The Death Panel for Charcot-Marie-Tooth Panels

Charcot-Marie-Tooth (CMT) disease is a category of hereditary neuropathy. Rather than 1 disease, CMT is a syndrome of several clinically and genetically distinct disorders (Table and for updated listings: http//www.molgen.ua.ac.be/CMTMutations/Mutations/MutByGene.cfm).[1] The various subtypes of CMT have been traditionally classified according to the nerve conduction velocities and predominant pathology (eg, demyelination or axonal degeneration), inheritance pattern (autosomal dominant, recessive, or X-linked), and the specific mutated genes, of which there have been >35 identified. Type 1 CMT or CMT1 refers to inherited demyelinating sensorimotor neuropathies, whereas the axonal sensorimotor neuropathies are classified as CMT2. By definition, motor nerve conduction velocities (MNCVs) in the arms are slowed to <38m/s in CMT1 and are >38m/s in CMT2. However, most cases of CMT1 are associated with MNCVs that are much slower. CMT1 and CMT2 usually begin in childhood or early adult life; however, onset later in life can occur, particularly in CMT2. Both are most commonly associated with autosomal dominant (AD) inheritance, although X-linked inheritance and autosomal recessive (AR) inheritance are also seen. The traditional classification of CMT into types 1 and 2 is widely used, but additional subtypes of CMT3 and CMT4 are also used to varying degrees. CMT3 refers to HMSNIII (hereditary motor and sensory neuropathy type III) in older classifications, and is characterized as a severe demyelinating or hypomyelinating neuropathy, with most patients having de novo dominant mutations in the common causative genes for AD CMT1 (*PMP22, MPZ*, and *EGR2*). CMT4 is an AR demyelinating polyneuropathy that typically begins in childhood or early adult life, although some classifications refer to these subtypes as AR CMT1 and the AR forms of CMT2 as AR CMT2. Intermediate forms of CMT with median or ulnar MNCVs between 25 and 45m/s are also present (see Table).

Given the large number of genes that can potentially cause CMT, the diagnostic approach to patients with a possible hereditary neuropathy can be daunting. In the United States, this has led to the use of large genetic panels that can be ordered through commercial laboratories. Unfortunately, these panels are often misused and lead to unnecessary and expensive testing. Guidelines have been published to help direct which genetic tests should be ordered based on inheritance pattern and MNCVs.[2] Nevertheless, many patients still have complete panels performed, including all CMT1-related genes in obvious CMT2 patients and vice versa. This problem is especially seen in the United States, but in many European and other countries, where individual gene diagnostic tests are available in noncommercial laboratories, it is not uncommon for inappropriate tests to be ordered especially testing for the chromosome 17 duplication in CMT2 patients.

In this issue of *Annals of Neurology*, Dr Shy's group report the results of genetic testing on their very large cohort of presumed CMT patients (787 patients, of whom 527 were genotyped) and propose a series of algorithms for genetic testing based on age of onset, inheritance pattern, and MNCVs.[3] Although there has been a recently published Practice Parameters suggesting a similar approach,[2] this article takes this a step further, offering a more refined approach backed by the results of their huge cohort of patients. One of the most important findings in this paper, especially in view of the expense involved in extensive CMT gene testing, is the finding that almost 92% of the 527 genetically defined CMT patients in their cohort had mutations in 1 of only 4 genes (*PMP22, MPZ, GJB1,* and *MFN2*). This finding is the basis of the useful algorithms they have devised. The authors propose initially testing only for CMT1A caused by *PMP-22* duplications in patients with a classical CMT phenotype with slow MNCV (15 < and ≤35m/s). Only if this is negative would they next screen for *GJB1* mutations (CMT1X) or *MPZ* (CMT1B), if there is clear male to male transmission. If these are negative, they suggest screening for point mutations in *PMP22, SIMPLE,* and *EGR2*. In patients with CMT and severely slow MNCVs (≤15m/s), they recommend screening for both the *PMP22* duplication and *MPZ* mutations in those patients who begin to walk after 15 months

TABLE : Classification of Charcot-Marie-Tooth Disease

Name	Inheritance	Gene Location	Gene
CMT1			
CMT1A	AD	17p11.2	*PMP22* duplication
CMT1B	AD	1q21-23	*MPZ*
CMT1C	AD	16p13.1-p12.3	*LITAF*
CMT1D	AD	10q21.1-22.1	*ERG2*
CMT1E	AD	17p11.2	Point mutations in *PMP22* gene
CMT1F	AD	8p13-21	*NEFL*
CMT1X	X-linked dominant	Xq13	*GJB1*
HNPP	AD	17p11.2	*PMP22*
CMT2			
CMT2A2 (allelic to HMSN VI with optic atrophy)	AD	1p36.2	*MFN2*
CMT2B	AD	3q13-q22	*RAB7*
CMT2B1 (allelic to LGMD 1B)	AR	1q21.2	*LMNA*
CMT2B2	AD	19q13	Unknown
CMT2C (with vocal cord and diaphragm paralysis)	AD	12q23-24	*TRPV4*
CMT2D (allelic to distal SMA5)	AD	7p14	*GARS*
CMT2E (allelic to CMT 1F)	AD	8p21	*NEFL*
CMT2F	AD	7q11-q21	*HSPB1*
CMT2G (may be allelic to CMT4H)	AD	12q12-q13	Unknown (may be *FGD4*)
CMT2H	AD	8q21.3	Unknown (may be *GDAP1*)
CMT2I (allelic to CMT1B)	AD	1q22	*MPZ*
CMT2J (allelic to CMT1B)	AD	1q22	*MPZ*
CMT2K (allelic to CMT4A)	AD	8q13-q21	*GDAP1*
CMT2L (allelic to distal hereditary motor neuropathy type 2)	AD	12q24	*HSPB8*
CMT2M	AD	16q22	*AARS*
CMT2X	X-linked	Xq22-24	*PRPS1*
CMT3 (Dejerine-Sottas disease, congenital hypomyelinating neuropathy)	AD	17p11.2	*PMP22*
	AD	1q21-23	*MPZ*
	AR	10q21.1-22.1	*ERG2*
	AR	19q13	*PRX*
CMT4 (AR CMT1)			
CMT4A	AR	8q13-21.1	*GDAP1*
CMT4B1	AR	11q23	*MTMR2*
CMT4B2	AR	11p15	*MTMR13*

TABLE : (Continued)

Name	Inheritance	Gene Location	Gene
CMT4C	AR	5q23-33	*SH3TC2*
CMT4D (HMSN-Lom)	AR	8q24	*NDRG1*
CMT4E (congenital hypomyelinating neuropathy)	AR	—	Probably includes *PMP22, MPZ,* and *ERG2*
CMT4F	AR	19q13.1-13.3	*PRX*
CMT4G	AR	10q22.2	*HK1*
CMT4H	AR	12q12-q13	*FGD4*
CMT4J	SR	6q21	*FIG4*
DI-CMT			
DI-CMTA	AD	10q24.1-25.1	Unknown
DI-CMTB	AD	19p12-p13.2	*DNM2*
DI-CMTC	AD	1p35	*YARS*

Modified from Amato AA, Russell J. Neuromuscular disease. New York, NY: McGraw-Hill, 2008.
CMT = Charcot-Marie-Tooth; AD = autosomal dominant; *PMP22* = peripheral myelin protein-22; *MPZ* = myelin protein zero protein; *LITAF* = lipopolysaccharide-induced tumor necrosis factor-alpha factor; *ERG2* = early growth response-2 protein; *NEFL* = neurofilament light chain; *GJB1* = gap junction associated protein B1; HNNP = hereditary neuropathy with liability to pressure palsies; HMSN = hereditary motor and sensory neuropathy; *MFN2* = mitochondrial fusion protein mitofusin 2 gene; LGMD = limb girdle muscular dystrophy; AR = autosomal recessive; *TRPV4* = transient receptor potential cation channel, subfamily V, member 4; SMA = spinal muscular atrophy; *GARS* = glycl-tRNA synthetase; *HSPB1* = small heat shock protein B1; *FGD4* = FGD1-related F actin binding protein; *GDAP1* = ganglioside-induced differentiation-associated protein-1; *HSPB8* = small heat shock protein B8; *AARS* = alanyl-tRNA synthetase; *PRPS1* = phosphoribosyl pyrophosphate synthetase 1; *MTMR2* = myotubularin-related protein-2; *MTMR13* = myotubularin-related protein-13; *SH3TC2* = SH3 domain and tetraticopeptide repeats 2; *NDRG1* = N-myc downstream regulated 1; *HK1* = hexokinase 1; *FIG4* = SAC domain-containing inositol phosphates 3; DI-CMT = dominant intermediate CMT; *DNM2* = dynamin 2; *YARS* = tyrosyl-tRNA synthetase.

of age, but only for the PMP22 duplication in those that walk before 15 months of age. If there is no *PMP22* duplication or *MPZ* mutation, they suggest sequencing *PMP22*.

Patients with CMT and intermediate MNCV 35 $<$ and $\leq$45m/s) usually have CMT1X or CMT1B. For patients with no male to male transmission, intermediate MNCVs, and a classical phenotype, the authors recommend first screening for *GJB1* mutations.[3] If this testing is negative, testing should proceed to *MPZ* mutations. Alternatively, if there is male to male transmission, patients should be first screened for CMT1B. As no patients with CMT1A had intermediate MNCVs, testing for a *PMP22* duplication would not be warranted. If testing for *MPZ* and *GJB1* is negative, then patients could be screened for mutations in rare genes associated with dominant intermediate forms of CMT including *DNM2* (DI-CMTB) and *YARS* (DI-CMTC). In patients with severe CMT2 in childhood (normal or only mildly slow MNCVs, if obtainable), screening should begin with mutations in *MFN2*, the cause of CMT2A. If this is negative, testing for *MPZ* and *GJB1* would be reasonable, as it would be initially for late onset patients, unless there was male to male transmission in the pedigree, in which case only *MPZ* screening is necessary.

The next generation of sequencing techniques including the use of gene chips, exome sequencing, and whole genome sequencing, may serve as cheaper alternatives to more efficiently screen for mutations in terms of cost and time in the future. These techniques are not widely available at present and would be too expensive for routine use, so the algorithms proposed in this paper are an excellent guide to rationale genetic testing of CMT patients currently. In the future, however, these newer techniques may be useful in identifying novel CMT-associated genes, particularly in CMT2, in which only about 30% of cases can be genotyped at present.

A hotly debated area is whether and when patients should have genetic testing. The authors touched on this, noting that testing can aid in prognosis and genetic counseling.[4,5] Further arguments for seeking a genetic diagnosis include the avoidance of unnecessary invasive tests, such as nerve biopsies, and in rare cases avoiding unnecessary trials of immunotherapy (eg, when there is diagnostic consideration of chronic inflammatory demyelinating polyneuropathy). However, one could play devil's

advocate and suggest that such testing from a clinical and pragmatic point of view often is not going to change management or help in the prognosis of an individual patient. Unfortunately, there are no specific treatments available for any of the subtypes of CMT. In terms of prognosis, there have been natural history studies done on some CMT subtypes with the primary aim of assessing outcome measures that may be useful in future clinical trials.[4,5] But what are you going to tell a patient if you genetically confirm they have CMT1A—that their impairment will increases by an average of 0.686 points/yr on the CMT Neuropathy Score (CMTNS) and by an average of 1.368 points/yr on the Neuropathy Impairment Score[4] or, in the case of CMT1X, that the CMTNS increased an average of 2.89 points/decade?[5] What do these numbers mean for an individual patient with CMT? Further, should we test for very rare mutations that occur in 1% or less of CMT patients? All these issues need to be discussed with patients and their families prior to ordering any genetic testing. Nevertheless, a strong argument for genetic testing and carefully following up phenotyped patients is to learn more about the natural history of all types of CMT, including the rare types, so that we can give more individualized prognoses in the future. We do not disagree with the authors' approach; these are just issues that we struggle with on a day to day basis, particularly given the costs of these studies. We fear it will only be more of a struggle in the future, but adopting a rational approach to genetic diagnosis as outlined in Dr Shy's paper should help.

Potential Conflicts of Interest

Nothing to report.

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