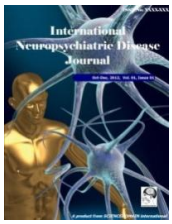

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Treatment of Catatonia Using Low Doses of Clozapine

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Authors' contributions

This work was carried out in collaboration between authors. Authors designed the case study and wrote the protocol. Author NFI managed the literature search and wrote the first draft of the manuscript with assistance from authors NRM and ZH. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Catatonia is a state of apparent unresponsiveness to external stimuli in a person who is apparently awake and which occurs in children, adolescents, and adults and is characterized by a variety of symptoms and signs of impairment of the expression of voluntary thoughts and movements.
Antipsychotics should be used with care as they can worsen catatonia and are the cause of neuroleptic malignant syndrome, a dangerous condition that can mimic catatonia and requires immediate discontinuation of the antipsychotic.
The use of atypical antipsychotics to treat catatonia remains anecdotal, owing to concerns that they may worsen catatonic symptoms.
We describe the case of good treatment response in low doses of clozapine in a adolescent with first psychotic episode –catatonic feature.

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Keywords: Catatonia; adolescent; clozapine; neuroleptic malignant syndrome.

1. INTRODUCTION

As a complex psychomotor syndrome, catatonia has been conceptualized by Northoff as a predominantly a cortical process dynamically interacting with subcortical regions, involving cognitive, emotional and behavioral circuits [1].

Clinicians caring for psychiatric patients with catatonic syndromes continue to face many dilemmas in diagnosis and treatment [2].

Differential diagnosis of catatonia involves three parts:

(a) recognizing the distinct cluster of signs of a catatonic syndrome;
(b) distinguishing catatonia from other movement disorders, including a range of other specific physiological and psychomotor syndromes that may share common features; and
(c) identifying sequelae and co-morbidity with other neurologic, medical, and psychiatric pathology.

Psychotropics that have been suggested and studied in the treatment of catatonia – including clozapine, other atypical antipsychotics, anticonvulsants, lithium, amantadine and others– have shown variable degrees of success [3]. More recently, benzodiazepines, especially lorazepam from modest to high doses, have been widely studied and used in the treatment of the various forms of catatonia, but most studies are small and have methodological shortcomings [4].

Presented here is a case report of a 16-year-old man appearing in a catatonic state that did not respond to lorazepam, as the catatonia clinical feature was exacerbated. On the basis of emerging evidence that atypical antipsychotics and weak N-Methyl-D-Aspartate (NMDA) receptor-antagonists may effectively treat catatonia, we treated our patient with clozapine in low doses, which resulted in a reduction in his catatonic symptoms.

The parents of the patient were informed that the medication has not allowed age to use it, they give their agreement for the treatment.

2. CASE PRESENTATION

A 16 year old patient who was brought to our Clinic of Psychiatry, University Clinical Center of Kosova, in the emergency room by his mother after he had become urinary incontinent, stuporous and mutistic. On presentation to the emergency, patient was not oriented to time, person, or place. He exhibited a blunted affect. His mental state changed approximately 2 weeks before and the patient's mother reported that he had been sleeping poorly and was not taking care of himself, stopped walking, refused to eat and drink, and developed generalized weakness. There was no prior history of neurologic disorder, psychiatric disorder, drug use, or another medical condition to suspect. Patient was autistic, somnolent, tachycardic with muscular rigidity.

Blood exams, urinalysis, basic metabolic profile, ammonia and thyroid function tests were normal.

After emergency evaluation, laboratory examinations revealed leukocytes, urine and blood cultures were all negative, lumbal puncture of Cerebro Spinal Fluid without change, EEG-registered diffuse nonspecific dysfunction of slowed wave with minor presentation (non specific findings), Computerized Tomography (CT-scan) and Magnetic Resonance Imagery (MRI) showed Cavum Septi Pellucidum (CSP) and an association between this developmental anomaly and a diagnosis of psychosis has been reported also in first psychotic episode [5]. Cavum Septi Pellucidum is a normal variant of Cerebrospinal Fluid space between the leaflets of the septum pellucidum. It is sometimes called the fifth ventricle**.** A CSP is present in 100% of fetuses, but over 85% of them fuse by 3-6 months of age meaning that a CSP is present in ~15% of the population.

The lack of evidence for a medical etiology of patients mental status change led us to consider psychiatric causes. According to DSM-IV-R criteria we find clinical feature of first psychotic episode-catatonia feature, based on Axis I. Axis II of Mental retardation was excluded while the patient had prior successful school results.

He scored a 29 on the Bush-Francis Catatonia Rating Scale.

The patient was admitted in adolescent psychiatric ward and started initially treated with lorazepam doses of 1 mg daily (see Table 1), which was gradually increased to 6 mg daily with no response during first week and

with exacerbation of his clinical symptoms, the treatment was discontinued it, as the effects were not sustained. The ECT was not available, in our Clinic.

We started than titration with low doses of clozapine 25mg daily (see Table 2), with permanent monitoring of eventually changes in his status.

There was no significant improvement in the first week and so therapeutic dose of clozapine was increased to 50mg daily in the fourth week of treatment with little response, gradual disappearance of urinary incontinence, and reduced rigidity of extremities.

The adherence to the treatment was good, and weekly blood drawing was in normal range.

Table 1. Dose response for lorazepam treatment

Week 1 Lorazepam	AM dose	PM dose	Total daily dose
Day 1	1mg	1mg	2mg
Day 2	1mg	2mg	3mg
Day 3	2mg	2mg	4mg
Day 4	2mg	3mg	5mg
Day 5	3mg	3mg	6mg
Day 6	3mg	3mg	6mg
Day 7	3mg	3mg	6mg

Table 2. Dose response for clozapine treatment

Clozapine	AM dose	PM dose	Total daily dose
Week 2	12,5mg	12,5mg	25mg
Week 3	12,5mg	25mg	37,5mg
Week 4	25mg	25mg	50mg
Week 5	25mg	25mg	50mg
Week 6	25mg	25mg	50mg

Approximately 5 weeks from the admission most of catatonic symptoms was improved and no serious side-effects (seizures, agranulocytosis) and collateral effects were observed. He later scored a 5 on the Bush-Francis Catatonia Rating Scale.

We discharged him after 6 weeks of hospitalization in therapeutic maintenance doses of 50 mg daily in good remission.

3. DISCUSSION

The exact pathophysiology of catatonia is not known, but several hypotheses regarding neurotransmitter dysfunction have been proposed. Decreased gamma-aminobutyric acid (GABA) activity has been observed in some patients with catatonia. This finding may explain the positive response that many catatonic patients show to benzodiazepines, which are $GABA_A$ agonists [6]. Agents that block dopamine-2 (D_2) receptors, such as typical antipsychotics, can induce catatonia in some patients; however, the scientific literature suggests that atypical antipsychotics may be effective in treating catatonia. These findings suggest that regulation of dopamine may be integral to the treatment of catatonia [7].

The recent scientific literature has shown that in addition to benzodiazepines, atypical antipsychotics and weak NMDA receptor-antagonists may be effective in treating catatonia [8]. Because our patient did not respond to lorazepam, we treated him with clozapine. Evidence indicates that classical antipsychotics may aggravate catatonia; however there are indications that atypical antipsychotics may be efficacious in nonmalignant catatonia.

All antipsychotics, typical as well as atypical, have relevant affinities for the dopamine D2 receptor. Blockade of dopamine receptors in the mesolimbic area is responsible for antipsychotic activity and in striatum cause extrapyramidal dysfunctions. The atypical antipsychotics also have minimal extrapyramidal side effects or EPS (parkinsonism, acute muscular dystonia, akathisia, malignant neuroleptic syndrome, tardive dyskinesia) or movement disorders at antipsychotic doses. Antipsychotic drugs with low affinity for the D2 receptor dissociate much more quickly from the receptor, and this low affinity/fast dissociation at the D2 receptor is the single best predictor of atypicality. Atypical antipsychotics antagonizes D2 receptor involving “Fast Off” theory of atypical antipsychotics which predicts their low doses in treatment of patients with psychosis in Parkinson’s disease as they are rapidly released from D2 receptors and less extrapyramidal side effects occur due to loose binding. Activity at D2 receptors is the basic property which unites atypical antipsychotics in their atypical behaviour irrespective of their different efficacy at different receptors.

Clinical features of Atypical Antipsychotics:

1. Lower affinity for D2 receptors
2. Higher affinity for 5-HT2 receptors [9].

A relatively low affinity for the D-2 dopamine (DA) receptor and high affinity for the 5-HT_2 receptor, producing a high 5-HT_2/D-2 ratio, best distinguishes atypical antipsychotics like clozapine from typical antipsychotic drugs. Through its weak antagonist action on D-2 DA receptors and a potent inhibitory effect on 5-HT_2 receptors, as well as its ability to increase DA and 5-HT release, clozapine may be able to permit more normal dopaminergic function in the anterior pituitary, the mesostriatal, mesolimbic and mesocortical regions. The numerous advantages of clozapine over typical neuroleptics are consistent with the primary importance of DA to the pathophysiology of schizophrenia. The secondary but still significant role of 5-HT in the action of clozapine may either be direct or via the effect of 5-HT on dopaminergic mechanisms [10].

Clozapine is extensively metabolized in the liver, via the cytochrome P450 system, to polar metabolites suitable for elimination in the urine and feces. The major metabolite, norclozapine (desmethyl-clozapine), is pharmacologically active. The cytocrome P450 isoenzyme 1A2 is primarily responsible for clozapine metabolism, but 2C, 2D6, 2E1 and 3A3/4 appear to play roles as well. The elimination half-life of clozapine is about 14 hours at steady state conditions.

The present case describe the good treatment response of first psychotic episode -catatonic feature in minimal doses of clozapine in 16 year old adolescent .The data from further studies describe the most high doses of treatment with clozapine in psychotic feature cases.

This is the first case described to have good therapeutic response in such minimal clozapine dosage. It was believed that clozapine would be a better choice of antipsychotic because of its lower risk of extrapyramidal symptoms as a result of lower dopamine-receptor affinity.

Clozapine has unique efficacy in improving treatment-resistant patients with chronic schizophrenia, but its role in the treatment of first-episode patients remains unclear [11]. In one study, 7 patients were treated with clozapine after unsuccessful trials of lorazepam and other atypical antipsychotics, and 6/7 (86%) experienced a beneficial effect following slow titration, a good overall response for treatment of catatonia [12].

However, clozapine is the first atypical antipsychotic drug, there are now many recent advancements in the field of atypical antipsychotics and newer drugs are developed which are much efficacious than clozapine. Also, we still recommend the use of benzodiazepines and ECT before considering clozapine. Hence there might be a wide scope for researcher to check the clinical effectiveness of others also in treatment of Catatonia.

4. CONCLUSION

This case study highlights usefulness of low doses of atypical antipsychotic –clozapine in the treatment of catatonia psychotic feature after unsuccessful treatment with benzodiazepine - lorazepam.

CONSENT

The identity of the case was concealed and obtaining informed consent is not applicable.

ETHICAL APPROVAL

All authors hereby declare that this case presentation was approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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