A novel p.Ala34Val variant in C19orf12 is associated with neurodegeneration with brain iron accumulation

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Abstract

Loss-of-function mutations in the C19orf12 gene may lead to mitochondrial membrane protein-associated neurodegeneration (MPAN), which is a subtype of neurodegeneration with brain iron accumulation disorders. It is manifest with juvenile-onset spastic paraparesis, dystonia, dysphagia, optic atrophy, decreased cognitive functions, and neuropsychiatric symptoms. Large amounts of iron are accumulated in the globus pallidus and substantia nigra pars reticulata due to abnormal brain iron metabolism. We report a novel C19orf12 (c.101C>T;p.Ala34Val) homozygous mutation in a Turkish man who presented with postural instability, slow gait and anxiety. Neuroimaging showed mild iron deposition in the basal ganglia and cortical atrophy. These results are consistent with the MPAN. This report demonstrates the importance of testing patients with spastic paraplegia, parkinsonism, motor axonal neuropathy, difficulty walking or dysarthria for MPAN.

Keywords: C19orf12, missense mutation, mitochondrial membrane protein-associated neurodegeneration (MPAN), neurodegenerative disorders, whole exome sequencing

INTRODUCTION

Neurodegeneration with brain iron accumulation (NBIA) is a very rare inherited heterogeneous neurodegenerative disorder. The prevalence is approximately 1/1,000,000 in the general population. To date, ten genes have been associated with different NBIA subtypes. Mitochondrial membrane protein-associated neurodegeneration (MPAN) has an autosomal recessive inheritance caused by loss of function mutations in C19orf12 gene. The C19orf12 gene encodes a highly conserved mitochondrial membrane protein, presumably involved in lipid homeostasis. Generally, frameshift, nonsense and missense mutations are detected in the second and third exons of the C19orf12 gene. About 110 cases have been reported worldwide so far. The age of onset is from early childhood to early adulthood. Clinical findings include muscle weakness and spasticity, extensor plantar response, dysarthria, dysphagia, dystonia, optic atrophy, urinary incontinence, cognitive retardation, and psychiatric symptoms. Magnetic resonance imaging (MRI) typically shows hypointensity in the globus pallidus and substantia nigra on T2-weighted imaging. We present here a 44-year-old male with progressive difficulty in walking from adolescence after normal early development, undiagnosed for 30 years until detailed genetic analysis reveals a mutation in C19orf12.

CASE REPORT

The patient was a 44-year-old male of Turkish ancestry with progressive dystonia, parkinsonism, and gait impairment. He was the second child of consanguineous Turkish parents (Figure 1A). There was no history of neurological disorders in his family. The patient started to slow down in movements 6 years ago. The patient’s complaints of slowing down movements, difficulty and stiffness in walking, and difficulty in self-expression appear. He was initially referred to psychiatry service by the family doctor; and was given treatment for anxiety and depression. As copper was found to be high in the urine, diagnosis of Wilson’s disease was suspected. However,
eye examination and serum ceruloplasmin were normal, and the urine copper repeated was also found to be normal (He used herbal medicine during the first urinalysis). Dopamine agonist was started for the parkinsonism. Due to the lack of response, levadopa + benserazide was later added. When the patient came to us, he was in an anteflexed posture, hypophonic and hypomimic. He had bilateral bradykinesia rigidity, and hyperreflexia of the deep tendon reflex. Eye examination was normal. In the evaluation of cognition, the minimental state examination score was 22/30 and the MOCA test was 25/30. The patient also had urinary incontinence and mild dysphagia. Since the patient’s response to levodopa was minimal, he was re-investigated. Brain MRI showed suspicious iron accumulation in the basal ganglia and diffuse cortical atrophy (Figure 2). On MRI T2-weighted sequence MR imaging, the hypointensity of the globus pallidus and substantia nigra was markedly increased as compared to the red nucleus. This was suggestive of iron accumulation in the basal ganglia (Figure 2). Gradient echo sequence (GRE) or susceptibility weighted imaging (SWI) images were planned for the patient. However, the patient refused to have the MRI again. After that, genetic tests for neuroferritinopathy were arranged.

Karyotype analysis indicated a normal 46, XY karyotype. Whole-exome sequencing (WES) of a DNA sample from our patient was performed by MGI (DNBSEQ-G400). The data analysis was by the Genemaster analysis programme. The WES analysis showed a novel homozygous missense c.101C>T; p.Ala34Val mutation in the exon of C19orf12 gene (Figure 1B). The segregation analysis of the parents showed that they were both heterozygous for the same mutation. The c.101C>T variant was predicted to be deleterious by in silico prediction programs (SIFT, Polyphen2 and Mutation Taster) (Figure 2). This variant is included in Clinvar as a variant of unknown/uncertain significance (VUS). This variant is classified as PM2 and PP2 according to ACMG (American College of Medical Genetics and Genomics). There is no individual in Genome Aggregation Database (gnomAD) whose genotype is homozygous for this allele frequency. Informed consent was obtained from the proband for the genetic test and publication of this report.

Figure 1. Pedigree of the family of the proband. Black symbol denotes affected individual (A). The results of the whole exome sequencing revealed a novel missense mutation in the C19orf12 gene (B).
Table 1: Characteristics of the C19orf12 variant detected in this study.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Location</th>
<th>Variant</th>
<th>Clinvar</th>
<th>SIFT</th>
<th>Polyphen2</th>
<th>MutationTaster</th>
</tr>
</thead>
<tbody>
<tr>
<td>C19orf12</td>
<td>Exon 2</td>
<td>c.101C&gt;T</td>
<td>Uncertain sign</td>
<td>Likely</td>
<td>Probably</td>
<td>Disease causing</td>
</tr>
<tr>
<td>NM_001031726.3 (rs544395324)</td>
<td></td>
<td>(p.Ala34Val)</td>
<td></td>
<td>pathogenic</td>
<td>damaging</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

NBIA constitutes a group of neurodegenerative disorders resulting in progressive dystonia, spasticity, parkinsonism, neuropsychiatric abnormalities, and optic atrophy or retinal degeneration.7 Mitochondrial membrane protein-associated neurodegeneration (MPAN) occurs less commonly and is inherited by an autosomal recessive fashion. The mono or biallelic C19orf12 mutations are cause of this condition.8,9 The function of C19orf12 remains uncertain, but it may be involved in mitochondrial function, lipid homeostasis, and coenzyme A metabolism. Thus, we have expanded the range of genetic causes associated with MPAN to include C19orf12 mutations.10 In our patient, we detected a novel homozygous (c.101C>T) missense mutation in exon 2 of the C19orf12 gene. This is a missense (p.Ala34Val) substitution that results in the amino acid substitution of valin for alanine at codon 34. This variant has not been previously reported in HGMD, Pubmed and other medical literature. There are no homozygotes in gnomAD for this variant.

According to ACMG, this variant is classified as an uncertain significance variant PM2 and PP2. The gait instability is the initial presentation in most patients with MPAN. The age of onset in patients with MPAN varies between 4 and 30 years.11,12 The initial symptom of our patient was in the second decade. Our patient was from a consanguineous family who had postural instability, loss of facial expressions, slow gait, and hypophonia. Brain MRI of the patients demonstrates hypointensity in the globus pallidus and substantia nigra and iron accumulation in bilateral globus pallidus, substantia nigra, and red nucleus.6 The MRI scan of the brain in our patient showed mild iron deposition in the basal ganglia and cortical atrophy. Ophthalmological abnormalities such as optic atrophy have been described in MPAN cases.13 Optic nerve atrophy was not seen in our patient.

There is no definitive cure for the disease and the management of patients is based on rehabilitation and symptomatic medication.4,10 In view of the role of brain iron deposition in the pathogenesis of NBIA, the current focus is the use of iron chelating agents in therapy.14,15 Recent clinical trial of a novel therapeutic chelating agent...
deferiprone that can cross the blood-brain barrier (3-hydroxy-1,2-dimethylpyridin-4-(1H)-one, DFP) has shown reduction in brain iron levels in globus pallidus. Although the clinical diagnosis of NBIA is difficult, age of onset, family history, clinical findings, and characteristic imaging abnormalities are helpful pointer to the clinical diagnosis. As highlighted in this case report, the application of next-generation sequencing (NGS) tests will improve diagnostic accuracy. The differential diagnosis with similar clinical phenotype include multiple system atrophy, Machado Joseph’s disease, Parkinson’s plus syndrome and Wilson’s disease.

We present here an adult Turkish patient with MPAN and a novel (c.101C>T;p.Ala34Val) disease-causing variant in the C19orf12 gene. Autosomal recessive neurodegenerative disease is more common in populations with high consanguinity, such as Turkey. Diagnosis of the specific genetic etiology of NBIA cases becomes difficult unless the genes and inheritance patterns involved in NBIA are known. Moreover, determining the genetic diagnosis in NBIA is important not only for understanding the individual effects of the disease, but also for variant screening of family members and giving genetic counseling for family planning.

ACKNOWLEDGEMENT

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DISCLOSURE

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Conflict of interest: None

REFERENCES