Automated prediction procedure for Charcot-Marie-Tooth disease

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Abstract— **The diagnosis of inherited peripheral neuropathies can be a challenging issue in several ways. Current research is focused on a multidisciplinary approach, developing new therapeutic strategies mainly involving online databases and repositories for sharing data and models used in some clinical trials. In this paper authors introduce the general architecture of an automated neural network based model for simulating the prediction procedure of Charcot-Marie-Tooth disease, according to the latest clinical studies.**

I. Introduction

Peripheral neuropathy describes damage to the peripheral nervous system. The nerve fibers most distant from the brain and the spinal cord malfunction first. While every peripheral nerve has a highly specialized function in a specific part of the body, a wide array of symptoms are reported. Some patients may experience temporary numbness, tingling, and pricking sensations (paresthesia), sensitivity to touch, or muscle weakness. Others may suffer more extreme symptoms, including burning pain (especially at night), muscle wasting, paralysis, or organ or gland dysfunction. More than 100 types of peripheral neuropathy have been identified, each with its own characteristic set of symptoms, pattern of development, and prognosis. Impaired function and symptoms depend on the type of nerves-motor, sensory, or autonomic-that are damaged. Motor nerves control movements of muscles under conscious control, such as those used for walking, grasping things, or talking. Sensory nerves transport information about sensory experiences, such as the feeling of a light touch or the pain resulting from a cut. Symptoms are related to the type of affected nerve and may be seen over a period of days, weeks, or years. Muscle weakness is the most common symptom of motor nerve damage. Sensory nerve damage causes a more complex range of symptoms because sensory nerves have a wider, more highly specialized range of functions. Damage to large sensory fibers lessens the ability to feel vibrations and touch, resulting in a general sense of numbness, especially in the hands and feet. Diagnosing peripheral neuropathy is often difficult because the symptoms are highly variable. A thorough neurological examination is usually required and involves taking an extensive patient history, following performing tests that may identify the causative gene of the neuropathic disorder, and conducting tests to determine the extent and type of nerve damage. The most common form of inherited peripheral neuropathy is Charcot-Marie-Tooth disease (CMT), also called Hereditary Motor and Sensory Neuropathy (HMSN) with estimated prevalence one in 2500 people [1]. CMT disease is a genetically heterogeneous group of conditions that affect the peripheral nervous system, characterized by degeneration or abnormal development of peripheral nerves, with a large range of patterns of genetic transmission [2]. In 1968, CMT was subdivided based on pathologic and physiologic criteria into 2 types: a predominant demyelinating process resulting in low conduction velocities (CMT1) and a predominant axonal process resulting in low potential amplitudes (CMT2). Genetic testing has improved the classification of specific CMT phenotype and allows for definitive diagnosis of about 70% of patients, since advances in cell biology have provided clues as to how particular mutations are linked to the disease. So far more than 30 genes have been identified to be associated with CMT. Some of the causative proteins have been the subject of many molecular biology studies, which have so far indicated that, the initial classification of neuropathy as demyelinating (CMT1), or axonal (CMT2), is somewhat artificial, since genetic overlap has become evident between the CMT1 and CMT2 phenotype. Moreover, there is not a good genotype-phenotype correlation and since great variability exists the diagnostic process has become complicated and therefore, there are still few answers to the questions about prognosis and treatment.

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II. Diagnostic Procedures

Today there is no single test or biomarker that can predict whether a particular person will develop CMT and a definitive diagnosis must follow a logical sequence of investigations [3-8]. A structured evaluation will involve the following steps:

- Definition of the clinical phenotype.
- Identification of the inheritance pattern.

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- Electrophysiological examination.
- Molecular analysis in order to identify the causative gene.

Recently with the advent of genetic testing, Magnetic Resonance Imaging (MRI) procedures as well as skin biopsy have been emerged as potential diagnostic tools for patients with uncertain molecular diagnosis or for patients with atypical presentation, although there have not been proved yet more efficient than electrodiagnostic techniques in cases of demyelinating pathology. With no specific diagnostic tools, physicians must focus on assessing natural history and clinical symptoms, including age of onset, disease severity and presence of uncommon associated features, in order to guide molecular investigations.

Nerve conduction studies should be done to assess the presence, degree, and pattern of nerve-conduction slowing. Diffuse and homogeneous nerve-conduction velocity slowing (<38m/s in upper-limb motor nerves) is classified as demyelinating CMT (CMT1 and CMT4), whereas normal or only mildly slowed nerve-conduction velocities (>38 m/s in median or ulnar motor nerves) with reduced compound muscle and sensory action potential amplitudes is classic of CMT2. Some of the main diagnostic problems occur in patients with intermediate nerve-conduction velocities. Subsequently, genetic tests are needed, which will determine the relative gene in that CMT subtype. A single laboratory cannot afford to undertake all the investigations. Therefore, requests for DNA testing need to take this limitation into account [8].

In typical cases, the signs and symptoms start in the first or second decade of life and the disease subsequently has a slowly progressive course. However, knowledge of the natural history, and age of onset is not a determinative factor in order to predict rate of progression, and overall severity. Disease course may vary depending on the CMT form, causative gene, and type of mutation. Moreover, substantial phenotypic variability occurs even within the same CMT type [9].

Autosomal-dominant inheritance is the most common pattern in CMT1 and most CMT2 and dHMN cases. However sporadic cases -occur as dominantly inherited disorders- may begin as a new mutation in a given patient. Knowing the genetic cause of a CMT patient is critical since family planning and prognosis require an accurate genetic diagnosis. However, the large number of CMT relating genes is often challenging for clinicians and patients (more than 30 genes and more than 44 distinct loci have been identified [10]. There is little information available to guide which gene to test and testing a patient for mutations in all commercially available CMT genes is not cost effective [11]. Therefore not every patient with a genetic neuropathy want or need to identify the genetic cause of their disease, due to several reasons, including high costs of commercial testing and fears of discrimination in their workplace [12]. For cases when the gene is not yet known or is recently identified, a serious issue arises while clinical laboratories do not provide commercial diagnostic testing. Competent genetic counseling is extremely important in clinical practice and selection of appropriate and rational testing must be considered carefully and discussed with the patient before proceeding with testing. Even comprehensive testing does not exclude novel forms of the disease.

The growing number of identified CMT genes and their proteins seems to be involved in the maintenance of normal nerve function and are necessary for the normal function of myelinated axons in the peripheral nervous system (PNS). A key question is whether all the pathogenic mutations associated with CMT lead to disease by mechanisms converging on a limited number of dysfunctional pathways, or alternatively, does each genetic mutation lead to peripheral nerve degeneration by a distinct mechanism [13]? Identifying the causative gene is only the beginning of unfolding the molecular mechanisms underlying major forms of CMT. A growing body of evidence has highlighted the role of mitochondrial dysfunction and the disruption of mitochondrial dynamics in CMT. Several hypotheses have been proposed to explain the role of fusion/fission dynamics in the mitochondrial lifecycle and maintenance. Mitochondrial dynamics describes the continuous change of shape and location of mitochondria, a process which has a key role for the distribution and reaction of mitochondria to functional requirements [14]-[18]. Neurons are particularly dependent on proper control of these dynamics, since defects in the dynamic nature of mitochondrial population cause neuronal dysfunction. Some of the possible mechanisms involving mitochondrial dynamics alterations, which can lead to Neurodegeneration, are: aberrant mitochondrial trafficking, altered interorganellar communication and impaired mitochondrial quality control.

III. Identification of the Correlations between Genotype and Phenotype

Genetic testing that has been made in different CMT types has showed that there is substantial overlap between CMT1, CMT2 and the intermediate forms, and between CMT2 and dHMN. Four genes can cause both CMT2 and dHMN, leading to a predominant motor neuronopathy and no (dHMN) or mild (CMT2) sensory neuronopathy. CMT2 is characterized as primarily axonal disorder. Studies from nerve biopsies reveal axonal loss with wallerian degeneration. CMT2 has a highly heterogeneous genotype and type 2A accounts for about 20 percent of CMT2. CMT2A is caused by mutations in the mitofusin2 gene (MFN2), which codes for a mitochondrial protein [19]. Current hypothesis propose that a mitochondrial transport

defect could be the cause of CMT2A. Targeting mitochondrial dysfunction might be a potential therapeutic approach.

Approximately 50% of CMT cases are accounted for CMT1A. This type seems to be caused by an alteration on PM22 gene. Studies have shown that it is the dosage of PMP22 that determines the type and the extent of the neuropathy [12].

Consequently, evaluation of the patient for whom genetic

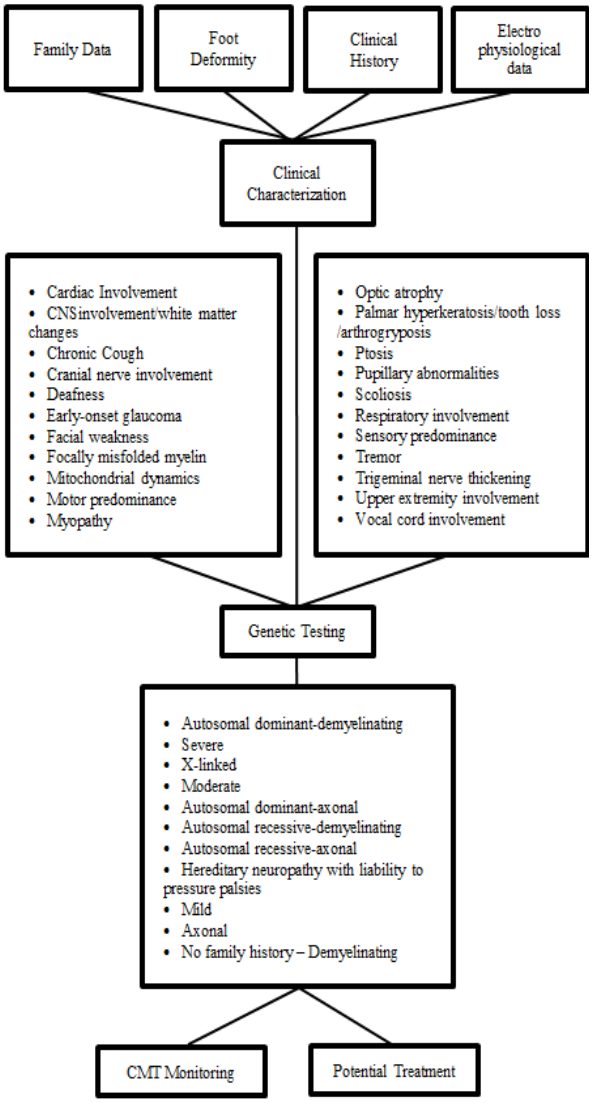

Fig. 1. The proposed multilayer neural network. The inputs are either CMT symptoms or unusual features and genetic tests and the outputs are the corresponding possible treatments and symptoms' monitoring.

testing is being contemplated should determine the target of the drug therapy. A focused treatment strategy includes a detailed examination for unusual phenotypic features suggesting specific genotypes. As experience with genotype–phenotype correlation grows, algorithms will likely become available that help guide genetic testing [20].

CMT also needs to be differentiated from other hereditary neuropathies, from acquired neuropathies, distal myopathies, motor neuron diseases, hereditary ataxias, mitochondrial disorders, hereditary spastic paraplegias, and leucodystrophies. Current treatment trials depend on knowing the genetic cause of a patient's CMT even if no cures are presently available [11]. Moreover patient's history can be falsely unremarkable, because of the extent of variable expression and oligosymptomatic patients who elude diagnosis. There is still no effective drug therapy for CMT [21,22]. Supportive treatment is limited to rehabilitative therapy and surgical treatment of skeletal deformities and soft-tissue abnormalities [9].

IV. The Neural Network Architecture

A clinical diagnosis approach will include several steps: At first the clinical evaluation; an approach to electrodiagnosis with commentary on technical and interpretative errors; clinical and diagnostic features of inflammatory hereditary neuropathy must be suspected. Although some patients have a clear disease history, other requires directed inquiry. Secondly, even when a hereditary neuropathy is clear, it can be difficult to make a genetic characterization. While the field of genotyping is expanding so rapidly, it is difficult to know what tests to order.

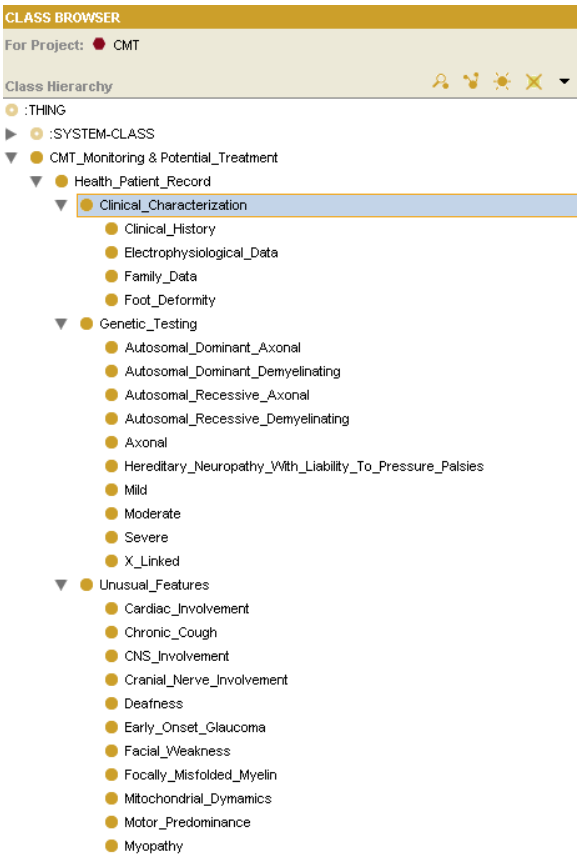

Fig. 2. The CMT classes in Protégé

In the proposed system, the patient diagnosis will be implemented using a multilayer neural network (Fig.1). Multilayer networks solve the classification problem for nonlinear sets by employing hidden layers, whose neurons are not directly connected to the output. The additional hidden layers can be interpreted geometrically as additional hyper-planes, which enhance the separation capacity of the network. The five feed forward layers that are be used in this study, the roles, the properties and their corresponding values, are based on recent studies concerning the diagnosis of CMT types [2, 19]. The input layer corresponds to the

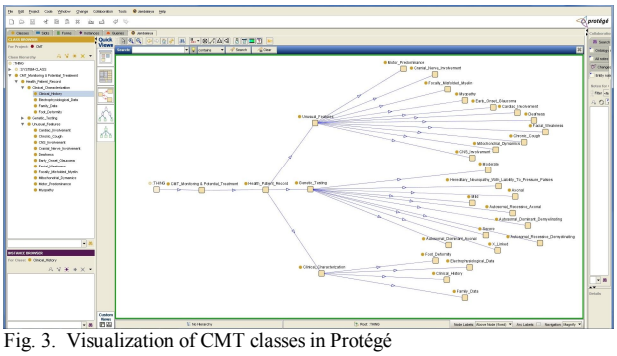

Fig. 3. Visualization of CMT classes in Protégé

first physician's evaluation (Family Data, Foot Deformity, Clinical History, Dissociation between Symptoms and Examination, Electrophysiologic Data, Negative Work-up for Acquired Etiologies, Mode of Inheritance) and it's highly associated with the most likely inheritance pattern leading to a general clinical classification. A third hidden layer concerning a few unusual pathophysiological features is then applied and linked to the clinical characterization in order to fed forward to the proper genetic test, avoiding useless and highly costing further testing. Finally the output layer correspond to CMT symptoms' monitoring and possible treatments available to patients their families and their physicians. While this is the first theoretical attempt for a decision support system on CMT, authors have already scheduled the implementation of this model through an ontology based framework using the Protégé platform [23].

In this paper we used Protégé Version 3.4.8 for the initial creation and visualization of the main ontology '*CMT Disease Ontology*' that will be used as an extension of the shared ontology '*Disease Ontology*'. The main class of the proposed system named '*CMT_Monitoring & Potential_Treatment*' will be used for progress monitoring and treatment of CMT Disease. Some of the subclasses of the system can be seen in Figures 2 and 3. The proposed system will handle (from storage to data association) various data, such as biomarkers, images or even more genetic material offering the opportunity to the physicians to decide more accurate and faster about the disease progression. In future work, supervised learning models will be used for the data training of the proposed neural network and retrospective patient data for its validation.

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