CASE REPORT

Levetiracetam induced irritability in organic personality disorder

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Levetiracetam is an antiepileptic drug with favourable pharmacological characteristics and demonstrated activity in improving seizure control. Studies have shown that levetiracetam can produce behavioural symptoms in children. Organic personality disorder is primarily characterized by a change of premorbid behaviour due to an organic impairment or disease of the central nervous system. The most common symptoms described were symptoms of depression, emotional instability, irritability and impulsive behaviour.

An 18 years old gentleman presented to the psychiatry department with complaints of hair loss, excessive concern about hair loss and irritability. Subsequently patient developed symptoms of irritability, ideas of reference and a firm belief and pre-occupation that his symptoms were secondary to his anti-epileptic medication side effects. The symptoms subsided with an adequate dose of risperidone and lorazepam with discontinuation of the anti-epileptic Levetiracetam.

Conclusion: Though the patient was on Levetiracetam the behavioural symptoms could be attributed to the brain lesions which are involved and can be managed effectively. The case in study hints a possible role of Levetiracetam in precipitation of behavioural symptoms in the individuals.

Key Words: *Personality disorder; Depression; Impulsive behavior; Palpitations*

INTRODUCTION

Levetiracetam is an antiepileptic drug with considerable evidence in improving seizure control. It was synthesized in the early 1980s, and initial pharmacologic studies with Levetiracetam explored its ability to facilitate cholinergic neurotransmission. In the early 90's, clinical studies were initiated in epilepsy patients as adjunctive therapy in refractory partial onset seizures [1]. Studies have shown that levetiracetam can produce behavioural symptoms in children. Children using levetiracetam have a risk of developing several behavioural side-effects such as aggression, hostility and nervousness compared to children who do not use levetiracetam [2].

Organic personality disorder brings about a change in the pre-morbid behaviour due to an impairment or disease of the central nervous system [3]. The most common symptoms described were symptoms of depression, emotional instability, irritability and impulsive behaviour. Psychopathological symptoms though unrelated to the eio-pathogenesis, showed some relation to the neuroanatomical location of functional disorders or damages. Frequent sites of such injury are the anterior temporal poles, lateral and inferior temporal cortices, frontal poles, and orbital frontal cortices.

There are several personality changes that affect the individual post traumatic brain injury. One of the problems frequently encountered is impulsivity which could is observed as verbal utterances, motor actions, snap decisions and poor judgement. Second would be that of irritability which could evolve into aggressive and assaultive behaviour. A third area of affective instability where there are exaggerated expressions of emotion associated with weeping and crying spells. This phenomenon occurs in other neurological disorders and has been called pathological affect, labile affect, pseudobulbar affect, and affective incontinence [4].

Study done by Mula, stated that it seems to be a problem more often in patients taking Levetiracetam than in those taking other antiepileptic drug [5]. The possibility of fast titration being a cause was considered but not clinically substantiated. However, the possibility that some patients are generally predisposed to develop this psychiatric reaction was considered. Few authors emphasized the previous psychiatric history, while others identified a specific genetic variation in dopaminergic activity that predisposes them to the personality change post Levetiracetam.

Hence it is important to consider personality disorders in individuals with traumatic brain injury despite the seemingly multifactorial causation.

CASE REPORT

An 18 years old male student, hailing from Kankanady, Mangalore, Karnataka had presented with a history of head injury and loss of consciousness following a road traffic accident on 24/05/2015 with diffuse axonal injury and fully recovered. Patient was treated at a different hospital for the same. Patient also developed post-traumatic generalized tonic-clonic seizures for which he was started on Levetiracetam. Over the period of recovery patient had adequate control of seizures with the medication (500 mg bd), which amounted to no seizures post discharge after adequate titration of the medication. Patient was brought to the Psychiatry Out Patient Department on 06/10/2016 with the complaints of hair loss since 6 months, excessive concern about hair loss since 6 months. There is no family or past history of excessive hair-fall, no cause (infections, wounds, etc.) that could be found by Dermatologist other than drug reaction, which it could be attributed to. The patient's mother had also reported a noticeable change in his personality, with irritability and assaultive behavior since 2 months.

During interview patient also reported subjective experience of anger, irritability and excessive concerns about hair loss. He had no complaints of cold/heat intolerance, palpitations, weight loss/gain, increased/decreased appetite. No complaints of hearing voices, seeing images, wandering behavior. No depressive symptoms or suicidal ideation. No history suggestive of manic symptoms. No history of sleep disturbances. No history of substance use. No significant past history and no contributory family history noted.

At the time of presentation, the patient was on Tab Levetiracetam 500 mg BD dosage. A provisional diagnosis of Organic Personality Disorder and Seizure disorder was made and the patient was admitted for diagnostic evaluation.

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Physical examination revealed no signs of acute physical trauma. BMI was calculated to be 19 kg/m^2. General physical examination and systemic examination were within normal limits and no residual neurological deficits. On mental status examination patient was found to be conscious-alert, with increased psychomotor activity, patient's talk was increased in tone and volume and had decreased reaction time, mood was reported as "unhappy", patient had an irritable affect, intact cognitive functions on MMSE and clinical evaluation. Patient had an Insight of Grade 1 (partially accepting that he had an illness and denying it at the same time).

Investigations revealed a normal EEG recording and all the blood investigations were within normal limit. Neurology consultation was obtained to assess any neurological deficits and to advice regarding the change in anti-epileptic medication as the patient had hair loss and irritability which could be attributed to the medication. Neurologist opined to consider changing antiepileptic. The patient was started on Risperidone and Lorazepam while the anti-epileptic was changed to Lamotrigine. The patient improved symptomatically and was advised to follow up on outpatient basis.

MRI report on follow up showed: multiple foci of blooming in the right frontal and temporal lobe, left parietal lobe, right cerebellum and dorsal midbrain on the left side-suggestive of chronic micro haemorrhages-likely sequelae of old diffuse axonal injury.

FINAL DIAGNOSIS

- Organic Personality Disorder (F07.0)
- Seizure disorder (R56.1)

DISCUSSION

Levetiracetam is a pyrrolidone derivative, developed from piracetam. It is presumed to act on presynaptic neurotransmitter release by binding to synaptic vesicle protein 2A (SV2A), a glycoprotein that is part of the membrane of presynaptic neurotransmitter-containing vesicles in neurons and neuroendocrine cells. Levetiracetam increases tissue concentrations of GABA, blocks the GABAA receptor, and reduces the excitatory effect of glutamate by modulation of AMPA receptors. Studies have suggested that Levetiracetam modulates neuronal cell function through other pharmacological mechanisms like the modulation of serotonergic and α2-adrenergic signalling and also μ-opioid receptors. Levetiracetam also regulates intraneuronal calcium levels via inhibition of N-type calcium channels. Other mechanisms of action as associated with Levetiracetam are modulation of presynaptic P/Q-type calcium channels and potassium channels, as well as upregulation of glutamate transporters in glial cells. It is not clear whether these mechanisms of action occur on their own or as a consequence of the interaction with SV2A. The broad pharmacological effect of Levetiracetam makes it difficult to determine the exact cause of Aggressive behaviour. The findings suggest that Levetiracetam's negative modulating effect on AMPA receptors contributes to increased aggressive behaviour. Undoubtedly, serotonin and GABA is involved in aggressive behaviour, but whether Levetiracetam might interfere with this mechanism is unclear [6]. Self-reported aggressiveness has also constantly been reported as a problem in individuals of all age groups on Levetiracetam. Treatment-emergent psychiatric adverse events of anti-epileptic drug are more frequently reported in patients with epilepsy and irritability, emotional lability is more frequently noticed with Levetiracetam [7]. Observational register of that self-reported symptoms suggested anger being more often a problem in patients taking Levetiracetam [8].

The above described patient presented with complaints of irritability and hair loss after starting anti-epileptic medication- Levetiracetam. It has been stated that Levetiracetam can cause irritability but the studies on this are few. This emphasizes the need for a detailed neurological and thorough physical examination along with neuroimaging in patients presenting with psychiatric disorders as well as to monitor the drugs the patient is on. Irritability can also be seen in organic mental disorders but in this patient the irritability improved with the change in the anti-epileptic medication thus indicating the possible effects of the medication - Levetiracetam.

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