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CASE REPORT



Control of seizures in a clozapine-treated schizophrenia patient, using valproate: a case report

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ABSTRACT

Schizophrenia is characterized by an adverse clinical course and poor psychosocial functioning, and causes problems in the social-cognitive sphere. Clozapine is a potent antipsychotic agent used in the treatment of psychotic disorders when other antipsychotic agents failed. It is seen that clozapine causes more seizures at therapeutic doses when compared to standard antipsychotic agents. Various mechanisms have been proposed for seizure onset. Clozapine can induce epileptogenic activity by inhibiting D4 receptors in mesolimbic system and cortex. Clozapine does not only exert its effects on H1 and Ach-Mus receptors but also on several receptors such as gamma-aminobutyric acid A, nicotinic acetylcholine, glutamate, and *N*-methyl-D-aspartate. Here, we discussed a woman with schizophrenia in whom atonic seizure was developed during clozapine treatment and treated successfully by valproic acid/sodium valproate. Atonic seizures should be considered in patients who have drop attacks during clozapine therapy and atonic seizures should be treated by using an anticonvulsant agent such as valproic acid/sodium valproate when it is inappropriate to reduce clozapine dose.

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Introduction

Schizophrenia is a psychiatric disorder which may disrupt functionality of both patients and their caregivers, and it may be refractory despite treatment with multiple antipsychotic therapies. Clozapine is a potent antipsychotic agent used in the treatment of psychotic disorders when other antipsychotic agents failed. It is recommended to switch clozapine in schizophrenia patients who did not respond to therapy, including at least two antipsychotics (one of these agents must be olanzapine) [1]. Marked improvement in symptoms of the patient with schizophrenia on clozapine (900 mg/day), aripiprazole (30 mg/day) and divalproex (25 mg/day) when aripiprazole was withdrawn and maintained treatment with clozapine (575 mg/day) and divalproex (1500 mg/day) suggests that one should cautiously considered which agent will be added in combination therapies [2]. Clozapine is a serotonin 5HT_{2A}-Dopamine D₂ antagonist and prototype for atypical antipsychotics [3]. Although clozapine use is associated with adverse effects such as sedation, hypotension, hyper-salivation, and less frequently agranulocytosis [4], it may also cause electroencephalogram (EEG) abnormalities and epileptic seizures. Here, we discussed a woman with schizophrenia in whom atonic seizure was developed during clozapine treatment and treated successfully by valproic acid/sodium valproate.

Case presentation

A 21-year-old female patient presented to our outpatient clinic with “insomnia, disorganized speech, inappropriate crying and laughter” episodes by her father. In her history, it was found out that she had been working in a fast-food restaurant as cashier and she had had a good relationship with her family and friends before the onset of symptoms. Inappropriate laughter episodes, wishing to be alone in her room, intrusion, disorganized speech, and behaviours had begun approximately 7 months ago. She had had persecutory delusions as people will be harmed and auditory-visual hallucinations had been developed. Subsequently, she had left the work and showed decrease in self-care. In psychiatric evaluation, the patient with poor self-care and restricted cooperation had blunt affection. She had normal orientation to place, time, and person. It was found that she had auditory and visual hallucination. She also had persecutory delusions and poverty of thought. Her thoughts were beginning as goal-directed but then they were usually deviating from topic and goal. Her connotations were dissipated with decreased attention and concentration. Her knowledge was limited. During examination, the patient suggested that she had no disease. She was lacking of insight. Her psychomotor activation was decreased. The patient had no comorbid physical or

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psychiatric abnormality in her history. In family history, it was found out that her mother had schizophrenia. No pathological finding was detected in complete blood count (CBC), biochemical tests, electrocardiogram, EEG, neuroimaging studies and neurological examination. Schizophrenia was diagnosed at psychiatric evaluation on the basis of DSM-5 diagnostic criteria. Clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). The patient's PANSS scores: positive scale 28, negative scale 33, and general psychopathology scale 48. Her initial Clinical Global Impression-Severity of Illness (CGI-SI) score was 6. She was prescribed haloperidol (20 mg/day), quetiapine (800 mg/day), and olanzapine (30 mg/day), which were maintained at therapeutic level over 6 weeks. However, no improvement was achieved in her complaints; thus, clozapine was started at dose of 25 mg/day, which was gradually up-titrated to 400 mg/day over 7 weeks. The remission was achieved at this dose. However, the patient experienced drop attacks due to sudden loss of strength, which occurred two to three times in a day. No finding of epileptic seizure such as contraction, loss of consciousness, urinary incontinence, or faecal incontinence was observed during drop attacks. Blood pressure measured at brachial region was within normal range during drop attacks. The patient had no history of epileptic seizure and no familial history of epilepsy. No abnormal finding was detected in repeated CBC, biochemical evaluations, and neurological assessment (EEG and brain MR imaging). Based on neurology consultation, this condition was attributed to clozapine-related atonic seizures; thus, dose of clozapine was tapered at the level of 300 mg/day. After a week, drop attacks were disappeared but she also experienced increase in delusions and hallucinations and clozapine dose was up-titrated to 400 mg/day with the addition of sodium valproate (gradually increased up to 1000 mg/day). Drop attacks were completely recovered while remission was achieved in psychotic symptoms one week after initiation of valproic acid/sodium valproate. Naranjo adverse drug reaction probability score was 7 in our patient, suggesting a probable association between clozapine and epilepsy [5]. At subsequent follow-up, she scored 2 on the clinical global impression-global improvement (CGI-GI) and achieved a PANSS scale total score of 28. No atonic seizure was observed during 3 months follow-up.

Discussion

Here, we presented atonic seizures following clozapine therapy, which was recovered with addition of valproic acid/sodium valproate in a female patient with schizophrenia.

In addition to blocking dopamine receptors, clozapine exerts its effects on a numerous receptor sites,

including norepinephrine, histamine, acetylcholine, and serotonin systems [6]. In addition to its effects in treatment-refractory schizophrenia, clozapine has shown to decrease suicidality and substance use, which occurs at an increased rate in patients with schizophrenia [7]. However, despite these positive effects, it is seen that clozapine causes more seizures at therapeutic doses when compared to other antipsychotic agents [8]. In a review on association between clozapine and seizure, it was reported that clozapine most frequently leads to tonic-clonic seizures, followed by myoclonic seizures, partial seizures, and atonic seizures [9]. Authors have suggested that some seizures are related to clozapine dose and plasma concentration while others are caused by a sudden increase in titration [10,11].

Regarding seizures associated to clozapine concentration, risk ratio was reported to be 0.6–2% for doses <300 mg/day, 1.8–4% for doses of 300–599 mg/day, and 5–14% for doses of 600–900 mg/day in the literature [12–14]. The incidence of seizures with clozapine was 6% and the risk of seizures increased with higher doses [15]. Indeed, one case report even reported that tonic-clonic seizures develop at lower clozapine dosages (200 mg /day) [16]. Another study reported higher antipsychotic-related seizure (ARS) risks with clozapine, thioridazine, chlorprothixene, and haloperidol than with risperidone, while aripiprazole involved a marginally lower risk of ARS [17]. However, the mechanisms that lower seizure threshold are not fully understood. Various mechanisms have been proposed for seizure onset. One is that clozapine reverses the inhibitor effect of GABA on 35S-t-butyl bicyclo phosphorothionate (35S-TBPS) [18]. Another important hypothesis is that mesolimbic areas are closely related to seizure initiation regions and clozapine can induce epileptogenic activity by inhibiting D4 receptors in mesolimbic system and cortex [8,19]. Another mechanisms proposed is that clozapine does not only exert its effects on H1 and Ach-Mus receptors but also on several receptors such as gamma-aminobutyric acid A, nicotinic acetylcholine, glutamate N-methyl-D-aspartate, serotonin 5-HT_{2A}, and strychnine-sensitive glycine [20–24].

It is recommended to reduce clozapine dose by 40–50% in first seizure and to add an anticonvulsant agent if seizure recurs [9]. In addition, primary anticonvulsant prophylaxis is recommended in patients at risk for epilepsy (history of seizures, febrile seizures, and head trauma), those with high clozapine plasma level (≥ 1300 ng/ml) and those receiving 600 mg/day clozapine [25]. A study state that seizure is not a contraindication to clozapine therapy and antiepileptic drugs can be used to prevent or treat clozapine-induced seizures [26]. Although it is recommended to avoid valproic acid in woman at reproductive age due to decreased fertility and increased polycystic ovaries [27], valproic

acid is most commonly used antiepileptic agent in clozapine-induced seizures [9]. We also reduced clozapine dose; however, we added valproic acid/sodium valproate as complaints were worsened.

Also, a case of schizophrenia comorbid for tetralogy of Fallot, without chromosome 22q.11.2 deletion or duplication, was treated successfully with a combination of clozapine and antiepileptic drugs [28]. It is unknown how valproic acid is effective in clozapine-induced seizures without exacerbating psychological symptoms although it alters activity of clozapine by reducing its plasma level [29]. Lamotrigine and gabapentin are other options in clozapine-induced seizures; however, carbamazepine should be avoided as there is a risk for bone marrow suppression when used in combination with clozapine [9].

Drop attacks occurring with up-titration of clozapine dose was considered as atonic seizures clinically despite a lack of epileptic discharge on EEG in our patient; dramatic response to valproic acid/sodium valproate had a positive effect on therapeutic process and compliance. Atonic seizures manifest as spontaneous drop attacks. However, it may be difficult to recognize such attacks. The drop attacks may be misleadingly interpreted as myoclonic flexion of knee joint or psychogenic. Interestingly, it was reported that drop attack and myoclonus were seen due to clozapine use in a case report [30]. Moreover, drop attack could be misleadingly attributed to hypotension; thus, blood pressure measurement during drop attack is important to clarify drop attacks. However, it should be kept in mind that there may be atonic seizures in patients who have syncope attacks, drop attacks, or who suddenly drop objects from his/her hands during clozapine therapy and atonic seizures should be treated by using an anticonvulsant agent such as valproic acid/sodium valproate, which are considered as potential risk for tonic-clonic seizures [31].

In Conclusion, although EEG abnormalities are commonly seen during clozapine therapy, they may be completely normal [9]. Thus, it is important not to switch treatment when EEG changes were detected during clozapine use; on the other hand, it is also important to manage this adverse effect in patients with normal EEG findings until clinic onset of seizures. Atonic seizures should be considered in patients who have syncope attacks, drop attacks, or who suddenly drop objects from his/her hands during clozapine therapy and atonic seizures should be treated by using an anticonvulsant agent such as valproic acid/sodium valproate when it is inappropriate to reduce clozapine dose.

Disclosure statement

No potential conflict of interest was reported by the authors.

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