Clinical Reasoning: A teenager with left arm weakness

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Section 1

A 16-year-old right-handed boy presented with left arm weakness. He had broken his right humerus in November 2015 and was in cast until January 2016. During that time, he noticed left arm weakness while carrying a heavy backpack. The weakness improved and he was able to play lacrosse during spring 2016. In summer 2016, he noticed substantial weakness of his left arm after rowing 7 km, and sought medical attention. He denied any pain or sensory symptoms, lower limb weakness, and bladder or bowel symptoms. There was no preceding illness or trauma. On neurologic examination in October 2016, there was atrophy of the deltoid, biceps, and periscapular muscles, as well as mild scapular winging. There was weakness of the following muscles (right/left; Medical Research Council [MRC] grades): deltoids (5/3), biceps (5/4), supraspinatus (5/4–), infraspinatus (5/4–). First dorsal interosseous, abductor digiti minimi, abductor pollicis brevis, finger extensors and flexors, wrist extension/flexion, brachioradialis, triceps, and rhomboids were 5/5. Tendon reflexes were 2+ throughout and sensory examination was normal.

Questions for consideration:

1. What is the localization for his presentation?
2. What are the differential diagnoses?

GO TO SECTION 2

Section 2

The patient in this vignette presented with painless recurrent left arm weakness in the distribution of C5-C6 myotomes. Weakness and atrophy suggested lower motor neuron involvement. This could result from lesions of the cervical spinal cord, anterior horn cells, roots, brachial plexus, peripheral nerves, or muscles. Intramedullary lesions (e.g., syringomyelia) typically involve spinothalamic tracts initially leading to dissociated sensory loss (not seen in our case) before extension to the anterior horn cells.¹ Anterior horn cell syndrome can be due to various disorders: poliomyelitis or acute flaccid myelitis (recurrent episodes make them unlikely); genetic motor neuronopathies: spinal muscular atrophy, Kennedy disease (unlikely as these disorders cause diffuse symmetric involvement with hypo/areflexia); distal hereditary motor neuronopathies (unlikely as there was no distal weakness), juvenile variant of amyotrophic lateral sclerosis (no upper motor neuron signs); and Hirayama

disease (unlikely as it presents with distal upper extremity weakness and atrophy).^{1,2} Lesions of the cervical roots (C5-6) could present in a similar way but lack of neck pain, sensory symptoms, and preserved biceps and brachioradialis reflexes made it less likely. Upper trunk brachial plexopathy could have similar presentation. Among these lesions, neuralgic amyotrophy usually presents with acute onset of pain (not seen in our case) followed by muscle weakness and atrophy. Multifocal motor neuropathy with conduction block can present with weakness and wasting with predilection for upper limbs.² Genetic myopathies, particularly facioscapulohumeral muscular dystrophy, could be considered in the differential due to the distribution of weakness. However, the patient did not have facial weakness.

Question for consideration:

1. What investigations can help to narrow the differential diagnosis?

GO TO SECTION 3

Section 3

The patient had 2 nerve conduction studies/EMG studies (table). The first study (October 2016) was interpreted as most consistent with left upper trunk brachial plexopathy (abnormal sensory studies point to postganglionic lesion as opposed to intraspinal process such as radiculopathy), entrapment neuropathies (median neuropathies at the wrists and left ulnar at the elbow), ulnar sensory neuropathies, and left medial plantar neuropathy. The second study after 3 months showed similar findings in the left median and ulnar nerves with superimposed chronic left suprascapular neuropathy. EMG ruled out anterior horn cell disorders and myopathy. MRI of the cervical and thoracic spine with contrast did not reveal extramedullary or intramedullary lesions or any nerve root thickening/enhancement, which could be seen in inflammatory, infectious, or neoplastic processes.

Laboratory testing showed normal blood counts, inflammatory markers, antinuclear antibodies, Lyme titers, B₁₂, and HbA1c.

Due to entrapment neuropathies at multiple sites, hereditary neuropathy with liability to pressure palsies (HNPP) was considered. A detailed family history was suggestive of neuropathy. The patient's mother had paresthesias of her hands and diminished ankle reflexes. His maternal grandfather had episodic sensory symptoms and weakness involving his arms. His maternal uncle had an EMG in his 20s and was told that he had a neuropathy.

Question for consideration:

1. Based on these findings, what test would you do to confirm the diagnosis?

Table Nerve conduction/EMG findings

Sensory nerves	Onset latency, ms	Amplitude, μ V	Conduction velocity, m/s
Bilateral median digit II, ulnar digit V, left LAC, left medial antebrachial cutaneous, and left medial plantar (first study); left median, ulnar, LAC (second study)	NR	NR	NR
Left radial	2.24	25.8	45
Left sural	2.97	18.3	47

Motor nerves	Distal latency, ms	Amplitude, mV	Conduction velocity, m/s
Left median APB	7.66	5	74
Right median APB	6.30	6.3	49
Left ulnar adductor digiti minimi	3.44	11.0	58 (Below elbow to wrist); 45 (across elbow)
Left peroneal extensor digitorum brevis	4.79	4.7	40
Left tibial adductor hallucis	5.31	10.3	40

Needle EMG	Spontaneous activity	Amplitude	Duration	Polyphasia	Recruitment
Deltoid (first study, normal in second study)	None	Normal	1+	1+	Normal
Infraspinatus (second study)	None	1+	1+	3+	2-

Abbreviations: APB = abductor pollicis brevis; LAC = lateral antebrachial cutaneous; NR = not recordable.

GO TO SECTION 4

Section 4

The family history suggested an autosomal dominant pattern of inheritance, which was consistent with the clinical diagnosis of HNPP. The patient underwent targeted genetic testing (sequencing and deletion/duplication analysis of 4 Charcot-Marie-Tooth disease [CMT] genes: *PMP22*, *MFN2*, *GJB1*, and *MPZ*), which revealed 1.4 Mb deletion involving 17p11.2 region including peripheral myelin protein 22 gene (*PMP22*) confirming the diagnosis of HNPP. The patient's weakness started to improve after 2–3 months after the second episode following rowing and he received physical therapy. At 8 months follow-up (June 2017), his left arm weakness improved and he denied any new symptoms. There was no atrophy of the periscapular muscles with only subtle weakness of the left infraspinatus. Overall, he had 2 painless episodes of left arm weakness (winter 2015–2016 and summer 2016) from brachial plexopathy and suprascapular neuropathy, with near complete recovery in between and clinically asymptomatic entrapment neuropathies of the upper limbs. He was counseled regarding the predisposition of recurrent symptomatic nerve palsies at the entrapment sites. Genetic counseling was offered following the diagnosis of HNPP. His mother declined genetic testing. The proband's sister was asymptomatic. Though family history was suggestive of autosomal dominant inheritance, we did not have genetic confirmation of the diagnosis in other family members.

Discussion

HNPP is characterized by recurrent entrapment neuropathy beginning in adolescence or young adulthood.^{3,4} HNPP is an autosomal dominant disorder caused by microdeletion of the *PMP22* gene and is allelic with CMT1A, which is caused by duplication of *PMP22*.^{5,6}

HNPP typically presents with painless focal mononeuropathies.^{3,4} About two-thirds of patients have preceding minor trauma/compression or physical exercise, which can account for the neuropathy.⁷ Our patient's episodes of weakness were preceded by carrying a heavy backpack and rowing.

The most common sites of mononeuropathy in HNPP are peroneal nerve at the fibular head, ulnar nerve at the elbow, and median nerve at the wrist. Other nerves include brachial plexus, radial nerve, and rarely hypoglossal or facial nerves.^{3–8} Other rare presentations of HNPP include recurrent positional sensory symptoms, progressive mononeuropathy, chronic polyneuropathy, and chronic inflammatory demyelinating polyneuropathy-like disorder.³

The diagnosis of HNPP is often delayed in early childhood during the first attack, as the presentation is often atypical.⁹ In a recent series of 12 children with HNPP, peroneal palsy was the commonest presentation, followed by brachial plexopathy.⁹ Four children had pes cavus and most patients had acroparesthesias (our patient did not have any of those features). Nerve conduction studies in this series revealed 3 major patterns: multifocal demyelination at the areas of nerve

entrapment, generalized demyelinating sensorimotor polyneuropathy, and a combination of both.⁹ All of them had electrophysiologic evidence of focal median neuropathy at the wrist. Our patient had left brachial plexopathy and superimposed left suprascapular neuropathy. In addition, he had multifocal demyelination at the entrapment sites (median nerve at the wrists, ulnar nerve at the elbow), which were clinically asymptomatic. Full recovery occurs in about 50% over days to months; incomplete recovery is fairly common. Our patient had near complete recovery from the 2 episodes. Early age at onset and frequent relapses are poor prognostic factors.⁹ A recently identified polymorphism in the *LITAF* gene when associated with *PMP22* deletion may lead to early-onset HNPP in some pediatric cases.¹⁰ The treatment for HNPP is mainly supportive with physical and occupational therapy.⁹ Patients should be counseled about preventative measures to avoid the risk for compression neuropathies.⁹

HNPP should be considered in a child with painless brachial plexopathy. In our patient, electrophysiologic findings of entrapment neuropathies at clinically asymptomatic sites were valuable clues to the diagnosis. A detailed family history over 3 generations was helpful in determining the autosomal dominant pattern of inheritance and guide genetic testing to confirm the diagnosis.

Author contributions

Dr. Ghosh: study concept and design, study supervision. Dr. Al-Ghamdi: acquisition of data. Dr. Al-Ghamdi, Dr. Vytopil, and Dr. Ghosh: analysis and interpretation. Dr. Ghosh, M. Vytopil: critical revision of the manuscript for important intellectual content.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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