REVUE NEUROLOGIQUE XXX (2016) XXX–XXX

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Update in Neurosciences

Classifications of neurogenetic diseases: An increasingly complex problem

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INFO ARTICLE

Article history:
Received 7 January 2016
Accepted 4 April 2016
Available online xxx

Keywords:
Classification
Charcot–Marie–Tooth
HSAN
Spastic paraplegia
Cerebellar ataxia

ABSTRACT

Neurodegenerative disorders represent a wide group of diseases affecting the central and/or peripheral nervous system. Many of these disorders were described in the 19th century, but our genetic knowledge of them is recent (over the past 25 years). However, the continual discovery of disease-causing gene mutations has led to difficulties in the classification of these diseases. For this reason, our present proposals for updating and simplifying the classification of some of these conditions (Charcot–Marie–Tooth diseases, distal hereditary motor neuropathies, hereditary sensory and autonomic neuropathies, hereditary spastic ataxias, hereditary spastic paraplegias and hereditary spastic ataxias) are expounded here.

1. Introduction

Neurogenetic diseases belong to a set of conditions induced by an abnormality in one or more genes that mainly code for proteins of the neuroectoderm and its derivatives. Since the 1980s, when the first genes were identified, a large number of genes have been implicated in these diseases. The description of gene alterations (especially an increase in their number) has complicated the classification of these hereditary, genetically heterogeneous conditions, which are also characterized by a multiplicity of clinical, electrophysiological and pathological phenotypes.

A salient example of this complexity is Charcot–Marie–Tooth disease (CMT), the most common inherited disorder of the peripheral nervous system, with an estimated average prevalence of up to 1/1214 [1]. Indeed, the wide variability of phenotypes (and especially the involvement of > 70 genes) has led to a system of classification that is increasingly difficult to understand even for experts in the field (Table 1). In a recent publication [2], the present authors made some proposals for simplifying this classification to render it accessible not only to neurologists and geneticists, but also to patients and their families. It is important to expound these proposals more widely to stimulate debate, with the aim to reach a consensus on a simplified and more accessible classification system. In

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http://dx.doi.org/10.1016/j.neurol.2016.04.005

addition, the essence of our present proposals is that it could also be applied to many other neurogenetic diseases as well as CMT. Furthermore, our proposed classification has the added advantage of being easily updated as new gene alterations are identified [3].

The present report deals with our proposals for CMT, sensory and autonomous hereditary neuropathies (HSANs), hereditary cerebellar ataxias (HCAs), hereditary spastic paraplegias (HSPs) and hereditary spastic ataxias (SPAXs).

2. Charcot–Marie–Tooth disease (CMT)

CMT is a heterogeneous syndrome with a multiplicity of clinical, electrophysiological, pathological and genetic phenotypes that are partly responsible for the complexity of the current classification. Clinically, patients with CMT present a somewhat homogeneous phenotype characterized by peroneal atrophy, skeletal anomalies (possibly), hollow foot arches and a reduction or loss of tendon reflexes. The variety of clinical phenotypes stems from the presence of additional clinical signs in certain patients, which can only be detected by a full clinical examination, including pyramidal signs, optic neuritis, deafness and retarded development, all of which have been previously listed elsewhere [2]. Recognition of these clinical signs may point to the involvement of certain genes, referred to as ''CMT-plus'' [4]; however, this designation is, in fact, no longer appropriate as the various gene changes can now be attributed to various subtypes of CMT. With regard to hereditary transmission in Western countries, most subtypes of CMT have an autosomal-dominant transmission (AD); in addition, there are also X-linked (XL) and autosomal-recessive (AR) forms, with the latter being more prevalent in Mediterranean countries (stemming from a high degree of consanguinity in that part of the world).

The complexity of the current classification is even greater for hereditary neuropathies of very early onset (which are, in fact, CMT): these include congenital hereditary neuropathy, congenital amyelination, congenital hypomyelinating neuropathy, Dejerine–Sottas syndrome, severe early-onset axonal neuropathy, early-onset hereditary motor sensory neuropathy of axonal type and congenital axonal neuropathy. However, our proposed classification does not find it useful to consider these forms as separate entities [2], but instead includes them as subtypes of CMT characterized by alteration of a given gene.

Based on electrophysiological findings, Dyck and Lambert [5,6] distinguished demyelinating from axonal forms. This dichotomy relies on the motor conduction velocity of the median nerve: cases where the velocity is > 38 m/s are regarded as ''axonal'', while those < 38 m/s are classified as ''demyelinating''; subsequently, an ''intermediate'' form was identified in patients with conduction velocities between 30 and 40 m/s [7,8]. The demyelinating forms are the most common (constituting around two-thirds of cases). Pathological findings have identified a variety of lesions classified not only according to type (demyelinating, axonal and intermediate), but also according to the mutated gene; for example, for the *MPZ* gene, abnormalities of myelin compaction are observed, while mitochondrial genes such as *MFN2* and *GDAP1* are responsible for mitochondrial alterations [9]. The characteristic microscopic lesions can only be identified by ultrastructural analysis of a nerve biopsy, which is nowadays only carried out in rare cases (for example, when the gene remains unspecified). Nevertheless, these pathological changes cannot always be explained by molecular genetics as, in many cases, the function of the protein coded by the mutated gene is not known. Yet, despite the wide genetic heterogeneity in CMT and with > 70 genes implicated in hereditary sensorimotor neuropathies, an analysis of recent studies, including large personal series [10,11], found that only four mutated genes caused 90% of CMT disease, including CMT1A (*PMP22* duplication), CMTX1 (*GDAP1*), CMT2A (*MFN2*), CMT1B (*MPZ*) and HNPP (*PMP22* deletion) [12].

Moreover, it seems logical to lump these forms of hereditary sensorimotor neuropathies together with the distal hereditary purely motor neuropathies (dHMNs), considering the clinical and molecular overlap between CMT and dHMNs.

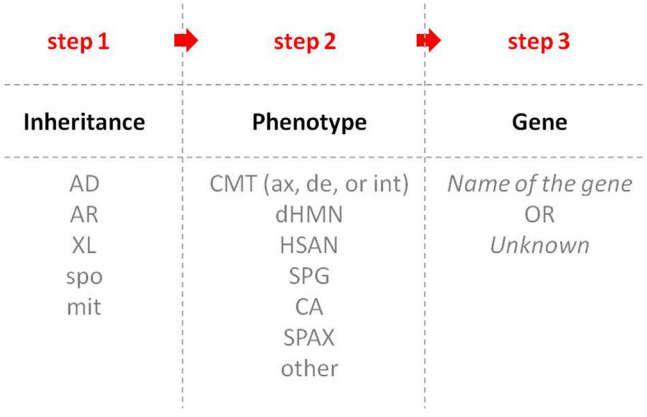

Fig. 1 – Schematic representation of the different steps in a new system for designating and classifying genetic disorders. AD: autosomal-dominant; AR: autosomal-recessive; XL: X-linked; spo: sporadic; mit: mitochondrial transmission; CMT: Charcot–Marie–Tooth disease; ax: axonal; de: demyelinating; int: intermediate; dHMN: distal hereditary motor neuropathy; HSAN: hereditary sensory and autonomic neuropathy; SPG: hereditary spastic paraplegia; CA: hereditary cerebellar ataxia; SPAX: hereditary spastic ataxia.

Please cite this article in press as: Vallat J-M, et al. Classifications of neurogenetic diseases: An increasingly complex problem. Revue neurologique (2016), http://dx.doi.org/10.1016/j.neurol.2016.04.005