CASE REPORT

A YOUNG MAN WITH HEREDITARY MOTOR AND SENSORY NEUROPATHY: A RARE GENETIC ASSOCIATION

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Abstract:

Hereditary motor and sensory neuropathies with early onset are uncommon conditions that include Dejerine-Sottas neuropathy, which begins in infancy, and congenital hypomyelinating neuropathy, which manifests in the early postnatal period. However, these two historically defined disease entities are only small parts of the clinical spectrum. It is well recognized that very early onset hereditary neuropathies are frequently caused by de novo dominant mutations in PMP22, MPZ, and EGR2. In addition, mutations in several other dominant and recessive genes for Charcot-Marie-Tooth disease may lead to similar phenotypes. A 20-year-old boy had complaints of weakness of both lower limbs for 1 year, followed by wasting and foot drop, which subsequently involved the upper limbs. Nerve conduction velocity and electromyography of both lower limbs revealed demyelinating sensory motor polyneuropathy. Histological examination of the sural nerve revealed a nerve trunk with perineural soft tissue, with the nerve bundles being irregular and separated by fibrous tissue bands. The later reveals small perivascular infiltration of chronic inflammatory cells, and no granuloma or AFB is seen. The genetic test of whole exome screening for heriditatory neuropathy showed pathogenic (PM2, PVS, PP5) with a gene impact of (NF2: c.363+1G>T), which is a rare entity in our case study to consider the diagnosis despite negative family history. We highlight this rare disease in young man with a high index of clinical suspicion for its diagnosis.

Keywords: Hereditary Motor and Sensory Neuropathy, Genetic association.

Introduction:

Hereditary motor-sensory neuropathy (HMSN), also as Charcot-Marie-Tooth neuropathy, is a common hereditary peripheral neuropathy that primarily manifests as progressive limb muscle weakness and muscle atrophy. As the disease progresses, symptoms of sensory and vegetative involvement may occur. According to clinical and electrophysiological characteristics, it can be categorized as demyelinating type, axonal type, or intermediate type. At present, the most common genetic pathogenic loci include PMP22, GJB1, MFN2, and MPZ, and this account for more than 90% of all subtypes of the disease. In recent years, with the development and application of gene sequencing technology, more than 90 pathogenic genes from other mutation sites and families have been discovered and reported. The prevalence is unknown, mainly due to the inexistence of detailed

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epidemiological studies, and it has been estimated at 2–16/100000.  The disease is associated with deletions in chromosome 17p11.2, where the peripheral myelin protein 22 (PMP22) gene is localized.

The authors report a case of a 20-year-old man who had complaints of weakness of both lower limbs for 1 year, followed by wasting and foot drop, which subsequently involved the upper limbs.

**Case report:**
A 20-year-old male non-diabetic, normotensive right handed person was admitted to our neurology department in September 2023 with the complaints of weakness of both lower limbs for 1 year, wasting of both lower limbs for 7 months, weakness and wasting of both upper limbs for 3 months, and bodyache for 3 months (Figure:1).

![Figure: 20 year old male with wasting of limbs.](image)

One year ago, the patient developed weakness in both lower limbs, whose onset was insidious and gradually progressive. Gradually, he noticed wasting of both lower limbs for 7 months, which started in the distal part of the lower limb. Then he also developed weakness and wasting of both upper limbs in the form of difficulty holding objects. Initially, these limb weaknesses did not hamper his daily activities, gradually impairing them. He also developed generalized bodyache, which is severe in nature, persists all day long, is aggravated by walking, and is relieved by taking rest. He feels tingling and numbness in his lower limbs. He was diagnosed with peripheral neuropathy in his local hospital and was given therapy with vitamin B1 and cobalamine. His symptoms were not alleviated, and then he was referred to our department. He is a non-smoker and non-alcoholic with normal bowel and bladder function and no H/O parental consanguinity, and none of his family members have this type of illness. He was immunized completely.

The patient has no anemia, lymphadenopathy, or thyromegaly. In his neurological examination, he found higher cerebral function, including speech, and the cranial nerve intact. There was wasting of almost all groups of muscles in both the distal and proximal groups of both lower limbs, more marked distally. There is wasting of the thenar and hypothenar muscles of the hands. Mainly, wasting is prominent in the left upper limb, followed by the right. Foot drop is present on the left. There was weakness (4/5) in the upper limb both proximally and distally, 3/5 in the distal, and 4/5 in the lower limbs. Tendon reflexes were decreased in all the extremities, and the Babinski signs were absent. All modalities of sensation are impaired in the lower limb up to the mid thigh and the upper limb up to the mid-forearm in the gloves and stockings pattern. There is the presence of Romberg’s sign. The bilateral finger-to-nose test and heel-knee-shin test were normal. The signs of meningeal irritation were negative, and the gait was high, stepping to the left. There is no nerve thickening.

An extensive laboratory test was performed (white blood cells and platelets count, sedimentation, C-reactive protein, liver function, phosphorous, calcium, magnesium, muscular enzymes, folic acid and vitamin B12, thyroid function, immunoglobulins, auto-antibodies, viral markers, and syphilis and CSF study) with normal results (Table I). Lower limb and foot X-rays were normal, as was the magnetic resonance of the vertebral column. Nerve conduction velocity and electromyography of both lower limbs revealed demyelinating sensory motor polyneuropathy. Histological examination of the sural nerve revealed a nerve trunk with perineural soft tissue, with the nerve bundles being irregular and separated by fibrous tissue bands. The later reveals small perivascular infiltration of chronic inflammatory cells, and no granuloma or AFB is seen. The genetic test of whole exome screening for heriditary neuropathy showed pathogenic (PM2, PVS, PP5) with a gene impact of (NF2: c.363+1G>T) (Table-II).
Discussion:

HMSN, also known as Charcot-Marie-Tooth neuropathy (CMT neuropathy), which was first described by Charcot, Marie, and Tooth in 1886, is a group of heterogeneous motor and sensory genetic neuropathies. 6 The pathology of reduced nerve conduction velocity, hypertrophic demyelination, and axonal lesions are the main pathological features of HMSN. Clinical symptoms include progressive weakness of the limb muscles, atrophy of the muscles, difficulty walking, and deformity of the feet. In a later stage, there is also evident damage to the sensory and vegetative nerves. Physical therapy and rehabilitation therapy are the only ways to control the disease, as there is currently no effective cure.
Early diagnosis can therefore positively and accurately guide HMSN patients to modify their lifestyle in order to minimize neurological damage to the greatest extent possible, thereby delaying or preventing the disease’s disability rate. 8 HMSN is a genetic illness that manifests itself in various ways. Autosomal dominant inheritance, autosomal recessive inheritance, X-linked dominant inheritance, and recessive inheritance are the genetic modes associated with HMSN. As of right now, the incidence of this disease has been linked to about 90 gene mutations, and its overall prevalence is about 1/2500.9 Several subtypes can be distinguished based on genetic loci and pathogenic genes. With over 70% of all subtypes, CMT1A is the most prevalent subtype, is caused by a mutation in the PMP22 gene, and is the most common subtype, accounting for more than 70% of all subtypes. The pathogenic loci GJB1, MFN2, and MPZ are also frequently found.10 In recent years, a few familial and sporadic HMSN cases caused by rare site mutations have been reported due to the widespread use of gene sequencing technology.11

This case study features a young man who initially had subtle lower limb weakness that progressively worsened. Over the course of seven months, he gradually noticed wasting in both lower limbs, beginning in the distal region. Then, he experienced wasting and weakness in both upper limbs. Higher cerebral function, including speech, and intact cranial nerves were observed in his neurological examination. Nearly all of the proximal and distal muscle groups in both lower limbs showed signs of wasting, with the distal wasting being more pronounced. The hands’ thenar and hypothenar muscles are wasting away. The left upper limb is more affected by wasting than the right. There was 3/5 distal weakness and 4/5 lower limb weakness, with the upper limbs weaker (4/5) both proximally and distally. All extremities had reduced tendon reflexes, and there were no Babinski signs. When wearing gloves and stockings, all sense modalities are compromised in the lower limb up to the mid-thigh and the upper limb up to the mid-forearm. There is a Romberg sign present. Both the heel-knee-shin test and the bilateral finger-to-nose test were normal. Meningeal irritations were negative, and the patient’s gait was left-sided high stepping. No thickening of the nerves occurs. The patient’s clinical symptoms and the aforementioned physical and clinical examinations supported the diagnosis of motor and sensory neuropathies. Extensive biochemisties had been done, which were negative. Nerve conduction velocity and electromyography of both lower limbs revealed demyelinating sensory motor polyneuropathy. Histological examination of the sural nerve revealed a nerve trunk with perineural soft tissue, with the nerve bundles being irregular and separated by fibrous tissue bands. The later reveals small perivascular infiltration of chronic inflammatory cells, and no granuloma or AFB is seen.

These findings indicate that the lower motor neuron was affected. An electrophysiological study indicated demyelinating sensory-motor polyneuropathy. Routine biochemistry and ganglioside antibodies in cerebrospinal fluid were negative. The above physical and clinical examinations, in conjunction with the clinical symptoms the patient had, supported a diagnosis of peripheral neuropathy. The genetic test of whole exome screening for heriditary neuropathy showed pathogenic (PM2, PVS, PP5) with gene Impact of (NF2: c.363+1G>T) is classified as a pathogenic variant. This result does support the previous report, as this variant may be an uncommon genetic sequence in Southeast Asia, like Bangladesh, and further study is to be done to support the study. The final diagnosis was young-onset hereditary motor and sensory neuropathy without family history with a rare genetic association. These findings indicate that the lower motor neuron was affected. An electrophysiological study indicated demyelinating sensory-motor polyneuropathy. Routine biochemistry and ganglioside antibodies in cerebrospinal fluid were negative. The above physical and clinical examinations, in conjunction with the clinical symptoms the patient had, supported a diagnosis of peripheral neuropathy. The genetic test of whole exome screening for hereditary neuropathy showed pathogenic (PM2, PVS, PP5) with a gene impact of (NF2: c.363+1G>T) is classified as a pathogenic variant. This result does support the previous report, as this variant may be an uncommon genetic sequence in Southeast Asia, like Bangladesh, and further study is to be done to support the study. The final diagnosis was young-onset hereditary motor and sensory neuropathy without family history with a rare genetic association.

**Conclusion:**

The clinical manifestations and electrophysiological results of this patient are consistent with the characteristics onset hereditary motor and sensory neuropathy with rare a genetic association (PM2, PVS, PP5) with gene Impact of (NF2: c.363+1G>T). It is a rare possible that this mutation is linked to hereditary motor and sensory neuropathy.

**Conflict of Interest:**

The author stated that there is no conflict of interest in this study

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Consent for publication:
Informed written consent was taken from the patient to publish details relevant to the disease and management.

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References: