

*Case report***LEVETIRACETAM AS A CAUSE OF DELIRIUM IN AN ELDERLY PATIENT: A CASE REPORT**Shahana Kasim^{1*}, Indu P V², Jayaprakashan K P³, Anil Prabhakaran⁴¹Junior Resident, Department of Psychiatry, Govt. Medical College, Thiruvananthapuram²Associate Professor, Department of Psychiatry, Govt. Medical College, Kozhikode³Associate Professor, Department of Psychiatry, Govt. Medical College, Thiruvananthapuram⁴Professor & HOD, Department of Psychiatry, Govt. Medical College, Thiruvananthapuram* Corresponding author: E-mail: shahanakasim@gmail.com

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ABSTRACT

Levetiracetam is a second-generation anticonvulsant. Delirium is not a well-known adverse effect of the drug. We present the report of an 80-year-old woman with a history of schizophrenia for 45 years and memory impairment for two years, who presented with worsening of confused, disoriented behaviour with sundowning, after being started on Tab. Levetiracetam for late-onset seizures. Examination revealed disorientation, fluctuation in the level of consciousness, impaired attention and psychotic symptoms. Physical examination was normal, except for gait disturbance. Relevant blood, urine and CSF investigations were also normal. Neuroimaging showed diffuse atrophy and small vessel ischemic changes. No focus of infection or metabolic imbalances could be identified. The possibility of delirium due to levetiracetam was suspected and, on cross-titration with sodium valproate, her delirium cleared. This report highlights that levetiracetam can cause delirium in the elderly, which brings forth the need for close monitoring while prescribing medicines in this population.

Keywords: anticonvulsant, acute confusional state in older adults, medication-induced delirium

INTRODUCTION

Levetiracetam is a second-generation anticonvulsant used for the treatment of epilepsy. Its mechanism of action is considered to be by indirectly enhancing gamma-aminobutyric acid (GABA) inhibition. It is mainly used in the treatment of convulsive

disorders, especially partial-onset seizures, myoclonic seizures, and idiopathic generalized epilepsy. In Psychiatry, it has been found to be useful in the treatment of acute mania, as an add-on treatment for major depression and as an anxiolytic agent. Some well-known adverse effects of levetiracetam are somnolence, ataxia, diplopia, memory impairment, paraesthesia,

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behavioural disturbances and even hallucinations.¹ Delirium is not a well-known adverse effect of the drug. Here, we present the case of an elderly woman with schizophrenia and memory impairment, who developed delirium following treatment with levetiracetam for late-onset seizures.

CASE REPORT

An 80-year-old woman, Mrs X, had presented to Psychiatry Out-patient Department (OPD) of a tertiary care teaching hospital in South Kerala with a history of continuous mental illness for past 45 years, with exacerbations and partial remissions. The exacerbations were characterized by auditory hallucinations, persecutory and grandiose delusions, poor self-care and agitated behaviour. She had received in-patient treatment and electroconvulsive therapy in the initial phase of her illness. After a period of six months, when her symptoms improved, medications were discontinued. Her suspicions and grandiose ideas remained and functioning never reached pre-morbid levels.

She also had memory impairment for the past two years, which was insidious in onset and gradually progressive. It was characterized by misplacing things, forgetting to have taken her meals and repeating whatever she told. The word-finding difficulty was also observed. There was no history suggestive of apraxias, agnosias or impairment in executive function. Her self-care was adequate, but she had occasional sleep impairment. She was not on any medications for these symptoms. She was on irregular treatment for type 2 diabetes mellitus and systemic hypertension for the past three years, with Tab. Metformin SR 500 mg bid and Tab. Cilnidipine 10 mg bid. Thyroidectomy was done about 20 years ago, details of which were

not available. She was not on thyroid hormone replacement therapy.

About 25 days prior to admission in our hospital, she had an episode of generalized tonic-clonic seizures. She was evaluated in the Medical Neurology OPD of a tertiary care teaching hospital and investigated for the causes of seizures. Following seizures, she had confused behaviour. She also had decreased sleep, assaultive and abusive behaviour, suspiciousness and hallucinatory behaviour. All relevant investigations, including blood, urine and CSF study and CT brain, were all within normal limits.

After three days, she was seen in another hospital, where her behavioural problems persisted for which she was given Tab. Quetiapine and Tab. Memantine. She was also started on Tab. Levetiracetam 500 mg bid for seizures and maintained on Tab. Cilnidipine for hypertension. After starting Tab. Levetiracetam, there was a worsening of confusion and psychosis, characterized by suspicions, agitation and intermittent aggressive behaviour.

On examination she was found to be drowsy, disoriented, with fluctuation in the level of consciousness, sundowning, impaired attention and inability to obey commands. Persecutory delusions, anxious mood and visual hallucinations were also observed. Physical examination showed a pulse rate of 88/minute and blood pressure of 120/80mm Hg. She was afebrile. Systemic examination, including examination of the central nervous system, was within normal limits, except for gait disturbance. She was already getting Tab. Levetiracetam 1000 mg/day, Tab. Quetiapine 100 mg/day, Tab. Memantine 10 mg/day and Tab. Cilnidipine 20 mg/day. Her symptoms worsened over the days and she was given Inj.

Haloperidol 2.5 mg intramuscularly for agitation, as required.

Relevant blood and urine investigations, including complete blood count, urine routine examination, fasting and post-prandial blood sugar, serum electrolytes, renal function test, liver function test and thyroid function test, were repeated and found to be within normal limits (See Table 1). EEG recording was normal. MRI Brain showed diffuse fronto-temporo-parietal brain atrophy and small vessel ischemic changes. Since infective and metabolic causes of delirium were ruled out, the role of drugs was considered. Levetiracetam was gradually cross titrated with sodium valproate and tapered off while maintaining the patient on other drugs. The dose of sodium valproate was optimized to 500 mg twice daily. Her symptoms improved: initially aggression, followed by suspiciousness, hallucinations and then orientation. The patient's mental status and gait improved over time and her sleep and appetite were also better. She was not re-challenged with levetiracetam. At discharge, she was conscious and oriented to time, place and person. Her psychomotor activity and talk were reduced, the mood was euthymic and there were no delusions or hallucinations. She was not co-operative for a detailed cognitive examination. She was maintained on Tab. Sodium Valproate 1000 mg/day, Tab. Quetiapine 100 mg/day, Tab. Memantine 10 mg/day and Tab. Cilnidipine 20 mg/day.

DISCUSSION

Delirium (acute confusional state) is a common condition in old age associated with high mortality. It can have a variety of aetiologies, including infections, metabolic derangements, trauma, surgery, systemic causes, toxins and certain medications. In the above-reported case, the American Psychiatric Association's

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for medication-induced delirium was fulfilled. This is substantiated by a disturbance in attention and awareness, which developed over a short period of time and fluctuated during the course of a day. There was an additional disturbance in cognition, and could not be explained by another neurocognitive disorder, or caused due to another medical condition, substance intoxication or withdrawal.² This patient had developed generalized tonic-clonic seizures 25 days prior to admission to our institution. After admission, it was found that she remained drowsy and disoriented, despite all investigations were normal. Prolonged delirium should be attributed to seizures alone, only if other possible medical conditions associated with delirium, including complications of anti-epileptic drug therapy, are excluded.³ Hence the role of medications in inducing delirium was considered. Although she was on medications like quetiapine and memantine, which could induce delirium, levetiracetam was tapered off first, considering the worsening of confusion and psychosis, as well as the emergence of gait disturbances after initiating the latter. On cross-titrating levetiracetam with sodium valproate, there was an improvement in her level of consciousness and orientation. Despite continuing quetiapine and memantine, her confusion cleared; psychosis and gait disturbance also improved.

Levetiracetam exerts its anti-epileptic effect by specifically binding to a 90-kDa-membrane protein, which is restricted to neuronal cells. It also blocks zinc and beta-carbolines from interrupting chloride influx in the GABA and glycine receptors. Mechanism of action of levetiracetam involves inhibition of N-type calcium channels, modulation of GABA and glycine receptors and binding to synaptic vesicle protein 2 (SVA 2). Although it has a good side

effect profile generally, psychiatric side effects are seen in up to 13.3% of adults. Of these, severe symptoms such as depression, agitation, hostility and psychotic behaviour are observed in 0.7% of patients.⁴ Some studies report that pre-existing psychiatric conditions may increase the probability of occurrence of behavioural side effects due to levetiracetam.⁵ Mood or affective symptoms and gait instability have also been reported with the use of levetiracetam in elderly.⁶

Although rare, there have been some reports stating levetiracetam as a cause for delirium, and exacerbation of psychosis, especially among the elderly. A case had been reported, of a 77-year-old Caucasian male who developed disorientation, agitation, and lethargy after initiation of levetiracetam to prevent post-traumatic seizures and was considered to be a case of delirium without psychotic features associated with levetiracetam.⁷ Another case was that of an elderly subject who presented with encephalopathy with levetiracetam. She had no renal failure, no concomitant valproate medication, and no other additional comorbidities.⁸ An 80-year-old woman with levothyroxine-treated hypothyroidism had developed acute confusion and paranoia after five days of substituting levetiracetam 1000 mg orally twice daily for phenytoin 100 mg orally twice daily to control new-onset, generalized seizures. Before starting levetiracetam, results of the patient's blood and urine tests, brain magnetic resonance imaging and cerebrospinal fluid examination were within normal limits. Delirium from levetiracetam was suspected. Therefore, the dosage was titrated downward to allow discontinuation of the drug; levetiracetam was replaced with pregabalin 150 mg twice daily. The subsequent improvement in mental status occurred within 14 days after administration of the last dose of levetiracetam.⁹

In our case, based on history, mental status examination, assessment of cognitive functions, physical examination and investigation results, a diagnosis of Levetiracetam-induced delirium was made, along with co-morbid schizophrenia and the possibility of underlying dementia. According to Naranjo Adverse Drug Reaction Probability Scale, a score of 6 was obtained,

Table 1. Investigation Results of Mrs X

| Sl. No. | Investigations | Result | Normal range |
|---------|---------------------------|------------------|---------------------------|
| 1 | Urine routine | WNL | |
| 2 | Hb | 12.2 g/dl | 12-15.5 g/dl |
| 3 | WBC count | 7800/cu.m m. | 4000- 11,000/cu.mm |
| 4 | FBS/PPBS | 94/129 mg/dl | 70-110/<140 mg/dl |
| 5 | S. Sodium/S. Potassium | 143/3.5 meq/l | 136-145/3.6- 5.4 meq/l |
| 6 | S. Calcium | 8.8 mg/dl | 8.5-10.5 mg/dl |
| 7 | S. Bilirubin | 0.5 mg/dl | 0.2-1.5 mg/dl |
| 8 | S. ALT/S. AST | 19/13 U/L | <40/<40 U/L |
| 9 | B. Urea | 22 mg/dl | 15-35 mg/dl |
| 10 | S. Creatinine | 1.0 mg/dl | 0.6-1.6 mg/dl |
| 11 | S. Ammonia | 22mg/dl | 7-20 mg/dl |
| 12 | S. T3 | 83 ng/dl | 83-180 ng/dl |
| 13 | S. T4 | 9.29 µg/dl | 5-12.5 µg/dl |
| 14 | S. TSH | 0.98 µU/ml | 0.34-5.2 µU/ml |
| 15 | HIV ELISA | Non- reactive | |
| 16 | VDRL | Non- reactive | |

which suggests levetiracetam as a probable cause for delirium in our case.¹⁰ Further, complete resolution of symptoms after stopping the drug supports the hypothesis.

CONCLUSION

This case report focuses on an elderly female patient with a history of psychiatric illness and recent onset of cognitive disturbances, who developed delirium and gait disturbance after initiation of levetiracetam for late-onset seizures. In the absence of other findings from history, examination and investigations, the possibility of Levetiracetam-induced delirium was considered. On removal of the offending agent, the symptoms of delirium and gait disturbance abated. Thus, the role of levetiracetam in the causation of delirium, especially in elderly people, is brought out. This case also highlights the need for close monitoring while prescribing medications for elderly patients.

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