Case Report

Possible levetiracetam induced encephalopathy presenting as electrical status epilepticus: An unknown occurrence

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ABSTRACT

Levetiracetam is a novel, broad spectrum anti-epileptic drug with proven efficacy in generalized as well as focal onset seizures. It has renal elimination with no hepatic metabolism. Levetiracetam induced encephalopathy is rarely reported in literature. Triphasic waves in the electroencephalogram are seen in toxic-metabolic encephalopathies of various aetiology like hepatic encephalopathy, uraemia. We report a patient who was on levetiracetam for acute symptomatic seizures and developed encephalopathy with electroencephalogram showing generalised triphasic waves. These triphasic waves disappeared with intravenous lorazepam but without clinical improvement in sensorium. The electroencephalographic abnormality appeared as electrical status epilepticus which got normalised on discontinuation of levetiracetam. This is the first report of levetiracetam induced encephalopathy presenting as electrical status epilepticus and also depicts electroencephalographic correlate of levetiracetam induced encephalopathy.

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1. Introduction

Levetiracetam (LEV) is a novel anti-epileptic drug having a broad spectrum anti-seizure activity in both generalized as well as focal onset seizures. It is a relatively well-tolerated anti-epileptic drug (AED) in both adults and children. It is a new AED with renal elimination and no hepatic metabolism.1 The most common adverse drug reaction (ADR) have been headache, somnolence, asthenia, drowsiness, behavioural disturbance, worsening of psychiatric symptoms and rarely paradoxical worsening of seizures.2 The behavioural and psychiatric side-effects with LEV include hostility, irritability, nervousness, anxiety and depression.3 Encephalopathy occurring following LEV administration is a rare occurrence. We report a patient who presented with acute meningoencephalitis and received LEV for solitary episode of seizure and developed encephalopathy after 4 days.

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Electroencephalography (EEG) was suggestive of electrical status epilepticus that got normalised on discontinuation of LEV.

2. Case report

A 46 year old lady presented to our hospital with the symptoms of fever associated with headache of 3 days duration, with one episode of generalised tonic clonic seizures (GTCS). Headache was diffuse, holocranial associated with vomiting. No visual disturbances, bulbar symptoms or limb weakness. No other comorbidities. On neurological examination, she was conscious but disoriented and used to talk irrelevantly. There was nuchal rigidity. Cranial nerves and motor examination was normal. No other localising or lateralising deficits. Complete haemogram revealed neutrophilic leucocytosis. Renal and hepatic functions were normal. Magnetic Resonance imaging (MRI) brain with contrast images did not show any parenchymal lesion or meningeal enhancement. Cerebrospinal fluid (CSF) analysis showed clear CSF, raised protein with normal glucose level and lymphocytic pleocytosis (protein-62 mg/dl; glucose 48 mg/dl; cells-38; lymphocytes-70%, neutrophils-30%).

Electroencephalogram (EEG) on day 2 after admission showed mild diffuse slowing of background rhythm with no epileptiform discharges. She was diagnosed as acute meningencephalitis probably of viral aetiology and was started on intravenous antibiotics (ceftriaxone), acyclovir and levetiracetam (loading dose 20 mg/kg followed by 500 mg 8th hourly). She had improvement in her sensorium as she became conscious, oriented and obeying to commands within 2 days of admission. CSF herpes simplex virus (HSV) polymerase chain reaction (PCR) was negative and hence acyclovir was stopped after 3 days.

There was decrease in her mental status on day 4 after admission as she became stuporous, not responding to verbal commands and opening eyes briefly to painful stimulus. There was no recurrence of convulsive seizures. Repeat serum electrolytes, calcium, renal and hepatic function including serum ammonia were within normal limits. Computed tomography (CT) of brain did not reveal parenchymal lesion. Repeat CSF showed decrease in cell counts (3/cumm). A possibility of non-convulsive status epilepticus was considered. EEG on day 4 after admission showed diffuse slowing of background rhythm with generalised, triphasic waves (Fig. 1). These triphasic waves disappeared on intravenous administration of lorazepam (4 mg) (Fig. 2). But there was no significant improvement in mental status. A possible drug induced encephalopathy causing non-convulsive status epilepticus was considered in view of non improvement in mental status despite disappearance of triphasic waves with lorazepam. LEV and ceftriaxone are known to cause non-convulsive status epilepticus with EEG showing triphasic waves. LEV was stopped first and substituted with clobazam. Ceftriaxone was continued. Within two days, there was gradual improvement in her mental status as she became conscious, oriented and started feeding herself. Repeat EEG showed normalisation of background rhythm with disappearance of triphasic waves.

![Fig. 1 — Electroencephalogram (EEG) (bipolar longitudinal montage, sensitivity 7.5 µV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, notch 50 Hz, speed 30 mm/s). Diffuse slowing (frequency 4–5 Hz) of background rhythm with generalised triphasic waves (red arrow).]
Fig. 2 — Electroencephalogram (EEG) (bipolar longitudinal montage, sensitivity 7.5 μV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, notch 50 Hz, speed 30 mm/s). There is disappearance of triphasic waves with intravenous administration of lorazepam, thereby suggestive of electrical status epilepticus.

Fig. 3 — Electroencephalogram (EEG) (bipolar longitudinal montage, sensitivity 7.5 μV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, notch 50 Hz, speed 30 mm/s). There is normalisation of EEG with background rhythm of 8–9 Hz after withdrawal of levetiracetam.
3. Discussion

Diffuse triphasic waves are the EEG patterns commonly observed in toxic-metabolic encephalopathies in adults. Initially, triphasic waves were thought to be specific for hepatic encephalopathy. However, they are often described in other etiologies of toxic-metabolic encephalopathies such as uremia, thyroid disease, hyperammonemia, hypoxia, cefepime intoxication in patients with chronic kidney disease and drugs like lithium, valproate and levodopa. Drug induced encephalopathy due to LEV has been rarely reported but has been reported due to many other AEDs. The mechanism of action of LEV is its action on synaptic vesicle protein SV2A and prevention of vesicle exocytosis and presynaptic neurotransmitter release. LEV undergoes minimum metabolism in blood via hydrolysis and eliminated through kidneys. It has superior pharmacokinetics with no hepatic metabolism, lack of significant drug interactions which makes it as a good choice for monotherapy. There are few reports on LEV induced encephalopathy in literature. Vulliemoz et al, (2009) reported a patient with renal failure who was on LEV (2000 mg/day) developed metabolic encephalopathy with triphasic waves due to accumulation of LEV. Bauer et al, (2008) reported a patient with idiopathic generalised epilepsy who developed encephalopathy due to LEV (3000 mg/day) when it was used as an add-on to oral valproate (2000 mg/day) therapy. Verma et al, (2013) reported a patient with localisation related epilepsy secondary to frontal lobe gliosis who presented with epilepsy partialis continua (EPC). Patient was on LEV initially and subsequently on oxcarbamazepine. After 2 days, patient became drowsy and on evaluation was suspected to have drug induced encephalopathy. On stopping LEV, patient had remarkable improvement in his state of consciousness along with normalization of EEG. According to authors, drug induced encephalopathy is one of the unusual side effects of LEV and a high index of suspicion is required for the diagnosis. Our patient had probable viral meningencephalitis who improved in her sensorium within 2 days with antibiotics, acyclovir. Acyclovir was stopped as soon as CSF HSV PCR came negative. On fourth day, she became stuporous with EEG triphasic waves due to accumulation of LEV. Bauer et al, (2008) reported a patient with idiopathic generalised epilepsy who developed encephalopathy due to LEV (3000 mg/day) when it was used as an add-on to oral valproate (2000 mg/day) therapy. Verma et al, (2013) reported a patient with localisation related epilepsy secondary to frontal lobe gliosis who presented with epilepsy partialis continua (EPC). Patient was on LEV initially and subsequently on oxcarbamazepine. After 2 days, patient became drowsy and on evaluation was suspected to have drug induced encephalopathy. On stopping LEV, patient had remarkable improvement in his state of consciousness along with normalization of EEG. According to authors, drug induced encephalopathy is one of the unusual side effects of LEV and a high index of suspicion is required for the diagnosis.

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4. Conclusion

Levetiracetam is a broad spectrum anti-epileptic drug with renal elimination and no hepatic metabolism. Encephalopathy due to LEV is of rare occurrence but there are case reports of its occurrence. A high index of suspicion is required for the diagnosis of LEV induced encephalopathy.

Conflicts of interest

All authors have none to declare.

Financial disclosure

None of the authors have any financial disclosure to make.

REFERENCES