ELSEVIER

Seminars in
Pediatric
Neurology

# Infantile-Onset *Myelin Protein Zero*–Related Demyelinating Neuropathy Presenting as an Upper Extremity Monoplegia

Eppie M. Yiu, MBBS, FRACP, PhD,[*,†,‡] Jithangi Wanigasinghe, MD, DCH, MPhil,[§] Mark T. Mackay, MBBS, FRACP, PhD,[*,†,‡] Michael Gonzales, MBBS, FRCPA,[‖] Garth A. Nicholson, MBBS, FRACP, PhD,[¶,#] and Monique M. Ryan, MBBS, FRACP, MMed[†,‡]

**We describe an infant with an early-onset demyelinating neuropathy who presented with an upper extremity monoplegia and progressive asymmetric weakness. Neurophysiologic testing revealed a generalized severe neuropathy with marked slowing of nerve conduction. The disproportionate severity and asymmetry of upper extremity involvement at presentation was atypical of inherited neuropathies, and an initial diagnosis of chronic inflammatory demyelinating polyneuropathy was considered. Nerve biopsy showed severe depletion of large myelinated fibers without inflammatory cells, and focally folded myelin sheaths were seen on electron microscopy. Genetic testing revealed a de novo heterozygous mutation in the *myelin protein zero* gene.**

Semin Pediatr Neurol ▮:▮▮▮-▮▮▮ 

## Introduction

Early-onset demyelinating neuropathies in childhood are uncommon and present a considerable diagnostic challenge. Although most have a genetic basis, acquired inflammatory neuropathies can also occur in early infancy. We report a child who presented in infancy with an upper extremity monoplegia, but who had widespread slowing of nerve conduction on neurophysiologic testing. Although a diagnosis of infantile chronic inflammatory demyelinating polyneuropathy was initially considered, features on the nerve biopsy were more consistent with an inherited neuropathy, and she was ultimately found to have a de novo heterozygous mutation of the *myelin protein zero* (*MPZ*) gene.

## Case Report

An 11-month-old female infant was referred with a 5-month history of decreased spontaneous movement of the left upper limb and generalized hypotonia. From 6 months of age, her parents noted decreasing use of the left upper limb. She reached across the midline with her right upper limb to grasp objects. Although she could hold objects placed directly into her left hand, she had no proximal movement and was unable to reach for toys on the left side. Hypotonia was also noted

[*]Department of Neurology, Royal Children's Hospital, Melbourne, Parkville, Victoria, Australia.
[†]Neurosciences Research, Murdoch Childrens Research Institute, Melbourne, Victoria, Australia.
[‡]Department of Paediatrics, The University of Melbourne, Parkville, Victoria, Australia.
[§]Department of Paediatrics, University of Colombo, Colombo, Sri Lanka.
[‖]Department of Anatomical Pathology, Royal Melbourne Hospital, Parkville, Victoria, Australia.
[¶]Northcott Neuroscience Laboratory, ANZAC Research Institute, University of Sydney, Concord, New South Wales, Australia.
[#]Molecular Medicine Laboratory, Concord Hospital, Concord, New South Wales, Australia.
Institution where the work was performed: Department of Neurology, Royal Children's Hospital, Melbourne, Australia.
E.M.Y. is supported by a National Health Medical Research Council, Australia (NHMRC) Early Career Fellowship (APP1073323). G.A.N. receives Grant support from the National Health Medical Research Council, Australia (APP104668). M.M.R. receives Grant support from the National Health Medical Research Council, Australia under The Centres of Research Excellence scheme (APP1031893). This work was made possible through Victorian State Government Operational Infrastructure Support and Australian Government NHMRC IRIISS.
Address reprint requests to Eppie M. Yiu, MBBS, FRACP, PhD, Department of Neurology, Royal Children's Hospital, Melbourne, 50 Flemington Rd, Parkville, Victoria, Australia. E-mail: eppie.yiu@rch.org.au, eppie.yiu@rch.org.au

http://dx.doi.org/10.1016/j.spen.2017.03.005
1071-9091/11/

from the first 2 months of life—she had head lag, was reluctant to roll, but at 6 months of age, was able to sit with support when placed.

Over the following 5 months, her neurologic deficits progressed. She developed proximal right upper extremity weakness, followed by bilateral proximally predominant weakness of the lower extremities. Her language, social development, hearing, and vision were normal.

On review of her history, she was born at term after a normal pregnancy to nonconsanguineous white parents and was well in the neonatal period. At 6 weeks of age, she was found to have excessive ligamentous laxity of the hips, without developmental hip dysplasia. She was managed in a Pavlik harness for 6 weeks. She had no respiratory or bulbar difficulties in the neonatal period. There was no family history of note.

Examination at 11 months of age indicated an alert and responsive infant with a head circumference and length on the 90th centile, and weight on the 50th centile. There was no muscle wasting or spinal deformity. She had axial hypotonia with increased head lag, a frog-legged posture, and an inability to lift her head when placed prone. She could sit without support when placed. Tone in all 4 limbs was reduced. She had no movement around the left shoulder girdle and only a flicker of flexion at the left elbow. There was no spontaneous extension of the wrist against gravity, and there was virtually no active movement of the left finger extensors or hand intrinsic muscles. She had a weak grasp on the left but was able to hold toys placed in her left hand. At rest, her left hand had an unusual posture with flexion at the interphalangeal joints in the fourth and fifth fingers, and extension of the index and third digits. The right upper limb also demonstrated marked weakness, with little movement at the shoulder girdle, some flexion with gravity eliminated at the elbow and a flicker of flexion and extension at the wrist, with a weak grasp on the right side.

Lower limb examination indicated flexible foot deformity with the foot and ankle in an everted and valgus position at rest. There was no antigravity hip flexion in the right lower limb, but this was preserved on the left side. Knee flexion and extension were relatively preserved, more so on the left than the right. Distal lower limb movements were comparatively active compared with other movements. The infant used her left lower limb to move and position her left upper limb. Reflexes were absent in the upper and lower limbs.

Cranial nerve examination was normal, including eye movements, facial movements, and bulbar function. Formal ophthalmologic examination was normal and no pupillary abnormalities were noted. Her hearing was normal on formal audiologic testing.

Magnetic resonance imaging of the brain and spine were normal. Extensive testing for inborn errors of metabolism, including testing of plasma and cerebrospinal fluid (CSF) amino acids, lactate and glucose, urine organic and amino acids, plasma carnitine and acylcarnitines, transferrin isoforms, white cell enzymes, fat-soluble vitamins, and very long-chain fatty acids, was negative. The CSF protein was mildly elevated (0.47 g/L; reference range: 0.2-0.4 g/L), with normal CSF cell counts.

Nerve conduction studies were performed at 11 months, and repeated at 13 months of age (Table). These showed a generalized severe sensorimotor demyelinating neuropathy with markedly slowed motor nerve conduction, prolonged distal motor latencies and absent sensory responses. The compound muscle action potentials were of very low amplitude. Temporal dispersion was present in the left ulnar response at 13 months of age. Electromyography at 13 months showed markedly decreased recruitment of high-amplitude, polyphasic motor unit potentials in the left deltoid muscle without active denervation. There was active denervation with frequent fibrillation potentials and positive sharp waves in the left extensor digitorum muscle.

A sural nerve biopsy showed severe depletion of large myelinated fibers, with focal thickening of myelin sheaths and active axonal degeneration. There were no inflammatory cell infiltrates. Numerous tomacula were identified on the teased fiber preparation. Thickening and excessive outfolding of myelin sheaths was noted on electron microscopy (Fig.). No onion bulbs were seen. Unmyelinated fibers appeared normal.

Given the asymmetric presentation and progressive course of weakness, a diagnosis of infantile chronic inflammatory demyelinating polyneuropathy was considered. The patient received an empiric 6-month trial of monthly intravenous

**Table** Nerve Conduction Studies

| Age and Side | Motor | | | | | | | | | Sensory | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Median | | | Ulnar | | | Tibial | | | Median | Ulnar |
| | MNCV | DML | CMAP | MCNV | DML | CMAP | MNCV | DML | CMAP | SNAP | SNAP |
| *11 mo* | | | | | | | | | | | |
| Right | NP | NP | NP | **16.9** | **8.3** | **0.1** | **2.4** | **18.3** | **0.4** | NP | NP |
| Left | NP | NP | NP | **23.8** | **8.3** | **0.6** | NP | NP | NP | **Absent** | NP |
| *13 mo* | | | | | | | | | | | |
| Right | **12.0** | **4.2** | **0.9** | **4.3** | **16.7** | **0.1** | NP | NP | NP | **Absent** | **Absent** |
| Left | **13.3** | **9.2** | **0.1** | NP | NP | NP | * | **17.5** | **0.1** | **Absent** | **Absent** |

Abnormal values are shown in bold type. CMAP, compound muscle action potential, amplitude in mV; DML, distal motor latency (ms); MNCV, motor nerve conduction velocity (m/s); mo, months; NP, not performed; SNAP, sensory nerve action potential, amplitude in μV.

*Proximal response absent.