Published Ahead of Print on February 2, 2018 as 10.1212/WNL.0000000000005074

ARTICLE

Updating the classification of inherited neuropathies

Results of an international survey

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Neurology® 2018;90:1-7. doi:10.1212/WNL.0000000000005074

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Abstract

Objective

The continual discovery of disease-causing gene mutations has led to difficulties in the complex classification of Charcot-Marie-Tooth diseases (CMT) that needs to be revised.

Methods

We recently published a proposal to update the classification of inherited neuropathies. The reactions from colleagues prompted us to diffuse the proposal and ask people if they would be ready for such a change. We therefore performed an internet survey (from October 1, 2016, to December 1, 2016) that included more than 300 CMT worldwide specialists (practitioners and scientists) from various countries. A questionnaire (with proposals to update and simplify the way in which CMT is classified) was sent by e-mail to all participants in the last International Charcot-Marie-Tooth and Related Neuropathy Consortium meeting held in Venice, September 8–10, 2016 (as identified through an e-mail list).

Results

Of the 107 CMT specialists who answered the survey, 65% considered that changes are needed and that our proposals constituted an improvement over the historical classification of CMT.

Conclusions

Based on recent proposals in the medical literature, these results highlight that most specialists think that changes are needed to the classification of CMT.

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Glossary

AD = autosomal dominant; **AR** = autosomal recessive; **Ax** = axonal; **CMT** = Charcot-Marie-Tooth disease; **CMTR** = Charcot-Marie-Tooth and Related Neuropathy Consortium; **De** = demyelinating; **dHMN** = distal hereditary motor neuropathy; **HSAN** = hereditary sensory and autonomic neuropathy; **In** = intermediate.

The increasing knowledge of Charcot-Marie-Tooth diseases (CMT) has led to many changes in the way in which CMT is classified since its first official nomenclature developed in 1968 by Dyck and Lambert.[1,2] Unfortunately, these often chaotic modifications have led to a dramatically complex classification,[3] thus increasing the risk of error of denomination.[4] Since 2015, our small working group has highlighted the need to harmonize the current CMT classification. We have thus proposed to update the classification of CMT (and related disorders) by using a 3-step (or modules) approach (figure 1). The first step is to indicate the mode of inheritance, which is crucial information for diagnostic purposes and genetic counseling: AD (autosomal dominant), AR (autosomal recessive), XL (X-linked), Spo (sporadic forms), or Mit (mitochondrial inheritance). The second module corresponds to the phenotype: either CMT or dHMN (distal Hereditary Motor Neuropathy); for CMT, we proposed adding the neurophysiologic hallmark "De" (demyelinating, instead of "1"), "Ax" (axonal, instead of "2"), or "In" (intermediate) after the term "CMT." The third step is to clearly indicate the "name of the gene" involved in the disease (with the possibility of putting the term "Unknown" in case of an unknown or as-yet undiscovered gene or mutation).[3] The same classification method has been proposed for HSAN (hereditary sensory and autonomic neuropathy).[5,6]

In September 2016, an oral presentation on this specific topic was given at the 6th International Charcot-Marie-Tooth and Related Neuropathy Consortium (CMTR) meeting in Venice-Mestre, Italy,[7] thus enabling stakeholders (clinicians and scientists) who are involved in the field of CMT and related hereditary neuropathy to be informed (with discussions about our proposals). We took this opportunity to conduct an internet survey, which was proposed to the members of this scientific community, to obtain their opinions on the subject.

Methods

Our aim was to target specialists in the field of CMT. The CMTR meeting is well-recognized in the field of hereditary neuropathy; more than 300 people from different continents and countries participated in the meeting held in Venice in 2016. As a result, this population was quite representative of the people (clinicians and scientists) interested in hereditary neuropathies.

We conducted an internet survey between October 1, 2016, and December 1, 2016. The link to complete the survey (table) was sent several times by e-mail with an introduction to 300 people. Participants were contacted via the e-mailing list from the CMTR meeting held in Venice. Additional physicians and scientists who are involved in CMT care and research were also contacted.

Results

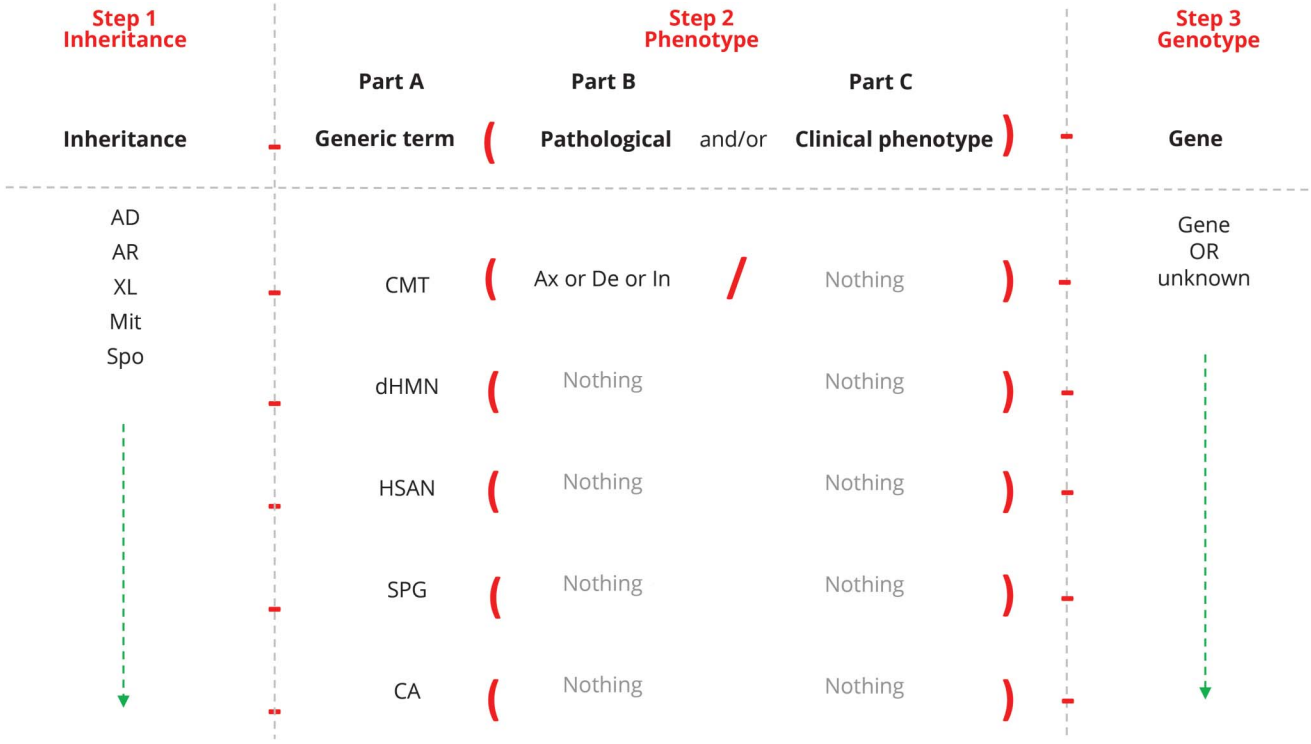
One hundred seven people from various countries (mainly France, Italy, and the United States) responded to the survey. The main results are displayed in figure 2. Most of the participants (81%) were between 30 and 60 years of age; 60% were physicians and 37% were scientists. The majority of the participants (65%) consider that our proposals constituted an improvement over the historical classification, whereas 23% want to keep the previous one. In each country, most of the participants consider our proposals constitute an improvement, except in the United States (28.6% thought it was an improvement) and Germany (42.3% thought it was an improvement) (figure 2). The results show that the answers do not differ between younger (<50 years) and older (≥50 years) participants.

Regarding the order of the 3 modules, 39% of the participants think the mode of inheritance should come first (as we proposed), whereas 33% believe the phenotype should be placed at the beginning. Ninety-one percent of the participants think the term "CMT" should be kept as a generic name for hereditary sensory and motor neuropathy (HSMN). For pure sensory neuropathy, 48% favor HSN over HSAN, although 41% think the opposite; 80% of the participants believe that the term "dHMN" should be kept for distal hereditary motor neuropathy. For the nerve conduction findings, 70% of the participants think the intermediate phenotype should be kept, and 68% favor our proposal to replace "1" with "De" and "2" with "Ax." Finally, 88% of the respondents thought that precise genetic information (mutation, duplication, or deletion) should be included in the classification of CMT.

Discussion

The problem of classifying things, particularly diseases, is an ancient one. Indeed, there is a need for people to have a system for classifying disorders so the diseases can be clearly named and so appropriate care can be given to the affected patients. This is particularly true in the field of hereditary disorders, where the ancient names and classifications based on numbers and letters now seem

Figure 1 Diagram explaining our proposals for denomination and classification of the various forms of CMT and other neurogenetic disorders



AD = autosomal dominant; AR = autosomal recessive; Ax = axonal; CA = cerebellar ataxia; CMT = Charcot-Marie-Tooth disease; De = demyelinating; dHMN = distal hereditary motor neuropathy; HSAN = hereditary sensory and autonomic neuropathy; In = intermediate; Mit = mitochondrial transmission; SPG = spastic paraplegia; Spo = sporadic form; XL = X-linked.

inappropriate. Indeed, there have been some recent attempts to solve such problems in hereditary ataxias and movement disorders.[8–10]

Following our recent publications on updating the classification of CMT and related disorders, we had many comments from colleagues worldwide, and most of the comments were encouraging. Some of these colleagues prompted us to conduct an internet survey to see whether a large consensus could be reached about the need to change the classification of CMT and related disorders. Although this kind of "democratic" approach is unusual, we thought that it would be much more informative because the results could reflect the feelings of the majority of people interested in CMT vs a small group of highly specialized physicians or scientists. Indeed, the results presented here do not reflect the position or ideas from the authors of this report; rather, they reflect the answers obtained from the survey responders.

This internet survey, although simple, appears to be very informative. The main point of interest is the fairly clear desire for change of almost all colleagues asked. This corresponds to the opinion that we have, which was reinforced after many informal discussions with physicians and scientists. This survey also has the merit of providing undeniable proof of this need for change. Moreover, recent and very concrete examples have clearly shown the limits of the current classification of hereditary neuropathies.[4] To take only the example of CMT2, there are more than 29 genes known in this category (involving axonal forms of CMT with both autosomal dominant and autosomal recessive transmission), but only 26 letters are available in the Roman alphabet, based on the OMIM (Online Mendelian Inheritance in Man) nomenclature. It is therefore urgent to ask serious questions on the subject of classification and to find solutions, which seems to be the opinion of most experts.

If we refer to the results obtained from this survey, our proposals are rather welcomed by the CMT community. Of note (and quite to our surprise), age was not decisive in the opinions about the need for changing the classification of hereditary neuropathy. However, there was a trend for people from the United States and Germany to favor the historical classification of CMT according to this survey. Whether this is related to the fact that no individual from these countries was involved in the process of designing our proposal would certainly require further investigation. The use of the 3 modules that we proposed seems relevant and accessible to optimally designate a particular type of CMT. Similarly, our choices of retaining the "axonal"

Table Online questionnaire about the proposed classification of CMT and related disorders

Who are you?	About nerve conduction findings
Surname (not mandatory)	Do you think the "intermediate" phenotype should be kept?
First name (not mandatory)	Yes
Your current condition	No
Physician	Do you think that it's a good idea to change 1 to "De," 2 to "Ax," and to say "In" for intermediate?
Scientist	Yes
Patient	No
Other	If you answered no to the previous question, please explain
Your age	Do you think "UNK" should be used if no nerve conduction studies are available?
20–29	Yes
30–39	No
40–49	About genetic findings
50–59	Do you think genetic findings should be included in the classification as we proposed?
60–69	Yes
70–79	No
>80	If you answered no to the previous question, please explain
The Country where you live/work	Do you think "UNK" should be used if no genetic information is available?
	Yes
Your general opinion about the proposal of a new classification of CMT and related disorders	No
What do you think about the current proposal (compared to the historical classification)?	Do you think "Spo" should be used for sporadic cases?
It's an improvement	Yes
I prefer to keep the historical classification	No
Don't know	Please use the space below if you want to add any other comment
About the order of information, you think	
The mode of inheritance should come first	
The clinical phenotype should come first	
The neurophysiologic information should come first	
The genetic information should come first	
Do you think CMT should be kept as a generic name for hereditary sensory and motor neuropathy?	
Yes	
No	
If you answered no to the previous question, what would be the best denomination in your opinion?	
Do you think HSAN is a good denomination for sensory neuropathy?	
Yes	
No, it should be replaced by HSN	

Continued

Table Online questionnaire about the proposed classification of CMT and related disorders *(continued)*

No, because when people grow older they develop motor signs
Do you think dHMN should be kept for distal motor neuropathy (even if nerve conduction studies show some sensory involvement)?
Yes
No
If you answer no to the previous question, please explain
Do you think it would be useful to add "p" for pyramidal, if pyramidal signs are present (for example, dHMNp)?
Yes
No

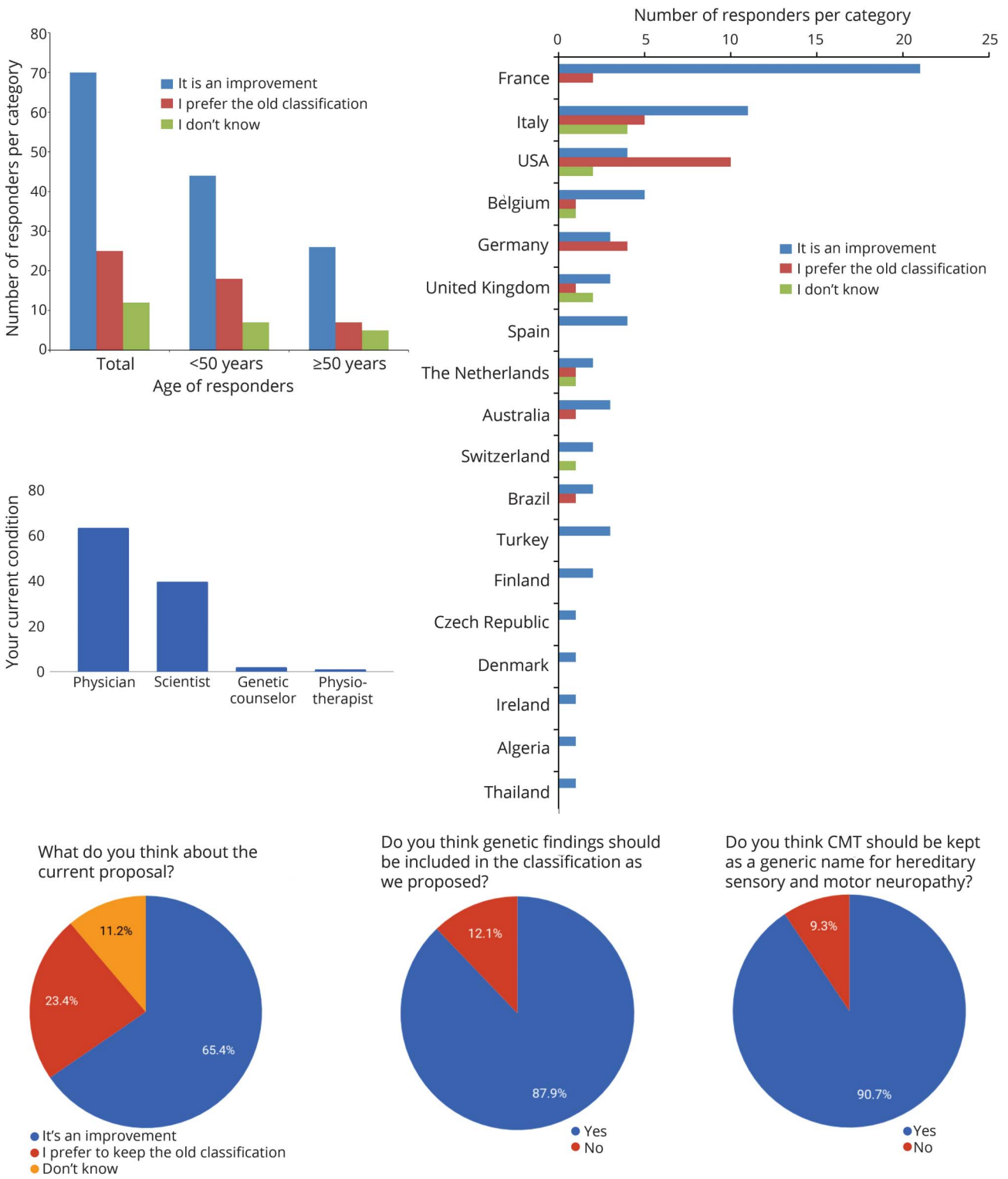
Abbreviations: Ax = axonal; CMT = Charcot-Marie-Tooth disease; De = demyelinating; dHMN = distal hereditary motor neuropathy; dHMNp = distal hereditary motor neuropathy pyramidal; HSAN = hereditary sensory and autonomic neuropathy; HSN = hereditary sensory neuropathy; In = intermediate; Spo = sporadic form; UNK = unknown.

and "demyelinating" categories (replacing "1" with "De" and "2" with "Ax") and adding the "intermediate" category ("In") seems to satisfy most. Cleary defining the name of the involved gene is also a strength of our proposition. The inheritance is another crucial parameter to indicate. Taking the example of *GDAP1*-related hereditary neuropathy, "CMT2H" becomes "AR-CMTAx-*GDAP1*," "CMT2K" becomes "AD-CMTAx-*GDAP1*," "CMT4A" becomes "AR-CMTDe-*GDAP1*," and "CMTRIA" becomes "AR-CMTIn-*GDAP1*," which appear clearer. One of the problems in classifying CMT and related disorders is that some data could be missing or uncertain. This is the case for mode of inheritance, nerve conduction findings, and genetic tagging. We therefore proposed to designate UNK (for "unknown") where appropriate, but this was not favored by responders. Indeed, another solution should be to simply discard the appropriate module for any single patient where data are missing. For example, a patient with CMT who has clear autosomal dominant CMT with demyelinating features but is missing genetic data could be designated "AD-CMTDe" instead of "AD-CMTDe-UNK."

The only main point of disagreement is the position of the 3 modules. For practical reasons, we opted to place the "inheritance" module first[3]; by doing so, we thought it would be easier to distinguish the different forms of CMT. Nevertheless, we consider that our proposals are applicable to other hereditary diseases (neurologic or not) with similar attempts in reclassification.[5,6] Thus, based on the responses of our colleagues (and to envisage a "universal process" of classification of genetic disorders), it would seem logical to arrange the phenotype in the first position: CMT, dHMN, HSAN, SPG (spastic paraplegia), CA (cerebellar ataxia), etc. The mode of transmission would come second, followed by the name of the gene. Thus, when national (or even global) databases of hereditary diseases are becoming increasingly important for clinical trials and research, this kind of classification would probably facilitate further studies and uses. In addition, it seems that this new layout of modules is preferable. Indeed, the "phenotype" module could include a first part (part A) for the generic term (e.g., CMT, SPG), then possibly a second part (part B) called a "pathologic hallmark," as for the CMT (De, Ax, In), and then (if necessary) another accessory part (part C) called a "clinical hallmark" for certain complex and heterogeneous diseases to definite ones (such as hereditary myopathies) (figure 1). The classification of hereditary diseases would thus be based on the assembly of the different modules and parts, such as a construction set in which all combinations and associations become possible, without the risk of being limited.

We are aware that this report has several drawbacks. The first one is that the results exposed here only reflect the opinion of approximately 100 people who are interested in CMT care and research. This may not be much of a limitation of this study because most recommendations that are established and published in medical fields usually involve far fewer people. Another drawback is that approximately two-thirds of the people who were recipients of the survey e-mails did not respond; thus, we do not know their opinions of our proposal, which is a common problem in democratic exercises. Why they did not respond certainly merits investigation, but the official e-mailing list provided by the CMTR meeting organization staff was accurate. The last drawback is that there may be various reasons why people would not favor our proposal, and we could not investigate all of these reasons or transcribe the free comments collected in this survey. Any change would have its detractors and defendants, and the results presented here reflect as many sides of the issue as possible. Finally, our proposition did not address the difficult emerging problem of patients with a complex phenotype, for

Figure 2 Main results of the survey



CMT = Charcot-Marie-Tooth disease.

example with overlapping motor neuropathy and myopathy or ataxia. However, no classification can realistically cover each individual problem and we think that, from a physician point of view, the most important clinical feature to be displayed in a classification is simply the most obvious one. Nevertheless, future discoveries in the field of hereditary disorder will probably drive changes in their classification.

Conclusions

The increasing number of genes that have been discovered (and the various additions made) over the years has resulted in a dramatic complication of the CMT classification. Through the simple survey that we performed, it is clear that the vast majority of CMT specialists want this method of classification to be modulated and simplified. As such, our proposals for modifications have been well received by the scientific community and may thus be a first step; however, the validation of a new classification method (possibly extended to other neurogenetic disorders) would require further discussions by expert working groups in a way that needs to be discussed within the scientific and medical communities.

Author contributions

Laurent Magy: study concept and design, acquisition and interpretation of data. Stéphane Mathis: drafting of the manuscript. Gwendal Le Masson: critical revision of the manuscript. Cyril Goizet: critical revision of the manuscript. Meriem Tazir: critical revision of the manuscript. Jean-Michel Vallat: study concept and design and critical revision of the manuscript.

Study funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Received September 22, 2017. Accepted in final form December 4, 2017.

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