CHARCOT MARIE TOOTH DISEASE

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ABSTRACT

Charcot-Marie-Tooth disease is a clinically heterogenous disorder with a prevalence of about 1 in every 2500. This disease is characterised by a progressive neuropathy which may present with a range of phenotypes. The classical phenotype of the disease generally includes distal muscular atrophy and skeletal deformities but varies with severity and age of onset. Electrophysiology is especially important for the current classification system of CMT, differentiating between CMT1, CMT2 and intermediate CMT subtypes. Over 60 causative genes have been identified for this disorder, owing to the advances that have been made in molecular techniques. Such techniques, especially Next-generation sequencing, have since revolutionised genetic testing and greatly expanded our knowledge of individual phenotypes and genotypes. Having said this, CMT is a continuously evolving field. In fact, although CMT is not associated with any particular treatment, clinical trials related to potential therapeutics are currently underway after presenting with positive outcomes in animal models. Although new techniques are being developed, diagnosis remains particularly focused on both the clinical and neurophysiological features, which in turn guides the application of Next-generation sequencing. Moreover, further research concerning epidemiology, as well as outcome measures is required to gain yet a better understanding of CMT and its subtypes, in hopes of developing specific treatment options and potentially even finding a cure so to subsequently improve the patients' quality of life.

LIST OF ABBREVIATIONS

CMT	Charcot Marie Tooth
NGS	Next- Generation Sequencing
SAP	Sensory Action Potential
HNPP	Hereditary Neuropathy with Liability to Pressure Palsy
CHN	Congenital Hypomyelinating Neuropathy
DSS	Déjèrine-Sottas Syndrome
PMP22	Peripheral Myelin Protein 22
MFN-2	Mitofusin-2
MPZ	Myelin Protein Zero
GJB1	Gap Junction Protein Beta 1
WES	Whole Exome Sequencing
WGS	Whole Genome Sequencing
P0	Protein 0
UPR	Unfolded Protein Response
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
cAMP	Cyclic AMP
NT3	Neurotrophin 3
CMTNS	CMT Neuropathy Scale

1.ORIGIN

Charcot Marie Tooth (CMT) disease represents a spectrum of hereditary neuropathies which are clinically and genetically heterogeneous. With an estimated prevalence of 1 in every 2,500 people (1), CMT is in fact among the most common inherited neuropathies (2).
Since its discovery over 120 years ago, substantial progress has been made in the discovery of causative genes. Most mutations in this disease primarily influence Schwann cells and peripheral axons (3). These may include radial or axonal transport proteins, transcription factors for Schwann cell differentiation, molecular chaperones or cytoskeletal, endosomal and mitochondrial proteins. Depending on the protein affected, the mutation can either cause axonal loss or demyelination (4), and this explains why clinical features, onset and severity tend to vary between subtypes of CMT.

The length-dependent deterioration of sensory and/or motor fibres typically characterizes the disease and leads to what is known as the classical CMT phenotype. This includes loss of sensation, depressed tendon reflexes, distal muscular atrophy and skeletal deformities (5). Symptoms tend to initially affect the lower limbs, particularly the intrinsic foot musculature, but can also progress to the peroneal and anterior tibialis muscles and eventually to the distal upper limbs (6). Similarly, gait difficulties are common due to the foot deformities that develop, including hammer toes and pes cavus (7). The pathophysiology of these skeletal abnormalities, particularly pes cavus, has been thought to be because of the loss of innervation of intrinsic foot muscles and can sometimes even progress to pronounced osseous changes (8,9). Having said this, the slow progression of the disease, typically presenting within the first 2 decades of life, leads to no significant alteration in life expectancy (10).

Furthermore, the classical CMT phenotype has also been described to include features seen on electrophysiology and nerve biopsy, particularly absent/reduced sensory action potential (SAP) amplitudes, reduced nerve conduction velocities (below 38m/s) and onion bulb formation along with demyelination and remyelination features (11).

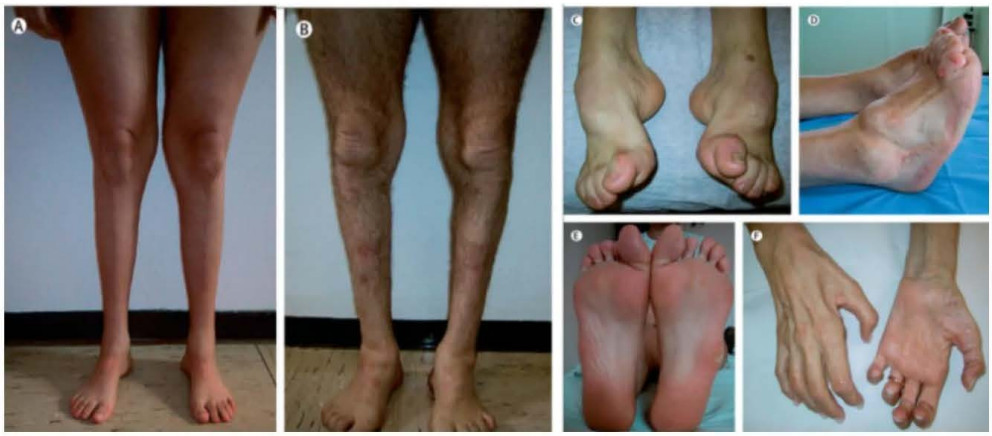

Figure 1 – Patients presenting with the classical CMT phenotype. A/B: muscular atrophy in the lower limb. C/D/E: foot deformities (pes cavus, callosities and high arches). F: wasting of the intrinsic muscles of the hand
Taken from *(Pareyson and Marchesi 2009)*.

2.CLASSIFICATION BASED ON ELECTROPHYSIOLOGY, NERVE BIOPSY AND INHERITANCE PATTERNS

Being that the clinical features of CMT subtypes are considered similar, ancillary diagnostic tests have been identified to assist in guiding genetic testing (12). Initially CMT was classified into demyelinating, axonal and intermediate forms on the basis of electrophysiology by using nerve conduction speeds in upper-limb motor nerves, specifically the ulnar and median nerves (5,13). Velocities less than 38m/s indicate demyelinating forms, specifically CMT1 and CMT4, while velocities greater than 38m/s indicate axonal forms, specifically CMT2. CMT1 is considered an AD demyelinating disorder, while CMT4 is typically considered an AR demyelinating disorder.

Further differentiation can then be achieved by sural nerve biopsy since CMT subtypes are found to show distinct myelin malformations. Demyelinating forms mainly exhibit onion bulb formations in Schwann cells, whereas axonal forms exhibit axonal degeneration and regeneration which characterises the subtype (10).

Intermediate velocities usually indicate X-linked CMT (CMTX1) or dominant-intermediate-CMT. This subtype can present with features of both demyelinating and axonal types and is considered the second most prevalent subtype of CMT (10). CMTX1 typically presents differently for males and females, with males exhibiting specific symptoms, including stroke-like symptoms, namely dysarthria and ataxia, as well as transient white matter hyperintensities on peripheral nerve MRI (9,14).

The third most frequent type of CMT is Hereditary Neuropathy with liability to Pressure Palsy (HNPP), typically presenting with recurring, temporary motor and sensory mononeuropathies which may lead to palsies in nerves or plexi (15). On biopsy, HNPP patients exhibit characteristic tomaculae, described as an excess of myelin ensheathing axons (12).

CMT3 is the subtype used to describe a group of early onset disorders; Congenital Hypomyelinating Neuropathy (CHN) and Déjèrine-Sottas syndrome (DSS). CHN, typically causing hypotonia in infants, is characterised by a defect in Schwann cells wherein peripheral nerves exhibit a lack of myelin and a very limited amount of basal lamina onion bulbs. On the other hand, DSS which is said to be the worst subtype of the disease, is typically characterised by an early onset, generally in infancy and exhibits delayed motor milestones as well as nerve hypertrophy (14).

Being an AR disorder, CMT4 is typically considered more severe than majority of CMTs. It contains all AR demyelinating subtypes, typically having an early onset with an involvement of proximal musculature. In fact, patients typically lose their ability to walk at a relatively early stage. Phenotype of CMT4 can sometimes also be complicated by vocal cord paralysis and sensorineural hearing loss (10).

Lastly, CMT5 is an AD disorder involving pyramidal features such as hyperreflexia (typically causing patients to be Babinski sign positive) or even spastic paraplegia. CMT6, on the other hand, has an early onset as well as a phenotype complicated by optic atrophy, commonly leading to vision loss (5).

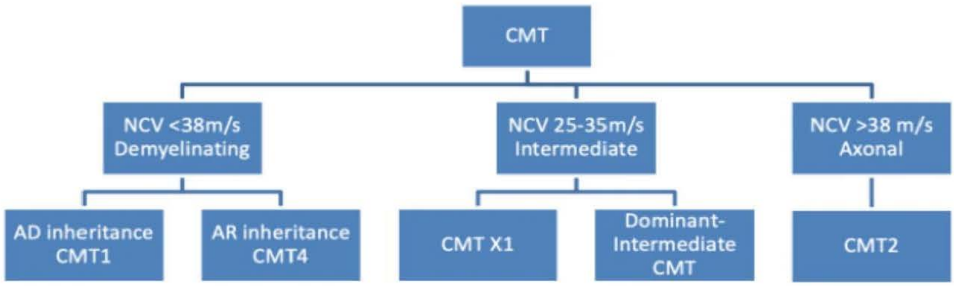

Figure 2 – Flow chart classifying the main CMT subtypes based on electrophysiology, inheritance patterns and/or clinical features. CMT: Charcot Marie Tooth Disease; NCV: Nerve Conduction Velocity; AD: Autosomal Dominant; AR: Autosomal Recessive.

CMT subtype	**Prominent characteristic of the subtype**
CMT1	AD Demyelinating form. CMT1A is the most common subtype of CMT. Intermediate NCV.
CMTX1	Exhibit features of both demyelinating and axonal types.
HNPP	Exhibit recurring, temporary motor and sensory mononeuropathies.
CMT2	NCV >38m/s, therefore axonal form. Patients exhibit both sensory and motor symptoms.
CMT3	Early onset. Includes Congenital Hypomyelinating Neuropathy (CHN) and Déjèrine-Sottas syndrome (DSS).
CMT4	AR Demyelinating form. Early onset and more severe. Patients exhibit involvement of proximal musculature.
CMT5	AD disorder characterised by pyramidal features.
CMT6	Early onset disorder characterised by optic atrophy.

Table 1: Summarised overview of CMT subtypes. CMT: Charcot Marie Tooth Disease; NCV: Nerve Conduction Velocity; AD: Autosomal Dominant; AR: Autosomal Recessive; HNPP: Hereditary Neuropathy with liability to Pressure Palsy

3.NOVEL GENES ASSOCIATED WITH EACH CMT SUBTYPE

The discovery of the first causative gene for CMT in 1991 has since led to advances in genetic testing wherein a genetic diagnosis is now achievable in approximately 70% of patients (10). With the use of NGS, studies have reported that in the majority of CMT patients, the etiology is a mutation in one of the following genes: the peripheral myelin protein 22 (PMP22), Mitofusin-2 (MFN-2), myelin protein zero (MPZ) or gap junction protein beta 1 (GJB1) gene (16) (figure 3). Whole exome sequencing (WES) and whole genome sequencing (WGS) are also considered very useful for identifying causative genes, thereby improving the diagnostic yield, especially when NGS panels do not detect any of the known pathogenic genes (17,18).

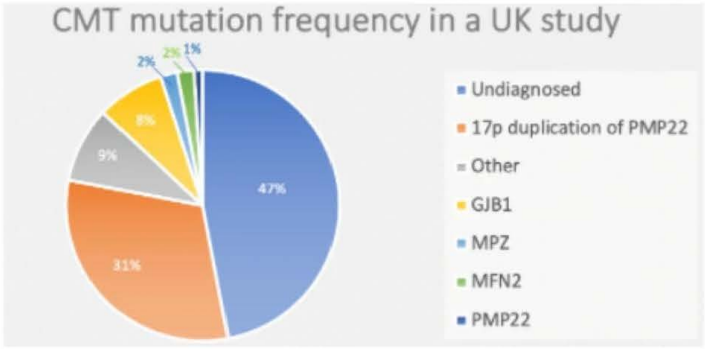

Figure 3: A pie chart demonstrating the breakdown of CMT cases presenting at a UK clinic (Murphy et al. 2012; Davidson et al. 2012). Adapted from (Rossor et al. 2013).

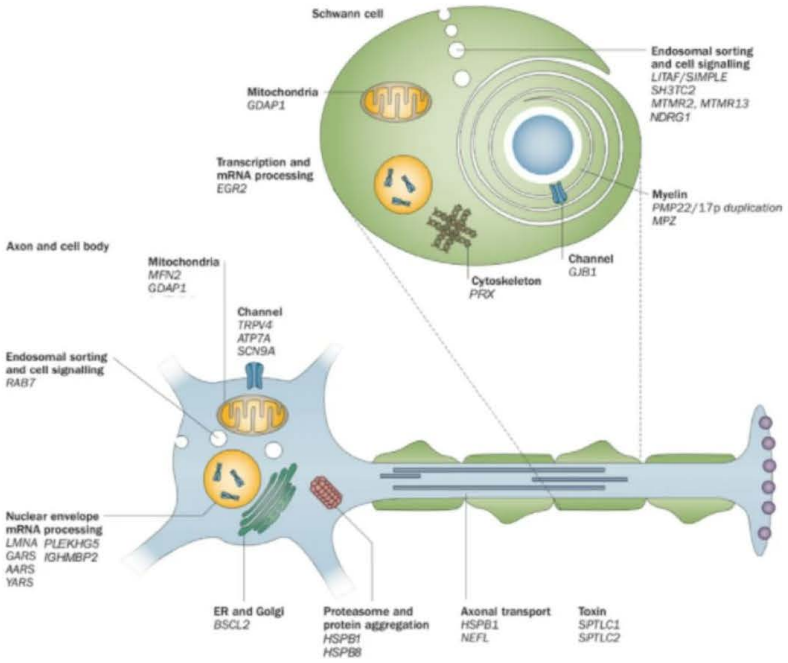

Figure 4: Location and function of some of the genes mentioned. Adapted from (Rossor et al. 2013)

4.MANAGEMENT

4.1.REHABILITATION

A multidisciplinary approach, along with ancillary services are currently the best method for managing CMT patients. Rehabilitation and instrument use, such as assistive orthopedic devices, plantars, ankle-foot orthoses and occupational therapy have been reported necessary for quality of life improvement and prevention of further complications. In fact, physical therapy has been found beneficial for both gait retraining as well as for maintaining a good posture (22,23).

4.2.SYMPTOMATIC TREATMENT

Now that studies have found pain to be a significant symptom of CMT, whether neuropathic or non-neuropathic, treatment prescribed to ease this symptom is essential for patient management. Examples may include nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants and tricyclic anti-depressants. While NSAIDs generally aid back or lower limb pain, the latter two drugs typically help treat the neuropathic pain that is associated with the disease (24).

Non-pharmacological pain management for CMT is also possible and includes maintaining an appropriate BMI and participating in regular physical activity of low intensity (25). In fact, exercise decreases the sensation of pain, ameliorates ambulation and reduces lower-limb weakness (26,27).

4.3.SURGICAL INTERVENTIONS

Orthopedic procedures used to manage CMT, specifically foot surgeries, include tendon transfers, osteotomies and plantar fasciotomies (28). Although they do not ameliorate lower limb strength or sensation, they have been found to improve gait difficulties by correcting complications such as hammertoes and pes cavus (29).Apart from foot deformities, surgical treatment may also be used to increase upper limb mobility or treat scoliosis which is exhibited in approximately 15-25% of cases (30).

4.4.DISEASE MODIFYING TREATMENTS

Presently, although CMT is not associated with any particular disease modifying treatments, many preclinical trials on animal models are underway, encouraging advances in potential therapeutics which can possibly be made use of by CMT patients in the near future (12).

Progesterone antagonists have been found advantageous in rat models bearing a PMP22 overexpression. These agents aim to downregulate PMP22 which is essential to combat the consequences caused by the novel duplication(1). In fact, research done on transgenic CMT1A rats reported improvements in both clinical features and neuropathology (31).

Through its effects on cAMP, ascorbic acid has been found to similarly reduce PMP22 expression in transgenic mice and has now advanced to the controlled trial phase. In fact, in a particular animal study, longer lifespans were even reported (32). Having said this, some studies have noted no therapeutic effect in humans, with minimal changes noted on the CMT neuropathy scale (CMTNS) (33–36). For this reason, further research is required about it's pharmacokinetic properties, especially due to side effects observed when large dosages are administered (37).

Neurotrophin 3 (NT3) has also demonstrated positive results for CMT1A models. In one study, when NT3 was applied to axons of mice ensheathed by CMT1A human Schwann cells, significant axonal regeneration was observed, leading to improvements in sensation and myelination of sural nerve (10). It has been reported that the mode of action for NT3 is through its effect on autocrine survival which promotes nerve growth (38).

Mutations in myelin structural genes (as are MPZ and PMP22) are thought to potentially cause a build-up of misfolded proteins or a stimulation of the UPR. Therapeutics such as curcumin have therefore been developed to target these pathomechanisms (29). In fact curcumin, has been seen to reduce ER stress by releasing the misfolded P0 or mutant PMP22 proteins from the ER of Schwann cells of CMT1B animal models (39). This decreases Schwann cell apoptosis, indirectly increasing axon myelination in demyelinating CMTs including those caused by PMP22 and MPZ gene abnormalities (40).

New techniques such as Induced Pluripotent Stem Cells (iPSCs) and RNAi are also currently under investigation. They can potentially be used for disease modeling so to effectively test new therapeutics. iPSCs are typically derived from skin biopsies of CMT patients and are artificially reprogrammed. Being human cell models bearing pathophysiological abnormalities, results using this technology could possibly be more beneficial than animal models when developing therapeutics (41).

5.CONCLUSION

Studies associated with Charcot Marie Tooth disease have increased dramatically recently, partly due to the advances made in genetic testing and sequencing. Increasing the genetic spectrum underlying the disease and gaining a better understanding of the disease's pathophysiology has led to the emergence of potential therapeutics, some of which are now progressing to the clinical trial phase.

Overall, CMT is an evolving disease and new technologies are constantly being developed to help guide research towards definitive cures. Having said this, under the circumstances, clinicians are still supporting patients and treating them symptomatically in hopes of alleviating as much

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