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Case Report

Calf Hypertrophy and Proximal Weakness in a 6-year-old Boy Mimicking Myopathy: A Case Report

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Abstract

We present a boy of 6 years old with proximal weakness and calf hypertrophy. Although clinically we thought of the case as muscular dystrophy, later through electrodiagnostic testing we found demyelinating sensory-motor polyneuropathy which was consistent with Charcot-Marie-Tooth (CMT1A) disease. Genetic analysis revealed duplication at 17p11.2 containing the PMP22 gene. We reviewed the literature about the association between CMT1A and calf hypertrophy. There are few reports in certain families of CMT1A where calf hypertrophy is a prominent feature rather than atrophy. The pathophysiological mechanism of hypertrophy is still unknown. Some authors mentioned that it is due to hypertrophy of type 1 muscle fiber. This study adds that hereditary neuropathy should be considered in a differential diagnosis of calf hypertrophy and limb weakness with or without atrophy. The utility of nerve conduction study and electromyography should be emphasized for these patients to reach a diagnosis. *[Journal of Current and Advance Medical Research, January 2025;12(1):44-47]*

Keywords: Calf hypertrophy; proximal weakness; CMT1A; PMP22; polyneuropathy

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Introduction

Hereditary neuropathies are a heterogeneous group of disorders of the peripheral nervous system both clinically and genetically. Charcot-Marie-Tooth (CMT) disease, also known as hereditary motor and sensory neuropathy (HMSN), is the most common cause of hereditary polyneuropathy, with a prevalence of approximately 1 in 2500 people[1]. Among all patients with CMT, CMT1 accounts for 60.0% cases[2]. CMT1A, an autosomal dominant demyelinating sensorimotor polyneuropathy, is the most prevalent among all CMT1 cases (70.0% to 80.0%), which results from a 1.5-Mb duplication at 17p11.2 involving the peripheral myelin protein 22 (PMP22) gene[3].

Similar to other forms of hereditary neuropathies, CMT1A is characterized by progressive weakness, muscle atrophy, and sensory deficit affecting the distal lower limbs more than the upper extremities. Pes cavus, hammertoes, muscle cramps, and postural tremors are often additional features[4]. Although calf muscle atrophy is a typical feature of CMT, some authors have reported calf muscle hypertrophy in some families with CMT[5]. Here we describe a 6-year-old boy with CMT1A who presented with calf hypertrophy and proximal weakness.

Case Presentation

A boy of 6 years old, 1st issue of a non-consanguineous parents, presented with complaints of developmental delay and progressive walking difficulty. The parents noticed that since his developmental age, he had delayed motor milestones and started walking by 28 months of age. He faced difficulties in sitting from a lying position and standing from a sitting position for the last 1 year. He also had difficulties in climbing stairs. He developed recurrent falls and walked on his toes for the last 6 months. He had no sensory complaints. His other domains of development (cognition, speech, socialization, and communication) were age-appropriate. He was delivered at term by caesarean section with average birth weight. His antenatal, perinatal, and postnatal periods were uneventful. His younger brother is normal to date. He had no family history of a similar illness. The child was well, alert, and cooperative. He had normal physical development: 22 kgs in weight and 112 cm in height. His head was normal in shape, and his circumference was 51.5 cm.

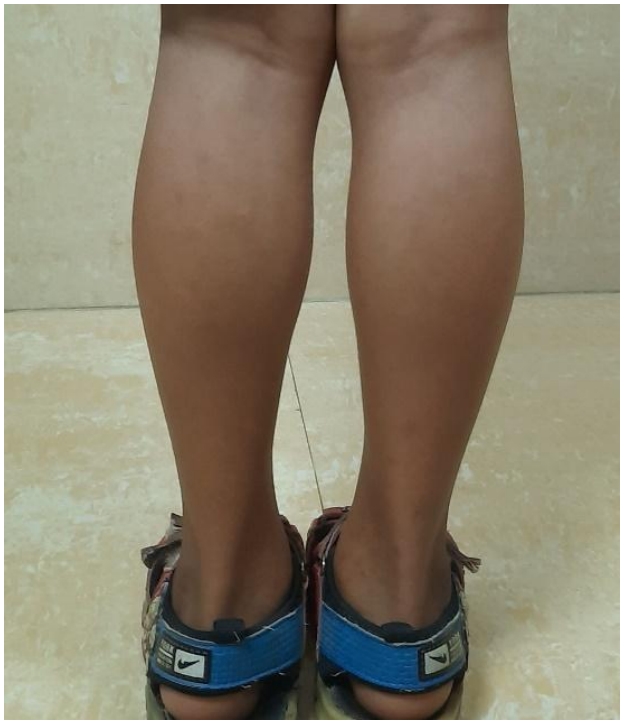

Figure I: Hypertrophy of Calf Muscle

All of his vitals were within normal limits. On systemic examination, he had calf hypertrophy which was symmetrical in both legs (Figure I), and a positive Gower´s sign. There was a slight tightening of the Achilles tendon without any foot deformity or muscle wasting. He had weakness in all four limbs but proximal weakness (3/5) was more than the distal weakness (4/5). All the reflexes were diminished with bilateral flexor plantar response. The child was not very cooperative for sensory examination. He had a waddling gait and walked on his toes. Other systemic examinations found no abnormality. A clinical diagnosis of Duchenne muscular dystrophy (DMD) was considered. However, Spinal muscular atrophy (SMA) type-3 could also cause a similar phenotype. His creatine phosphokinase (CPK) level was 72U/L which was within the normal limit. Nerve conduction study (NCS) and electromyography (EMG) revealed demyelinating sensory-motor polyneuropathy, which was suggestive of CMT1. Then we considered genetic analysis, which documented duplication of the entire 17p11.2 segment associated with classical CMT1A. As no definite treatment was available, supportive care like exercise training and orthopaedic shoes were given.

Discussion

The cardinal clinical features of the reported case were calf hypertrophy, limb weakness predominantly proximal, and hyporeflexia. All these clinical signs suggested a myopathic process and we clinically thought of the case as DMD. But there was a poor clinical correlation with the investigation findings. Calf hypertrophy has also been found in juvenile proximal SMA type 3, central core and centronuclear myopathy, benign X-linked muscular dystrophy of Becker type, autosomal recessive limb-girdle muscular dystrophy, acid maltase deficiency, and polymyositis[6].

When CPK level turned out normal, we went for NCS and needle EMG as it is a useful tool to differentiate myopathy from neuropathy and neuronopathy. Surprisingly it revealed demyelinating sensory-motor polyneuropathy with relative symmetry and absence of conduction block which was suggestive of CMT1. CMT1 is characterized by Motor nerve conduction velocities (MNCVs) below 38 m/s at upper limbs, compound muscle action potential (CMAP) amplitude usually within normal range but may be reduced due to secondary axonal loss. In CMT1A, MNCVs are usually uniformly slow in all nerves, with a mean range of 17–21 m/s. Very slow MNCVs (< 10 m/s) are suggestive of early-onset CM1B, CMT1E, or demyelinating recessive phenotypes (CMT4). Reduced CMAP amplitude and normal or mildly slowed MNCVs (mostly above 45 m/s at upper

limbs) were found with CMT2[7]. In our case, the mean MNCV in the upper limb was 28 m/s and the lower limb was 21 m/s which were suggestive of CMT1A. Sensory nerve conductions showed absent sensory nerve action potentials in the ulnar, median, and sural nerve. Needle EMG of tibialis anterior muscle showed mild spontaneous activity with reduced recruitment and polyphasic long-duration motor unit potentials. Examination of gastrocnemii did not reveal spontaneous motor unit activity or repetitive discharges. One study stated that MNCV is uniformly below 38 m/s in the median or ulnar nerves in PMP22dup and above 40 m/s in MFN2 mutation, whereas GJB1 and MPZ mutations result in more variable electroneurographic phenotypes[8]. These findings are consistent with our study.

Although the cardinal feature of CMT is distal muscle weakness and atrophy[4], there are few reports of calf muscle hypertrophy in some families. In a study, Uncini et al. have described a cohort of 6 cases (age, 25-79 years) belonging to three generations with CMT1A where all had calf hypertrophy. Five of that cohort also had pes cavus, leg weakness, and muscle atrophy. The calf enlargement was true muscle hypertrophy as per the histopathological report[9]. Mukherjee et al. have reported a boy of 4 years with CMT1 who presented with muscle hypertrophy and progressive weakness. Analysis of PMP22 found a heterozygous deletion in exons 1-5, which confirmed the diagnosis of CMT1[10]. Sakashita et al[11] described three relatives with CMT1 where calf muscle enlargement was the most prominent feature. None of those patients had atrophy of leg muscles. In another study, six members originating from two families with CMT were noted to have enlarged calf muscles[12]. Thomas et al[13] described a 55-year-old man with CMT1A who presented with incapacitating muscle cramps and calf muscle hypertrophy having 17p11.2 duplication.

During the last two decades, a molecular genetic diagnosis has become available for the majority (50–80%) of CMT1 patients, especially for those with AD disease[3,14]. Three genetic defects (PMP22 duplication, GJB1, or MPZ subtle mutation) were responsible for approximately 90% of detectable mutations in patients with demyelinating CMT1[8]. Genetic analysis of our case found duplication in chromosome 17p11.2 encompassing the PMP22 gene, causing CMT1A, which is the most common hereditary neuropathy[15].

In CMT1, muscle atrophy may not be evident in the early stage of the disease in patients with considerable subcutaneous fat[4]. Our reported case had calf hypertrophy without any evidence of muscle atrophy. The pathophysiological mechanisms responsible for muscle enlargement in neurogenic disorders are still unclear[9]. However, few studies mentioned that true calf hypertrophy was mainly due to hypertrophy of type 1 fibers in contrast to fat accumulation in the dystrophic process[9-12]. Some authors have proposed that the muscle enlargement in CMT may be a compensatory product of daily physical activity by way of a work-induced type 2 fiber hypertrophy and stretch-induced type 1 fiber hypertrophy. Indeed, muscle biopsy has demonstrated types 1 and 2 fiber hypertrophy in some patients[9,11,12]. Hyperexcitability of peripheral nerves may contribute to hypertrophy, which can be observed as continuous muscle unit activity on electromyography[5]. This mechanism is, however, unlikely in our patients as gastrocnemius muscles did not show any continuous motor unit activity on EMG.

Some studies highlighted that calf hypertrophy might be genetically determined[11,16]. Both affected members showed a duplication of the entire segment 17p11.2, which has been thought to be responsible through segmental trisomy and a gene dosage effect of the CMTIA phenotype[17]. However, the exact genetic mechanism and characterization of new genes may explain why some patients of CMT present with muscle atrophy while others present with calf hypertrophy.

Conclusion

It is well known that phenotypic expression varies in CMT1 families even in the members of the same generation. Our patient adds a phenotypic variation associated with CMT1A. CMT should be considered in the list of differential diagnoses of patients with calf hypertrophy and proximal weakness even in the absence of expected clinical features of hereditary neuropathy. NCS and EMG play a vital role not only in the diagnosis of CMT1 but also in deciding which genetic defect to be analyzed first.

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None

Conflict of Interest
The authors have no conflicts of interest to disclose

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Contributions to authors: BD and Saha were involved in study compiling, and manuscript writing. All were involved in case diagnosis and management. All authors read and approved the final manuscript.

Data Availability
Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate
Written informed consent was obtained from the legal guardian of the patient.

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