Mitochondrial Membrane Protein–Associated Neurodegeneration: A Case Series of Six Children

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Abstract

Neurodegeneration with brain iron accumulation (NBIA) is a group of genetic disorders with a progressive extrapyramidal syndrome and excessive iron deposition in the brain, particularly in the globus pallidus and substantia nigra. Mitochondrial membrane protein–associated neurodegeneration (MPAN), a subtype of NBIA, is caused by mutation in the orphan gene *C19orf12*. A slowly progressive gait disorder from generalized dystonia and spasticity and cognitive impairment constitute the main features of MPAN. The *C19orf12* p.Thr11Met mutation is frequent among Turkish patients with MPAN. Here, we report the clinical manifestations and genetic study results of six Turkish patients with MPAN due to different mutations from previous.

Keywords: Children, *C19orf12* mutations, mitochondrial membrane protein–associated neurodegeneration

Introduction

Neurodegeneration with brain iron accumulation (NBIA) comprises a heterogeneous group of disorders with accumulation of iron in the brain, mostly basal ganglia.[1] Mutations within *C19orf12* have recently been identified in patients with NBIA.[2] This gene *C19orf12* codes for a mitochondrial membrane protein and the acronym MPAN. *C19orf12* protein is localized in mitochondria and endoplasmic reticulum. Pathogenic mutations in this gene are postulated to cause dysfunction of lipid homeostasis in mitochondria.[3]

The clinical progression of mitochondrial membrane protein–associated neurodegeneration (MPAN) is similar to that of classical pantothenate kinase–associated neurodegeneration (PKAN), but the age of onset is later and the symptoms are milder.[2,4] We reported the clinical manifestations and genetic study results of Turkish six patients with MPAN due to different mutations from previous mutations.

Case Reports

Patient 1 was a 14-year-old boy who presented with progressive difficulty in walking. The first neurological symptom developed at the age of 10 years was gait impairment with frequent falls while walking. Over the following years, behavioral disorders, slight cognitive impairment, dysarthria, and abnormal involuntary movements developed. The parents were consanguineous. His neurological examination revealed hypomimia, bradykinesia, mild dysarthria, intentional tremor, dystonia, and spasticity of both lower limbs with exaggerated deep tendon reflexes. Eye fundus examination was normal. Magnetic resonance imaging (MRI) of brain revealed symmetric, hypointensity of bilateral globus pallidus, and substantia nigra in the T2-weighted images [Figure 1]. Nerve conduction studies were normal. The homozygous mutation p.M124Ifs*17 (c.371_372insT) in *C19orf12* gene was detected. This patient was previously published.[5]

Patients 2 and 3 were siblings. Patient 2 was a 12-year-old girl who was admitted to our hospital for difficulty in walking from 9 years of age. Her parents were consanguineous. Her neurological examination revealed mild dysarthria and dystonia, intentional tremor, and spastic gait. Patient 3 was her brother, and his symptom was gait impairment. The ophthalmologic examinations of two patients were normal.

Patient 4 was a 17-year-old girl and cousin of patients 2 and 3. She had progressive gait impairment, dystonia, bradykinesia,

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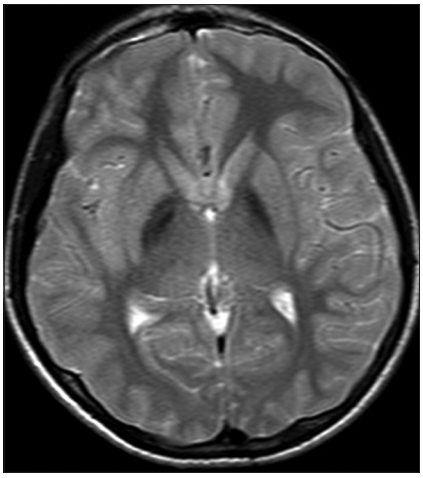

Figure 1: Symmetric, hypointense lesions in the globus pallidus and substantia nigra in T2-weighted images of brain imaging

cognitive impairment, behavioral disturbances, visual failure, and spasticity. Onset of the disease was around age 10 years with behavioral disturbances and gait impairment. Ophthalmological examination revealed optic atrophy. The electromyography revealed axonal neuropathy. Patients 2, 3, and 4 had bilateral globus pallidus and substantia nigra hypointensity on T2-weighted. In these three patients, *C19orf12* gene sequencing analysis was performed and a novel homozygous mutation c. 166_167insG (p.Ala56Glys*16) was detected.

Patient 5 was a 17-year-old girl who presented with difficulty in walking and vision loss. Her neurological examination revealed optic atrophy, dysarthria, dystonia, intentional tremor, behavioral disturbances, cognitive impairment, and spastic gait. Brain MRI showed hypointensity in globus pallidus and substantia nigra and cerebellar atrophy. The homozygous mutation p.M124Ifs*17 (c. 371_372insT) in *C19orf12* gene was found.

Patient 6 was a 15-year-old boy and was brought with gait impairment, behavioral disturbances, and mild cognitive decline from 10 years of age. Neurological examination was characterized by a mild dysarthria and dystonia, behavioral disturbances, visual failure, intentional tremor, and spastic gait.

Discussion

Since the discovery of the first major gene causing neurodegeneration with NBIA in 2000, significant progress has been made in delineating the genetic and clinical features of various forms.[1] MPAN is a new identified subtype of NBIA, caused by mutations in *C19orf12* gene, described primarily in Polish cohort.[2] MPAN is thought to be the third most frequent subtype of NBIA after PKAN- and PLA2G6-associated neurodegeneration, accounting for about 5% in international patient series and up to 30% within specific populations.[2,4,6]

The clinical symptoms associated with MPAN are similar to classical PKAN, but the age of onset is later, and expression of symptoms is milder in MPAN.[2,4] MPAN symptoms can manifest from early childhood to early adulthood, with a broad phenotypical spectrum, including spasticity, dystonia, parkinsonism, optic atrophy, motor axonal neuropathy, autonomic dysfunctions, cognitive decline, and psychiatric disturbances. Key clinical features are pyramidal and extrapyramidal signs, cognitive decline, neuropsychiatric abnormalities, optic atrophy, and motor axonal neuropathy in patients with MPAN. In almost all cases, the optic atrophy has been noted. Nearly 50% of cases have had a motor axonal neuropathy.[2]

Hartig *et al*.[2] reported the clinical and genetic findings in 24 patients with MPAN. They found that the most common presenting symptoms were speech and gait difficulties. In other study, Skowronska *et al*.[7] described the common symptoms as spasticity, dysarthria, parkinsonism, and dystonia in 14 patients with MPAN. Hogart *et al*.[4] detected cognitive decline (100%), spasticity (91.3%), dysarthria (90.4%), dystonia (71.4), optic atrophy (74%), and parkinsonism (47.8%). We detected developmental gait difficulties (100%), spasticity (83.3%), dystonia (66.7%), cognitive decline (66.7%), and parkinsonism (66.7%). Two patients had optic atrophy and one patient had motor axonopathy.

Radiological findings of MPAN are also helpful for the differentiation of MPAN from other NBIA disorders. Iron accumulation in the globus pallidus and substantia nigra may be observed, but the "eye of the tiger" sign is not typical for MPAN and, if present, less prominent than in PKAN.[2,4] We found hypointensity on T2-weighted images in globi pallidi and substantia nigra in MRI of all our patients. We did not detect the eye of the tiger sign in any patient. Cerebellar atrophy was found in one patient.

Very different mutations have been described in *C19orf12* in previous publications including frameshift mutations, missense mutations, nonsense mutations, and splice-site mutations. The *C19orf12* p.Thr11Met mutation is frequent among adult Turkish patients with MPAN in previous reports.[8,9] Olgiati *et al*.[8] described clinical and neuroradiological findings in 15 patients with MPAN from nine families from Turkey, who all harbor the same homozygous mutation (c.C32T [p. Thr11Met]). Dogu *et al*.[9] described two consanguineous families with a homozygous *C19orf12* p.Thr11Met mutation. In another case, Yilmaz *et al*.[10] reported a novel homozygous mutation p.L121Q (c.362 T > A) in a 14-year-old girl. We have found two novel homozygous mutations in six patients.

In conclusion, especially in patients with NBIA with cognitive decline, optic atrophy, motor axonal neuropathy, and psychiatric findings but without the typical radiological eye of the tiger sign, genetic testing of *C19orf12* should be performed to confirm the clinical diagnosis and provide genetic counseling to the families.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of

the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from the parents of the children included in the study.

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Conflicts of interest

There are no conflicts of interest.

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