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OBM Neurobiology

Case Report

Lamotrigine-Associated Progressive Dysphasia and Cognitive Dysfunction

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Academic Editor: Bart Ellenbroek

OBM Neurobiology
2021, volume 5, issue 2
doi:10.21926/obm.neurobiol.2102091

Received: December 01, 2020
Accepted: April 11, 2021
Published: April 20, 2021

Abstract

Lamotrigine is generally accepted as a well-tolerated medication with few cognitive side effects. Here, we report a case of a 62-year old female with a severe, rapidly progressive dementia-like process which was completely reversed after reduction of lamotrigine. Associated findings included hyperreflexia with clonus, ataxia, Wernicke-like dysphasia, global cognitive impairment, burst suppression on electroencephalogram (EEG), and bilateral parietal hypo-metabolism on fluorodeoxyglucose-Positron Emission Tomography (FDG-PET). To our knowledge, this is the first case of a severe neuropsychiatric syndrome attributed to lamotrigine at the Food and Drug administration (FDA) recommended dose and not associated with epileptic activity.

Keywords

Reversible cognitive dysfunction; lamotrigine adverse effects; anticonvulsant adverse effects; encephalopathy; organic mental disorders; language disorder; paraphasias; myoclonus; toxicity at approved dose; hyperreflexia.

1. Introduction

While most antiepileptic drugs can cause neurocognitive adverse effects, lamotrigine is known for its superior profile over other antiepileptic drugs for minimizing cognitive adverse effects and even improving cognitive functions [1, 2]. There are rare reports of neurocognitive adverse effects attributed to lamotrigine, but these are in association with epileptiform activity or high doses of lamotrigine [3-6]. Here, we present a case of severe neurocognitive effects attributed to lamotrigine at the Food and Drug Administration (FDA) recommended dose of 200 mg daily.

2. Case Report

A 62-year-old female presented to the geriatric psychiatry service with a 2-month subacute onset of progressive 'word-salad' dysphasia, global confusion and disorganization, and inability to perform activities of daily living (ADLs). She had no prior history of cognitive or speech impairments, nor seizures. Her family history was notable for depression and dementia in her parents. Her medical history included psoriasis. She was a non-smoker, a social drinker, and previously worked as a clerk.

Ten weeks prior, she was on our service for a severe depressive episode. Although her historical diagnosis was major depressive disorder, her symptoms - including racing thoughts, restlessness, insomnia, and agitated mood - suggested mixed episodes of bipolar disorder. She responded well to 10 sessions of electroconvulsive therapy (ECT). Following ECT, at the time of discharge, lamotrigine was initiated at 25mg daily with instructions to titrate over six weeks per manufacturer specifications to the FDA recommended target dose of 200mg daily (2.88mg/kg/d). At the same time, we switched her home quetiapine to risperidone upon her request, due to cost. We continued prior home medications including mirtazapine, citalopram and trazodone.

According to her outpatient psychiatrist, she initially did well with the exception of continued restlessness, attributed to akathisia from risperidone. Trials of benztropine, hydroxyzine, and propranolol were added without benefit over the next seven weeks. At this time, approximately three weeks before she was referred back to our hospital, she was taken off risperidone and switched back to quetiapine. Despite this, her restlessness continued, and she developed progressive confusion and disorganization, gait instability, and executive dysfunction. She soon became too cognitively impaired to provide any history or care for herself. At her next outpatient appointment, she was unable to complete a Folstein mini-mental status examination (MMSE) [7] or draw a clock (Figure 1) [8]. Quetiapine, hydroxyzine, and mirtazapine were discontinued; gabapentin and lorazepam were started for ongoing severe restlessness; and lamotrigine was continued at 200 mg/day. Unfortunately, she continued to deteriorate cognitively, as well as functionally, and she required re-hospitalization.

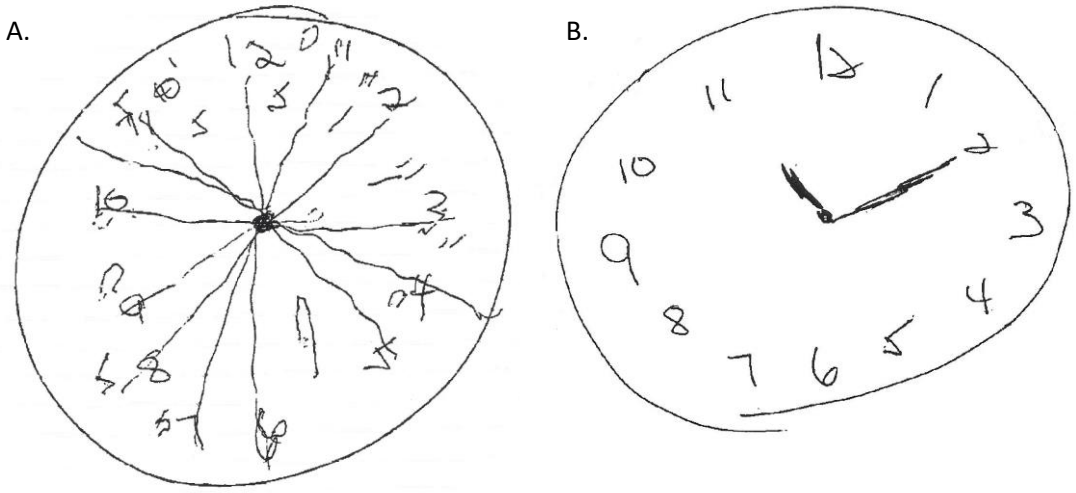

Figure 1 Clock drawings on and off recommended dose of lamotrigine. (A) Clock drawing at 3rd outpatient visit: 10 weeks after lamotrigine initiation and 5 weeks after recommended dose achieved. (B) Clock drawing after decreasing lamotrigine for several days.

Upon re-admission 10 weeks later, she was disheveled and uncooperative. Her thoughts were incoherent and illogical, and she had intermittent visual hallucinations. She required extensive prompting to follow single-step commands. Her language consistently exhibited loose associations and at times deteriorated to frank word salad. She was only oriented to person and being in a hospital, and she could not perform an MMSE. She had an unsteady gait and symmetric hyperreflexia in all extremities with 2-3 beat clonus in bilateral ankles. She had oral canker sores and psoriasis on her elbows bilaterally, but no other rashes or sores.

Initial work-up revealed a urinary tract infection, which was successfully treated with a seven-day course of nitrofurantoin, but with no neurocognitive improvement. Serum tests including electrolytes, complete blood count, ammonia, rapid plasma reagin, thyroid function, cobalamin, folate, and thiamine levels were all unremarkable. Brain magnetic resonance imaging showed minimal white matter disease with unremarkable ventricles and sulci. We restarted quetiapine out of concern for affective psychosis causing 'word salad', but her dysphasia did not improve.

Speech pathologists described a Wernicke-like dysphasia with phonemic paraphasias, marked difficulty with automatic speech, and poor auditory comprehension. Primary progressive dysphasia was considered due to the rapid onset and progression. However, a fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) scan revealed hypo-metabolism in the bilateral parietal lobes with relative sparing of the primary motor and sensory cortex (as shown in the Supplemental Digital Content), most often consistent with Alzheimer's dementia.

Continuous video electroencephalography (EEG) for three days did not reveal any seizure activity or inter-ictal epileptiform discharges, but did show generalized slowing, frontal intermittent rhythmic delta activity, and a burst suppression pattern. A lorazepam challenge produced no clinical or EEG changes. Cerebrospinal fluid tests including protein, cell counts, beta-amyloid and tau levels, protein 14-3-3, and a full panel of viral studies were all unremarkable. There was no evidence of autoimmune limbic encephalitis on brain magnetic resonance imaging

(i.e. no enhancement in the limbic areas) or cerebrospinal fluid studies (i.e. no elevation in cerebrospinal fluid protein). Additionally, she had no evidence of aseptic meningitis on physical exam or in cerebrospinal fluid studies.

With no reversible cause identified, her differential diagnosis included very rapid onset of Alzheimer's and Creutzfeldt-Jacob Disease. Indeed, her prognosis was very poor. Only then was it noted that the onset and progression of her decline coincided with titration of lamotrigine. At the FDA recommended dose of 200 mg/day (with verified administration of that dose during the 2 ½ week hospitalization), and with no medications inhibiting lamotrigine's metabolism, there was no clinical indication to obtain a lamotrigine level. We tapered lamotrigine to 100 mg over the next 8 days and monitored her cognitive function with serial clock drawings and MMSEs. Dramatic and rapid improvement was noted. Her MMSE score improved from a 0/30 to a 30/30, her clock drawing markedly improved (Figure 2), and her gait returned to normal. She was discharged with a plan to continue tapering off lamotrigine. While we had interest in a follow-up EEG and FDG-PET scan at that time, they were not clinically indicated in the context of a complete recovery.

She returned to our service eight months later for another depressive episode off of lamotrigine, at which time she scored 28/30 on MMSE. A repeat 1-hour EEG (which was recommended by the ECT service) was normal. She again received ECT with remission of depressive symptoms and no complications.

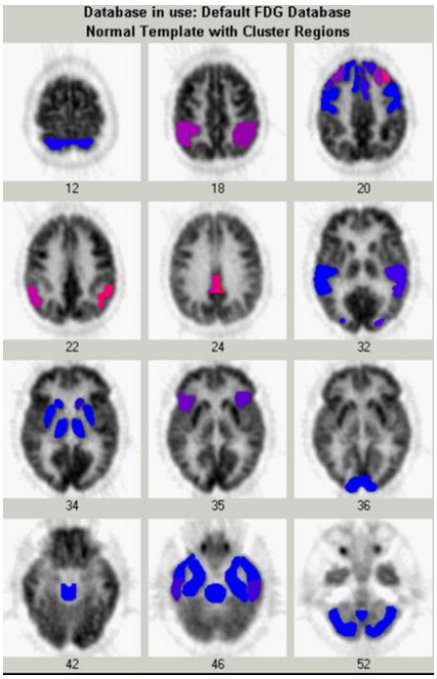

Figure 2 Hypometabolism in bilateral parietal lobes associated with severe cognitive dysfunction on lamotrigine. PET Scan: The patient was imaged on a GE Discovery whole body PET/CT scanner approximately 60 minutes after the intravenous administration of F18-fluorodeoxyglucose. A standard brain protocol was performed. At visual assessment, there is decreased uptake in the bilateral parietal lobes with sparing of the sensory-motor cortex, at least 3 standard deviations below database values. There are also more subtle areas of hypometabolic activity in the bilateral frontal regions. Standard deviations below normal: Blue 2-3, Purple 3-4, Pink 4-5, Red 5-6.

3. Discussion

This case demonstrates a unique presentation of a severe, progressive, and debilitating neurocognitive dysfunction with prominent dysphasia – along with abnormal EEG and PET findings - which was induced following the initiation of lamotrigine, rapidly progressed for 6 weeks, and then promptly reversed following lamotrigine taper, returning to normal cognitive function (see Figure 3).

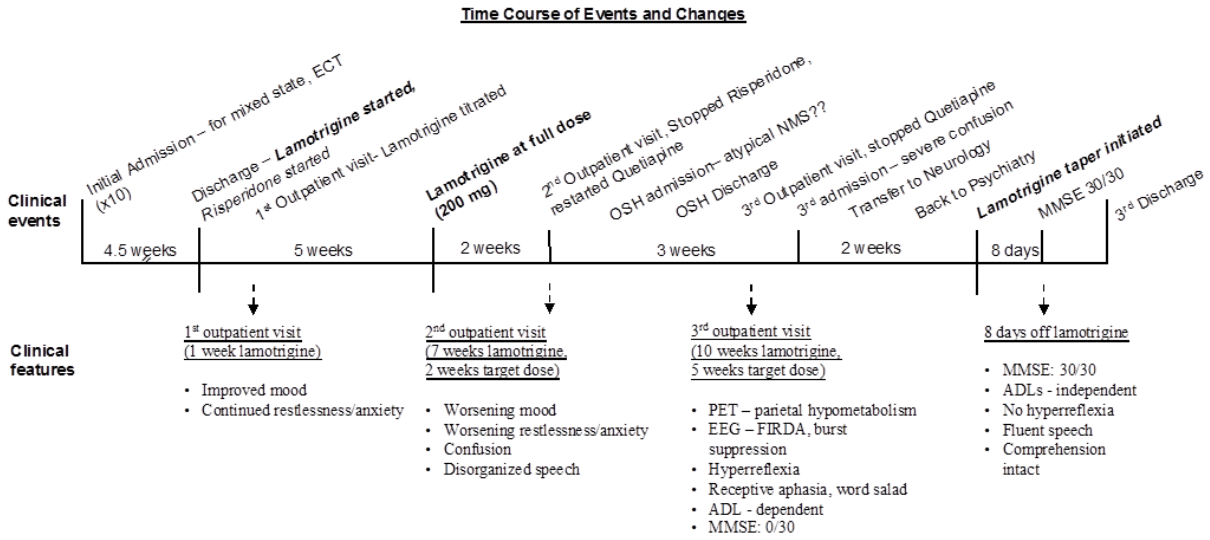

Figure 3 Time course of lamotrigine initiation, clinical deterioration, taper and resolution. Other medication changes included risperidone and quetiapine, but did not temporally correlate with deterioration and resolution.

Reports of adverse neurocognitive or behavioral reactions related to lamotrigine are rare. Our review of the literature found only a handful of case reports describing neuropsychiatric adverse reactions, none of which were comparable to those experienced by our patient. Additionally, none of the previous case reports describe the profound language and cognitive impairments seen in our case, nor were they associated with significant EEG changes (burst suppression pattern) or FDG-PET abnormalities (parietal hypo-metabolism). A series of six case reports described psychotic symptoms such as visual hallucinations, paranoia, agitation, and incoherent thoughts in epilepsy patients treated with lamotrigine [3]. In all but one of these cases, the patients were on higher doses of lamotrigine (i.e. 250 mg/day - 700 mg/day) and some in combination with valproic acid. In each case, the symptoms remitted when the lamotrigine was reduced and/or withdrawn, and they found no evidence of the symptoms being "post-ictal" [3]. Another series of case reports in nine children with epilepsy (and several with developmental delay) described a variety of neurobehavioral symptoms including self-injurious and violent behaviors, severe insomnia, extreme volatility, hallucinations, and hyperactivity [4]. Lamotrigine dosing ranged from 0.7mg/kg/d to 14mg/kg/d at the time when the behavioral symptoms appeared. All nine children had significant improvement or resolution of their behavioral symptoms following the withdrawal

or reduction of lamotrigine [4]. One case report did describe similar language impairments in a nine-year old epileptic patient with borderline intellectual functioning at baseline who was treated with non-toxic levels of lamotrigine; however, this was attributed to a paradoxical increase in epileptogenic EEG activity [5]. Hennessy and Wiles also reported a case in a semiconscious epileptic patient with symptoms including primitive reflexes, ataxia, hemiplegia, and muteness, which was associated with a "toxic serum level" of 19mg/L (reference range 1-4mg/L) and reversed when lamotrigine was reduced [6].

The primary limitation to our report is that no lamotrigine serum levels were obtained, therefore, we cannot determine whether this patient's response was due to toxicity, or simply an adverse effect. It is worth noting that a therapeutic serum concentration range of lamotrigine as a mood stabilizer has not been established, and routine monitoring of lamotrigine serum levels is not recommended. This report then raises the question as to whether obtaining levels should be recommended, and a range established, to guide clinicians treating patients with mood disorders. In fact, this patient was taking the FDA recommended dose for bipolar depression (200mg daily, or 2.88mg/kg/day) with no known concomitant metabolic-inhibiting medications. She had normal renal and hepatic function. Therefore, toxic serum levels of lamotrigine were less likely, though not impossible. For example, a genetic variant in uridinglucuronyl transferase (UGT) 1A4 has been reported to cause unpredictably high serum levels [9] via metabolic shunting to the cytochrome P450 system, and production of a toxic arene oxide intermediate metabolite [10]. Therefore, we can simply conclude that her deficits occurred at the recommended dosage, in the absence of known pharmacokinetic interactions or metabolic risk factors; and questions the current recommendations regarding serum levels in this patient population.

Another limitation to our conclusion is that other medication changes were made during this period. However, as shown in figure 3, none were temporally correlated with her clinical deterioration, or more notably, her improvement.

4. Conclusions

To our knowledge, this is the only documented case of FDA recommend doses of lamotrigine producing such severe clinical and objective neurocognitive findings. Additionally, these side-effects were not associated with epileptogenic activity. This case re-impresses the importance of considering iatrogenic etiologies, even when not described in the literature.

Author Contributions

JCB and JLB both contributed to the writing of this report and preparation of figures.

Funding

This work was supported by the National Institutes of Health, R25DA020537.

Competing Interests

The authors have declared that no competing interests exist.

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