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Very Early Use of Clozapine in a Case of Very Early-Onset Schizophrenia

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Case Report

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ABSTRACT

Schizophrenia is a chronic disorder that affects 1% of the population and causes serious impairment in functioning. If symptoms associated with schizophrenia begin before the age of eighteen, it is called early-onset schizophrenia (EOS), and if it starts before the age of thirteen, it is called very early-onset schizophrenia (VEOS). Although there are many studies on the prevalence and risk factors of schizophrenia in the adult population, there are not enough studies yet on VEOS. Although the number of studies on this topic is limited, it is known that these cases have a more severe course than adult-onset schizophrenia. In very early-onset schizophrenia, it has been determined that the loss of gray matter continues from the onset of the disease, which accelerates during adolescence. Early diagnosis of cases and early initiation of treatment are critical, as neurocognitive deterioration is more rapid and severe. Also, treatment resistance is not uncommon. Clozapine, which has never been the first choice in the pediatric population due to its possible adverse effects, should be considered as a treatment option in these cases. In this paper, we will present the successful management of a 10-year-old boy with schizophrenia using clozapine. Following clozapine treatment, the patient's psychotic symptoms considerably decreased and there were no severe side effects. There was a significant improvement in the patient's daily functionality. It would be useful for clinicians to keep in mind clozapine, which is not a frequently used agent in the child-adolescent population, as a treatment option in treatment-resistant VEOS cases.

Keywords: Şizofreni, Klozapin, Çocuk, Ergen

Çok Erken Başlangıçlı Şizofreni Vakasında Klozapinin Çok Erken Kullanımı

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ÖZET

Şizofreni toplumun %1'ini etkileyen ve işlevsellikte ciddi bozulmalara neden olan kronik bir hastalıktır. Şizofreni ile ilişkili belirtiler on sekiz yaşından önce başlıyorsa erken başlangıçlı şizofreni (EBŞ), on üç yaşından önce başlıyorsa çok erken başlangıçlı şizofreni (ÇEBŞ) olarak adlandırılmaktadır. Erişkin popülasyonda şizofreninin yaygınlığı ve risk faktörlerini araştıran pek çok çalışma olmasına rağmen ÇEBŞ ile ilgili henüz yeterli çalışma bulunmamaktadır. Bu konuyla ilgili çalışma sayısı sınırlı olsa da bu vakaların erişkin başlangıçlı şizofreniye göre daha ağır seyrettiği bilinmektedir. Çok erken başlangıçlı şizofrenide gri madde kaybının hastalığın başlangıcından itibaren devam ettiği, ergenlik döneminde ise hızlandığı tespit edilmiştir. Nörobilişsel bozulma daha hızlı ve şiddetli olduğundan, vakaların erken tanısı ve tedaviye erken başlanması kritik öneme sahiptir. Ayrıca tedavi direnci de nadir değildir. Muhtemel istenmeyen etkileri sebebiyle hiçbir zaman pediatrik popülasyonda birinci tercih olmayan klozapin, bu olgularda tedavi seçeneği olarak akla gelmelidir. Bu yazıda 10 yaşındaki şizofreni hastasının klozapin ile başarılı tedavisini sunacağız. Klozapin tedavisinden sonra ciddi bir yan etki görülmedi ve hastanın psikotik semptomları önemli ölçüde geriledi. Hastanın günlük işlevselliğinde anlamlı bir düzelme oldu. Çocuk-ergen popülasyonunda kullanımı sık olmayan bir ajan olan klozapinin, tedaviye dirençli ÇEBŞ vakalarında bir tedavi seçeneği olarak klinisyenler tarafından akılda tutulması yararlı olacaktır.

Anahtar Kelimeler: Schizophrenia, Clozapine, Child, Adolescent

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Introduction

Schizophrenia is a chronic disorder that affects 1% of the population and causes serious impairment in functioning.[1] If symptoms associated with schizophrenia begin before the age of eighteen, it is called early-onset schizophrenia (EOS), and if it starts before the age of thirteen, it is called very early-onset schizophrenia (VEOS).[2] Although there are many studies on the prevalence and risk factors of schizophrenia in the adult population, there are not enough studies yet on VEOS.

The course of schizophrenia may exhibit more severe in early-onset cases.[2,3] In very early-onset schizophrenia, it has been determined that the loss of gray matter continues from the onset of the disease, which accelerates during adolescence.[4] Early diagnosis of cases and early initiation of treatment are critical, as neurocognitive deterioration is more rapid and severe.[5,6]

Second-generation antipsychotics are considered the first-line treatment option for children and adolescents with early-onset schizophrenia.[7] But approximately 20-30% of patients with schizophrenia are unresponsive to treatment.[8,9] Treatment-resistant schizophrenia refers to patients with schizophrenia who, despite two different trials of antipsychotics at the required dose and for the required duration, continue to exhibit poor functioning with moderate to severe positive or negative symptoms or disorganization over an extended period of time.[10] Clozapine is a potent antipsychotic agent used in treatment-resistant schizophrenia cases.[11] Still, considering its adverse effects, it is not used as the first choice.[2] In addition, there is no FDA approval or treatment guidance on the use of clozapine in pediatric population.[12,13]

There is a limited number of case reports in the literature regarding the use of clozapine in EOS cases. Because VEOS cases are even rarer than EOS cases, there are much fewer case reports of clozapine use. Therefore, in this paper, successful treatment with clozapine in a ten-year-old boy with a diagnosis of treatment-resistant VEOS will be presented.

Case

A 10-year-old boy was brought to our clinic by his family. His symptoms were persecutory delusions, grandiose delusions, self-talk, disorganized behaviors, decreased communication, negativism, and agitation. The parents said that these complaints had been present for about a year. The boy, was no longer able to go to school due to the complaints mentioned, and had very limited communication, including with his family.

There was no significant developmental delay in his history and he had no known chronic disease. The boy was living with an older brother who is fifteen years older than him, his mother and father. The patient's mother was followed with schizophrenia for 20 years and is currently in remission with risperidone 3 mg/day.

The patient, who was examined in detail in different centers and diagnosed with schizophrenia, was initially started on risperidone treatment (4 mg/day) and used this treatment for four months. It was switched to aripiprazole because of unresponsiveness to treatment. Although aripiprazole 15 mg/day was used for three months, there was no significant improvement in psychotic symptoms. In our first evaluation, the PANSS score was 158, and the CGI-S score was 7. Since he did not benefit from aripiprazole, it was planned to switch to olanzapine treatment. Olanzapine was gradually increased to 20 mg/day and was used at this dose for 6 weeks. There was a partial response to olanzapine, with a PANSS score of 141 and a CGI-S score of 6. The case was evaluated by a committee of three experienced psychiatrists who confirmed the diagnosis of schizophrenia based DSM-5 and recommended switching to clozapine due to lack of adequate response to three different antipsychotics. Complete blood count, troponin, CRP tests and cardiology consultation (including Echo, ECG) were requested before clozapine treatment. Neurologic evaluation is not mandatory before starting clozapine, but we requested a detailed neurologic evaluation including MRI and EEG in our case due to the presence of VEOS; no problem was found here either. And the clozapine treatment was started gradually.

Weekly complete blood count and height-weight-blood pressure follow-ups were continued for 24 weeks. The dose of clozapine was increased up to 300 mg/day within six months. The patient's persecution and grandiosity delusions ceased, his disorganized behaviors decreased significantly, his interpersonal communication increased, his self-talk decreased, and his negativism and agitation ended. All blood counts were within normal range at the start of clozapine, during the follow-up period and at the end of six months. The patient who lost weight during the disease process was 142 cm (75-90th pctl) and 38 kg (75-90th pctl) when clozapine treatment was started. In six months of clozapine treatment, he was 147 cm (90-97th pctl) and 48 kg (97th pctl). Sedation, hypersalivation, headache were observed during clozapine therapy. Hypersalivation was evident after the dose was increased above 200 mg/day. Tropicamide drops were used for hypersalivation, and paracetamol was used for headaches. After clozapine therapy PANSS score was 87, and the CGI-S score was 3. There was a significant improvement in the patient's daily functionality. The patient was now able to attend school on a full-time basis. It was planned to follow up the case with clozapine 300 mg/day treatment once a month.

(The parents gave written consent for the publication of this report and the patient provided assent.)

Discussion

In this paper, a successfully management with clozapine therapy of a case 10-year-old with VEOS was presented. In the literature review, few studies could be found on managing very early-onset schizophrenia cases. It seems that these cases are difficult to diagnose and to access effective treatment. In addition to medication, multidimensional support is needed.[14] We came across very few reports on the long-term use and follow-up of clozapine in these cases.[15] These cases are sometimes managed with alternative

combined pharmacotherapies.[16] Bailly et al. started clozapine after using two different antipsychotics in a 10-year-old case of VEOS, and no adverse effects were observed.[17] Mozes et al. used clozapine in four patients with VEOS. They encountered hypersalivation, subclinical EEG changes, mild tardive dyskinesia, stereotypical movement seizures, and enuresis nocturna during clozapine use.[18] In another study of patients using clozapine, it was reported that sedation and hypersalivation were the most common complaints reported by more than 90% of patients.[15] Other common adverse reactions (reported in 10-60% of patients) were enuresis, constipation, weight gain, and nonspecific EEG changes; it has been learned that neutropenia is reported in 6-15% of cases but is usually transient, and agranulocytosis is rare (<0.1%).[15]

Schizophrenia is an important disease in which genetic factors play a role in its etiology.[19] As expected, schizophrenia was found to be strongly associated with schizophrenia and related disorders in first-degree relatives.[19] The patient's mother was also receiving treatment with a diagnosis of schizophrenia. To the best of the researchers' knowledge, the relationship between genetic factors and onset of schizophrenia has been little investigated. Further studies on this subject are needed.

Clozapine was found to be superior for positive and negative symptoms treating schizophrenia.[11] Considering the possible side effects of clozapine, it has never been the agent of first choice in EOS.[2] Since schizophrenia started at a very early age in this patient, neurocognitive deterioration was rapid and severe, and the symptoms didn't improve with three previously used antipsychotics, so we switched to clozapine. There were no serious adverse events after clozapine treatment, and the patient's psychotic symptoms significantly improved. VEOS is more severe, and resistance to treatment is commonly seen. But very few cases have been found in the literature regarding the use of clozapine in those patients.[20] In conclusion clinicians would be well advised to keep clozapine in mind as a treatment option in cases of treatment-resistant VEOS. When there is an indication to switch to clozapine treatment, it would be in the best interest of these children and adolescents to start this treatment without delay.[21] However, further research is needed to investigate the consequences of long-term clozapine use in these cases.

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