Charcot-Marie-Tooth disease

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Charcot-Marie-Tooth disease (CMT) is a hereditary monogenic peripheral nerve disease

Charcot-Marie-Tooth (CMT) (AKA peroneal muscular atrophy, AKA Hereditary Motor and Sensory Neuropathy (HMSN)): Up to 7 types (the most common form is autosomal dominant, but X-linked recessive forms also exist). CMT Types 1 & 2 together make up the most common inherited disorder of peripheral nerves (up to 40/100,000). The most common forms involve demyelination. Progressive loss of motor (primarily distal LE) and, to a lesser degree, sensory function (predominantly proprioception and vibration), with atrophy in UEs & LEs. Earliest findings: pes cavus with hammertoes, foot drop, and frequent ankle sprains. Patients are more susceptible to entrapment neuropathies due to underlying compromise of peripheral nerves. Patients with Type 1 usually maintainability to ambulate, whereas Type 2 usually loose ambulation by their teenage years.

Variants in the gene encoding myelin protein zero (MPZ) lead to CMT, and different variants have different clinicalphenotypes. A variant site, namely, c.389A > G (p.Lys130Arg), in the MPZ gene has been found in Chinese people. The pathogenicity of this variant has been clarified through pedigrees, and peripheral blood-related functional studies have been conducted.

Whole-exome sequencing and Sanger sequencing were used to detect the c.389A > G (p.Lys130Arg) variant in the MPZ gene in family members of the proband. Physical examination was performed in the case group to assess the clinical characteristics of MPZ site variants. The expression of MPZ and phosphorylated MPZ in the blood of 12 cases and 12 randomly selected controls was compared by RT-qPCR, Western blotting, and ELISA.

The proband and 12 of her family members presented the AG genotype with different clinical manifestations. The expression of MPZ mRNA in the case group was increased compared with that in the control group, and the levels of MPZ and phosphorylated MPZ in peripheral blood were higher than those in normal controls.

The heterozygous genotype of the c.389A > G (p.Lys130Arg) variant in the MPZ gene mediated the increase in MPZ and phosphorylated MPZ levels in peripheral blood and was found to be involved with CMT [1)].

Charcot-Marie-Tooth disease 1 A (CMT1A) results from a duplication of the PMP22 gene in Schwann cells and a deficit of myelination in peripheral nerves. Patients with CMT1A have reduced nerve conduction velocity, muscle wasting, hand and foot deformations and foot drop walking. Here, we evaluate the safety and efficacy of recombinant adeno-associated viral vector serotype 9 (AAV2/9) expressing GFP and shRNAs targeting Pmp22 mRNA in animal models of Charcot-Marie-Tooth disease 1 A. Intra-nerve delivery of AAV2/9 in the sciatic nerve allowed widespread transgene expression in resident myelinating Schwann cells in mice, rats and non-human primates. A bilateral treatment restores expression levels of PMP22 comparable to wild-type conditions, resulting in increased myelination and prevention of motor and sensory impairments over a twelve-month period in a rat model of CMT1A. We observed limited off-target transduction and immune response using the intra-nerve delivery route. A combination of previously characterized human skin biomarkers is able to discriminate between treated and untreated animals, indicating their potential use as part of outcome measures [2)].

Wang et al. identify a set of miRs that are candidate biomarkers for clinical trials in CMT1A. Some of the miRs may reflect Schwann cell processes that underlie the pathogenesis of the disease [3)].

Case series

Fourteen participants with CMT Type 1A were recruited into a randomized, two-arm study. Baseline assessments included measures of disease severity, posturography, physical function, and patient-reported outcome measurements. All participants received one fall education session. Participants were randomized to either 12 weeks of balance training or 12 weeks of usual activities. The intervention comprised a home-based, multi-sensory balance training and proximal strengthening program, supported by three home visits from a physiotherapist.

Thirteen participants completed the study. The intervention was successfully implemented and well tolerated, with high participation levels. Functional measures of balance and walking showed strong effect sizes in favor of the training group. Posturography testing demonstrated moderate improvements in postural stability favoring the intervention group. Inconsistent changes were seen in lower limb strength measures.

The intervention was feasible to implement and safe, with some evidence of improvement in balance performance. This supports future studies to expand this intervention to larger trials of pragmatic, home-delivered programs through current community rehabilitation services and supported self-management pathways [4)]

1)
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