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Case Report / Olgu Sunumu

Juvenile-onset Mitochondrial-membrane Protein-associated Neurodegeneration with Late Diagnosis

Geç Tanı Konan Juvenil Başlangıçlı Mitokondriyal Membran Proteini ile Ilişkili Nörodejenerasyon

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Abstract

Neurodegeneration with brain iron accumulation (NBIA) encompasses a number of heritable disorders affecting children and adults characterized by diverse clinical manifestations and brain iron deposition detected on magnetic resonance imaging (MRI). The most frequent NBIA subtypes are pantothenate kinase-associated neurodegeneration, phospholipase A_2-associated neurodegeneration, fatty acid-2 hydroxylase-associated neurodegeneration and mitochondrial-membrane protein-associated neurodegeneration (MPAN). Here, we report a male patient presenting with optic atrophy, progressive cognitive and movement impairment, bilateral hypointensity of the basal ganglia on T2-weighted MRI and proven mutation for MPAN. The NBIA disorders can remain undiagnosed for 3 to 30 years. In children developing optic atrophy, NBIA should be taken into consideration.

Keywords: Mitochondrial protein associated neurodegeneration, neurodegeneration with brain iron accumulation, C19orf12

Öz

Beyinde demir birikimi ile seyreden nörodejenerasyon [neurodegeneration with brain iron accumulation (NBIA)], çeşitli klinik belirtiler ve manyetik rezonans görüntülemede (MRG) tespit edilen beyinde demir birikimi ile karakterize, çocukları ve yetişkinleri etkileyen bir dizi kalıtsal bozukluğu kapsar. En sık görülen NBIA alt tipleri pantotenat kinaz ile ilişkili nörodejenerasyon, fosfolipaz A_2 ile ilişkili nörodejenerasyon, yağ asidi-2 hidroksilaz ile ilişkili nörodejenerasyon ve mitokondriyal membran proteini ile ilişkili nörodejenerasyondur (MPAN). Burada optik atrofi, ilerleyici bilişsel bozukluk, hareket bozukluğu, T2 ağırlıklı MRG'de bazal ganglionlarda bilateral hipointensite ile başvuran ve MPAN için kanıtlanmış bir mutasyon tespit edilen bir erkek hastayı sunuyoruz. Beyinde demir birikimi ile seyreden nörodejeneratif bozukluklar 3 ila 30 yıl boyunca teşhis edilmeden kalabilir. Optik atrofi gelişen çocuklarda NBIA düşünülmelidir.

Anahtar Kelimeler: Mitokondriyal protein ilişkili nörodejenerasyon, beyin demir birikimi ile nörodejenerasyon, C19orf12

Introduction

Neurodegeneration with brain iron accumulation (NBIA) signifies a number of inherited neurological disorders defined by genetic and clinical heterogeneity with variable progression (1,2). Beginning in infancy or adulthood, NBIA leads to cognitive decline, psychiatric disturbances, akinetic-rigid parkinsonism and optic atrophy or retinal degeneration (2,3). Diagnosis of NBIA is confirmed by genetic testing, brain magnetic resonance imaging (MRI) and clinical presentation. Iron accumulation in basal ganglia marks a distinctive feature of NBIA (4). To date, ten genes (*ATP13A2, C19orf12, C0ASY, CP, DCAF17, FA2H, FTL, PANK2, PLA2G6, WDR45*) have been identified as associated with particular NBIA subtypes. We present a case of NBIA with C19orf12 mutation diagnosed by using MRI.

Case Reports

Thirty-one -year-old male had been followed up since childhood due to bilateral optic atrophy presenting with a

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gradual visual impairment, which was attributed to time spent in the incubator after birth. Visual field assessment at the age of 21 revealed areas of deterioration of retinal sensitivity in the intermedial zone with relative shallow central scotoma of the right eye and wider angiosarcoma with deterioration of retinal sensitivity in the intermedial zone of the left eye. At the same time, brain MRI showed symmetrical calcifications of the striatum and mesencephalon nuclei.

Five years later, progressive balance problems were noted causing frequent falling. The same year, antiepileptic drug levetiracetam was introduced because of frequent falls and onetime loss of consciousness. Electroencephalogram showed diffuse dysrhythmic changes with a mild temporooccipital focus and independent left frontotemporal focus with abortive spike-and-wave bursts, polymorphic delta activity, paroxysmal tendency and vulnerability to provocation methods. Patient had sepsis after birth. At the age of 5, he had head injuries due to falling from a height but without brain concussion. There was no history of convulsive elements. There was no history of neurologic diseases in family.

Over the next months, further cognitive decline and scarce vocabulary were observed. Serum levels of magnesium, copper, calcium (Ca), phosphorus were in the reference range, while ceruloplasmin and parathyroid hormone (PTH) were below the reference range. Head computed tomography (CT) showed bilateral basal ganglia calcifications.

Presumption of hypoparathyroidism and vitamin D hypovitaminosis with Ca disposal in basal ganglia and ataxia was made and vitamin D therapy was initiated. Cerebrospinal fluid markers were typical for neurodegenerative diseases [neuron-specific enolase 98.15 ug/l, tau protein 1558 ng/l, beta amyloid (1-42) 1080 ng/l]. Sanger sequencing analysis revealed normal range of the allelic variants of the spinocerebellar ataxia (SCA1, SCA2, SCA3, SCA6, SCA7).

Control brain MRI showed hypointense signal in the striatum and mesencephalic nuclei indicative of calcifications or iron accumulation. In the following year, based on the normal serum PTH, Ca and phosphate levels, diagnosis of hypoparathyroidism was excluded. The molecular genetic testing for hereditary hemochromatosis (HH) was performed. Mutations of human factors engineering (HFE)-associated hemochromatosis (p.C282Y, p.H63D, p.S65C) were not found.

At the age of 28, dysarthria, left-side predominant intention tremor, ataxia and impaired eye movements were detected with no limb weakness. A neuropsychological evaluation showed mild mental retardation. Over the following year, brain MRI and CT were performed. MRI showed hypointense signal in the globus pallidus, subthalamic nuclei and mesencephalic nuclei indicative of iron accumulation in the nigrostriatal pathway. CT scan did not show any calcifications. Clinical exome sequencing revealed frameshift variant c.279delT (p.Ala94ProfsTer25) in the *C19orf12* gene and definite diagnosis was established. General health deterioration, cognitive decline and dysphagia were present at the age of 31 years in our patient. Neuropsychological testing, through which all cognitive domains were tested, showed personality changes accompanied by impaired affective functioning and mild intellectual disability (Figures 1, 2).

Discussion

Mutations in chromosome 19 open reading frame 12 gene have been identified as the molecular genetic cause of mitochondrial-membrane protein-associated neurodegeneration (MPAN) (4). MPAN accounts for 5-10% of all NBIA subtypes (2). Even though MPAN mostly follows autosomal-recessive pattern of inheritance,

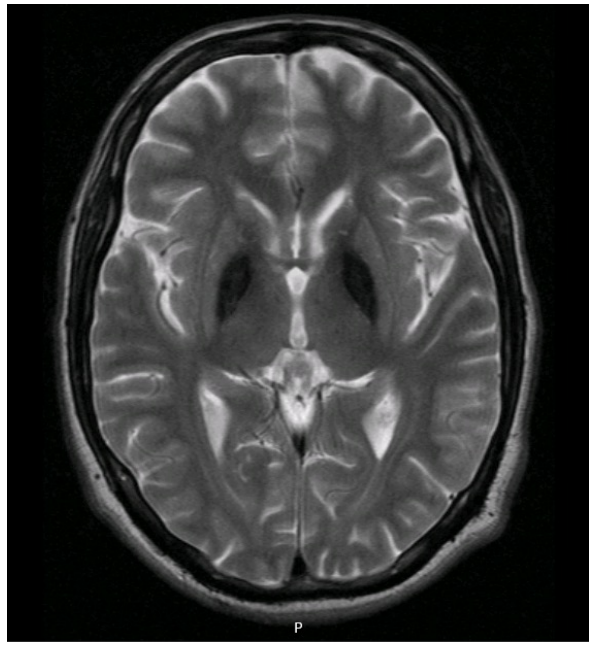

Figure 1. MRI T2 hypointensities are seen bilaterally in the area of the globus pallidus
MRI: Magnetic resonance imaging

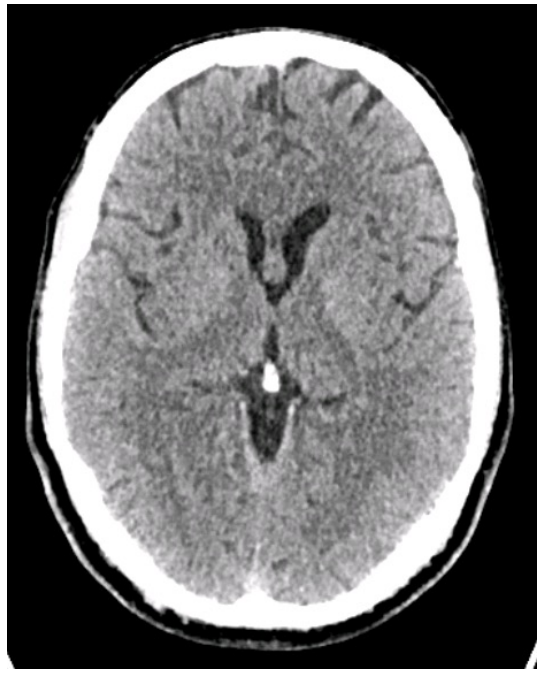

Figure 2. Normal brain CT scan, without calcifications in basal ganglia
CT: Computed tomography

autosomal-dominant mode of inheritance has been reported recently (2,4). An array of mutations was allocated throughout the coding region of C19orf12 including frameshift, missense and nonsense mutations (1,4,5). We identified the heterozygous C19orf12 frameshift mutation c.279delT resulting in premature termination codone at position 25 of the new reading frame. The variant was previously noted in OHSU International NBIA Respository (2).

Consisting of three exons, the *C19orf12* gene codes for two alternative mRNA isoforms and proteins (6). Encoded transmembrane protein is not only confined to mitochondria as previously thought (4,5,7), but is also present in endoplasmic reticulum and mitochondria associated membrane (8). It is postulated that the protein plays a major role in fatty acid biogenesis and branched-chain amino acid (valine, leucine and isoleucine) degradation proposing likeness to other NBIA proteins, including PKAN2, PLA2G6 and FA2H (4,5).

Studies suggest mutations are likely to impair the correct localisation of the protein in the membrane thus mutant C19orf12 protein being present in the mitochondrial matrix as well as mitochondrial membranes, while the wild-type C19orf12 protein is solely found in mitochondrial membranes (8). C19orf12 protein is known to be implicated in the removal of the dysfunctional mitochondria by selective autophagy, whereas the mutant protein causes accumulation of the altered mitochondria leading to neuronal degeneration and death (8).

Despite ubiquitous expression (brain, adipocytes, blood cells), C19orf12 leads to degeneration preferentially in neurons which is accordant with clinical features and MRI findings (5). Our patient presented with optic atrophy early in life corresponding with previously documented initial symptoms of juvenile-onset MPAN (4).

Initially, ataxia and retinopathy led us suspect spinocerebellar ataxias, but the diagnosis was excluded by molecular testing (9). HH was considered due to iron depositions in basal ganglia, ataxia, dysarthria and cognitive impairment (10). However, HFE-associated hemochromatosis mutations were not found.

Although, a mutation specific to MPAN was revealed, significant phenotypic overlap between NBIA subtypes was apparent. Other than MPAN, optic atrophy and retinal degeneration are seen in early stages of fatty acid-2 hydroxylase-associated neurodegeneration (FAHN) (11), atypical pantothenate kinase-associated neurodegeneration (PKAN) or Hallervorden-Spatz disease (12), and advanced stage of phospholipase A_2-associated neurodegeneration (PLAN) (12). Symptoms present in our patient that could resemble FAHN were progressive intellectual decline, dysarthria, ataxia and gait changes (11). Apart from MPAN, parkinsonism and slowed saccadic eye movements are indicative of PKAN (1,13).

Most of the patients with early-onset MPAN have slow progression and survival beyond twenties, as seen in our patient, in contrast to abrupt progression seen in childhood-onset PKAN and PLAN.

Pathohistological examination, acknowledged in previous studies, has revealed neuronal loss and gliosis and proved the presence of iron deposits, axonal spheroids, alpha-synuclein positive Lewy bodies and tau inclusions in basal ganglia (the substantia nigra and the globus pallidus) and neocortex implying a similar pathogenesis of the NBIA disorders (2,4,5).

First MRI and CT interpretations displayed symmetrical calcifications of basal ganglia. The next one considered iron accumulation based on the hypointense signal on T2-weighted imaging (T2WI) and no calcifications on CT scan. Apart from disease duration, age affects the radiological picture as well. Globus pallidus and substantia nigra physiologically become hypointense on T2WI around the age of ten when compared with the signal in white matter (14). While both calcifications and iron accumulation can have isointense or hypointense signal on T2WIs (1), T1-160 weighted images of calcifications are hyperintense and most of those of iron accumulation are isointense.

Even though T2 low intensity signal in the globus pallidus and substantia nigra is a well know hallmark of MPAN (15), it can be present in other NBIA subtypes. Yet another distinctive feature of MPAN, present in one-fifth of patients, is linear T2 hyperintensity of the medial medullary lamina between globus pallidus externa and interna that becomes more evident over time (4,5,15). In contrast to PKAN, eye-of-the-tiger sign is absent in MPAN (4). CT scans may be more convenient when making a distinction between calcifications and iron deposits (15). Calcifications on CT scan of our patient with MPAN weren't reported in literature (15) leading us to conclude that the mistake was made when analysing early CT images of our patient since this was not seen in second CT scan five years later.

The NBIA disorders can remain undiagnosed for 3 to 30 years. The reason behind it is rarity of occurrence, variety of symptoms prevalent in other well-known disorders and unavailability of genetic testing. In children developing optic atrophy, NBIA should be taken into consideration.

Ethics

Informed Consent: Written consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.B., Analysis or Interpretation: K.G.J., D.O., Literature Search: R.P., M.F., Writing: R.P., M.F.

Conflict of Interest: No conflict of interest was declared by the authors.

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