distal prominent tetraparesis (MRC 2/5 distal LE, 3/5 distal UE), DTR absent in upper and lower extremities, generalized twitching of all limbs, bilateral pes cavus and hammer toes
Electrophysiology	Nerve conduction studies	Low and disperse distal CMAPs, after discharges. Sensory NCSs unremarkable.	Bilateral low and disperse tibial CMAPs, after discharges. Sensory NCSs unremarkable.	Bilateral absent tibial motor responses and low amplitudes in the peroneal motor and sural nerves.	Bilateral absent tibial and peroneal motor responses. Low ulnar and median CMAPs, after discharges. Temporal dispersion and motor conduction block. Sensory NCSs unremarkable.
Imaging	Imaging findings*	Negative	Negative	Negative	Hepatosplenomegaly
Laboratory	Laboratory findings	Unremarkable	Unremarkable	Unremarkable	CK level increased to 900 IU/L (normal 1–145 IU/L).
	CSF findings	Normal protein levels with no atypical cells. OCB negative	Normal protein levels with no atypical cells. OCB negative	Mildly elevated protein levels (51.7 mg/dl) with no atypical cells, OCB negative	n. d.
	Serum neuronal autoantibodies	None	Neuropil staining on live hippocampal neurons and immunoreaction with as yet uncharacterized neuronal cell surface antigens.	None	None
	Genetic tests	Unremarkable[1]	n. d.	Unremarkable[2]	Unremarkable [3]
Treatment and Prognosis	Treatment	CBZ (200 mg/d, due to skin rash discontinued), LTG (100 mg/d), GBP (900 mg/d) IVMP (5 days), IVIG (2 gr/kg) Prednisolone (40 mg/d, 6 months)	CBZ (800 mg/d), PGB (300 mg/d), IVIG (2 gr/kg), IVMP (7 days), Prednisolone (40 mg/d, 6 months)	GBP (1200 mg/d)	IVIG (2 gr/kg in 5 days, 0.4 gr/kg every 3 months for 6 months)
	Treatment response	Mild-moderate response	Good response	Mild response	Mild response
	Follow-up duration	2.5 years, mild-moderate improvement of symptoms	3 years, complete remission of symptoms	2.5 years, mild decline of gait disturbance	1.5 years, mild improvement

CBZ: Carbamazepine; CMAP: Compound muscle action potentials; CNS: Central nervous system; CSF: Cerebrospinal fluid; DML: Distal motor latency; DTR: Deep Tendon Reflexes; GBP: Gabapentin; F: Female; IVIG: intravenous immunoglobulin; IVMP: Intravenous methylprednisolone; LE: Lower extremity; LTG: Lamotrigine; M: Male; MRC: Medical Research Council; NCS: Nerve conduction studies, n. d.: Not done, NR: Nonresponsive; OCB: Oligoclonal bant; PBG: Pregabalin; PNH: Peripheric nerve hyperexcitability; UE: Upper extremity.

* Including cranial and spinal magnetic resonance imaging (MRI), computerized tomography (CT) scans of the chest and abdomen, mammography in female patients, pelvic ultrasonography (USG) and positron emission tomography (PET) of the whole body.

[1] Including molecular testing of PMP22 duplication and deletion and whole exome sequencing

[2] Including molecular testing of PMP22 duplication and deletion

[3] Including molecular testing of PMP22 duplication and deletion, histidine triad nucleotide binding protein 1 (HINT1), and whole exome sequencing

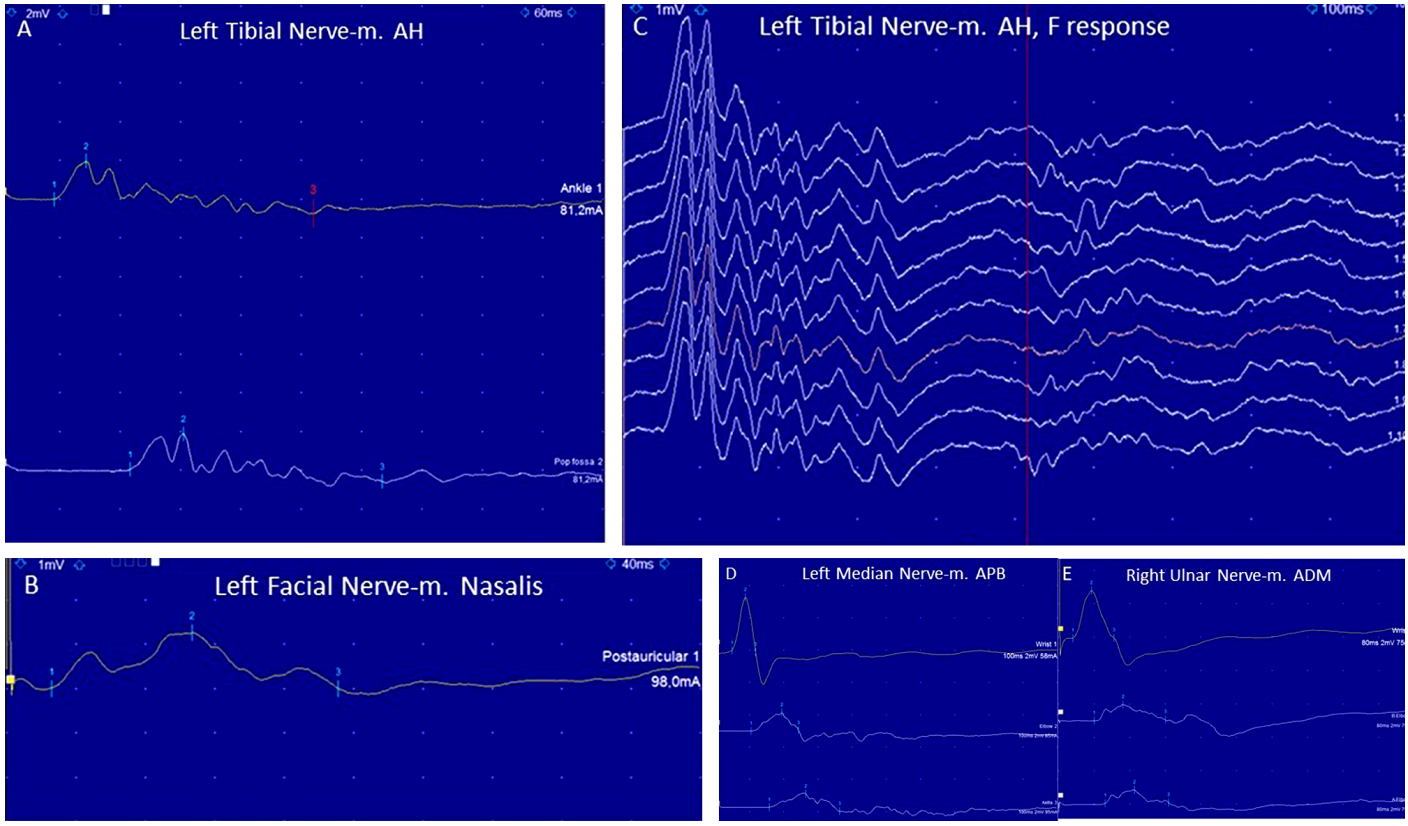

Figure 1. a–e. Nerve conduction studies demonstrated increased temporal dispersion and reduced amplitude of the compound muscle action in the posterior tibial and facial nerve in patient 1 **(a, b)**. Following supramaximal electric stimulation of the posterior tibial nerve, the F-wave study of the tibial nerve shows prolonged posterior discharges **(c)**. Nerve conduction studies demonstrated partial conduction block and increased temporal dispersion in the left median nerve and right ulnar nerve of patient 4 **(d, e).** (**ADM:** Abductor digiti minimi; **AH:** Abductor Hallucis; **APB:** Abductor pollicis brevis; **m:** Musculus).

Prior to immunotherapy, we screened sera to determine the serological background of the illness using immunofluorescence assay (IFA) and immunoblotting tests for paraneoplastic antibodies (anti-Hu, Yo, Ri, Ma2, CV2, Amphiphysin), cell-based assay for N-methyl-D-aspartate receptor, Contactin associated protein 2 (CASPR2), leucine-rich glioma inactivated 1 (LGI1), GABAB-receptor, AMPA-receptor antibodies, radioimmunoassay for anti-acetlycholine receptor and ELISA for anti-glutamic acid decarboxylase antibody tests. Furthermore, antibodies to neuronal surface antigens were detected by using cultured hippocampal neurons of P1 rat pups, as described elsewhere (2). Investigations for well-characterized anti-neuronal antibodies proved negative for all patients except patient 2.

Patient 1

A 18-year-old woman, presented with continuous twitching of bilateral periorbital, perioral and perinasal muscles of 1-year duration. In addition, she was experiencing lower extremity weakness, exercise intolerance, painful muscle cramps in the legs and twitching of distal muscles. Neurological examination showed involuntary continuous twitching of the of the muscles around the mouth, eyes, nose, chin, hands and feet (online resource 2; video 1–4). Immunotherapy and AEDs provided a mild improvement in her symptoms. The patient refused plasma exchange therapy.

Patient 2

A 37-year-old woman, presented with a 5-month history of painful cramps, fasciculations and paresthesia in the lower limbs, generalized muscle twitches and stiffness, hyperhidrosis, weight loss and insomnia. On neurological examination, she had prominent fasciculations on her lower extremities. Serum IgGs of patient 2 showed neuropil staining on live hippocampal neurons. Immunotherapy and AEDs provided a marked improvement in her symptoms. Three years later the clinical picture remained stable after discontinuing prednisolone and antiepileptic drugs. Electrodiagnosis in the follow-up revealed normal motor and sensory responses with chronic neurogenic changes in bilateral S1 innervated muscles.

Patient 3

A 54-year-old male presented with weakness in his lower extremities, progressive difficulty in walking, painful cramps, hyperhidrosis, weight loss and insomnia for the last 2 years. Neurological examination revealed bilateral distal lower extremity weakness, more prominent on the left side and fasciculations in bilateral gastrocnemius and hamstring muscles. Treatment with gabapentin provided a moderate improvement in cramps. The patient refused immunotherapy. After 2.5 years gait disturbance worsened.

Patient 4

A 15-year-old male born from consanguineous parents developed gait impairment, frequent cramps and generalized twitching in the extremities for the last 1 year. Neurological examination revealed steppage gait with bilateral pes cavus and hammer toes and distal prominent tetraparesis. Immunotherapy with intravenous immunoglobulin (IVIG) provided mild improvement in his symptoms after a 1.5 year follow-up.

DISCUSSION

Clinical and electrophysiological manifestations of PNH with neuropathy may be observed in patients with voltage-gated potassium channel (VGKC)-complex-antibodies and histidine triad nucleotide binding

Table 2. Summary of nerve conduction studies

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)/Gender	18, F	37, F	54, M	15, M
Motor NCS				
Median nerve				
Distal latency (ms)	2.4	2.8	2.9	4.1
Amplitude (mV)				
Wrist-APB	**3.9**	8.3	10.7	**4**
Elbow	**3.2**	7.1	9.7	**1.0**
CV (m/s)	75	66.7	54	**42**
Ulnar nerve				
Distal motor latency (ms)	2.3	2.4	2.2	**4.3**
Amplitude (mV)				
Wrist-ADM	6	8.6	11.4	**2.7**
Below elbow	5.2	8.3	11.4	**0.8**
Above elbow	**4.4**	8.4	11.2	**0.5**
CV (m/s)				
Below elbow	**49**	68.9	54	**44**
Above elbow	**40**	75.9	60	**24**
Tibial nerve				
Distal motor latency (ms)	5.4	5.5	**NR**	**NR**
Amplitude (mV)				
Ankle-AHB	**2**	**0.9**	**NR**	**NR**
Popliteal fossa	**1.9**	**0.8**	**NR**	**NR**
CV (m/s)	52	43.7	**NR**	**NR**
Peroneal nerve				
Distal motor latency (ms)	3.2	3.1	6.1	**NR**
Amplitude (mV)				
Ankle-EDB	**1.9**	3.2	**0.7**	**NR**
Below knee	**1.6**	2.6	**0.5**	**NR**
Above knee	**1.6**	2.5	**0.4**	**NR**
CV (m/s)				
Below knee	40	47	**38**	**NR**
Above knee	39	52.6	41	**NR**
Sensory NCS (antidromic stimulation)*				
Median nerve				
Amplitude (μV)	31.9	47.8	11.5	19.6
CV (m/s)	79	59.1	53	51
Ulnar nerve				
Amplitude (μV)	33	45	11.7	11.1
CV (m/s)	67	59.5	51	47
Sural nerve				
Amplitude (μV)	31.5	16.4	**4**	20.7
CV (m/s)	56	62.2	58	55

ADM: Abductor digiti minimi; AHB: Abductor hallucis brevis; APB: Abductor pollicis brevis, CV: Conduction velocity; EDB: Extensor digitorum brevis; F: Female; M: Male; NR: Nonresponsive.
Abnormal values are marked with bold.
* Ringed electrodes are used to test the sensory nerves in the fingers. The sensory nerve action potentials amplitude is measured from baseline to negative peak. Median sensory studies are recorded from middle finger, stimulation site is middle of the wrist, distal distance: 14 cm. Ulnar sensory studies are recorded from little finger, stimulation site is medial wrist, distal distance: 11 cm. Sural sensory nerve is recorded from posterior to the lateral malleolus, stimulation site: posterior lateral calf, distance: 14 cm.

protein 1 (HINT1) gene mutations (4,5). Despite extensive serologic and genetic investigations, no definitive etiology was found in our cohort. VGKC-complex-antibodies are found in around half of PNH patients and lead to loss of function of the complex and hyperexcitability of the motor nerve. Although the clinical features of Case 1 were similar to Isaac syndrome, they resembled Morvan syndrome despite the absence of other typical features such as insomnia symptoms, lethargy, or hallucinations exhibited in Cases 2 and 3 (3). However, antibodies against the VGKC-complex were not detected in our patients. A patient with normal muscle strength showed antibodies against neuronal surface antigens and a permanent response to immunotherapy, indicating putative autoimmunity to uncharacterized neuronal antigens. Chronic alcohol use may have contributed to the neuropathy findings of Case 3.

Although clinical features of our patients (particularly Case 4) were compatible with hereditary neuropathy with PNH, our genetic screening failed to show mutations of genes associated with PNH (KCNA1, KCNQ2) or hereditary axonal motor neuropathy with PNH (HINT1) (4,5). Whole exome sequencing did not reveal any abnormality in two patients with young onset, suggesting an acquired etiology or involvement of non-exomic factors. Nevertheless, hereditary etiology should be considered in young-onset cases with associated polyneuropathy and genetic investigation should include non-exomic gene variants.

Nerve conduction studies of the patients were compatible with pure motor neuropathy with abnormal temporal dispersion and sensory-motor axonal polyneuropathy. In patient 4, motor conduction blocks were observed with the proximal stimulations of the upper extremities. In three patients, prolonged posterior discharges defined as recurrent late potentials following M waves and as a sign of PNH were observed (6). Neuromyotonic discharges have been reported in inflammatory demyelinating neuropathies (7,8). Multifocal demyelination may cause distal conduction block in some motor axons and this may facilitate ectopic impulse generation and ephaptic transmission between adjacent demyelinated nerve fibers distal to the site of conduction block site, resulting in sustained motor unit activity (8).

Distinguishing features of our treatment-responsive patient were the presence of neuronal-surface antibodies and a relatively milder disease course. This case series highlights the importance of early recognition of the clinical phenotype and administration of immunosuppressive agents or plasma exchange in patients with idiopathic PNH and neuropathy. In brief, our case series indicates the high prevalence of neuropathy in PNH and highlights anti-neuronal antibody positivity and early diagnosis as potential favorable prognostic factors.

Acknowledgments: We would like to thank the patients who participated in this study.

Informed Consent: Written informed consent was obtained from the patients for the publication of this case report.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- OA, LB, ET; Design- OA, LB, TAU, ET; Supervision- OA, LB, TAU, ET; Resource- OA, LB, TAU, ET; Materials- ET; Data Collection and/or Processing- OA, LB, TAU, ET; Analysis and/or Interpretation- OA, LB, TAU, ET; Literature Search- LB, ET; Writing- LB, ET; Critical Reviews- LB, ET.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: None.

REFERENCES

1. Sawlani K, Katirji B. Peripheral nerve hyperexcitability syndromes. Continuum (Minneapolis, Minn.)23(5, Peripheral Nerve and Motor Neuron Disorders) 2017;1437–1450. [Crossref]
2. Irani SR, Alexander S, Waters P, Kleopa KA, Pettingill P, Zuliani L, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain. 2010;133;2734–2748. [Crossref]
3. Dalakas MC. Autoimmune neurological disorders with IgG4 Antibodies: a distinct disease spectrum with unique IgG4 functions responding to Anti-B cell therapies. Neurotherapeutics. 2022;9;741–752. [Crossref]
4. Peeters K, Chamova T, Tournev I, Jordanova A. Axonal neuropathy with neuromyotonia: there is a HINT. Brain. 2017;140;868–877. [Crossref]
5. Zimoń M, Baets J, Almeida-Souza L, De Vriendt E, Nikodinovic J, Parman Y, et al. Loss-of-function mutations in HINT1 cause axonal neuropathy with neuromyotonia. Nat Genet. 2012;44;1080–1083. [Crossref]
6. Harrison, TB, Benatar M. Accuracy of repetitive nerve stimulation for diagnosis of the cramp-fasciculation syndrome. Muscle Nerve. 2007;35;776–780. [Crossref]
7. Odabasi Z, Joy JL, Claussen GC, Herrera GA, Oh SJ. Isaacs' syndrome associated with chronic inflammatory demyelinating polyneuropathy. Muscle Nerve. 1996;19;210–215. [Crossref]
8. Meriggioli MN, Sanders DB. Conduction block and continuous motor unit activity in chronic acquired demyelinating polyneuropathy. Muscle Nerve 1999;22:532–537. [Crossref]