CASE REPORTS

Charcot–Marie–Tooth disease

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Abstract

Charcot–Marie–Tooth (CMT) disease is a group of genetic peripheral neuropathies that is associated with a broad variety of clinical genetic features. Most CMT syndromes are characterized by a progressive muscle weakness and atrophy with a distally pronounced sensory dysfunction. Bone deformities as *pes cavus* or hammertoes are frequent. The severity of disability varies considerably between different subclasses. Physical examination, electrophysiological testing and family history are current methods to investigate a patient affected by CMT. We used these methods for clinical assessment of two cases. Whenever available molecular genetic testing establishes the certain diagnosis and defines the type of CMT.

***Keywords*:** Charcot–Marie–Tooth disease, electrophysiology, molecular genetic testing.

Introduction

Charcot–Marie–Tooth (CMT) is the generic name for a group of genetic peripheral neuropathies characterized by a chronic motor and sensory polyneuropathy. Prevalence is approximate to 1:2500. This group of disorders is associated with a broad variety of clinical and genetic features [1, 2]. The typical clinic signs are progressive distal muscle weakness and atrophy often associated with mild to moderate sensory loss, depressed tendon reflexes, bone deformities and high-arched feet. A careful family history and physical examination could establish the clinical diagnosis. Electrophysiological studies – electromyography (EMG) and nerve conduction velocity (NCV) – are also useful. Because there are more than 40 different genes and loci candidate for CMT, as often as possible molecular genetic testing define the type of CMT. However, in all cases is necessary to exclude many other causes of acquired (non-genetic) neuropathies [3].

Patients and methods

Case no. 1

Clinical assessment

A 10½-year-old girl was brought for evaluation and rehabilitation for a foot deformity. She was the single child for her parents. Past medical history revealed her mother's pregnancy and delivery was normal. There were not unusual problems in her perinatal period and she experienced no serious illnesses or injuries in her childhood. Her developmental milestones had been met on schedule and she walked by age 1 year. By the age 6, she presented fatigability in walking and started to have frequent falls.

Physical examination revealed bilateral lower extremity weakness, more distal than proximal, with generalized hipo-/areflexia: deep tendon reflexes (graded on a scale of 0–4) were 1/4 (knee reflex), 0/4 (ankle reflex) and bilaterally symmetrical. Deep-tendon reflexes were 4/4 in the arms and plantar reflexes were flexor. Cranial nerves were normal. She had a postural hand tremor and Romberg's sign was absent. Sensory examination and coordination was normal.

She had shortening of tendon Achilles, bilateral foot drop and *pes cavus* deformity secondary to a plantar flexion of the first metatarsal with an elevated medial longitudinal arch, and a fixed heel varus, atrophy of intrinsic foot muscles (*extensor digitorum brevis* and *abductor hallucis*) and presence of callosity (Figures 1 and 2).

She showed impossibility in heel walking and tiptoe walking and no dorsiflexion of her toes. Ankle angle during passive dorsiflexion was 0^0, active plantar flexion was 45^0, and the ability to raise on the heel was 1 cm. Muscle strength of flexo-extensor ankle and toe muscles, manually assessed using the standard Medical Research Council (MRC) scale, was 1/5 for *tibialis anterior*, 1/5 *extensor digitorum longus*, 1/5 *extensor hallucis longus*, and 4/5 for *triceps suralis*. Motor strength was 5/5 in the arms, hip flexors, and quadriceps (Figures 3–5). We also identified a double curve scoliosis, right thoracic and left lumbar curve, associated with thoracic kyphosis (Figure 6).

Clinical findings indicated a hereditary motor and sensory neuropathy (HMSN) or Charcot–Marie–Tooth disease (CMT).

Family history

Family history revealed that her father presents fatigability in walking, leg cramps and dysesthetic sensations developed in his feet. Tendon reflexes were hypoactive 1/4 at the ankles and normal elsewhere. His neurological examination was otherwise normal. Another family member, her father's sister, 38-years-old was known to have presence of cramps, clumsiness in walking and running, difficulty in heel walking (Figure 7).

Electrophysiological study

Electromyography (EMG) was used to help differentiate whether the patient's deficits were myogenic or neurogenic. EMG of the *tibialis anterior* showed a neurogenic with long duration and large amplitudes of polyphasic waves.

Nerve conduction studies (NCS) were done to distinguish between demyelinating and axonal pathologies and were tested with surface electrodes. Conduction velocity was recorded in ulnar and tibial nerves using conventional methods. They revealed severe slowing of the conduction velocity: tibial 14 m/s and ulnar 16.5 m/s bilaterally (normal range 42–47 m/s in the legs and 50–55 m/s in the arms). These findings identify the problem as Charcot–Marie–Tooth disease type 1 predominantly demyelinating (see *Discussions*).

Her parents' conduction velocity was also recorded. Normal findings on her mother but the father showed a slowing of nerve conduction velocity: tibial 28 m/s and ulnar 32 m/s.

Laboratory investigations

Laboratory investigations, included complete blood cell count, immunological profile (erythrocyte sedimentation rate, serum protein electrophoresis, complement, rheumatoid factor), blood sugar, electrolytes, liver function, renal function, creatine-kinase activity, were normal.

Case no. 2

Clinical assessment

The patient is a 13-year-old girl, the second child for her parents, with a history of lower extremity weakness that began 6 years before. Medical history revealed her mother's pregnancy and delivery was normal, birth weight 3500 g, born with a tight nuchal cord (umbilical cord around the neck), intense cyanosis, the 1-minute Apgar score was 7, the 5-minute was 9, occipital cephalohematoma, resorbed and resolved completely within three weeks.

Her neuromotor and cognitive development was normal without developmental disabilities. By the age of seven she presented weakness of both lower extremities which had progressed over time and was associated with significant distal muscle wasting of lower extremities and hands.

She had *pes cavus* deformity with complete foot drop, hammer toes, calluses over the pressure points in the middle lateral border of foot, associated with foot slapping, unsteadiness, frequent falls, with impossibility in heel walking and tiptoe walking and no dorsiflexion of her toes.

On neurological examination, muscle weakness was more pronounced in the legs than in the arms, but in both upper and lower extremities, and proximal muscles were not involved. Weakness was found exclusively in distal muscles (manual motor testing MRC): 1/5 for *tibialis anterior*, 1/5 *extensor digitorum longus*, 1/5 *extensor hallucis longus*, 4/5 *triceps suralis*, 5/5 for quadriceps in lower limb and 1/5 finger extensor, 2/5 wrist extensor, and 5/5 for biceps and triceps in upper limb.

Deep tendon reflexes were 1/4 (knee reflex), 0/4 (ankle reflex), 2/4 (biceps, triceps and brachioradialis reflexes) and bilaterally symmetrical. Plantar reflexes were flexor. Cranial nerves were normal. She had decreased vibratory sensation in the lower extremities and abnormalities of position sense in her feet. Coordination was normal.

Family history

The family history showed some similar deformities of the feet in her mother's brother and her grandmother but less severe (Figure 8).

Electrophysiological study

Electromyography (EMG) of the *tibialis anterior* showed an increase of amplitudes with long duration of polyphasic waves, indicating an active denervation-reinnervation process, demyelinating type 1 Charcot–Marie–Tooth disease (axonal type 2 EMG findings consist of decreased amplitude of sensory potentials, fibrillations and positive sharp waves in the distal limbs, suggesting denervation).

Nerve conduction velocity (NCV) showed symmetrically decreased nerve conductivity: tibial 17 m/s and ulnar 9 m/s bilaterally. Her parents' conduction velocity was also recorded, but with normal findings on her mother and a slowing of NCV on her father: tibial 29 m/s and ulnar 34 m/s.

Laboratory investigations

No laboratory abnormalities were found.

Discussions

Myelin in the peripheral nervous system is generated by Schwann cells, which enwraps axons with multiple layers of its plasma membrane, resulting myelin sheath responsible for rapid propagation of action potentials along the neuron. Axons and Schwann cells are anatomically and functionally closely connected and tightly regulate each other. Breakdown of this complex system results usually in peripheral neuropathies [4].

Charcot–Marie–Tooth inherited neuropathies (CMT) were first described independently by Charcot JM and Marie in France [5] and by Tooth HH in England [6]. The heterogeneous nature and different forms of inheritance of this group of disorders were soon recognized. Dejerine H and Sottas J described more severe infancy-onset cases [7] and Roussy G and Levy G described cases associated with tremor [8].

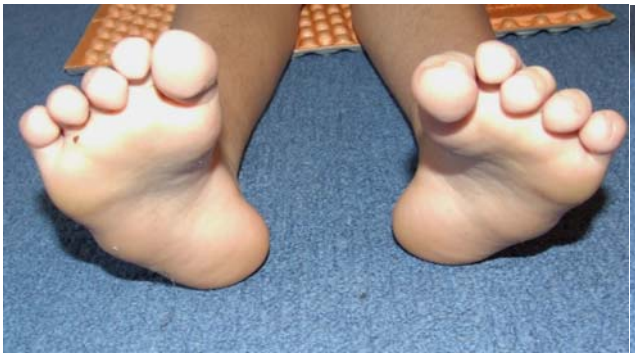

Figure 1 – ***Typical cavus deformity, clinical aspect***

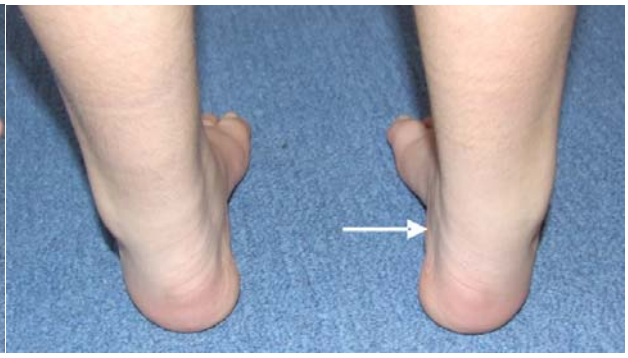

Figure 2 – ***Varus deformity, clinical aspect***

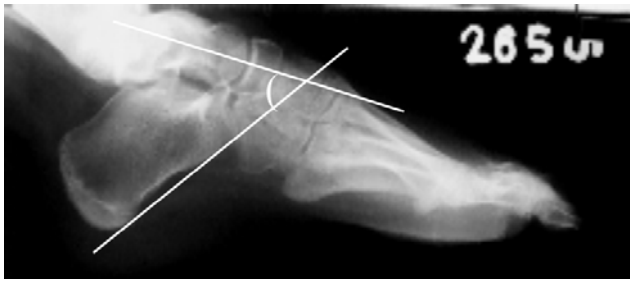

Figure 3 – ***X-ray foot, sagittal plane view: high arches, increased calcaneal inclination and increased metatarsal declination, talocalcaneal angle 400 (normal 150–300)***

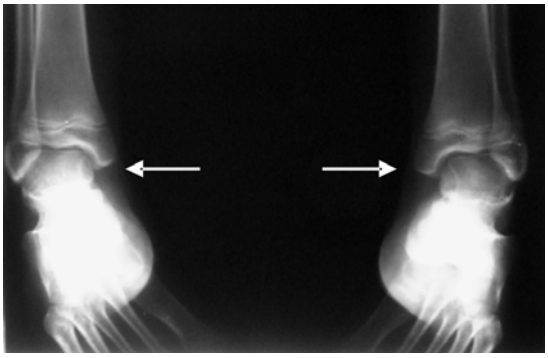

Figure 4 – ***X-ray foot, medial plane view***

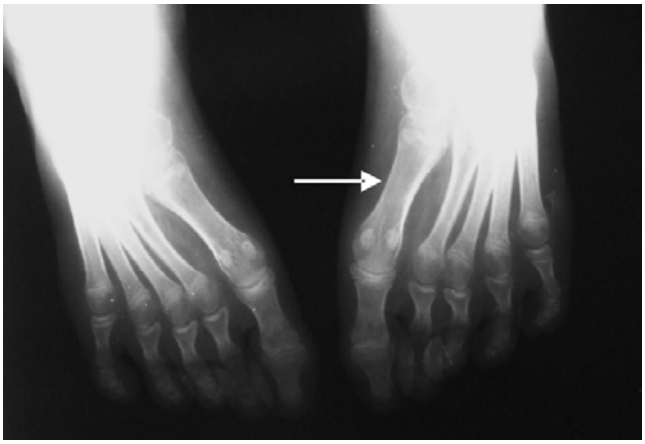

Figure 5 – ***X-ray metatarsus adductus (varus) deformity in both feet***

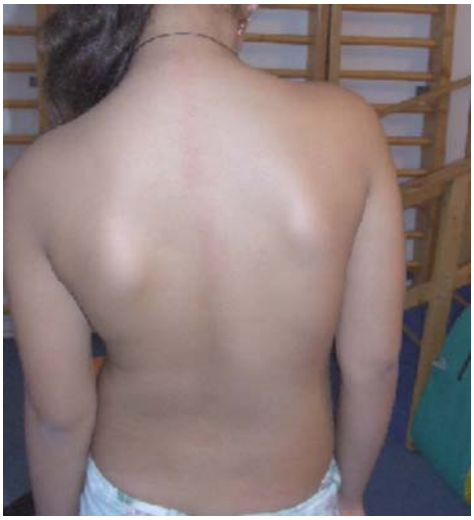

Figure 6 – ***Double curve scoliosis, right thoracic and left lumbar curve***

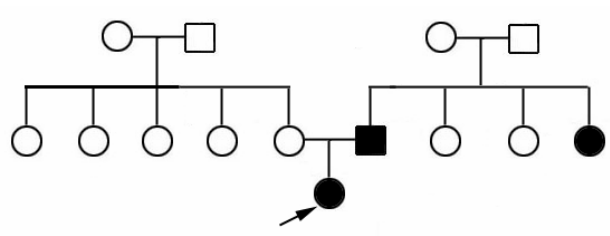

Figure 7 – Pedigree of case no. 1

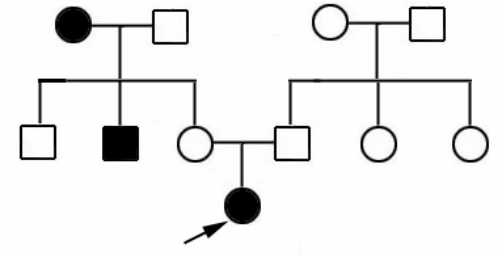

Figure 8 – Pedigree of case no. 2

Neurophysiologic testing performed beginning with 1960s [9] allowed the classification of CMT into two groups, one with slow nerve conduction velocities and histologic features of a hypertrophic demyelinating neuropathy (hereditary motor and sensory neuropathy type 1 or CMT1) and another with relatively normal velocities and axonal and neuronal degeneration (hereditary motor and sensory neuropathy type 2 or CMT2). When molecular genetic tests become available (early 1990s) patients with both CMT1 and CMT2, while often clinically similar, were found to be genetically heterogeneous.

Now a large and ever increasing number of genetic subtypes have been described, and modern techniques in molecular and cellular biology have clarified the role of different proteins in the physiology of peripheral nerve conduction [10]. In CMT group, mutations in several different genes cause similar disease phenotypes, but also different mutations affecting the same gene can lead to different disease phenotypes. However, classification is especially difficult when different mutations in a single gene are associated with both autosomal dominant and autosomal recessive inheritance, and/or both axonal and demyelinating neuropathy [11]. A common classification uses as main criteria the inheritance patterns and molecular genetics:

▪ CMT1, characterized by abnormal myelin, with an autosomal dominant mode of inheritance, is the most frequently (about 50% from all cases).

▪ CMT2, having the main feature axonopathy, also an autosomal dominant form, is on the second place (approximately 20–40%).

▪ Intermediate form, an autosomal dominant combination of myelinopathy and axonopathy in individual is rare.

▪ CMT4 is a rare group of progressive motor and sensory axonal and demyelinating neuropathies, with typical phenotype, but autosomal recessive inheritance.

▪ X-linked CMT is characterized by a moderate to severe motor and sensory neuropathy in affected males and usually mild to no symptoms in carrier female and is responsible for approximately 10–20% from cases.

In studied cases, the inheritance is autosomal dominant. In first case, CMT disorder is paternally inherited, but, conversely, the second seems to be maternally inherited, because, although proband's mother is not affected, in mother family there are two members with some deformities of the feet that could be due to a mild form of CMT. This is an example of incomplete penetrance and variable expressivity. Penetrance of CMT1 is usually nearly 100%, but the wide range in age of onset and severity may result in under-recognition of individuals with mild or late-onset disease. Some cases of CMT disease result from a new mutation and occur in people with no history of the disorder in their family [12].

Electrodiagnostic studies (electromyography and nerve conduction studies) are pivotal in the evaluation of polyneuropathy, whether acquired or inherited. They can both confirm the presence of polyneuropathy and, more important, identify the pathophysiology as demyelination or axonal degeneration. Electrodiagnostic studies are used to classify patients as having Charcot–Marie–Tooth disease type 1 (predominantly demyelinating) or type 2 (axonal) based on nerve conduction velocity. Demyelinating neuropathy results in slowing of nerve conduction velocities, which are measured in the largest, fastest-conducting myelinated nerve fibers [13].

However, loss of these large myelinated nerve fibers because of axonal degeneration is also associated with some degree of slowing of nerve conduction velocity, but to a lesser extent than in a demyelinating neuropathy, and this slowing is proportional to the degree of axonal loss. In practice, nerve conduction velocities less than 80% of the lower limit of normal provide evidence of demyelination, if substantial axonal loss has not occurred, whereas those between 80–100% of the lower limit of normal are of indeterminate significance. A cutoff for median nerve conduction velocity of 38 m/s (normal 50 m/s) can be used to distinguish between demyelinating and axonal forms of Charcot–Marie–Tooth disease [14].

In both cases presented here, the electrodiagnostic studies showed evidence of demyelinating forms of Charcot–Marie–Tooth disease. This interpretation is consistent with several clinical features of cases. For the first patient, the data is also consistent with the electrophysiological and pathological evaluation of his father. Therefore, we believe these patients have the demyelinating form of Charcot–Marie–Tooth disease type 1 (CMT1).

CMT1 usually become symptomatic between age five and 25 years. Clinical severity is variable, from extremely mild disease almost unrecognizable by the patient and physician to marked weakness and disability [15, 16]. The typical presenting symptom of CMT1 is weakness of the feet and ankles. The initial physical findings are depressed or absent tendon reflexes with weakness of foot dorsiflexion at the ankle. The typical adult individual has bilateral foot drop, symmetrical atrophy of muscles below the knee (stork leg appearance), atrophy of intrinsic hand muscles and absent tendon reflexes in both upper and lower extremities. Proximal muscles usually are not affected [17]. Mild to moderate sensory deficits of position, vibration, and pain/temperature commonly occur in the feet. Pain, especially in the feet, is reported by 20–30% of patients. Less than 5% of individuals become wheelchair dependent. Life span is not shortened [18].

CMT1 – as well as the others subtypes of CMT – can be further subdivided primarily on molecular genetic findings [19]. Each of these subtypes is identified based on detection of a mutation in the causative gene: *PMP22* – Peripheral myelin protein 22 (subtypes 1A and 1E), *MPZ* – Myelin P_0 protein (subtype 1B), *LITAF* – Lipopolysaccharide-induced tumor necrosis factor-alpha factor (subtype 1C), *EGR2* – Early growth response protein 2 (subtype 1D), and *NEFL* – Neurofilament light polypeptide (subtype 1F). The CMT1 subtypes are often clinically indistinguishable.

However, some distinct features, like scoliosis, appear sporadically. Scoliosis has been reported with the p.Arg359Gln mutation in EGR2 (subtype 1D) and also in a CMT1A case [20]. We noticed in first case a double curve scoliosis, right thoracic and left lumbar curve, associated with thoracic kyphosis.

Conclusions

Charcot–Marie–Tooth peripheral neuropathies have a heterogeneous nature and different forms of inheritance. Modern techniques in molecular and cellular biology revealed a large and ever increasing number of genetic subtypes. In CMT group, mutations in several different genes cause similar disease phenotypes, but also different mutations affecting the same gene can lead to different disease phenotypes. Penetrance of CMT1 is usually nearly 100%, but the wide range in age of onset and severity may result in under-recognition of individuals with mild or late-onset disease. Electrodiagnostic studies (electromyography and nerve conduction studies), physical examination and family history are pivotal in the evaluation of polyneuropathy, whether acquired or inherited.

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