Original Article - Case Study

Late-onset cerebellar ataxia in an adult with a novel mutation in the CLN5 gene

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ABSTRACT

Neuronal ceroid lipofuscinosis (NCL) is a neurodegenerative disorder which mostly presents in early life and is associated with a premature death. Here, we report a 50-year-old Saudi male who presented with cerebellar ataxia and whole exome sequencing identified a previously undescribed, homozygous mutation in the CLN5 gene (c.562T>C; p.Phe188Leu). This mutation was predicted to be pathogenic based on bioinformatics tools scoring; PolyPhen-2 (1) and SIFT (0.0). He did not have a visual impairment, cortical atrophy or cognitive decline, which were reported in previous adult cases associated with CLN5 mutation. This case, therefore, further expands the molecular and clinical phenotype associated with CLN5 mutation. It also highlights the role of next-generation sequencing analysis in providing early insights and diagnosis of rare hereditary disorders.

Keywords

Neuronal ceroid lipofuscinosis, adult-onset, cerebellar ataxia, whole-exome sequencing, CLN5 mutation.

Abbreviations

Neuronal ceroid lipofuscinosis (NCL), endoplasmic reticulum (ER), Magnetic resonance imaging (MRI), ceroid lipofuscinosis neuronal protein 5 (CLN5), Whole exome sequencing (WES).

INTRODUCTION

Neuronal ceroid lipofuscinosis (NCL) is a genetically heterogeneous group of neurodegenerative disorders, characterized by the intralysosomal accumulation of auto-fluorescent lipopigments in neural and peripheral tissues1. Mutations in at least 14 genes (CLN1-CLN14) have been identified to cause various forms of NCL2. The CLN5 gene located on chromosome 13q22 encodes for ceroid lipofuscinosis neuronal protein 5 (CLN5), which is a soluble lysosomal protein. Its precise function remains unknown3. A recent study reveals the possible role of CLN5 in mitochondrial energy homeostasis and activation of mitophagy4. It has been shown that mutant CLN5 protein is retained in the endoplasmic reticulum (ER) and it does not reach the lysosome, indicating that CLN5 mutations affect ER-lysosomal trafficking3,5. CLN5 disorder is inherited in an autosomal recessive pattern. Bi-allelic mutations in CLN5 result in a phenotype characterized by motor impairment, visual loss, seizures and cognitive regression3,6. The onset of symptoms is either in childhood or up to early
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adulthood (4-17 years). Here, we report a case in which the cerebellar ataxia associated with CLN5 mutation, developed in late-adult life.

CASE REPORT

A 50-year-old Saudi male was referred to the neurology clinic with a history of progressive unsteady gait for ten years and slurred speech for six years. He did not have seizures or visual impairment. His parents were first cousins, and there was no history of similar illness in the family. On examination, he had ataxia, dysarthria, bilateral horizontal nystagmus, dysmetria and dysdiadokokinesis. He had no muscle atrophy, or weakness and sensations were intact. His vision was normal, and there was no cognitive decline. Magnetic resonance imaging (MRI) of the brain

Figure 1. Radiological, molecular and lymphocyte abnormalities in a 50-year-old Saudi male with cerebellar ataxia and a homozygous mutation in the CLN5 gene (c.562T>C; p.Phe188Leu) (A) Sagittal and (B) axial views of MRI brain showing cerebellar atrophy; (C) Sanger sequence chromatograms of CLN5 showing the normal control, unaffected heterozygous carrier, and affected patient with a homozygous mutation. The arrow indicates a single base T > C transition in exon 3 of CLN5; (D) Electron microscopy of peripheral lymphocytes showing focal collections of intra-lysosomal storage material.
showed cerebellar atrophy, most significantly involving the vermis (Figure 1A, B). There was no cerebral atrophy. Whole exome sequencing (WES) revealed a novel pathogenic homozygous missense mutation in CLN5 (c.562T>C; p.Phe188Leu), which was confirmed by Sanger sequencing (Figure 1C). Subsequent electron microscopic examination of peripheral lymphocytes showed focal collections of storage material with the ultrastructure of fingerprint bodies (Figure 1D). Family screening could not be performed, since his parents were deceased and healthy siblings refused to be tested.

**DISCUSSION**

NCL associated with CLN5 mutation was initially reported in Finnish population, in Europe9. Later, patients from a diverse ethnic background were diagnosed to have CLN5-related disease3,8,9. It mainly presents in younger age, varying from infancy to the second decade of life. There is only one previous report of two Italian siblings presenting in the mid-50s8. We presume that specific CLN5 mutations have a less severe impact on the CLN5 protein, initially preserving its residual function. It, therefore, takes longer to cause significant damage, resulting in late onset of the disease.

Using WES, we identified a novel homozygous mutation in exon 3 of the CLN5 gene; a single base T > C transition that caused a substitution of phenylalanine to leucine at codon 188 (c.562T>C; p.Phe188Leu). The c.562T nucleotide is highly conserved throughout evolution, as is the corresponding amino acid phenylalanine. The p.Phe188Leu mutation was predicted to be pathogenic by using two bio-informatics tools, such as PolyPhen-2 (http://genetics.bwh.harvard.edu /ph2/) and SIFT (http://sift.bii.a-star.edu.sg/), which give a score representing the probability that an amino acid substitution is damaging. PolyPhen-2 revealed a score of 1.0 (range - 0.0: tolerated; 1.0: deleterious) and SIFT a score of 0.0 (range- 1.0: tolerated; 0.0: deleterious). This mutation was not present in the 1,000 Genome project database, 1,000 Arab exomes and 700 Saudi exomes databases. Demonstration of characteristic membran-bound inclusion bodies in lymphocytes further supported the diagnosis of NCL10,11.

In the previous report, Italian siblings presented with cerebellar ataxia, mild cognitive, visual impairment, and cortical atrophy associated with CLN5 mutation4. Our patient had cerebellar ataxia but no cognitive loss, cortical atrophy or visual disturbance. Hence, this case further expands the spectrum of neurological phenotypes associated with CLN5-related adult-onset NCL.

Saudi Arabia has one of the highest incidence rates of autosomal recessive diseases, and NCL constitutes 5% of the neurodegenerative disorders seen in children12. This is the first report of cerebellar ataxia associated with CLN5 mutation, presenting in a middle-aged Saudi adult. It emphasizes the need for considering genetic testing even when there is no family history of a similar disorder. Molecular diagnosis also facilitates preventive reproductive measures in such cases where no curative treatment is available.

**CONCLUSION**

Adult-onset cerebellar ataxia associated with CLN5 mutation is a rare disease. This case expands the neurological phenotype of CLN5 disease and suggests that it should be considered in the differential diagnosis of late-onset cerebellar ataxia even when there are no visual failure, seizures or cognitive decline. WES is not only facilitating the early diagnosis of rare diseases with novel mutations, but is also expanding the spectrum of associated phenotype.

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**Conflict of Interest**

The authors declare no conflict of interest.

**References**


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