Charcot-Marine-Tooth (CMT-2) Polyneuropathy Syndrome: A Case Study.

Arbind Kumar Choudhary, Sadawarte Sahebrao Kishanrao

Abstract: Charcot-Marie-Tooth disease (CMT) refers to the inherited peripheral neuropathies affect approximately one in 2500 people; they are among the most common inherited neurological disorders. The majority of CMT patients have autosomal dominant inheritance, although X-linked dominant, and autosomal recessive forms also exist. The majority of cases are demyelinating although up to one third appear to be primary axonal or neuronal disorders. A patient of 9-year-old girl, visited our hospital because of began to suffer from an insidious onset of progressive distal weakness and numbness, and muscle twitching in both in her upper and lower limbs. Nerve conduction studies showed, sensory nerve conduction (SNCV) of bilateral median and ulnar nerve was reduced in upper limb and bilateral sural nerve was reduced in lower limb, While in case of motor nerve conduction (MNCV) bilateral median and ulnar nerve was reduced in upper limb and common peroneal nerve (CPN), as well as posterior tibial nerve was decreased leg. F response latencies were markedly prolonged in patient. Family history along with electrophysiological studied showed; It was typical case of autosomal dominant CMT 2 axonal neuropathy. CMT is currently an untreatable disorder and at the moment the treatment of CMT is only supportive, as there are no drugs available that would halt the disease symptoms. The care of a CMT patient is challenging for the health care team.

Keywords: CMT, Neuropathy, Nerve conduction, Polyneuropathy.

1. Introduction

Charcot and Marie [1] described an unusual slowly progressive form of muscular atrophy characterized by weakness and wasting of the feet and leg muscles followed by involvement of the hands. That same year, Tooth [2] independently described the peroneal type of progressive muscular atrophy with essentially the same clinical features. Charcot-Marie-Tooth (CMT) Disease is one of the most common forms of inherited peripheral neuropathies with the prevalence of one in 2500 individuals [3]. CMT is actually a heterogeneous group of disorders of the peripheral nerves also referred to as the hereditary motor and sensory neuropathies (HMSN) [4]. CMT can be inherited *X-linked, autosomal dominant* and *autosomal recessive.* CMT can run in a family, even when there is no obvious family history of it. In part, this is because CMT can be inherited in three different ways that aren't always easy to trace through a family tree. When CMT is passed on in an autosomal dominant pattern, it can be easy to recognise in the family tree. In contrast, X-linked or autosomal recessive types of CMT might seem to occur "out of the blue." In landmark studies, Dyck and Lambert [5] subdivided hereditary motor and sensory neuropathies (HMSNs) into dominantly inherited demyelinating HMSN1 (CMT1) and dominantly inherited axonal HMSNII (CMT2) forms, based on electrophysiological and neuropathological criteria [5] . CMT 1 if the patient has an autosomal dominantly inherited demyelinating neuropathy; CMT 2 if the neuropathy is dominantly inherited and axonal. A motor NCV value of 38 m/sec in the median nerve is often used as the division to separate CMT1 from CMT2 [6].

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CMT1 patients demonstrate severely reduced motor nerve conduction velocities (NCVs < 38 m/s) the amplitude of the motor and sensory action potentials is greatly reduced due to demyelination. NCVs of CMT2 patients are nearly normal (>38 m/s) the amplitude of the motor and sensory action potentials are greatly reduced due to axonal loss [6, 7]. Intermediate forms of CMT (NCVs between 25 and 45 m/s) 3 show signs of both demyelination and axonal loss. There are some exceptional cases, however, so these figures should be used as a guide only.

2. Methodology

Nerve conduction study (NCS) was carried out in a quiet room of neurophysiology laboratory at a temperature of 26^0 to 30^0C by using Neuroperfect-2000. The nerves (median and radian for motor and sensory) in upper limb and the nerves (Common peroneal, posterior tibial for motor and sural for sensory) in lower limb were stimulated sub-cutaneous along their course where they are relatively superficial. The skin resistance was reduced by rubbing with spirit swab; the active electrode was placed over muscle belly and reference electrode over tendon. The nerve conduction examination were done, by stimulating motor and sensory nerves at specific sites, The intensity of stimulus was increased gradually until the muscle action potential is viewed and recorded the time it takes for the stimulus to be sensed by the recording electrodes. E-1 is placed over the mid-portion of a muscle belly to record the distal motor latency (DML). The motor nerve action potential (MNAP) had been recorded at their respective places. The recording electrode was placed directly over the nerve to record the sensory nerve action potential (SNAP). The nerve conduction velocity (NCV) is calculated by measuring the distance between stimulation sites and then dividing by the latency difference.

3. Case study:

A patient of 9-year-old girl, visited our hospital because of began to suffer from an insidious onset of progressive distal weakness and numbness, and muscle twitching in both in her upper and lower limbs. She was apparently alright 7-years before, then she complained of difficulty in walking, falls down during walking, not able to stand up, not able to

get up from lying down position without support, not relieved on taking medication, The typical presenting symptom was slowly progressive lower leg muscle weakness, and hand muscles were affected later on in the disease course. Patient had difficulty to walk on her heels, or to move part of his leg against an opposing force. *Past history:* normal delivery, term child, 3.5kg, no complication, cried after birth, vaccination was given on schedule. *Family history*: The family history was including CMT-like symptoms, combined with signs of nerve damage. Families showed an autosomal dominant pattern of inheritance with CMT2. In family father was also clinically and electrically affected (figure 2) while mother was normal. Out of two, only one sibling was affected with disorder symptom like CMT2. The onset of symptom was in late childhood, with slowly progressive disease. *Clinical examinations* disclosed mild muscle weakness and muscle atrophy in hands and feet, abnormal gait, Mild distal sensory impairments were noted in the pin-prick, temperature, touch, vibration, and position senses. In addition, intrinsic hand muscle wasting and postural hypotension were also observed. General Hyporeflexia was observed in both upper and lower limbs and also looking for sensory loss, Patient's *deep tendon* reflexes (like the knee-jerk reflex) was reduced. Examination of the patient revealed foot deformities (pes caus and hammer toes), bilateral foot drop, and also had continuous body weight loss (Figure 1a). Cranial nerves were intact. There were no signs of upper motor neuron disease, bulbar symptoms, tremor or progressive cognitive problems were observed in the patient. There was no speech disturbance, cardiac and respiratory difficulty, Chest X-ray and sleep cycle was normal. *Laboratory examinations*, including complete blood counts, blood sugar, blood pressure, thyroid function, liver function, renal function, Creatine kinase and serum phosphate and Ca^{2+}were all normal. *Neurophysiological examinations:* Nerve conduction studies showed, sensory nerve conduction (SNCV) of bilateral median and ulnar nerve was reduced in upper limb and bilateral sural nerve was reduced in lower limb, While in case of motor nerve conduction (MNCV) bilateral median and ulnar nerve was reduced in upper limb and common peroneal nerve (CPN), as well as posterior tibial nerve was decreased in lower limb (table 1 & 2). F wave is a late response resulting from antidromic activation of motor neurons involving conduction to and from spinal cord. F response latencies were markedly prolonged in patient (table 3).

4. Discussion

Nerve damage, or *neuropathy*, causes muscle weakness and wasting, and some loss of sensation, in the extremities of the body: the feet, the lower legs, the hands and the forearms. Clinical manifestations of CMT include slowly progressive distal weakness, wasting, and sensory loss, which spreads proximally as the disease progresses. Delayed responses are a sign of demyelination and small responses are a sign of axonopathy. Thus, NCV is often used to distinguish between CMT1 and CMT2. The majority of cases with CMT2 show an autosomal dominant inheritance pattern. However, some of the CMT2 cases are caused by recessively inherited mutations [8]. CMT1 is characterized by marked slowing of the nerve conduction velocity (NCV) and hypertrophic nerves due to repeated segmental demyelination and remyelination with onion bulb formations [9] while CMT2 is characterized by reduction in CMAP and SNAPamplitudes, which slowly progresses over the years, reflecting axonal degeneration [5]. Nerve conduction is usually normal or mildly slowed, depending on the amount of large diameter fiber loss. Sometimes nerve conduction is preserved early in the course of the disease and progressively decreases over decades. However, nowadays, a nerve biopsy for diagnosis is considered to be obsolete. Many people with CMT eventually develop contractures (stiffened joints) that result in deformities of the feet and hands. The contractures occur because as some muscles around a joint weaken, others remain strong, contracting and positions. For example, as muscles that lift the foot at the ankle become weak, muscles that lower and curl the foot downward contract and tighten, causing the most common type of foot deformity - a shortened foot with a high arch (pes cavus). As the contracture gets worse, the toes can become locked in a flexed position. *Autosomal* means the mutation occurs on a chromosome other than the X or Y. Therefore, autosomal diseases affect males and females equally. *Autosomal dominant* means one copy of a defective gene is enough to cause disease. In that case, a person who inherits the defective gene from a parent will have the disease, as will the parent.

Limitation of the study:

Limitation of this finding can be overcome by further diagnosis, which can be done by using needle *electromyography (EMG)*, which measures the electrical signals in muscles, and less commonly, *nerve biopsy*, which involves the removal and examination of a small piece of nerve. Next, if the diagnosis is still consistent with CMT, *genetic testing or karyotyping can be done* to find the exact region of genetic defects or mutation. Insufficient observations are unable to find out exact cause about this possible diagnosis.

Conclusion:

CMT is currently an untreatable disorder and at the moment the treatment of CMT is only supportive, as there are no drugs available that would halt the disease symptoms. The therapy consists mainly of orthopaedic surgeries, rehabilitation, symptomatic treatment of pain and depression and surgical corrections of foot and hand deformities. Exercise is encouraged with the individual's capability and in fact many patients remain physically active.

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Conflict of interest

The authors declared no conflict of interest.

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TABLE 1: *MNCV (Upper and Lower limb)*

NERVE	Rec – Stim Site	Distance (mm)	Latency difference(ms)	NCV(m/s)
Rt. CPN	EDB- ANKLE EDB-FIB.HEAD	75 415	5.88 9.74	12.75 42.60
Lt. CPN	EDB- ANKLE EDB-FIB.HEAD	78 420	4.50 9.10	17.33 46.15
Rt. PTN	Abd. Halls- ANKLE Abd. Halls- POP. FOSSA	110 415	8.35 11.63	13.17 35.68
Lt. PTN	Abd. Halls- ANKLE Abd. Halls- POP. FOSSA	100 420	5.80 9.50	17.24 44.21
Rt. Median	APB-WRIST APB-ELBOW	80 250	2.50 6.12	32.00 40.84
Lt. Median	APB-WRIST APB-ELBOW	70 240	3.00 6.20	23.33 38.71
Rt. ULNAR	ADM-WRIST ADM-ELBOW	70 250	2.88 6.17	24.31 40.51
Lt. ULNAR	ADM-WRIST ADM-ELBOW	80 240	2.75 5.63	25.45 42.63

TABLE 2: *SNCV (Upper and Lower limb)*

NERVE	Rec – Stim Site	Distance (mm)	Latency difference (ms)	NCV (m/s)
Rt. SURAL	Laterals Malls-MID CALF	165	4.75	34.73
Lt. SURAL	Laterals Malls-MID CALF	170	4.60	36.95
Rt. Median	2nd Digit -WRIST	135	2.80	48.21
Lt. Median	2nd Digit- WRIST	140	2.65	52.83
Rt. ULNAR	5th Digit - WRIST	130	2.75	47.27
Lt. ULNAR	5th Digit - WRIST	120	2.60	46.16

TABLE 3: *F WAVE (Upper and Lower limb)*

NERVE	Distance (mm)	Latency difference (ms)	Velocity (m/s)
Rt. CPN	80	25.13	3.2
Lt. CPN	70	24.25	2.9
Rt. PTN	100	25.50	3.92
Lt. PTN	110	23.26	4.73
Rt. Median	70	27.50	2.54
Lt. Median	75	24.63	3.04
Rt. ULNAR	75	29.50	2.54
Lt. ULNAR	80	25.63	3.12

Figure 1: *Foot drop of patient*

Figure 2: *Foot drop of patient's father*