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Case Report **Open Access**

Zolpidem in treatment resistant adolescent catatonia: a case series

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Abstract

Catatonia is a well-established psycho-motor disorder occurring in the background of various psychiatric and medical disorders. Catatonia is commonly associated with psychiatric disorders, especially affective disorders followed by schizophrenia. However, almost 20% occur in the background of different medical and neurological disorders which need to be properly examined and investigated. Catatonia is a serious medical and psychiatric emergency condition; most probably caused by alteration in GABAergic circuits and basal ganglia. If untreated, catatonia can cause life threatening complications like dyselectrolemia, respiratory aspiration, venous thromboembolism, acute renal failure and cardiac arrest because of poor oral intake, immobility and muscular rigidity. The risk of mortality or serious life threatening events further increases in cases of children and adolescents. In children and adolescents, thus, it becomes even more important to diagnose catatonia early and start appropriate treatment. Lorazepam is considered to be the first line treatment and is safe both in adults and children. But evidence is scarce for treatment of lorazepam-resistant adolescent Catatonia. In this report we discuss two adolescent patients diagnosed with catatonia with no medical or neurological disorders in the background. Neither of the patients responded to lorazepam alone or even after augmentation with second generation antipsychotic (olanzapine). Zolpidem, like lorazepam, has a positive allosteric effect on GABA A Receptors (GABAAR) and has been used in some cases successfully to treat resistant catatonia. Here we used zolpidem 30 mg/day in divided doses with marked improvement in few days in all the symptoms. Both cases were discharged on zolpidem extended release (ER) three times a day and maintained well through the next two follow ups in over a two month period. Zolpidem can be a good alternative for children and adolescents in resistant cases.

Keywords: Adolescent catatonia; catatonia; zolpidem; lorazepam; benzodiazepines; treatment-resistant catatonia

Introduction

Catatonia is a psychomotor disorder associated with various mental and neurological disorders. It is characterized by a variety of motor symptoms including stupor, posturing, catalepsy, waxy flexibility, mutism, negativism, mannerisms, stereotypic behaviour, and extreme agitation (1).

Catatonia is a psychiatric emergency and it increases the risk of certain medical complications and mortality due to dehydration, immobility, and sympathetic nervous system hyperactivity, which are usually associated with catatonia. These conditions can lead to hypernatremia, pneumonia, rhabdomyolysis, sepsis, pulmonary embolism, renal and liver dysfunction, deep venous thrombosis, arrhythmia and neuroleptic malignant syndrome (2). It is found to be more severe in the younger age group (3). In adolescents it increases the risk of premature death up to 60 fold in comparison to the general population of the same sex and age (4).

It becomes crucial to diagnose and treat adolescent catatonia early to avoid serious complications. Although DSM-5 (1) has no separate criteria for child and adolescent catatonia, it is challenging to identify adolescent catatonia in the early stages because its presentation might be different from adult catatonia, and it can be complicated by an existing developmental disorder. The commonly used scale for adults, Bush Francis Catatonia Rating scale (BFCRS), has also been used widely in children and adolescents (5). Cohen incorporated some changes in BFCRS to make it more child and adolescent oriented, including separating refusal to drink/eat from social withdrawal, replacing automatic obedience with automatic compulsive behaviour, adding incontinence as a regressive behaviour of

catatonia. The resulting instrument is a modified version of the BFCRS called the Paediatric Catatonia Rating Scale (6).

Benzodiazepines are the mainstay treatment for catatonia in adults (7) as well as in children (8). Augmenting lorazepam with second generation antipsychotics can be helpful. Although antipsychotics increase the risk of side effects including malignant catatonia and neuroleptic syndrome (6), favourable results have been found in some lorazepam-resistant cases (9). Zolpidem is another alternative in resistant cases. Zolpidem challenge test is found to be useful in initial improvement in symptoms and hence in diagnosing catatonia in adults (10) as well as in adolescents (11). There are case reports which showed a beneficial effect of zolpidem in treatment of catatonia (12). Here we present two adolescent cases of acute onset catatonia with no underlying neurological cause, who were initially tried on lorazepam with no or minimal improvement. With close monitoring of side effects by regular examination and relevant investigations in both patients, lorazepam was augmented with second generation antipsychotic. They showed no improvement with the combination, and then zolpidem was started after favourable results of a zolpidem challenge test.

Case 1

Background

A 15-year-old adolescent female from an urban background presented with an acute onset illness of around one month duration. There was no history suggestive of any past psychiatric, medical or neurological disorder, any substance use, childhood trauma or any other contributory personal or family history. The illness started acutely with irritability, unprovoked physical aggression, undressing herself in public and inability to sleep. Toward the end of the last week before presentation to the emergency department, she developed decreased social interaction, inability to speak, maintaining a posture for long time, decreased oral intake, and sudden unprovoked undirected agitated behaviour.

Presentation and assessment

The patient presented in the emergency department of a tertiary neuropsychiatry centre. On examination, she showed mutism, active negativism, withdrawn behaviour, staring, posturing, and rigidity of all the limbs; BFCRS Score was 20. No other neurological sign was found. Vitals including blood pressure, pulse rate, temperature and SpO2 were within normal limits.

Initial investigations including Complete Blood Counts (CBC), Random Blood Sugar (RBS), Liver Function Test (LFT), Kidney Function Test (KFT), Serum Electrolytes (SE), Serum Ammonia, Creatine Phosphokinase (CPK) and Non Contrast Computed Tomography (NCCT) head were found to be within normal limits.

Management

On the basis of examination and investigations a provisional diagnosis of catatonia was entertained in the background of psychosis and the patient was shifted to a psychiatric unit for further evaluation and management. After favourable results with a lorazepam challenge test, she was started on lorazepam 2 mg intravenously three times a day along with supportive therapy. The patient was observed for next 2 days on the same regimen on which she would show only transient improvement (lasting for 20-40 minutes) in mutism and oral intake after lorazepam injection with no response in other catatonic symptoms. Intravenous lorazepam was augmented with an oral second generation antipsychotic (SGA). Olanzapine 10 mg/day resulted in no added response in any of the symptoms for the next 3 days. The patient was planned to start on zolpidem therapy before use of Electroconvulsive Therapy (ECT), as use of ECT is restricted in children and adolescents as per Mental Healthcare Act 2017 of the government of India.

She was given a zolpidem challenge test on the 6th day with a 10 mg Immediate Release (IR) tablet, after which she showed some improvement in rigidity, posturing and mutism in the next 30 minutes. She was then started on oral zolpidem IR 30 mg/day in divided doses along with oral olanzapine 10 mg/day. Intravenous lorazepam was gradually stopped. After 3 days of zolpidem, she had shown complete response in all the catatonic symptoms. She was discharged on oral zolpidem Extended Release (ER) 12.5 mg three times a day along with olanzapine 10 mg/day. The patient maintained well for the next two months during follow-ups and thereafter planned to taper off and stop zolpidem.

Case 2

Background

The second case was a 14-year-old adolescent male. Similar to the previous case, there was no history suggestive of any past psychiatric, medical or neurological disorder, any substance use, childhood trauma or any other contributory personal or family history. He had history of acute onset illness of 20 days duration, which started with remaining withdrawn, decreased verbal output and decreased oral intake. Symptoms worsened after a week, and gradually he completely stopped taking food or drink orally, stopped interacting with anyone both verbally and non-verbally, would maintain a posture for long time and later on started repeating the same phrases

or words again and again without any stimuli and developed stiffness in whole body.

Presentation and assessment

The patient presented in the emergency department of a tertiary neuropsychiatry centre on around the 20th day of illness. On examination all the vitals including blood pressure, pulse rate, temperature, and SpO2 were within normal limits. On mental status examination, mutism, negativism, withdrawn behaviour, posturing, occasional episodes of verbal stereotypy, and rigidity of all the limbs were found, BFCRS Score was 22. No other neurological sign was established. Initial investigations including CBC, RBS, LFT, KFT, S.E., S. Ammonia, CPK and NCCT head were within normal limits.

Management

The patient was provisionally diagnosed as a case of catatonia and shifted to the Psychiatric Unit. A lorazepam challenge test was given, and he showed some improvement in oral intake 15 minutes after the injection. He was started on intravenous lorazepam 2 mg three times a day along with supportive therapy. By the next week he showed improvement in oral intake and started taking food by himself (BFCRS=18), but there was no improvement in any other catatonic symptoms. Thus intravenous lorazepam was augmented with olanzapine 10 mg/day. In the 2nd week he showed improvement in verbal stereotypy apart from oral intake, but all other symptoms persisted. Moreover he developed abnormal behaviour of persistent pacing around the ward which was considered a part of olanzapine induced akathisia, and olanzapine was stopped. The patient was kept on intravenous lorazepam 6 mg/day and propranolol up to 40 mg with no improvement in the next 4 days. All the investigations were repeated along with serum ceruloplasmin, serum copper, 24 hour urinary copper, and MRI of the brain to rule out other causes of movement disorder. All the investigations were within normal limits and the brain MRI showed no significant changes. After ruling out all the causes, persistent pacing behaviour was considered to be an automatic compulsive movement which can be seen in children and adolescents with catatonia. The patient was resistant to intravenous lorazepam alone and with olanzapine. In this case also, zolpidem challenge test was performed, and some improvement was observed in pacing behaviour and mutism after about 30 minutes. Henceforth he was started on oral zolpidem IR 30 mg/day in divided doses, and over the next week, the patient showed significant improvement in all the catatonic symptoms with no significant side effects. The patient was discharged on oral zolpidem ER 12.5 mg three times a day and remained asymptomatic for next 2 months of follow-ups, after which zolpidem was tapered off and stopped.

Discussion:

Catatonia effectively responds to lorazepam and ECT, and lorazepam is considered as first line treatment irrespective of the underlying cause (7). Although benzodiazepines are used extensively to treat catatonia and accepted to be a first choice, they demonstrate around only 79% remission rate (13).

The exact pathophysiology of catatonia is unclear, but there are some proposed theories of underlying mechanism. It has been proposed that catatonia is the result of motor manifestations of intense inner anxiety(14). Hence, benzodiazepines through facilitatory action on the GABA-A Receptor (GABAAR) improve the catatonic symptoms (15).

It is also proposed that the catatonia is characterized by hypokinetic and hyperkinetic movements similar to Parkinson's disease which is suggestive of dysfunction of different neuronal motor circuits. One of the important circuits which can be included in causing inhibition and excitation of movements, comprises a circuit from the primary motor cortex (PMC) to the thalamus, and back to the PMC. Another circuit, corticocortical circuit, is considered to control motor organisation and speed, and includes the PMC, the supplementary motor area (SMA), and the medial prefrontal cortex (16). The SMA is found to initiate the inhibitory process to the basal ganglia, and automatic motor control depends on the concentration of GABAAR in the SMA (17). Reduced concentration of GABAAR is found in the SMA and motor cortical areas in cases of catatonia (18). The decreased concentration of GABAAR in the SMA and motor cortex leads to decreased inhibition, initiation, and control of motor movements, and this possibly leads to symptoms of catatonia. Benzodiazepines increase inhibitory action in the CNS through their positive allosteric action on GABAAR, a pentameric ligand gated channel. A total of 19 subunits of GABAAR have been identified (α1-α6, β1- β3, γ1-γ3, δ, ε, π, θ, ϱ1-ϱ3) which in different combinations form a multitude of GABAAR subtypes. Benzodiazepines non-specifically bind to the α(+)/γ2(−) subunit interface in different subtypes of GABAAR (19).

Here we had two adolescent cases who did not respond to the first line treatment of lorazepam alone for adequate dose and duration nor along with a SGA as an augmenting agent. Both patients showed significant improvement with zolpidem therapy (30 mg/day) in the next 3-4 days with no significant side effects and also remained asymptomatic on zolpidem ER 12.5 mg three times a day for the next two

months of follow up without any significant side effects.

Zolpidem like benzodiazepines is a positive allosteric modulator of GABA-A receptors, but it specifically binds to the alpha 1 subunit of GABAAR unlike lorazepam which non-specifically binds to different subtypes of GABAAR (20). Zolpidem has already been used successfully in cases where benzodiazepines were not effective (10, 12). The zolpidem challenge test is also proposed for catatonia screening based on existing studies. For example, a French study confirmed prompt response within 20 minutes after zolpidem administration in all patients (21), and a beneficial response was seen in other case reports(11, 12).

By reviewing the neuropathology of catatonia, action of benzodiazepines and zolpidem, and seeing improvement with zolpidem in many cases along with the response seen in our two lorazepam-resistant cases, we can arrive at following possibilities:

(I) In different patients, catatonia might occur through deficiency of different subtypes of GABAAR

(II) In some cases, catatonia might occur through specific deficiency of the alpha 1 subunit of GABAAR

(III) Zolpidem may be beneficial in lorazepam-resistant cases of catatonia in children and adolescents. It can be tried before ECT and in cases where ECT is contraindicated or restricted

Although the evidence in the favour of zolpidem for treatment of catatonia is scarce, it may be an effective treatment in lorazepam-resistant cases, especially in children and adolescents. Larger studies are required to confirm zolpidem's efficacy.

Ethical considerations

Written informed consent was taken from parents of both the patients for publication.

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Declaration of conflicting interest

The authors declare no conflict of interests in preparing this report.

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