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Original Research Paper

General Medicine

A CASE REPORT OF HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES

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ABSTRACT Hereditary neuropathy with liability to pressure palsy is an autosomal dominant demyelinating disorder. In individuals with numerous compressive neuropathies, hereditary neuropathy with liability to pressure palsies (HNPP) should be taken into consideration.Here We present a case of 49-year-old man who exhibited right upper and lower extremity weakness with tingling and numbness of right upper limb and lower limb. Electrophysiological studies showed widespread, multifocal, motor > sensory, chronic peripheral neuropathy affecting the upper and lower limbs.Type: demyelinating >> axonal.Genetic studies showed Heterozygous deletion of PMP22 gene (upstream, exons 1-5) along with flanking regions encompassing TEKT3 and COX10 genes were detected.Treatment for this usually self-limiting illness is debatable, in this instance, patient was managed conservatively following which there is an improvement in patient condition.

KEYWORDS :

INTRODUCTION

Hereditary neuropathy with liability to pressure palsy (HNPP), is demyelinating neuropathy which is recurrent and episodic.Because the chromosome with the deleted PMP22 gene is inherited, people with HNPP only have one copy of the PMP-22 gene[1].HNPP is inherited in an autosomal dominant manner [2]and it is similar to Charcot–Marie–Tooth1A. A 1.5-Mb duplication on chromosome 17p11.2 causes CMT1A, a subtype of CMT (Charcot-Marie-Tooth)[3]. Although various mono neuropathies can arise, they frequently do so at common compression or entrapment sites[4]. The prevalence of HNPP is unknown; it is estimated at 7:100,000-16:100,000 population. The actual prevalence may be higher because of under-diagnosis.[5]Patients typically present in their second or third decade of life with painless numbness and weakening in the distribution of single peripheral nerves [6]. These problems begin after modest compression or trauma or without a discernible initiating reason, and they resolve on their own over the course of a few days to a few weeks [7] . Because Tomacula, which stands for localised thickening of the myelin sheath, it is also known as tomaculous neuropathy and it frequently appears in both sensory and motor nerves in HNPP[8].It has been demonstrated that some drugs, including vincristine, make the neuropathy in CMT and HNPP worse [9],[10] .The diagnosis of HNPP is established in a patients with suggestive clinical findings and electro physiologic studies and either the 1.5-Mb deletion involving PMP22 (in 80%), or a PMP22 sequence variant (in 20%) identified by molecular genetic testing.[11]

CASE REPORT

A 49-year-old male with history of relapsing-remitting weakness of random limbs was admitted to MGM kamothe in July 2022 with complaints of weakness of right lower limb for more than 6 months, weakness of right upper limb over 15 days.

At age of 10 years, the patient developed left upper limb weakness for which he was treated conservatively with physiotherapy in Lucknow following which symptoms slowly started improving, after that in 1993 patient developed right lower limb weakness without any apparent cause which later improved after 2-3 months. In 2019 patient again developed left upper limb weakness which also later improved after 3-4 months. The patient has occasional tingling and numbness of the right upper limb and lower limb for 2 years along with weakness of the right lower limb for 6 months and right upper limb for 15 days. Patient is also a known case of type 2 diabetes mellitus for past 3 years.

On neurological examination, the patient is found to be having power (1/5) in his right shoulder and elbow muscle groups of the right upper limb and lower limb muscle groups were normal (5/5). Tendon reflexes were normal in all extremities. There are decreased sensations over the right wrist. There is no dysdiadochokinesia, finger-to-nose test and the heel-knee-shin test was normal.

Family history reveals that the patient's father has a history of weakness in the right upper limb which resolved completely. Patient's daughter has tingling in her hands and legs easily but never had any episodes of weakness.

In laboratory investigations, complete blood counts, liver function tests, and renal function tests are normal.

Nerve Biopsy was not done as patient has given negative consent Nerve Conduction study of the daughter was done which showed evidence of a widespread, multifocal, motor> sensory, demyelinating peripheral neuropathy affecting the upper and lower limbs

Nerve Conduction Study and Needle EMG showed following Findings

Sensory nerve conduction velocities

Motor nerve conduction

Nerve Conduction Studies is suggestive of widespread, multifocal, motor > sensory, chronic peripheral neuropathy affecting the upper and lower limbs of demyelinating >> axonal type.

To differentiate between an acquired vs inherited cause of multifocal demyelinating peripheral neuropathy, nerve conduction study of his daughter (asymptomatic) was done which showed evidence of a widespread, multifocal, motor >

sensory, demyelinating peripheral neuropathy affecting the upper and lower limbs (asymptomatic).

SNC

Nerve / Sites	Rec. Site	Onset Lat ms	Amp.2-3 µV	Dist. cm	Vel. m/s	COMMENTS
R Median - Digit II (Orthodromic)						
Index Finger	Wrist	3.70	2.4	14	37.9	Low amplitude and slowed
L Median - Digit II (Orthodromic)						
Index Finger	Wrist	3.96	4.3	13.5	34.1	
R Ulnar - Digit V (Orthodromic)						
Little Finger	Wrist	NR	NR			No Response
L Ulnar - Digit V (Orthodromic)						
Little Finger	Wrist	3.49	6.5	10.5	30.1	Low amplitude and slowed
L Sural - Ankle (Calf)						
Calf	Ankle	NR	NR	12		
R Sural - Ankle (Calf)						No Response
Calf	Ankle	NR	NR	12	NR	
R Superficial peroneal - (Ankle-calf)						
Lower leg	Ankle	NR	NR	12	NR	

SNC

Nerve / Sites	Rec. Site	Onset Lat ms	Amp.2-3 µV	Dist. cm	Vel. m/s	COMMENTS
R Median - Digit II (Orthodromic) repeat						
Index Finger	Wrist	3.80	3.1	13	34.2	Low amplitude and slowed
R Ulnar - Digit V (Orthodromic) repeat						
Little Finger	Wrist	NR	NR			No Response
R Median - Digit I (Orthodromic)						
Thumb	Wrist	4.43	3.2	11	24.8	Low amplitude and slowed
L Median - Digit I (Orthodromic)						
Thumb	Wrist	4.17	6.5	11.5	27.6	
R Radial - Superficial Branch						
Forearm	Base of Thumb	3.59	5.1	12	33.4	Low amplitude and slowed
L Radial - Superficial Branch						
Forearm	Base of Thumb	2.86	16.2	12	41.9	Mildly attenuated + slowed
R Lateral antebrachial cutaneous						
Cubital Fossa	Lateral Forearm	3.54	4.8	12	33.9	Low amplitude and slowed
L Lateral antebrachial cutaneous						
Cubital Fossa	Lateral Forearm	2.66	16.6	12	45.2	Normal amplitude but slowed

Electrodiagnostic findings showed large motor unit potential, polyphasic with reduced interference in most of the sample muscle fibres which is consistent with Hereditary Neuropathy with liability to Pressure Palsies.

MNC

Nerve / Sites	Rec. Site	Latency ms	Amp.3-4 mV	Amp.1-2 mV	Area %	Dur. ms	S.Dur. %	Dist. cm	Vel. m/s	COMMENTS
R Median - APB										
Wrist	APB	4.84	11.7	8.1	100	5.89	100	7		
Elbow		10.00	11.3	7.1	95.2	5.89	100	23	44.6	TL:Prolonged CMAP: Normal MNCV: slowed
Arm		12.34	10.7	6.8	102	6.04	103	11	46.9	
L Median - APB										
Wrist	APB	5.89	7.4	5.0	100	4.69	100	7		
Elbow		11.15	6.6	4.4	93.6	5.10	109	24	45.6	
Arm		13.75	6.6	4.2	90	6.04	118	11	42.2	
R Ulnar - ADM										
Wrist	ADM	4.43	12.5	8.0	100	5.10	100	7		
Below ME		9.74	11.4	6.9	93.8	5.36	105	23	43.3	TL:Prolonged CMAP: Normal MNCV: slowed across elbow > forearm.
ME		10.63	11.3	6.8	96.1	5.57	104	26	41.9	
Above ME		13.44	10.5	6.2	94.9	5.99	107	11	29.7	
Supraclav fossa		20.00	7.8	5.0	96.2	6.20	103			
L Ulnar - ADM										
Wrist	ADM	4.27	12.9	8.6	100	5.26	100	7		
Below ME		9.11	12.2	8.0	85.1	5.68	108	23	47.5	TL: Prolonged CMAP: Normal MNCV: slowed across elbow > forearm
ME		10.21	11.7	7.7	99	5.83	103	26	43.6	
Above ME		12.86	10.8	7.0	80.2	6.25	107	12	32.0	
R Axillary - Deltoid										
Supraclav fossa	Deltoid	4.22	15.2	6.6	100	12.03	100			Normal
R Musculocutaneous - Biceps										
Supraclav fossa	Biceps	4.69	15.7	11.0	100	8.39	100			
R Median - FCR										
Elbow	FCR	2.66	16.8	10.0	100	9.32	100			Normal
Above elbow		4.58	16.6	8.2	90.8	10.16	109	11	57.1	
R Peroneal - EDB										
Ankle	EDB	4.38	0.4	0.2	100	11.51	100	8		CMAP: severely attenuated MNCV: slowed
Fib head		15.83	0.2	0.2	65.3	12.55	109	34	29.7	
L Peroneal - EDB										
Ankle	EDB	NR	NR	NR	NR	NR	NR	8		Normal
R Peroneal - Tib Ant										
Fib Head	Tib Ant	2.66	12.8	6.4	100	12.29	100			
Above fib head		5.42	12.0	5.8	98.9	12.03	97.8	10	36.5	CMAP: Normal MNCV: mildly slowed
L Peroneal - Tib Ant										
Fib Head	Tib Ant	3.70	14.7	7.4	100	13.23	100			
Above fib head		6.41	14.0	6.9	92.5	13.49	102	10	36.9	
L Tibial - AH										
Ankle	AH	5.05	6.3	3.8	100	7.97	100	8		CMAP: Mildly attenuated MNCV: slowed
Pop fossa		15.63	4.1	2.5	72	10.21	128	37	35.0	
R Tibial - AH										
Ankle	AH	5.00	9.4	6.9	100	6.77	100	8		CMAP: Normal MNCV: mildly slowed
Pop fossa		15.16	6.8	4.8	75.6	7.76	115	39	38.4	
L Tibial - Gastroc										
Pop Fossa	Gastroc	3.80	13.1	9.8	100	11.25	100			Normal
R Tibial - Gastroc										
Pop Fossa	Gastroc	4.32	24.2	16.5	100	11.09	100			

TL:Terminal Latency, CMAP: Compound Motor Action Potential, MNCV: Motor Nerve Conduction Velocity

Genetic Studies Showed

Heterozygous deletion of PMP22 gene (upstream, exons 1-5) along with flanking regions encompassing TEKT3 and COX10 genes were detected within the detection limits of MLPA(multiplex ligation dependent probe amplification.

RESULTS*

PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS IDENTIFIED

Sl. No.	Deletions /Duplications	No. of exons deleted/duplicated †	MLPA probe ratio (Dosage quotient) ¥	Disease (OMIM)	Inheritance	Classification
1.	Heterozygous deletion	*PMP22* (upstream, exons 1-5)	0.50 – 0.53	Hereditary neuropathy with liability to pressure palsies	Autosomal dominant	Pathogenic

ADDITIONAL FINDINGS: NO VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

DISCUSSION

This patient, who had HNPP confirmed by pathology and genetic testing, had signs of weakness and numbness as a result of compression. Our patient here presented with relapsing and remitting type of weekness. Numerous neuropathic dysfunctions, including those of the bilateral motor and sensory nerves, were discovered by additional clinical and electrophysiological investigations. Investigations on immunology, infectious diseases, and neurotoxins were fruitless. The extensive clinical distribution, sensory loss, and genetic discoveries eliminated other diagnostic possibilities including spontaneous or inherited neuralgic amyotrophy.

F Wave

Nerve	F min ms	COMMENTS
L Tibial - AH	69.95	Prolonged
R Tibial - AH	67.97	
R Median - APB	34.32	
L Median - APB	34.53	
R Ulnar - ADM	38.59	
L Ulnar - ADM	36.67	

H Reflex

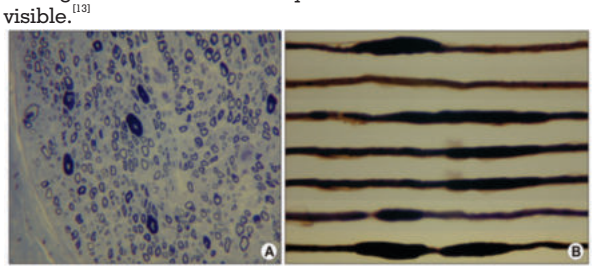
Nerve	H Amp pp mV	H lat ms	COMMENTS
L Tibial - Soleus	1.5	37.03	Normal amplitude + prolonged latency
R Tibial - Soleus	1.2	40.83	

EMG Summary Table

	At Rest	MUAP	Interference Pattern	Comments
Muscle	.	.	.	.
L. Deltoid	None	Large motor unit potentials +Large wide polyphasics	Mildly reduced	Chronic Partial Denervation
L. Triceps brachii	None	Areas of Large wide polyphasics	Mildly reduced	Chronic Partial Denervation
R. Deltoid	None	No motor units	Nil	Possible complete conduction block
R. Infraspinatus	None	Large triphasics	Severely reduced + fast firing units	Conduction block pattern
R. Biceps brachii	Positive sharp waves	Large triphasics	Severely reduced + fast firing units	Severe Conduction block pattern + Active denervation
R. Brachioradialis	None	Large triphasics	Severely reduced+ fast firing units	Conduction block pattern
R. Triceps brachii	None	Large motor unit potentials +Large wide polyphasics	Mildly reduced	Chronic Partial Denervation
R. First dorsal interosseous	None	Large motor unit potentials	Mildly reduced	Chronic Partial Denervation
R. Tibialis anterior	None	Large motor unit potentials +Large wide polyphasics	Mildly reduced	Chronic Partial Denervation
L. Vastus medialis	None	Large motor unit potentials	Mildly reduced	Chronic Partial Denervation

In HNPP patients, the pathological results of nerve biopsies typically reveal sausage-like swellings that are myelin sheath thickenings (tomacula). However, molecular genetic testing has essentially taken the place of nerve biopsies.[12] Given that up to 50% of people with the PMP 22 gene deletion are asymptomatic and have normal findings on a clinical neurological evaluation, genetic testing has consistently been helpful in HNPP families.

Light microscopy—In sural nerve biopsies of patients with HNPP many fibres were found to be thinly myelinated, some showed profound hyper-myelination or redundant myelin foldings and occasional early onion bulb formations were visible.[13]



Transverse semithin section of sural nerve. Thickening of myelin sheath (tomacula) are occasionally seen (A. Toluidine blue, ×400). Consecutive lengths along one teased myelinated fiber from the sural nerve of a patient with HNPP demonstrates multiple characteristic tomacula (B. Osmium tetroxide, ×400).

HNPP is treated conservatively, with the main focus on techniques to prevent minor trauma and compression in sensitive locations. Special considerations could be needed at work or school as a result.Activity modification and protective padding are important in the prevention of compression neuropathies such as ulnar neuropathy, carpal tunnel syndrome, and peroneal neuropathy. Combining protective gear like elbow and knee pads with activity modification measures like avoiding repetitive hand motions, cutting down on time spent crossing your legs, kneeling, and resting on your elbows is recommended.[14]

For HNPP, as of now no accepted medical therapy is available. Splints or pads can be used on the wrist or arms to prevent the nerves from being compressed as well as precautions to avoid or adjust activities and postures (such as resting on the elbows) that aggravate symptoms. Those who still have a residual foot drop may require an ankle-foot orthosis permanently. The treatment of pain may involve using over-the-counter analgesics or prescription medications for peripheral neuropathy. Nerve damage may be prevented by wearing safety equipment while playing sports, using pressure-relieving pads, and staying away from repetitive motions or activities.

HNPP does not influence life expectancy, but the long-term prognosis for quality of life is dependent on the severity and frequency of episodes as well as whether pain and impairment continue.In this case.patient improved with conservative management without any residual deficit.

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