CASE REPORT

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Mitochondrial Membrane Protein-Associated Neurodegeneration as The Cause of Psychosis

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Abstract

Hallucinations and delusions can be an initial symptom of many medical conditions as well as psychiatric disorders. These medical conditions can be endocrinological, immunological, neurological or genetic diseases. NBIA (Neurodegeneration with Brain Iron Accumulation) is a very rare genetically inherited mixed disorder that can occur with neurological, psychiatric or neuropsychiatric symptoms. MPAN (Mitochondrial Membrane Protein-Associated Neurodegeneration) is a recently described NBIA subtype. In this article, MPAN case with visual hallucinations and cognitive destruction was discussed. Also, we aimed to present the clinical features of MPAN and to underline the importance of the physical and neurological examination and the combination of findings with appropriate tests in the process of diagnosis.

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INTRODUCTION

The majority of psychosis patients in early adulthood are diagnosed with schizophrenia spectrum disorders or mood disorders. However, psychosis may be a symptom of neurological, endocrine, immunological or genetic disease [1]. Many various medical illnesses can occur with isolated psychotic symptoms and a significant proportion of them have disease-specific treatment [2].

An organic psychotic disorder is a psychiatric disorder in which hallucinations and delusions are seen as distinct secondary to an underlying original organism. Disorders whose clinical appearance is similar to schizophrenia but which are understood to be manifestations of a non-psychiatric disorder are grouped in DSM-5 under the title of psychosis disorder due to another medical condition [3]. In order to make this diagnosis, the physician must evaluate the history, physical examination or laboratory findings that this disorder is the direct pathophysiological result of another health condition [4]. The disease that causes psychosis can rarely be genetically transmitted. When the diagnosis of a genetically transmitted disease is determined, close relatives of the patient can be given genetic counseling and the possibility of misdiagnosis decreases in relatives who are at risk of showing the disease [5]. It also plays an important role in preventing the disease for future generations.

Neurodegeneration with brain iron accumulation (NBIA) is defined as a heterogeneous inherited group of neurodegenerative diseases especially in the basal ganglia, substantia nigra and other parts of the brain with excessive iron accumulation [6]. The prevalence of NBIA, which is a very rare disease group, in the general population is less than 1/1000000 [7]. NBIA subtype mitochondrial membrane protein-associated neurodegeneration (MPAN) is caused by mutations recently found in C19orf12 which encodes a protein localized in the mitochondrial membrane [8]. MPAN was first described by Hartig in Poland in 2011. Although the clinical picture is not specific, it's often seen with combinations of neurological and psychiatric symptoms in ages ranging from early childhood to late adulthood [9]. Neurological findings of MPAN include gait disorders, signs of pyramidal system, parkinsonism, dystonia, muscle atrophy, dysphagia, dysarthria, incontinence, ocular motor disorder and cerebellar findings. Optic nerve atrophy is often accompanied by motor axonal neuropathy. Accompanying psychiatric findings were reported as cognitive impairment, hallucinations, learning difficulties, anxiety, hyperactivity and obsessive-

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compulsive disorders [10,11]. In the literature, 14 MPAN cases in Poland in 2017, it was stated that patients had spastic paraparesis or tetraparesis, optic neuropathy, dysarthria, dystonia and parkinsonism [8]. Parkinsonism, pyramidal findings, psychiatric disorders, cognitive impairment, walking and speech disorders were reported among the most common findings in 15 MPAN cases from 9 families screened for c19orf12 mutation in our country [12]. In this article we aimed to discuss the MPAN case that admitted to the psychiatry outpatient clinic with complaints such as visual hallucinations, speech disruption, forgetfulness and tremors without a history of psychiatric illness in the past.

Case Presentation

A 32-year-old high school graduate, a single male patient came to the psychiatric outpatient clinic with his father and his own will. He applied with the complaints of seeing a human-like presence with tall bare feet, black clothes and green eyes both in the dark and during the day, which started 2 years ago and simultaneous tremors, forgetfulness and speech impairment. In the first psychiatric examination, he was compatible with his chronological age, had moderate self-care and was willing to communicate with the interviewer. His speech was blocky; reaction time was prolonged, thought speed was slow. His thought content was poor, affect was restricted. He had no insight. His spontaneous attention, concentration and psychomotor activation were reduced. He was admitted to the clinic for further examination and treatment, considering that he may have psychotic disorder as a preliminary diagnosis.

When the patient's history deepened, he was born 7 months out of twin pregnancies with a normal vaginal route, as the seventh out of ten siblings. One month after birth, his twin died for an unknown reason. His neurological development was normal. School success is good, with no class repetition, no noticeable problems with friends and teachers. The functionality of the patient was good until the last two years. Premorbid personality was mentioned as extrovert, harmonious, responsible in good relationships with people. According to the information received from the family, the patient's older sister died at the age of 38 due to a disease with muscular involvement and her 37-year-old brother had symptoms similar to his older sister. It was learned that his parents were cousins, his aunt and father's aunt also had illnesses with the same symptoms as his older sister. Thereupon, a neurology consultation was requested.

In his neurological examination, consciousness was open and cooperation was limited. The resting tremor was present in both hands and legs. His muscle tone had decreased. He had rigidity in the bilateral elbow and knee joint. Achilles clone was evaluated as one positive (+). Kent EGY intelligence test performed at the time of hospitalization was evaluated as 67 points (Mild Mental Retardation) and Minimental Examination: 11 points (moderate to severe cognitive impairment). When the patient's laboratory results were examined in detail, no findings could be obtained to explain the current situation. Primarily, the patient was thought to have a genetic-transmitted disease with neuropsychiatric findings.

The cranial magnetic resonance imaging (MRI) results showed symmetrical hypointensity in the globus pallidus and substantia nigras and laminar streaks in the globus pallidus in the T2 flair and gradient series. After the cranial MRI was taken, the patient was asked for a consultation from the neurosurgical department and the opinion was obtained that there was no mass. Considering the patient's age with clinical information, it was interpreted as compatible with NBIA. (Figure 1) The family tree of the patient was made. (Figure 2) In light of all these data, the diagnosis of NBIA was considered in the foreground and genetic testing was recommended to the family. The family stated that blood was drawn from all family members about 5 years ago but they did not know what the consequences were. An epicrisis was requested from the neurology clinic where the patient's sister had been treated in the outer center. However, as a result of insufficient information, a verbal conversation was spoken to the doctor who had previously followed the patient's sister. According to the information received from the outer center neurology doctor, blood was taken from all family members, a genetic test was performed and C19orf12 mutation was detected in the family members who were sick. As a result, the patient was diagnosed with mitochondrial membrane protein-associated neurodegeneration (MPAN). However, neuropsychiatric findings were predominant in our patients while motor neuron findings were dominant in other sick siblings.

In treatment, pramipexole 0.250 mg 2x1 was started symptomatically in order to improve the quality of life for the patient with the complaint of tremors in the hands. It was gradually increased to 1 gram per day. Patient's tremor was decreased in the second week of treatment. The patient had no hallucinations during this period. Antipsychotic treatment was not started to avoid the worsening of extrapyramidal findings. The family was told about the disease and directed to genetic counseling.

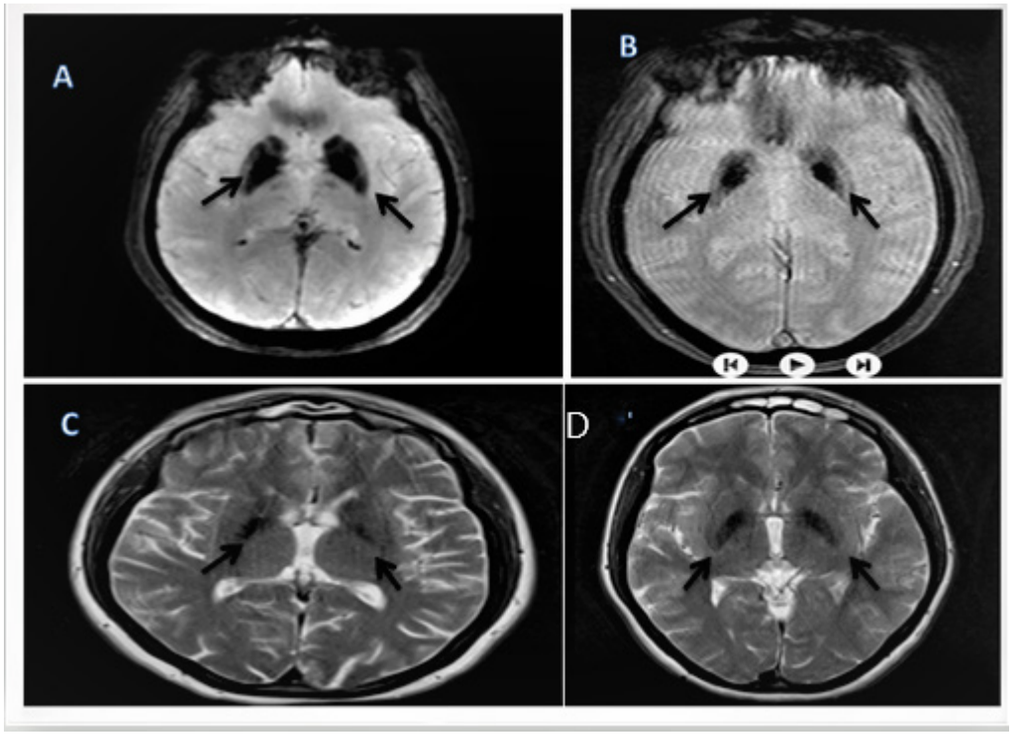

Figure 1 . Symmetrical hypointensity in basal ganglia (arrow)

A-Cranial magnetic resonance imaging (MRI) of our patient in 2019
B-Cranial MRI of the sick brother in 2019
C-Cranial MRI of the ex-sister in 2012
D-Cranial MRI of the sick aunt in 2012

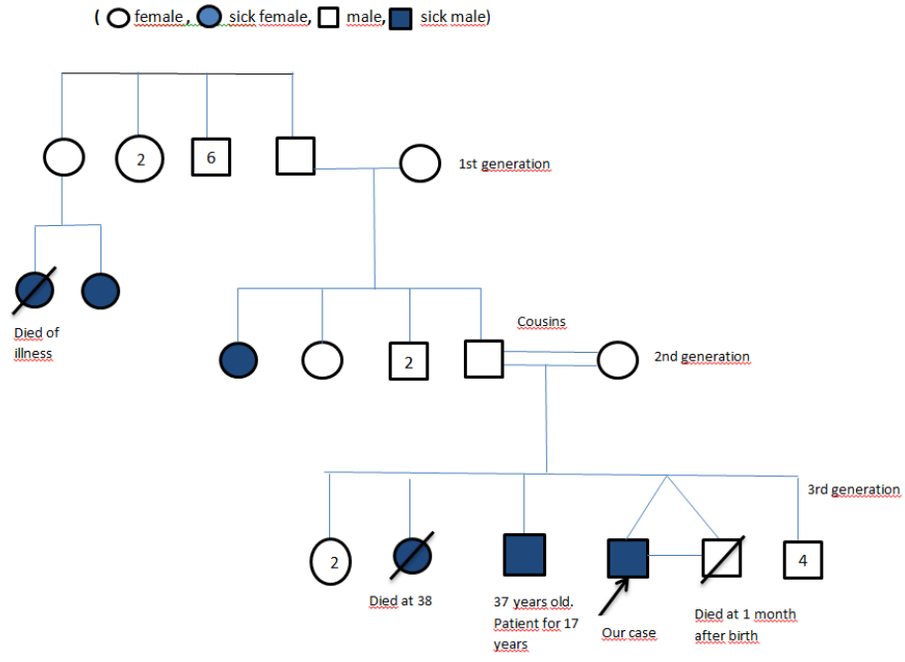

Figure 2. Family tree of the case

DISCUSSION

The first psychotic attack can occur at any age and is secondary to psychiatric or other hidden diseases. Caution about organic etiology is of great therapeutic importance as early diagnosis can help the initiation of disease-modifying treatments early [13]. In this article, we present a case of MPAN, which is an extremely rare cause of organic psychosis with neuropsychiatric findings, which started acutely 2 years ago with visual hallucinations. When the symptoms are compared both in primary psychosis and secondary psychosis due to organic causes, it is seen that they are similar. However, visual hallucinations are more common in secondary psychosis while core schizophrenia symptoms, auditory hallucinations, pre-disease schizoid personality and family history are more dominant in primary psychosis. In our case, visual hallucinations, acute and late symptom onset, premorbid history, mild neurological findings and family history were among the reasons suggesting organic etiology.

Although the role of structural neuroimaging methods in clinical psychiatry is uncertain, they are certainly useful in establishing the pathophysiology and differential diagnosis of psychiatric disorders [14]. Structural neuroimaging methods provide valuable information, especially in the first episode psychosis and late-onset psychosis in non-evident neurological conditions. The rarity of the demonstrable organic causes of psychotic diseases in the clinical setting takes the physician away from the investigation of these organic causes. As a result, organic-based disorders can not be diagnosed when they occur only with psychiatric symptoms or psychiatric diagnoses are made. From this point of view, first-episode psychosis, late-onset psychosis, suspicious neurological findings, presence of an electroencephalographic abnormality and accompanying physical illness symptoms require the investigation of the link between the psychotic state and organic disease [15].

The symmetrical hypointensity in basal ganglia in T2 flair in cranial MRI of our case played an important role in the diagnosis. In addition, the same finding in the cranial MRI of the sick brother indicated hereditary disease. (Figure 1) The differential diagnosis, according to the clinical table, was made by taking into consideration the hereditary diseases that can show a psychosis table. In particular, accumulating diseases in the brain were prioritized and Wilson's disease was excluded because of normal copper and ceruloplasmin levels and brain imaging findings did not comply. Also abetalipoproteinemia, a hereditary disease accompanied by psychosis was ruled out as a result of normal peripheral propagation. Although the symptoms of the patients in the family were different, the diagnosis of MPAN became definitive with the learning of the C19orf12 mutation in the patient's siblings as a result of the same cranial MRI findings, detailed family history and detailed investigation of the medical records in our case. Based on this fact, the importance of taking a detailed disease history, performing a physical, neurological examination and combining the findings with appropriate tests in all cases suspected of organic etiology was once again emphasized in the diagnostic process.

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