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CASE REPORT

A Case Report and Literature Review of Charcot-Marie-Tooth Disease Type 2F in a Family

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Objective: To report the clinical and genetic characteristics of a rare Charcot-Marie-Tooth disease type 2F (CMT2F) pedigree, and to explore the phenotypic diversity and diagnostic essentials of the mutation in combination with literature review.

Methods: The clinical data, electrophysiological findings, and genetic testing results of the proband and pedigree members were retrospectively analyzed, and relevant literatures were reviewed for comparative analysis.

Results: Both patients had an onset in middle and old age (50/66 years), presenting with distal lower limb muscle weakness (Grade III), muscle atrophy, absent tendon reflexes, pes cavus, and sensory abnormalities. Serum creatine kinase (CK) was elevated (474 U/L), and electromyography indicated axonal peripheral nerve damage. Genetic testing revealed a heterozygous mutation of HSPB1 gene c.418C>G [p.Arg140Gly], which was verified by co-segregation in the pedigree. Literature review showed that this mutation causes axonal transport dysfunction by impairing the chaperone function of HSP27.

Conclusion: This study expands the phenotypic spectrum of late-onset CMT2F, with some patients showing mild elevation of serum CK. It provides new clinical evidence for the pathogenicity of this mutation.

Keywords: Charcot-Marie-Tooth disease, HSPB1 mutation, HSP27, hereditary neuropathy, axonal degeneration

Introduction

Charcot-Marie-Tooth disease (CMT) is a group of hereditary peripheral neuropathies characterized by progressive distal motor and sensory dysfunction of the limbs.[1–3] With a global incidence of approximately 1/2500, it exhibits high clinical and genetic heterogeneity.[4] The common inheritance patterns of CMT include autosomal dominant inheritance, while autosomal recessive inheritance, X-linked dominant inheritance, and X-linked recessive inheritance are less frequent.[5] Based on nerve conduction velocity (NCV), CMT can be classified into demyelinating type (CMT1), axonal type (CMT2), and intermediate type. Among them, CMT2 accounts for about 20–30% and is caused by various gene mutations.[6–8]

CMT2F is a rare subtype of CMT2, which is caused by mutations in the HSPB1 gene and mainly manifests as adult-onset distal axonal damage.[9] HSPB1 encodes heat shock protein 27 (HSP27), which is involved in cellular stress protection and maintenance of axonal stability. Mutations in HSPB1 can lead to pathogenesis through mechanisms such as affecting mitochondrial function and axonal transport.[10] This article reports a CMT2F family carrying the HSPB1 c.418C>G mutation and discusses its clinical heterogeneity in combination with relevant literature.

Proband

A 66-year-old male presented on October 31, 2024, with 5-year progressive bilateral lower limb weakness and gait instability, worsening over 1 year. Examination revealed:

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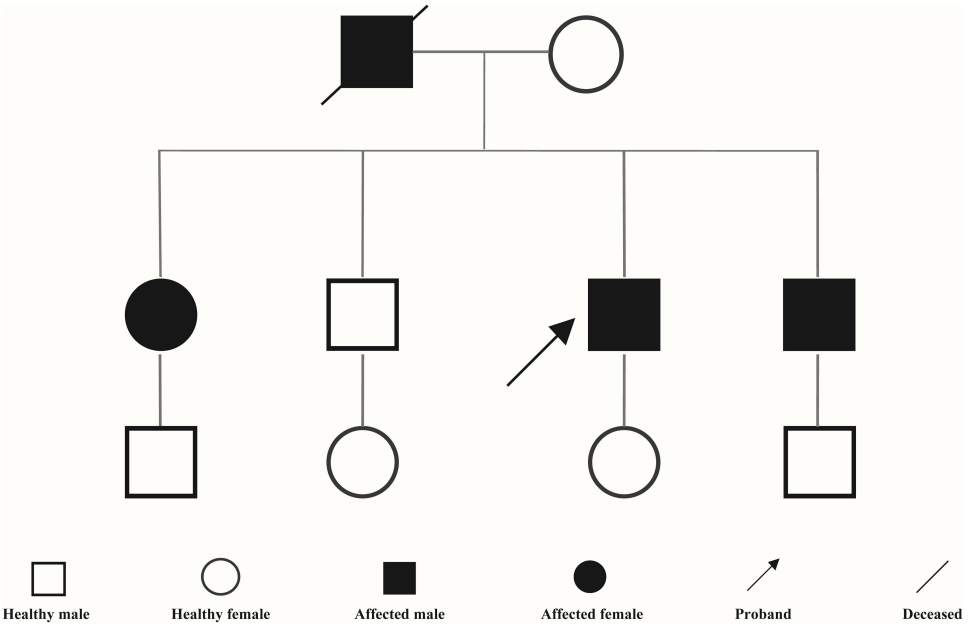

Figure 1 Pedigree of the CMT2F Family.

- Muscle strength: Grade III (lower limbs)
- Bilateral calf atrophy
- Absent tendon reflexes
- Pes cavus
- Elevated CK (474 U/L; normal <19 U/L)
- EMG: Axonal-dominant peripheral neuropathy

Whole-exome sequencing (Beijing Quanpu Medical Laboratory) identified a heterozygous HSPB1 mutation [c.418C>G (p.Arg140Gly)], classified as likely pathogenic (ACMG criteria: PS3_Supporting+PS4_Moderate+PM1 +PM2_Supporting+PP3). Phenotypic analysis (HPO: HP:0003202, HP:0007340, HP:0009049) and electrophysiological findings (sensory involvement) distinguished this case from HMND3, confirming CMT2F diagnosis. Two variants of uncertain significance (SEPTIN9, PEX13) were excluded due to clinical inconsistency. The patient received supportive care with stable follow-up.

Family Study

The pedigree chart is shown in Figure 1 (Pedigree of the CMT2F Family). The proband's father, younger brother, and elder sister developed similar symptoms at 47, 50, and 46 years of age, respectively. The proband's father has passed away, and his mother shows no obvious clinical phenotype. The proband's younger brother presented with diminished tendon reflexes but refused to undergo muscle enzyme tests and electromyography. Next-generation genetic testing (Figure 2. Second-generation validation results of the HSPB1 gene variant [NM_001540.5(HSPB1):c.418(exon2)C>G (p. Arg140Gly)] in the pedigree) revealed that both the proband and his younger brother carried the heterozygous mutation of HSPB1 gene [NM_001540.5 (HSPB1): c.418 (exon2) C>G [p.(Arg140Gly)]].

Discussion

Comparison of the Present Case with the Typical Phenotype of CMT2F

The typical manifestations of CMT2F are distal symmetric motor-sensory neuropathy with an onset age of 20–50 years, characterized by weakness of both lower limbs, muscle atrophy (so-called "stork leg" appearance), diminished/absent tendon reflexes, and pes cavus, with electrophysiological findings indicating axonal damage.[9,11] In the present case, the

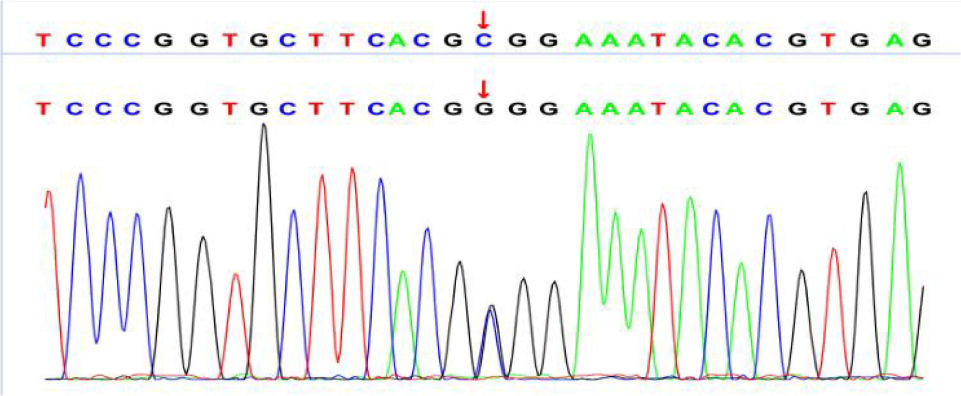

Figure 2 Second-generation validation results of the HSPB1 gene variant.

proband had a late onset at 66 years, while his younger brother had a typical onset at 50 years. The phenotypic characteristics of this pedigree are consistent with the genetic pattern of CMT2F. The delayed onset age of the proband is speculated to be related to the insidious progression of the disease and neglect of early symptoms, which is in line with the literature-described feature that "CMT2F has an insidious onset and is prone to missed diagnosis"[9] Therefore, a definitive diagnosis requires the combination of electrophysiological examinations and genetic testing.

To further clarify the phenotypic correlation, the characteristics of the present case and those of CMT2F reported in the literature are summarized in Table 1.

Notably, the proband in this case showed a mild elevation of serum creatine kinase (CK) (474 U/L), which is uncommon in CMT. Previous studies have indicated that CK levels in CMT2F patients are mostly normal or mildly elevated. This is primarily attributed to the pathological nature of CMT, which involves length-dependent axonal degeneration or segmental demyelination, leading to denervation atrophy of distal muscles (without direct damage to muscle fibers). Moreover, this atrophic process progresses slowly, accompanied by protease activation and orderly degradation of the cytoskeleton, preventing massive release of intracellular CK from muscle cells into the bloodstream. Therefore, elevated serum CK is infrequent in CMT cases, and even when present, it is mostly mild (typically < 3 times

Table 1 The Characteristics of the Present Case and Those of CMT2F Reported in the Literature

Features	The Proband in this Case	The Proband's Younger Brother	Typical Manifestations of CMT2F	Literature-Reported Cases of HSPB1 Mutations[11]
Age of onset	66 years old (late-onset)	50 years old (typical)	Aged between 20 and 50 years old	Ages from 25 to 60 (with intrafamilial variation)
Motor symptoms	Weakness in both lower extremities and muscle atrophy	Both lower limbs are weak and unsteady to walk	Distal muscle weakness (mainly lower limbs), "crane leg" changes	Distal muscle weakness and slow progression
Feel symptoms	Slight sock sensation loss	The lower limbs are cold	Sock cover - glove-like loss of sensation (lighter)	Some cases with subclinical paresthesia (eg, decreased SNAP amplitude)
Other physical signs	High arch, tendon reflex disappears	Tendon reflex disappears	High arch, tendon reflexes are weakened/absent	Occasionally, foot edema and abnormal skin temperature are seen
Electrophysiological characteristics	Median nerve CMAP 3.2mV (↓), normal conduction velocity	Refusal to detect	Axonal damage (CMAP/SNAP amplitude ↓)	Axonal injury is predominant, and the conduction velocity is normal or slightly slowed
Gene mutation	HSPB1 c.418C>G (p. Arg140Gly)Heterozygosity	HSPB1 c.418C>G (p. Arg140Gly) Heterozygosity	HSPB1 pathogenic mutations (eg, 135F, P39L, etc)	Most of them are heterozygous mutations and are autosomal dominant

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the upper limit of normal). In this case, the elevated CK was not accompanied by manifestations of inflammatory myopathy such as myalgia or muscle edema. Combined with the electrophysiological findings indicating axonal damage, this supports that the elevated CK is an atypical laboratory feature of CMT2F rather than a primary myopathy.

Phenotypic Diversity of CMT and Its Implications for Clinical Diagnosis

CMT exhibits remarkable phenotypic diversity. In addition to the typical distal motor-sensory dysfunction, atypical manifestations have been reported, such as postural tremor, optic atrophy, vocal cord paralysis, proximal muscle weakness, and deafness.[12–15] These atypical manifestations suggest that clinicians should be vigilant about the "atypical initial symptoms" of CMT to avoid misdiagnosis.

Pathogenic Mechanisms of HSPB1 Mutations and Advances in Treatment

It was first reported by Evgrafov et al in 200410 that CMT2F is caused by dominantly inherited mutations in the HSPB1 gene, which encodes heat shock protein 27 (HSP27).[16] HSP27 belongs to the small heat shock protein superfamily and plays a key role in cellular processes such as molecular chaperoning, antioxidant stress response, anti-apoptosis, and maintenance of axonal stability.[17] The core mechanisms by which HSPB1 mutations induce CMT2F include:

① Impaired molecular chaperone function, which leads to abnormal assembly of neurofilament proteins and subsequent axonal transport dysfunction;[18,19]

② Mitochondrial dysfunction: HSPB1 is involved in the dynamic regulation of mitochondria, and mutations may affect energy metabolism, resulting in chronic axonal damage.[20,21] Studies have demonstrated that CMT2-causing mutations in this gene induce multiple defects, including abnormalities in mitochondrial morphology, function, and localization. For instance, expression of mutant HSP27 (S135F) in HT22 mouse hippocampal neurons results in enlarged mitochondrial morphology and significant impairment of mitochondrial respiratory chain function;[22] in transgenic mouse models of CMT2F harboring S135F or P182L mutations, reduced α-tubulin acetylation levels in the sciatic nerve are observed, accompanied by severe defects in mitochondrial axonal transport;[23]

③ Increased susceptibility to oxidative stress: mutant HSPB1 reduces the defense capacity of neurons against oxidative damage, accelerating axonal degeneration.[24] The c.418C>G (p.Arg140Gly) mutation in this pedigree is located in the highly conserved α-crystallin domain of HSP27, and this mutation significantly reduces protein stability.

Latest Therapeutic Approaches and Prognosis

Currently, there is no definitive cure for CMT2F, and treatment mainly focuses on symptomatic support. Rehabilitation therapy (including orthoses and balance training) can delay muscle atrophy;[25] gabapentin or pregabalin can relieve neuropathic pain; emerging therapies such as the heat shock protein activator Arimoclomol have been shown in Phase II clinical trials to partially restore HSP27 function and slow disease progression.[25] In terms of prognosis, CMT2F typically progresses slowly, with a lower disability rate than demyelinating CMT subtypes. However, approximately 20% of patients may require ambulatory aids after 20 years of disease duration. The patient in this case has remained stable following symptomatic treatment, and long-term prognosis requires further follow-up.

Conclusion

This study reports a CMT2F pedigree carrying the HSPB1 p.Arg140Gly mutation, confirming that this mutation can cause late-onset distal motor-sensory neuropathy, with some patients exhibiting mild elevation of serum CK. These findings enrich the clinical evidence for this mutation. The phenotypic diversity of CMT, including atypical manifestations, suggests that in clinical practice, for patients with adult-onset peripheral neuropathy, a definitive diagnosis requires the combination of neuroelectrophysiological examinations and genetic testing. Particularly for familial cases, the possibility of rare gene mutations such as HSPB1 should be vigilant.

Ethics Statement

According to the regulations of Lanzhou Petrochemical General Hospital (Fourth Affiliated Hospital of Gansu University of Traditional Chinese Medicine), anonymous case reports do not require approval from the ethics committee.

Informed Consent Statement

The patient involved in this case report has been fully informed about the details of the case and the publication of accompanying images, and has provided written informed consent for the publication of this case report and all related materials.

Disclosure

The authors report no conflicts of interest in this work.

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