Charcot-Marie-Tooth type 1A disease from patient to laboratory

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Abstract

Charcot-Marie-Tooth (CMT) disease is a well-known neural or spinal type of muscular atrophy. It is the most familiar disease within a group of conditions called Hereditary Motor and Sensory Neuropathies (HMSN). The disease was discovered by three scientists several years ago. Several genes are involved as the causative agents for the disease. Hundreds of causative mutations have been found and research work for the identification of a novel locus and for the treatment of CMT1A is going on. This review article was planned to gather information on CMT disease and updates on its treatment.National Center for Biotechnology Information(NCBI) and PubMed were searched for data retrieval. Molgen database, which is the exclusive site for CMT mutation, was the other source of articles. Different aspects of the CMT disease were compared.Advancements in the finding of the causative gene, discovery of the novel Loci are the current issues in this regard.CMT disease is incurable, but researchers are trying to get some benefits from different natural compounds and several therapeutic agents.Various groups are working on the treatment projects of CMT1A. Major step forward in CMT research was taken in 2004 when ascorbic acid was used for transgenic mice treatment.Gene therapy for constant neurotrophin-3(NT-3) delivery by secretion by muscle cells for the CMT1A is also one of the possible treatments under trial.

Keywords: Charcot-Marie-Tooth disease, Peroneal dystrophy, Ascorbic acid, Nerve conduction velocity, Demyelintion.

Introduction

Charcot-Marie-Tooth (CMT) sickness is a well-known neural or spinal style of muscular atrophy. It is the most common sickness with a bunch of symptoms also referred as Hereditary Motor and Sensory Neuropathies (HMSN). Marie, together with his pupil Charcot in February 1886, explained five cases of this progressive muscular atrophy that was speculated to be caused by myelopathy. This

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work was Charcot's last prominent contribution to orthodox neurology.[1] In the running year (1886), Howard H. Tooth delivered his thesis at the University of Cambridge titled "The peroneal type of progressive muscular atrophy". Prime atrophy of the skeletal muscle was described by him and he assumed the condition to be a peripheral pathology. Even older reports could also be recognised in literature.[2] CMT sickness may be a clinically and genetically heterogeneous cluster of body process peripheral neuropathies and represents the foremost frequent genetic disorder(s) moving the system, with a prevalence rate of 36/100,000.[3]

The syndrome has distinct features of slow progression of wasting and weakness of distal muscles, the gloves and feet, caused by degeneration of the peripheral nerves, nerve roots, as well as the spinal cord, with wastage of reflexes, loss of cutaneous sensations and development of foot drop. Optic atrophy is usually present.

Classification

Based on electrophysiological and pathological studies, CMT has been divided into 2 large distinct groups.[4] CMT type 1 (CMT1, HMSNI), the demyelinating type, that shows mild to harsh reduction in motor nerve conduction velocities (NCV), absent muscle stretch reflexes, and the formation of onion bulb appears in nerve biopsy. CMT type 2 (CMT2, HMSNII), the neuronal form, shows normal or moderate reduction in motor NCVs and decreased amplitude, normal muscle stretch reflexes, and no hypertrophic characteristics on nerve biopsy. This classification imply that the demyelinating form of CMT1 may be caused by an abnormality of Schwann cells. Latest classification was done in 2009[5] (Table).

Delineation was suggested in the 1970s focusing on assemblage of most general CMT variants as HMSN. In CMT1 the myelinating Schwann cells are affected, while axons are devolved in CMT2. In addition, these two autosomal dominant inherited CMT categories, recessive and X-linked demyelinating and axonal CMT subtypes, have been described and also included in the HMSN classification.[6] Focusing on the severity of motor or sensory deficiency, other CMT variants were grouped mainly into distal hereditary motor neuropathies (distal HMN) and hereditary sensory and autonomic

Table: Genetic classification of Charcot-Marie-Tooth disease major types.

CMT1A	17p11.2	PMP22	Peripheral myelin protein 22	118220
CMT1B	1q22	MPZ	Myelin protein zero	118200
CMT1C	16p13.1-p12.3	SIMPLE/LITAF	SIMPLE	601098
CMT1D	10q21.1-q22.1	EGR2	Early growth response protein 2	607678
CMT1E	17p11.2	PMP22	Peripheral myelin protein 22	118220
CMT1F	8p21	NEFL	Neurofilament triplet L protein	607684
CMT2A	1p36	MFN2	Mitofusin 2	118210
CMT2B	3q21	RAB7	Ras-related protein Rab-7	600882
CMT2B1	1q21.2	LMNA	Lamin A/C	605588
CMT2B2	19q13.3	Unknown	Unknown	605589
CMT2C	12q23-q24	Unknown	Unknown	606071
CMT2D	7p15	GARS	Glycyl-tRNAsynthetase	601472
CMT2E/F1	8p21	NEFL	Neurofilament triplet L protein	607684
CMT2F	7q11-q21	HSPB1	Heat-shock protein B1	606595
CMT2G	12q12-q13	Unknown	Unknown	608591
CMT2H	8q21.3	Unknown	Unknown	607731
CMT2I	1q22	MPZ	Myelin protein zero	118200
CMT2J	1q22	MPZ	Myelin protein zero	118200
CMT2K	8q13-q21.1	GDAP1	Ganglioside-induced differentiation protein 1	214400
CMT2L	12q24	HSPB8	Heat shock protein B8	608673
CMT4A	8q13-q21.1	GDAP1	Ganglioside-induced differentiation protein 1	214400
CMT4B1	11q22	MTMR2	Myotubularin-related protein 2	601382
CMT4B2	11p15	SBF2/MTMR13	SET binding factor 2	604563
CMT4C	5q32	SH3TC2	SH3TC2	601596
CMT4D	8q24.3	NDRG1	NDRG1 protein	601455
CMT4E	10q21.1-q22.1	EGR2	Early growth response protein 2	607678
CMT4F	19q13.1-q13.2	PRX	Periaxin	145900
CMT4G	10q23.3	Unknown	Unknown	605285
CMT4H	12p11.21-q13.11	FGD4	FRABIN	609311
CMT4J	6q21	FIG4	FIG4	611228
DI-CMTA	10q24.1-q25.1	Unknown	Unknown	606483
DI-CMTB	19p12-13.2	DNM2	Dynamin 2	606482
DI-CMTC	1p35	YARS	Tyrosyl-tRNAsynthetase	608323
DI-CMTD	1q22	MPZ	Myelin protein zero	607791
CMTX	Xq13.1	GJB1	Gap junction -1 protein, connexin 32	302800

neuropathies (HSAN).[7] Lately, clinical and genetic imbrications have been described between CMT neuropathies and hereditary spastic paraplegias. Besides, scattered cases with more complex clinical phenotypes involving other tissues, such as skin and bone, have been reported, further complicating the original CMT classification.[8-10]

Inheritance

CMT disease commonly unfolds in childhood or adolescence and moves sluggishly, but may come down in adults; more common in males than in females. Its cause is unfamiliar. The affected child has normal intelligence, and a normal life span. It is transferred as an autosomal dominant or in recessive fashion in some families and as X-linked mode in others. The most familiar mode of inheritance for CMT is autosomal dominant,

which describes that where one parent has CMT, there is a 50% (1 in 2) chance of each and every child to get affected.

There are three unique inheritance forms that encircle all the many variations of CMT: Autosomal Dominant Inheritance; Autosomal Recessive Inheritance; and X-Linked Inheritance.

Symptoms

Persons with CMT go through symmetric, slowly progressive distal motor neuropathy of the hands and legs, usually starting in the first to third decade and resulting in weakness and atrophy of the muscles in the feet and/or hands. Pescavus foot disfigurement is common. Inspiteof the fact that CMT disease is usually explained as "painless," the neuropathy of CMT may be painful.[11]

Clinical appearance is similar for CMT disease originating by mutations in many different genes engaged in very diverse affairs, coding for structural myelin proteins, gap-junction forming proteins, cytoskeleton elements, enzymes, transcription factors, and many more. Improper function of all these proteins, even when mainly affecting myelin, ultimately results in axonal deterioration which is length-dependent.[12,13]

Major clinical symptoms of CMT disease are a combination of the motor and sensory neuron type, which shows the sensory-motor neuropathy. The symptoms are length-dependent, which can be partial paralysis or result in muscle atrophy which leads to loss of reflexes but a number of patients will keep the reflexes in axonal type of CMT disease.

Motor neuropathy prevailing for long period of time will result in foot distortion, which can be in any form like hammer toes and pescavus feet. The symptoms of the disease also appear in hands as the disease progresses. Genes are involved in both sensory and chronic neuropathies, but sensory neuropathies are not frequent. Symptoms of the sensory dysfunction frequently appear in almost 70% patients and include the failure of vibration, joint sensation succeeded by the loss of pain and temperature sensation in hand and foot. Axonal and demyelination forms cannot be distinguishedon the basis of clinical symptoms (Figure-1).

On the basis of electrophysiological exploration, CMT sickness can be categorised into two types:the demyelinating form, which has the characteristic of sluggish NCV; usually <38 m/s), and the second form is axonal form that is hooked up with normal or subnormal NCV; and lowered compound muscle action potential.

Genetics

CMT disease is defined by a clinically and genetically miscellaneous group of neuropathies that include all categories of Mendelian inheritance patterns. More than 1,000 different mutations have been found in 80 disease-affiliated genes. Genetic research on CMT has resulted in the discovery of genomic disorders and helped in understanding the effects of copy number variation and the mechanisms of genomic rearrangements.[14]

The inaugural CMT locus was mapped in 1982 and 30 years of genetic research has not only led to successful exploration of 80 disease-causing genes, but also initiated the discovery of unfamiliar genomic mechanisms.[15] Loci and genes for CMT and affiliated peripheral neuropathies were initially identified using genetic linkage analysis, positional cloning, or candidate gene methodologies. As

Figure-1: Close-up pictures of the feet showing severe pescavus and varus, toe clawing and atrophy.Close up pictures of the feet illustrating moderate pescavus and toe clawing that almost disappears during standing up.
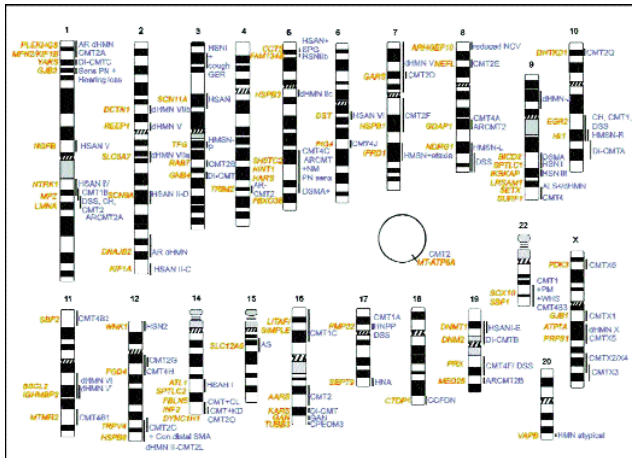
Figure-2: Genes and loci for Charcot-Marie-Tooth (CMT) and related inheritedperipheral neuropathies.

the Human Genome project was completed in 2001[16] the development of high-throughput technologies, such as whole genome mapping (WGM), whole genome sequencing (WGS), and whole exome sequencing (WES) accelerated the gene and mutation discovery in CMT research[17] (Figure-2).

In spite of the fact that CMT seems to resemble an acquired neuropathy — a type of nerve damage responsible for diabetes, immunological abnormalities or vulnerability to certain chemicals or drugs — it isn't caused by anything a person does, and it is not contagious,which means that it can be transferred from one generation to the next.

Diagnosis

NCV studies are performed to evaluate the presence, degree and pattern of conduction slowing along motor and sensory nerves, and in proximal as well as in distal segments. Conduction slowing provides indirect evidence of myelin dysfunction and is usually considered a sign of demyelination or hypomyelination. However, NCV reduction may also be caused by other mechanisms, including abnormalities of ion channels, of nodes and paranodes, and of Schwann cell-axon interactions.[18] The degree of axonal damage and loss of fibres are reflected in a reduction in amplitude of compound muscle action potential (CMAP) for motor nerves, and of sensory nerve action potential (SNAP) for sensory nerves. Both axonal and demyelinating CMT ultimately end in loss of axons and in reduction of CMAP and SNAP amplitudes.[19]

Combined effects of lower leg weakness and foot deformities are really severe, but not solely helpful in

diagnosis. A neurologist will examine the patient physically to look for extremities' weakness and sensory loss. The neurologist will start cross-questioning about the symptoms and conditions. To look for sensory loss, the neurologist will usually test the patient's deep tendon reflexes (like the knee-jerk reflex), which are reduced or absent in most people with CMT. During this primary testing, the neurologist will also inquire about patient's family history. Family history of the person suffering from CMT-like symptoms and nerve damage in physical exam can lead to the CMT or some other hereditary neuropathy. The neurologist may perform a NCV test to calculate the momentum of electrical signals travelling through nerves. It is performed by putting surface electrodes, analogous to those used for electrocardiograms, on the skin at various points over a nerve. One electrode delivers a mild shock that enhances an electrical response in the nerve, and the others record this response as it travels through the nerve.

CMT1A
PMP22 Gene Dosage Change: Potential Therapy for CMT1A

Alterations of PMP22 gene dosage result in two different disease entities. Approximately 50% of CMT cases are resulted by CMT1A, resulted by 1.4-Mb duplication on chromosome 17 containing the PMP22 gene; deletion of the same region results in Hereditary neuropathy with liability to pressure palsies(HNPP) (Figure-3). The dosage of PMP22 is believed to be responsible.[20]

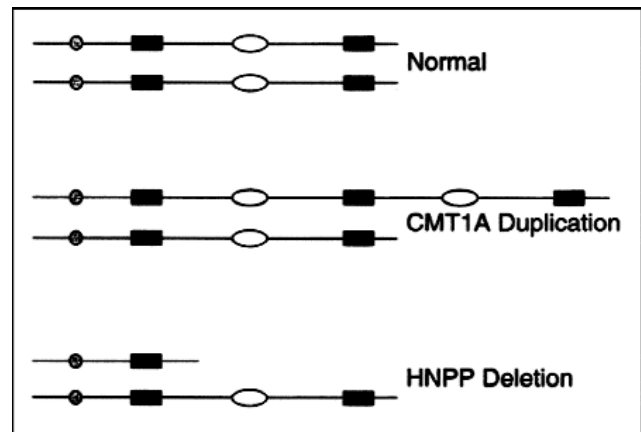The commonest form of CMT disease is CMT1A.The mean

Figure-3: Structure of CMT1A duplication and HNPP deletion. Chromosome 17 homologues are depicted with filled circle representing the centromere, filled rectangles corresponding to the flanking CMT1A-REP repeat, and the open oval depicting the PMP22 gene. The chromosome 17p short arm is not drawn to scale and the 1.5 Mb tandem duplication and 1.5 Mb deletion are not visible by conventional clinical cytogenetics techniques.

age for the appearance of clinical symptoms is 12.2±7.3 years. NCV less than 38m/s can be easily diagnosed and is independent of age.

The search for the CMT1A disease gene was misdirected and impeded because some chromosome 17 genetic markers that are linked to CMT1A lie within the duplication. Matise[21] demonstrated that the ratio of transmission of the disease is disturbed by the presence of the unexplored duplication, that the undetected presence of a duplication distorts transmission ratios, inhibit fine localisation of the disease gene, and increase the false evidence of linkage heterogeneity. Similar method was designed by them on the basis of the presence of a tandemly duplicated marker. Other researchers[22] developed a fast, informative, cheap and easily understandable non-radioactive test for CMT1A duplication finding based on microsatellite polymorphism. The accuracy was higher in this method as CMT1A duplication was detected in 76% of 56 unrelated patients.

In spite of the fact that there is no cure for CMT, there are multiple therapies like physical therapy, occupational therapy, braces and other orthopaedic devices. Even orthopaedic surgery can aid individuals to manage with the disabling signs of the disease. Some pain-killer drugs can also be suggested for the patients who have intense pain. Such interventions can immensely improve life and function for CMT patients.

Although medical professionals are involved in many stages and forms of treatment, the patients themselves are responsible for much of the management of CMT. In mid-90s researchers executed the expansive dispensation of PMP22 ribonucleic acid (RNA) in various mesodermal and ectodermal tissues of growing mice, also in the villi of the matured gut, indicating a broader biologic importance for PMP22 in cell multiplication or specialisation.[23]

One year later a mouse model was created by bearing the PMP22 gene as well as the major portion of the duplicated region in CMT1A.[24] One of the transgenic line eight copies of human deoxyribonucleic acid (DNA) was injected into mouse chromosome and it showed the symptoms of the CMT1A, intense demyelination in the peripheral nervous system, and the existence of onion bulb formations.

Few years later, another set of researchers[25] created a transgenic model for CMT, but it was to check the over-expression of PMP22 gene in the presence of tetracycline. Over-expression of the gene resulted in demyelination. Over-expression is almost normal when the mice were fed on tetracycline. It was also noticed that when over-expression was switched off, correction also started in a few days. The study supposed that even adult mice were sensitive to the level of expression of PMP22 with regard to homeostasis of the myelin sheath. Another study also noticed that the antagonist of progesterone, on a pristone, reduced the over-expression of PMP22 and had remarkable effect on male mice, as noticed by maintenance of large axons and better NCV. The study supposed that a reduction in over-expression of PMP22 may have a positive effect on disease pathways[26] (Figure-4).

After the test of some chemical effects, some hormones were also tested by some researchers. For example, it was observed that progesterone showed significant effect on PMP22 gene expression both invitro and invivo.[27]

He observed that in mutant mice over-expressing PMP22, with ascorbic acid treatment, phenotype was improved as well as improvement in motor function was also noticed which resulted in increased survival. Ten-fold decrease of PMP22 RNA in sciatic nerve was also observed. A 2004 study found that ascorbic acid was the promoter of myelination, and suggested the mechanism of PMP22 suppression through inhibition of cyclic adenosine monophosphate (cAMP).[28]

Several dominant MPZ mutations, including R98C, present as an infantile onset of dysmyelinating neuropathies. Saporta et al made an R98C 'knock-in'
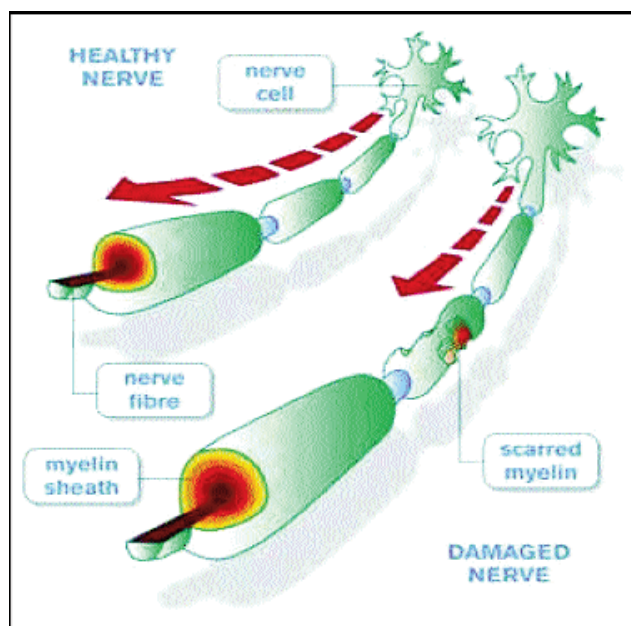

Figure-4: Charcot-Marie-Toothcauses demylination of the nerve fibres.

mouse model of Charcot-Marie-Tooth type 1B, where a mutation encoding R98C was targeted to the mouse Mpz gene. Both heterozygous (R98C/+) and homozygous (R98C/R98C) mice expand flaw, irregular nerve transmission velocities and morphologically unusual myelin; R98C/R98C mice are more cruelly affected. MpzR98C is retained in the endoplasmic reticulum of Schwann cells and provokes a transitory, canonical unfolded protein response. R98C/R98C Schwann cells are developmentally arrested in the promyelinating stage, whereas development is delayed in R98C/+ mice. Hence, a potential link between the gathering of MpzR98C in the endoplasmic reticulum and a developmental holdup in myelination occurs. These mice give a form by which we can begin to recognize the early onset dysmyelination seen in patients with R98C and alike mutations.[29]

Two teams described the first preclinical studies to illustrate proof of principle in support of AAV1.NT-3 gene therapy for constant NT-3 delivery by secretion by muscle cells for the familiar type of the CMT neuropathies, CMT1A. CMT1A is a popular prototype of a myelin disease by histological and electrophysiological standard, but at the moment exhibits a clinical phenotype typical of a length-dependent neuropathy resulting from preferential distal axonal loss.[30,31]

Earlier studies have described that in animal models of CMT, in addition to axonal pathology, there is wasted nerve regeneration.[32]

Increased myelin thickness in trembler nerves with NT-3 gene therapy from the earlier proposed inhibitory role for NT-3 in myelination[33] but supported an opposite role for NT-3 as shown by more recent in vivo studies.[34]

They reported a long-term efficacy of NT-3 gene therapy on TrJ nerve pathology comparing single-stranded and self-complementary vectors, treatment duration, doses and promoters. The biological systemic effect of NT-3 is intermediate midst which is loose from the muscle as showed with long-lasting therapeutic serum NT-3 levels and functional, histopathological and electrophysiological improvements observed not only in the vector-injected limb but also in the contralateral limb. The long-playing positive result of this treatment paradigm was certified with continuous improvement of magnetic field (MF) densities and connectivity map (CMAP) amplitudes over time. Studies carried for 40 weeks depicted obvious increased MF densities and CMAP amplitudes compared to 20 weeks post-treatment and baseline values. Moreover, correlative functional breakthrough was accomplished between grip strength and CMAPs that has potential for relevance in future clinical trials.

Zarife Sahenk, a neurologist and principal investigator at the Centre for Gene Therapy at Nationwide Children's Hospital in Columbus, Ohio, is running her research on gene therapy for CMT1A. She declared that mice with a CMT1A-like disease improved from a solo injection of genes for the NT-3 protein into a leg muscle. The gene delivery vehicle was the shell of a type 1 adeno-associated virus (AAV1). Now, Sahenk is continuing her research in NT-3 gene therapy for CMT, with the eventual result of moving towards a human trial." I have a National Institute of Health (NIH) grant to compare two different promoters ['on switches' for genes] at different doses to assess the efficacy of AAV1-NT3 gene therapy in this CMT1A mouse model," Sahenk said recently. "Efforts such as this are an essential step towards finding therapeutics for an ultimate clinical trial."[35]

Conclusion

Although CMT disease is incurable, but researchers are still trying to get some benefits from different natural compounds and several therapeutic agents.Various groups are working on treatment of CMT1A. A breakthrough happened in 2004 when ascorbic acid was used for transgenic mice treatment. Since then work is going on, but still no drug is used for human trials but hopefully it will happen soon.Based on current knowledge, intakes of vitamin C in excess of 400mg/d are not expected to provide additional benefits as cells are already saturated and the Institute of Medicine has set an upper limit of 2g/d which, albeit restrictive, would prevent adverse effects and, consequently, increase attrition. The randomised clinical trial carried out thus far confirm the tight control of ascorbic acid's pharmacokinetics and prove its tolerability at one and two years.

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