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Case Report / Olgu Sunumu

Is Aripiprazole the Most Appropriate Option in the Treatment of Niemann Pick Type C Disease Psychosis?

Aripiprazol Nieman Pick Psikozunda En Uygun Tedavi Seçeneği midir?

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Abstract

Niemann Pick Type C (NPC) is a rare autosomal recessive lysozomal depot disease. It has highly heterogeneous appearance characterized by progressive neurological deterioration and premature death. The disease manifests itself as visceral, neurological, psychiatric disorders alone or in various combinations. The clinical presentation varies according to the age of onset. A 17-year-old girl was referred with the diagnosis of NP-C, consulted by Pediatric Metabolism Department due to the referential and persuasion delusions. After Psychiatric examination and psychometric evaluations the patient was given the diagnosis of acute psychotic episode and mental retardation. We started the risperidone treatment after evaluations. After risperidone treatment epileptic seizures have occurred. After controlling the seizures, we switched the risperidone treatment to aripiprazole. Aripiprazole treatment and psychosocial intervention of the patient whose psychotic symptoms have diminished continues. NP-C disease is a rare disease and may cause psychiatric symptoms. The questioning of developmental history and associated neurological symptoms in juvenile-onset psychotic conditions may suggest underlying NP-C disease. There is no much research with respect to treatment of psychiatric symptoms seen in NP-C. In this case report, the treatment of NP-C disease with psychiatric symptoms and treatment of psychiatric symptoms were emphasized. Aripipirazole might be an option for treatment of psychotic symptoms seen in NP-C.

Keywords: Adolescent, Metabolic Disorder, psychosis

Özet

Niemann Pick Tip C (NPC) nadir görülen otozomal resesif lizozomal depo hastalığıdır. Progresif nörolojik bozulma ve erken ölüm ile karakterize oldukça heterojen bir görünüme sahiptir. Hastalık kendisini tek başına veya çeşitli kombinasyonlarda visseral, nörolojik, psikiyatrik bozukluklar olarak gösterir. Klinik tablo başlangıç yaşına göre değişir. Çocuk Metabolizması Bölümü'nden NP-C tanısı ile takipli 17 yaşında kız hasta referansiyel ve perseküsyon sanrıları nedeniyle danışıldı. Yapılan psikiyatrik muayene ve psikometrik değerlendirmelerden sonra hastaya akut psikotik atak ve mental retardasyon tanısı konuldu. Değerlendirmelerden sonra risperidon tedavisine başlandı. Risperidon tedavisinden sonra epileptik nöbetler meydana geldi. Nöbetleri kontrol ettikten sonra risperidon tedavisini aripiprazole çevirildi. Psikotik belirtileri azalan hastanın aripiprazol tedavisi ve psikososyal müdahalesi devam etmektedir. NP-C hastalığı nadir görülen bir hastalıktır ve psikiyatrik semptomlara neden olabilir. Juvenil başlangıçlı psikotik durumlarda gelişim öyküsü ve ilişkili nörolojik semptomların sorgulanması, altta yatan NP-C hastalığını düşündürebilir. NP-C'de görülen psikiyatrik semptomların tedavisi ile ilgili çok fazla araştırma bulunmamaktadır. Bu olgu sunumunda NP-C hastalığının psikiyatrik semptomlarla tedavisi ve psikiyatrik semptomların tedavisi vurgulanmıştır. Aripipirazol, NP-C'de görülen psikotik semptomların tedavisi için bir seçenek olabilir.

Anahtar Kelimeler: Ergen, metabolik hastalık, psikoz

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1. Introduction

Niemann - Pick disease type C (NP-C) is a rare autosomal recessive disorder with an estimated incidence of 1 / 100,000 births (1). NP-C is characterized by the accumulation of non-esterified cholesterol in various tissue lysosomes because of a biochemical defect in the intracellular metabolism of exogenous cholesterol (2-5). The disease can present with visceral, neurologic, and psychiatric symptoms, and its clinical findings vary according to age (1,5,6). NP-C can present with various clinical phenomena. The prenatal-perinatal–onset type often presents with visceral conditions such as neonatal cholestasis and liver failure. Neurologic disturbances are not seen in the neonatal period. The early-infantile–onset type often manifests with motor mental retardation and hypotonia;late-infantile–onset type usually presents with walking disorder, apraxia, delayed speech, catalepsy, and vertical supranuclear gaze paralysis (VSGP), and the juvenile-onset type commonly presents with failure in school, ataxia, VSGP, epileptic seizures and catalepsy. The latter is the most common form. The adult-onset type often manifests with VSGP, ataxia, dystonia, dementia, and psychiatric symptoms (5,6). In patients presenting with psychiatric symptoms, the age of diagnosis is later 6. The diagnosis is made by the presence of filipin staining in the fibroblast culture of biopsy taken from skin or by showing the mutation in NPC1-2 genes (1). The only known treatment is miglustat, which is used to prevent progressive neurologic symptoms in adult and pediatric age groups (3,7).

In this article, we aimed to present a patient with NP-C who had juvenile-onset psychotic symptoms to draw attention to this rare metabolic disease, which may present with psychiatric symptoms, and to discuss the psychiatric symptoms of NP-C and its treatment and to contribute to the literature.

2. Case

A 17-year-old female was referred to the Ankara University Faculty of Medicine, Child and Adolescent Psychiatry Department by the Pediatric Metabolic Diseases Department with symptoms of explosive sudden anger and skepticism. In her history, it was learned that after the onset of miglustat treatment due to NP-C disease, the patient became easy to anger, had anger-control problems, and talked obsessively about a one subject with her friends she was living with. Her family stopped the treatment of miglustat due to the sudden anger explosions at their own discretion. In her history, it was learnt that she had been followed up with a pre-diagnosis of NP-C at an external center due to having downward gaze paralysis when she was aged 10 years, that the metabolic tests, electroencephalogram (EEG), and cranial magnetic resonance imaging (MRI) performed at that time were normal, and that the diagnosis of NP-C was genetically confirmed approximately three years ago.

In the prenatal, natal, postnatal history of the patient, who was born term through a normal spontaneous vaginal delivery with a birth weight of 3500 gr, it was found that the patient completed her developmental steps on time. She was admitted to a child psychiatrist for the first time when she was aged 10 years because of her low school achievement. Psychiatric and psychometric examinations revealed mild ‘mental retardation’ at that time. In her family history, it was learned that there was no kinship between the parents, that her sister was followed up with diagnoses of epilepsy, NP-C, and mental retardation, and that her uncle's daughter died of epilepsy when she was aged 18 years.

A psychiatric examination showed that she was consciousness, her orientation to place and time was intact, but orientation to persons was impaired. Her appearance was appropriate for her age and socioeconomic status. Her instant memory was intact, her short-term memory was impaired and her long-term memory was intact. It was observed that she was distracted during the examination and her intelligence was clinically slightly retarded. Her speech was dysarthric and was difficult to understand, her flow of thoughts was inappropriate, and her thoughts were

filled with derailment and flying ideas. In the content of her thoughts, she had referential delusions against her friends. Her abilities to judge, and to abstract were impaired. She had visual hallucinations in the form of cat, dog, and human, and she had auditory hallucinations in the form of hearing voices about herself. She had no olfactory or tactile hallucinations. Her affect was superficial and her mood was dysphoric. Her psychomotor activity was slow.

The treatment of risperidone was initiated with a NP-C pre-diagnosis presenting juvenile-onset psychotic symptoms and a dosage of 2 mg/day was titrated slowly due to possible neurologic and metabolic adverse effects. The patient, who had a reduction in positive psychotic symptoms and anger bursts, had a generalized tonic clonic seizure in the second year of treatment with risperidone 2 mg/day. Risperidone therapy was discontinued due to the recommendation of the Pediatric Neurology Clinic. An EEG showed epileptic abnormalities in bilateral frontal regions and levetiracetam 2000 mg/day was started. The patient's generalized tonic clonic seizures continued and oxcarbazepine 600 mg/day was started and no seizures were observed following oxcarbazepine treatment. An MRI scan revealed cerebral atrophy. Upon the continuation of the patient's referential delusions, persecution delusions and visual hallucinations, she was redirected to our clinic by the Metabolic Diseases department. Before treatment, the Positive and Negative Syndrome Scale (PANSS) was performed and the positive symptoms (P) subscale scorewas 26, the negative symptoms (N) subscale scorewas 30, and the general psychopathology (G) subscale scorewas 52.

A pediatric neurologist recommended evaluating the use of antipsychotics in terms of epilepsy. Aripiprazole 2.5 mg/day and haloperidol 18 mg/day were initiated in the patient who had no active seizures. After a month, haloperidol was gradually reduced and ceased and the aripiprazole dosage was gradually increased to 7.5 mg/day, according to the clinical response.

The family was given psychosocial training on psychotic symptoms and course. Eight sessions of cognitive behavioral therapy for social skills were administered to the patient. With aripiprazole treatment, sudden anger bursts, flying thoughts, auditory-visual hallucinations, and psychomotor retardation were improved completely. Her referentiality reached a tolerable level. In the PANSS applied in the third month of treatment, the P subscale score was 12, the N subscale score was 14, and the G subscale score was 25. In the PANSS applied in the eighth month of aripiprazole treatment, the P subscale score was 10, the N subscale score was 13, and the G subscale score was 22. The patient is currently being treated with 7.5 mg/day aripiprazole and the treatment compatibility is good.

Written informed consent was obtained from the patient's family.

3. Discussion

Juvenile-onset NP-C, the most common form of NP-C, is often accompanied by failure in school, ataxia, vertical supranuclear gaze paralysis, epileptic seizures, and catalepsy (5). According to our patient's medical history, and psychiatric and psychometric examinations, it was found that her symptoms began at the age of 10 years in the form of a limitation of eye movements in down gaze and decreased success at school. As a result of a genetic examination, an NPC-2 gene mutation was detected and the patient was diagnosed as having NP-C with juvenile-onset psychotic symptoms. Psychiatric problems are common in juvenile and adult-onset NP-C types (8). Juvenile-onset type often manifests with school problems, failing courses, and learning problems. The leading psychiatric findings are cognitive decline and psychosis (5,8). These findings tend to increase in patients over the age of 16 years (8). People with NP-C may exhibit paranoid delusions, auditory-visual hallucinations, thoughts that comment about themselves, behavioral disorder, self-mutilation, and social isolation (8,9). Other psychiatric disorders are reported as depressive disorder, bipolar disorder,

obsessive-compulsive disorder, and destructive-aggressive behaviors (6).

In addition, psychiatric disorders seen in patients with NP-C may be resistant to treatment (6,8). It was observed that the decrease in the school success, diagnosis of mild mental retardation, auditory and visual hallucinations, and referential delusions seen before treatment were compatible with the literature on the course of NP-C. In addition, no publication was found showing that the use of miglustat caused anger-control problems.

The only known treatment for the disease, miglustat, reduces the storage of lysosomal lipid in neuronal and glial cells, preventing the progression of neurologic symptoms (7). There are no known psychiatric adverse effects of miglustat treatment (7). When the literature on miglustat was examined, it was thought that psychiatric symptoms seen in our case were not related to the drug, but might be associated with the clinical presentation of NP-C. In the literature, antipsychotic drug use is recommended for the treatment of psychotic symptoms in the course of NP-C (10). In a systematic review of Bonnetiet al., it was reported that 22 of 50 patients with NP-C were using psychopharmacological drugs and 12 of 22 patients were using antipsychotic drugs (olanzapine, risperidone, haloperidol) (11). In a review published in 2017 on psychiatric presentation of NP-C, it was reported that psychotic symptoms could be resistant to treatment and atypical antipsychotics could be useful, but could also worsen the clinical picture due to causing dystonia (12). In 2014, an adolescent girl from Belgium reported that psychotic symptoms were in remission with olanzapine depot form (13). A male adolescent showing partial improvement with risperidone, an atypical antipsychotic, was reported (14). A patient who did not respond to olanzapine and risperidone and responded partially to haloperidol but developed dystonia was reported from Hungary. Haloperidol was ceased and aripiprazole, which has relatively fewer extrapyramidal system adverse effects, was initiated but the patient still developed dystonia. It was reported that the antipsychotic drug treatment was discontinued and the patient was followed up with miglustat treatment for 3 years. It was reported that the psychotic symptoms of the patient completely disappeared in the third month of treatment and did not repeat in the follow-up (15).

As seen in our case, epileptic seizures, which can be seen in the course of NP-C, can be triggered during antipsychotic treatment of psychotic symptoms. There was epilepsy in the family history of our patient. Therefore, the risk of epilepsy should not be attributed only to NP-C in our case. Concomitant epilepsy should be investigated before the treatment of psychotic symptoms in NP-C and treatment options should be reviewed according to the presence of epilepsy. Aripiprazole may be considered as a safer choice than other antipsychoticsin the treatment of patients with NP-C with psychotic symptoms associated with seizures due to the lower risk of development of dystonia and possible metabolic adverse effects. However, animal studies and larger double-blind randomized placebo-controlled studies on the use of aripiprazole and miglustat in patients with NP-C with psychotic symptoms and more extensive are needed.

As a result, NP-C is a rare disease that can be accompanied by psychiatric symptoms. In juvenile-onset psychosis, the questioning of developmental history and accompanying neurologic symptoms may suggest underlying NP-C disease. The aim of this case presentation was to draw attention to this rare disease and to the treatment of psychiatric symptoms, and to provide treatment alternatives to the literature.

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