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A Review on Charcot-Marie-Tooth Disease

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Abstract: *Charcot-Marie-Tooth (CMT) disease is a group of inherited peripheral neuropathies characterized by progressive muscle weakness, sensory loss, and foot deformities. It is caused by mutations in genes responsible for myelin sheath formation or axonal function, leading to impaired nerve conduction and muscle atrophy. CMT is classified into demyelinating (CMT1), axonal (CMT2), and intermediate forms based on electrophysiological and genetic findings. Clinical manifestations include foot drop, high-arched feet, hand weakness, and reduced reflexes, with symptoms typically appearing in childhood or early adulthood. Diagnosis is based on clinical evaluation, nerve conduction studies, and genetic testing. While no cure exists, treatment focuses on symptom management through physical therapy, orthotic support, pain management, and, in some cases, surgical intervention. Advances in genetic research and potential therapies, including gene therapy and neuroprotective strategies, hold promise for future treatment..*

Keywords: Charcot-Marie-Tooth

I. INTRODUCTION

Charcot–Marie–Tooth (CMT) disease, also known as hereditary motor and sensory neuropathy (HMSN), is a genetically heterogeneous group of hereditary peripheral nerve diseases, mainly affecting peripheral axons and Schwann cells, with an estimated preva lence of 1:2500 individuals [1]. Originally, patients with CMT were described by Virchow, Eulenburg, Friedreich, Osler, and others as those with a disorder of peroneal muscular atrophy until, in 1886, Jean-Martin Charcot and Pierre Marie and Henry Tooth indepen dently described this neuropathy, and the name CMT has since been used [2]. As a length-dependent motor and sensory neuropathy, the disorder features a slowly progres sive muscular atrophy, starting in the feet (presenting as pes cavus or hammertoes) and legs and moving to the upper extremities , with segmental vasomotor disturbances, while the proximal muscles and muscles on the trunk, shoulders, and face have relatively high integrity
[3] .These are the usual phenotypes of the disease, as there are also some CMTtypes with much more severe phenotypes. By detection of specific alleles, mutations, genotypes, or karyotypes, genetic testing can also be used as a method for disease determination. For example, CMT1A usually detected with MLPA (multiplex ligation-dependent probe amplification) is caused by mutations in the peripheral myelin protein 22 gene (Pmp22), most often duplications and less commonly point mutations, which may cause a severe phenotype [4]. With the clinical application of genetic testing in disease assessment, CMT diagnostic methods were simplified, and decision-making processes in neuropathy were improved [4,5].

High throughput next-generation sequencing (NGS) technologies allow for thousands to billions ions of DNA fragments to be simultaneously and independently sequenced [6]. With NGS approaches, novel genes attributing to CMT development have been uncovered, and our knowledge of the pathogenic mechanisms behind CMT is improving. The further sub classification of CMT based on genetic heterogeneity has been conducted with the NGS approach. of DNA fragments to be simultaneously and independently sequenced [6]. With NGS approaches, novel genes attributing to CMT development have been uncovered, and our knowledge of the pathogenic mechanisms behind CMT is improving. The further sub-classification of CMT based on genetic heterogeneity has been conducted with the NGSapproach Although oral pain killers and supportive, rehabilitative, and surgical regimes may be helpful in the management of symptoms, the gene-specific treatments in current development are the most promising treatment modalities for neuropathy cures, for example, antisense

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oligonucleotide (ASO) treatments.Here, we review the pathogenic mecha nisms of and management perspectives on CMT disease. opment are the most promising treatment modalities for neuropathy cures, for example, antisense oligonucleotide (ASO) treatments.Here, we review the pathogenic mecha nisms of and management perspectives on CMT disease.(7)

Charcot-Marie-Tooth (CMT) disease is the most common genetic neuropathy affecting 1 in 3 2,500 people [8]. Although the motor symptoms may attract the most attention, a large survey (N = 407) revealed that over three-quarters of patients with CMT experienced pain and over four fifths numbness [9]. Among

genetically diagnosed patients with CMT1A, 29% had neuropathic pain. Allodynia was the most specific neuropathic pain symptom [10]. Although there is no known cure for this slowly progressive disease, there are treatments such as physical and occupational therapy, orthotics, and pharmacotherapies to manage symptoms.

The medications used for pain management are varied and included aspirin, nonsteroidal anti inflammatory medications, acetaminophen, tricyclic antidepressants, anticonvulsants, and opioids [11].

The National Academy of Sciences reported that there was conclusive evidence indicating that cannabis was effective for chronic pain among adults [12]. There was also moderate evidence that cannabis was effective for improving shortterm sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome or chronic pain [13]. Clinical practice guidelines are now emerging recommending that chronic pain patients can be treated with medical cannabis [13]. Surveys of cannabis dispensary members have identified a harm reducing substitution effect where they reduce or stop using other medications, especially opioids after starting cannabis. There is currently no published information about medical cannabis ,that is specific to CMT. The objective of this exploratory study was to obtain CMT patient's perspectives regarding the benefits and risks of medical cannabis. [14]

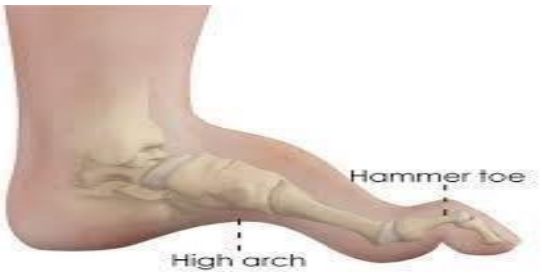

Figure no.1

Figure no. 2

SIGNS AND SYMPTOMS OF CHARCOT MARIE TOOTH DISEASE

Weakness in your legs, ankles and feet.
Loss of muscle bulk in your legs and feet.
High foot arches.
Curled toes (hammertoes)
Decreased ability to run.
Difficulty lifting your foot at the ankle (footdrop)
Awkward or higher than normal step (gait)

DIAGNOSIS OF CHARCOT MARIE TOOTH DISEASE

The approach for the diagnosis of CMT subtypes and other hereditary neuropathies depends on a line of clinical-lab oratory reasoning that begins with the definition of the phenotype, identification of the inheritance pattern, elec trophysiological study, and ends with molecular analysis. Nerve biopsy may be necessary in selected cases.(15)

The autosomal dominant inheritance pattern is the most commonly found and is seen in cases of CMT1 and in most cases of CMT2. It is important to remember that CMTX1 is transmitted in a dominant way linked to X chromosome, which is characterized by the absence of transmission between men, with women carrying the mutation in hetero zygosis presenting a milder phenotype than the male indi viduals. Sporadic cases may occur and represent a diagnostic challenge, such as de novo mutations, which are particularlyassociated with CMT1A (by duplication of PMP22) and muta tion of MFN2 (related to CMT2A2) but may also occur in other types of CMT.(15,16)

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Family history, in some cases, may be less elucidative, since there is great variability of gene expression with many oligo symptomatic carriers. Summoning relatives of the patient referred to as "healthy" for performing electrophysiolog ical test and a detailed physical examination may reveal important findings.[17]

VELECTROPHYSIOLOGICAL EVALUATION

The electrophysiological test corresponds to an important step in the evaluation of individuals with suspected hered itary neuropathy and may be necessary for the planning of genetic tests. The study of nerve conduction (NCS) corre sponds to the pillar of electrophysiological investigation in these cases.

The main objective is to differentiate between demyelinating and axonal forms, or even to seek evidence for intermediate types. The NCS can be easily performed in the relatives of the index case helping to define the pattern of inheritance. For NCS at least three sensory nerves (sural, median and ulnar nerves) and three motor nerves (fibular, tibial and medial nerves) should be examined. Ideally, the evaluation should be supplemented with needle electromyography and somatosensory evoked potential.[18].

NERVE BIOPSY

Prior to the accessibility of the molecular test, the histo pathology of the peripheral nerve was the most important tool in the diagnostic process of hereditary neuropathies. Currently, indications for peripheral nerve biopsy are restricted to select cases, in which diagnostic determina tion was not possible, despite a broad investigation of the mutations of the most commonly involved genes. Another possible scenario is one in which there is an important suspi cion of sporadic hereditary neuropathy, but, however, causes of acquired neuropathies need to be excluded (19,20)

GENETIC TESTING

The introduction of new generation sequencing (NGS) as a research tool in the field of hereditary neuropathies has allowed a progressive drop in the cost of wholeexome sequencing (WES). The trend of this evolution is to make many diagnostic algorithms by sequential testing of partially obsolete genes. However, it is important to remember that, despite the emergence of this new scenario, the cost of WES still remains quite high for use in the clinical routine[25]

TREATMENTS OF CHARCOT MARIE TOOTH DISEASE

There is currently no effective pharmacological therapy in CMT. Most of the disease management is related to rehabil itation therapy and surgical treatment of skeletal deformities. Patient followup should be multidisciplinary, including the assistance of neurologists, orthopedists, physiatrists, physio therapists, and nurses. Prescription of orthoses for lower limbs is recommended for patients with the classic CMT phenotype. Moderate phys ical exercises and stretching in order to avoid osteoskeletal complications are generally well tolerated. Patients with spine and limb deformities will commonly require corrective ortho pedic surgeries.(226)

Fatigue can also be a complaint in CMT and is probably asso ciated with different factors, including reduction of muscle strength and possible reduction in cardiorespiratory capacity. Obstructive sleep apnea syndrome is also common in CMT and its correction may have a positive response in improving fatigue in these patients. Modafinil was a drug that showed benefit in this symptom in a small series of cases.(26)

Emerging Drug Treatments:

Manypromising compounds targeting pathophysiological pathways are being tested as CMTtreatments. Given the role of PMP22 dosing in the pathogenesis of CMT1A, treat ment efforts have focused on reducing PMP22 expression. [27] Pmp22 transcription is a cAMP-induced action, as two binding sites for cAMP response element binding proteins (CREBs) reside in the Pmp22 promoter. [28].

Gene Therapies

Gene therapy is the treatment of a disease through transferring genetic material into cells of the patients [28].

Recently, RNA interference (RNAi) techniques have been extensively investigated as potential therapeutic strategies for CMT. RNAi involves the interaction between RNA and corresponding mRNA to form double-stranded RNA (dsRNA) that effectively inactivates the target gene .[29]

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Current gene editing technology is laying the foundation for the formulation of future disease therapies [30]. Discovered in the adaptive immune system of bacteria and archaea, the CRISPRbased gene editing system, consisting of Cas9 endonuclease and guide RNA (gRNA), has great potential in the treatment of genetic diseases, including CMT1A, by directly targeting diseasecausing genes. [31] By designing a CRISPR/Cas9 system with a TATA-box of Pmp22, gene expression of PMP22 can be downregulated to preserve myelin and axons using intraneural injections. [32]

Stem Cell Research

Patient-specific induced pluripotent stem cells (iPSCs) can be differentiated into rel evant cell type(s) for the in vitro confirmation of disease mechanisms and targets using models that accurately simulate the pathogenesis of CMT disease [33,34]. Although rare clinical treatment with iPSCs has emerged to date, patient-specific iPSCs-based culture systems including microfluidic chips, organoids, and assembloids have been identified as a particularly powerful platform for disease modeling and preclinical studies. [35] An iPSC-derived self-organizing organoid model is more likely to capture biologically mean ingful features of the disease and capture the physiological complexity. For CMT1A, iPSC-derived human organoids have been applied to further evaluate amelioration effect on myelin defect by downregulation of PMP22. [36] Luet al. reported that an iPSC line derived from the GARS (G294R) family with fibular atrophy was successfully induced, and the mutated gene loci were repaired at the iPSC level using CRISPR/Cas9 technology for the treatment of CMT2D123. The surprising results indicated that a combination of CRISPR/Cas9 and iPSCs is a potential therapeutic method for CMT. In addition to iPSCs, other types of stem cells, such as Schwann cells derived from dental pulp stem cells (DPSCs), which are typically obtained from third molar extractions and present minimal ethical concerns due to their origin as medical waste, can also be utilized for studying demyelinateing neurodegenerative diseases. [37]

Therapeutic Education and Genetic Counseling

Proper therapeutic education and genetic counseling are important for patients with CMTandtheir families. Therapeutic education includes awareness, information, learning, and psychological and social support aimed at helping the patient understand the disease and treatments, participate in care, take charge of his or her state of health, and encourage, as far as possible, the maintenance of daily activities [38]. Genetic counseling is crucial for CMT patients to comprehend and adjust to the medical, psychological, and familial implications of genetic factors contributing to the disease [39].

Emerging Perspectives for CMT Disease

There are various of administration methods for current pre-clinical and clinical treat ment on CMTs(drugandgene therapies). Generally, two fundamentally different routes include localized injection versus widespread delivery [40].

RISK FACTORS OF CHARCOT MARIE TOOTH DISEASE

Charcot-Marie-Tooth disease is hereditary, so you're at higher risk of developing the disorder if anyone in your immediate family has the disease.

Other causes of neuropathies, such as diabetes, may cause symptoms similar to Charcot-Marie-Tooth disease. These other conditions can also cause the symptoms of Charcot-Marie-Tooth disease to become worse. Medications such as the chemotherapy drugs vincristine (Marqibo), paclitaxel (Abraxane) and others can make symptoms worse. Be sure to let your doctor know about all of the medications you're taking.

II. CONCLUSION

Conclusions Studying the biology of CMT has revealed a stunning variety of mechanisms involved in the pathology of the peripheral nervous system and has provided insights into the process of neurodegeneration in general. These discoveries have revolutionized our understanding and led to the identification of common pathways, which can provide a rational basis for therapeutic strategies. Genetic diagnosis of CMT is becoming increasingly available. However, accurate phenotypic evaluation is of high importance for natural history studies and the elaboration of reliable outcome measures for future clinical trials. Finding adequate therapeutic options for patients with CMT remains a challenge; however, ongoing clinical trials represent the recent rapid advances that dominate the field.

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