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Beneficial cognitive effect of lamotrigine in severe acquired brain injury: A case report

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ABSTRACT

Background: Acquired brain injuries (ABI) can cause various negative sequelae, including cognitive impairment, leading to poor functional outcomes for patients. Evidence is limited on pharmacological interventions to effectively improve the cognitive status of these patients. This study aims to provide evidence for the use of lamotrigine to improve the cognitive status of patients with severe ABI.

Case presentation: We report the case of a 29-year-old man who suffered a severe traumatic brain injury secondary to a motor vehicle collision. When admitted to our rehabilitation program three months later, he was in a minimally conscious state, achieving Level III on the Rancho Los Amigos Cognitive Scale. Post-traumatic seizures were well controlled with levetiracetam. Multiple neurostimulants including methylphenidate, amantadine, and venlafaxine were trialed with minimal benefit, thereby prompting the switch of his antiepileptic medication to lamotrigine five months after his injury. The introduction of lamotrigine was followed by relatively rapid and significant improvement in arousal, cognition and communication that preceded levetiracetam being tapered. The patient continued making functional gains over the following year while using lamotrigine.

Conclusions: Lamotrigine may potentially provide cognition-enhancing effects independent of its known antiepileptic properties in patients with severe ABI. Further research is required on the role of lamotrigine in patients with ABI.

1. Background

Acquired brain injuries (ABI) can leave patients with a variety of negative sequelae, including physical disability, cognitive dysfunction, and behavioural impairments. Regarding traumatic causes of ABI (TBI), the global burden has increased significantly in the past few decades with approximately 27 million incident cases and 55 million prevalent cases worldwide in 2016, caused primarily by falls and road injuries [3]. These injuries not only adversely affect the life of individuals and their families, but also result in a burden to health-care systems and economies. As such, it is imperative to find effective treatments for ABI patients.

At the time of this writing, the FDA stated that they have "not yet cleared or approved any standalone medical products that are intended to specifically diagnose or treat TBI" [18], and there is minimal accepted pharmacological intervention to improve cognitive status for moderate to severe ABI patients except for methylphenidate, donepezil and rivastigmine [2]. As an anticonvulsant and mood stabiliser, lamotrigine has been widely used for epilepsy and bipolar disorder as well as augmentation for treatment-resistant depression [4]. Meanwhile, there is evidence of its cognitive benefit for patients with bipolar disorder [7,13], in ischemic animal brain models [6], and possibly for the elderly individuals with dementia [16]. However, the published evidence for lamotrigine's role in patients with moderate to severe ABI, while

Abbreviations: ABI, acquired brain injury; TBI, traumatic brain injury; CT, computerized tomography; VP shunt, ventriculoperitoneal shunt; RLACS, Rancho Los Amigos Cognitive Scale; EEG, electroencephalogram; AED, antiepileptic drug; SLP, speech language pathologist.

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suggestive of benefit, is limited. Specifically, several case reports and series have suggested that lamotrigine has led to improvement in mood [11] and behavior [12], as well as functional outcomes in ABI patients [17]. Showalter and Kimmel (2000) observed cognitive improvement in patients with severe ABI when switching anticonvulsants (phenobarbital, phenytoin and/or carbamazepine) to lamotrigine; however, the authors did not explain whether their finding was a result of the reduction in the side effects of anticonvulsants and/or better seizure management. The current case report adds to the literature by demonstrating evidence of the potential cognitive benefit of lamotrigine independent of its impact on seizure management and minimization of side effects. Reporting of this case has been done following the CARE guidelines [15].

2. Case presentation

The patient is a 29-year-old right-handed Caucasian male who suffered a severe ABI secondary to a motor vehicle collision. On arrival to the hospital, the patient had a Glasgow Coma Scale of 3/15. Computerized tomography (CT) scan demonstrated multiple intracranial injuries, including subdural hematoma, subarachnoid hematoma and signs of diffuse axonal injury involving the bilateral frontal, temporal and occipital parenchyma. He underwent urgent decompressive craniectomy due to the significant mass effect of his brain injury (see Fig. 1). His recovery was complicated by central venous sinus thrombosis, hydrocephalus that required ventriculo-peritoneal (VP) shunt insertion (Codman valve at 100 mmHg) and then its replacement with an external ventricular drain (EVD) after VP shunt-related infection and septic shock, replacement of craniectomy flap along with another EVD as the prior EVD unexpectedly came out, and later the replacement of this second EVD with another VP shunt (Codman medium pressure fixed valve), all of which occurred before being transferred to our rehabilitation unit.

The patient was admitted to the ABI Rehabilitation Program subsequent to medical stabilization three months following his initial injury. He was in a state of minimal consciousness in keeping with Rancho Los Amigos Cognitive Scale (RLACS) Level III. Specifically, he required total assistance including bed mobility and transfers, and used a gastrostomy tube for feeding and medication with no oral intake. He responded inconsistently to external stimuli (e.g. opening his eyes to verbal commands without tracking visually or following commands). His mother reported occasional verbal output of one or two words. He showed positive frontal release signs including palmomental and grasp reflexes. He developed significant spasticity bilaterally and had minimal

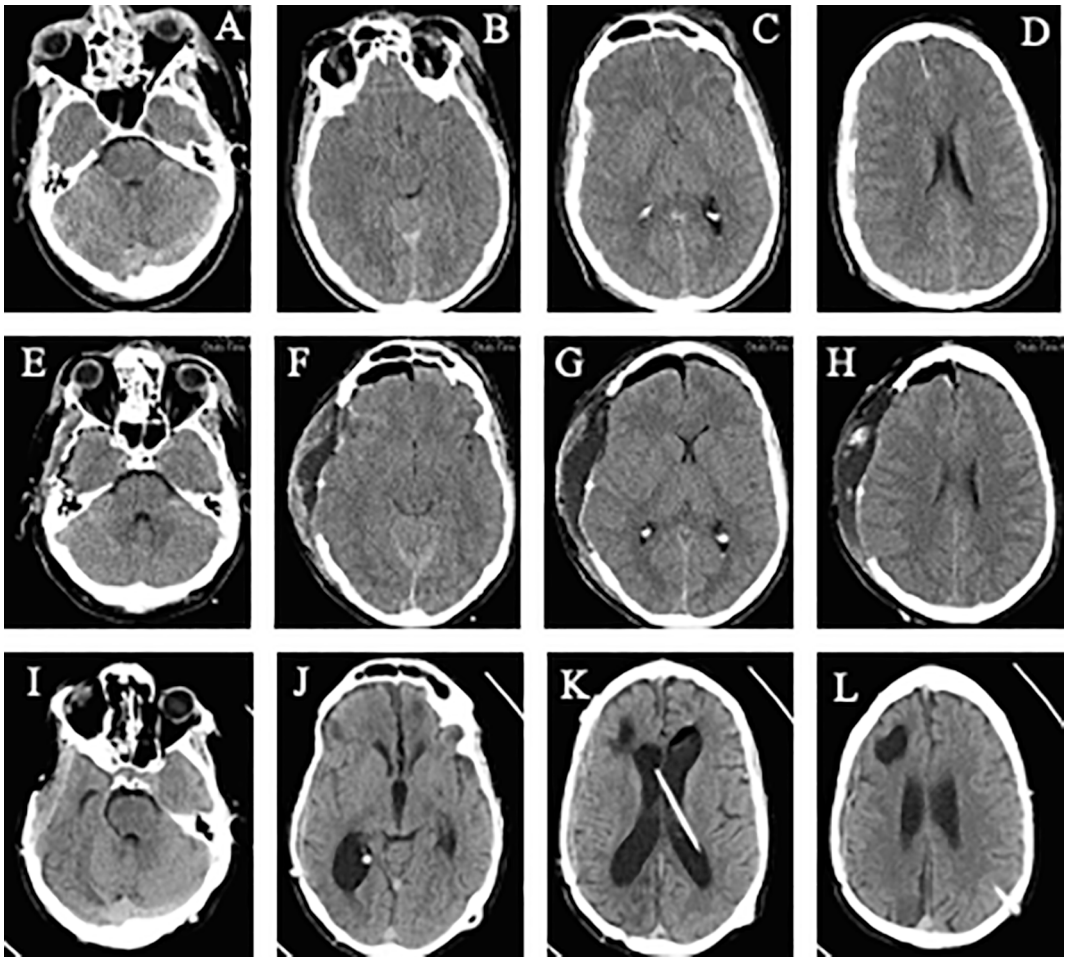

Fig. 1. Non-contrast CT head images after traumatic brain injury. A-D: Head CT scan right after traumatic brain injury demonstrated multiple punctate hemorrhagic foci at the gray-white junctions involving bilateral frontal, temporal and occipital parenchyma suggestive of diffuse axonal injury, evidence of diffuse cerebral edema with increased intracranial pressure and mild leftward midline shift, small right cerebral convexity and parafalcine acute subdural hematoma, and small volume subarachnoid hemorrhage over bifrontal convexity. E-H: Head CT scan one day after injury showed status post right-sided decompressive craniectomy and evacuation of subdural hematoma with small volume pneumocephalus, improvement in the midline shift and patency of the cerebral convexity sulci, ongoing increased intracranial pressure with mild diffuse cerebral edema, and a possible focus of early ischemia in right anterolateral frontal cortex. I-L: Head CT scan four months post injury demonstrated mild hydrocephalus with a VP shunt placed via a left parietal approach (without transependymal CSF leakage), focal encephalomalacia in frontal, temporal and parietal lobes, a small right frontal porencephalic cyst, and stable subdural collections.

purposeful movements in his right upper extremity.

He was on levetiracetam (1500 mg BID) and a tapering dose of lacosamide (25 mg BID for 1 week before discontinuation) for seizure prophylaxis when he was admitted to the rehabilitation unit. These antiepileptic drugs (AEDs) were started because EEG one month prior to admission noted epileptiform discharges from the left frontocentral region associated with chewing. Subsequently, no epileptiform abnormality was identified in two repeat EEGs later that month other than diffuse nonspecific slowing of the background activity, with persistent asymmetric suppression over the right hemisphere; As such, lacosamide was gradually tapered to discontinuation, keeping him on levetiracetam 1500 mg BID (Fig. 2).

Neurostimulants amantadine and methylphenidate, and antidepressant venlafaxine were trialed in an attempt to improve the patient's cognitive status (see Fig. 2 for details). However, there was no observable benefit from these medications, and some adverse effects were noted. Specifically, a higher dose of amantadine (100 mg BID) led to probable seizures in the form of "zoning out spells" and a reduced level of alertness and awareness when an EEG demonstrated sharp waves in the right temporal region. Methylphenidate resulted in an increased stiffness and tachycardia consistent with dysautonomia. His function gradually returned to baseline after these medications were discontinued. Another major pharmacological change was the switch of baclofen 15 mg TID to dantrolene 100 mg TID for spasticity management, in an attempt to minimize cognitive adverse effects. In addition, onabotulinumtoxinA injections were performed, which were followed by surgical release of the right quadriceps tendon and Achilles's tendon lengthening for spasticity and contractures.

Since there was no improvement in his cognitive status with the aforementioned management, we decided to switch his AED to lamotrigine based on our clinical observations of cognitive benefit of lamotrigine in some ABI patients that our team had encountered. Five months after injury when the patient was in a minimally conscious state, lamotrigine was started at 25 mg daily with slow up-titration. Clear functional improvement in the patient's cognitive status was noted following the initiation of lamotrigine starting at 25 mg daily. While the patient previously had minimal verbalizations (e.g. occasionally one or two words while being with family), two weeks after starting lamotrigine (on 50 mg daily) he was able to produce a short sentence, recognize and verbally indicate when he needed to use the urinal, and initiate a question (e.g. asking for water). At that point, his speech language pathologist (SLP) started a trial of oral intake, and by the fourth week (on lamotrigine 50 mg BID) the SLP documented that he was improving in all areas of intervention and able to participate in a fulsome rehabilitation program. Visual tracking had improved as well as right arm motor function, and he could respond to his name. His cognitive function continued to improve, and by the fifth week (lamotrigine 50 mg BID) he could state his birth month and day correctly, and sometimes even location and season. At that time, he had achieved RLACS Level VI, being able to consistently follow simple commands, retain learning for familiar tasks he performed pre-injury, and demonstrate increased awareness of self, situation, and environment. Lamotrigine was gradually titrated up to 200 mg BID over thirteen weeks in total. Six weeks after the initiation of lamotrigine, we started to taper levetiracetam, which did not cause setbacks to his functional progress. Similarly, the venlafaxine was tapered off by the 30th week, which also did not negatively affect his functional progress.

One complication that occurred during his lamotrigine trial was VP shunt malfunction, which was associated with fatigue, agitation and verbal aggression, but without loss of his cognitive gains. Neurosurgery revised his shunt through the removal of the previous medium pressure Codman Valve and replacement with a programmable Codman Valve set at 80mmH_2O. However, his behavior persisted after the shunt revision. In an attempt to determine whether lamotrigine was contributing to his behavior, his dose was decreased from 200 mg BID to 150 mg BID; however, this led to drowsiness and a reduced responsiveness. As such, lamotrigine was increased back to 200 mg BID. Subsequently, risperidone 0.5 mg BID was added for his behavior. Propranolol was also trialed for his behaviour, but this was discontinued as it was either non-beneficial or worsened his aggression. He was medically optimized

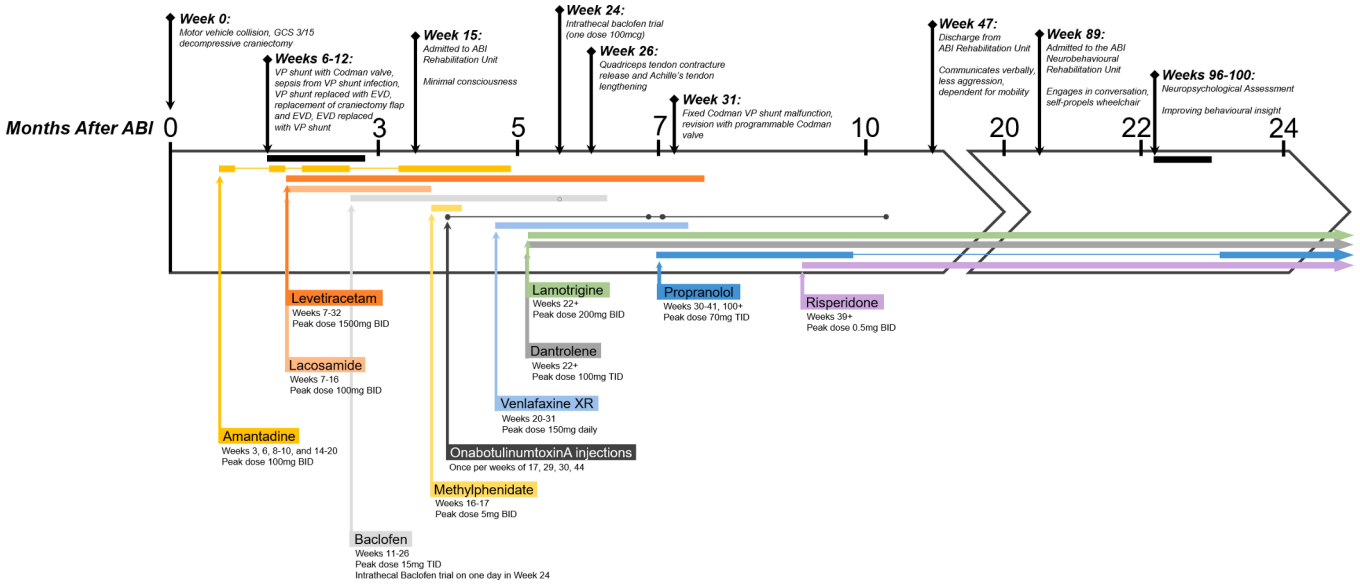

Fig. 2. Timeline summarizing pharmacological and surgical interventions and neuropsychological assessment. The major medication changes during the patient's admission in the ABI rehabilitation program are demonstrated. Colored bars represent medication duration of use. Lamotrigine was initiated approximately 5 months after injury and was gradually titrated up to 200 mg BID over thirteen weeks in total. Levetiracetam 1500 mg BID was used for seizure prophylaxis before being tapered off during lamotrigine up-titration. The patient was on a tapering dose of lacosamide 25 mg BID for 1 week before discontinuation in the beginning of his stay in the rehabilitation program. Amantadine 50 mg BID was used at the time of his admission to the rehabilitation program, and the increase of amantadine to l00mg BID led to probable seizure activities; therefore, it was discontinued. Methylphenidate was trialed with a maximum dose of 5 mg BID but was discontinued following his increased symptoms of dysautonomia. Venlafaxine was trialed with a dose up to 150 mg daily over 2 months before being discontinued. Baclofen 15 mg TID was used for spasticity before being switched to dantrolene 100 mg TID. Propranolol was trialed for behavior that was followed by risperidone later during his stay in the rehabilitation program, and risperidone remained at 0.5 mg BID.

before being discharged to complex continuing care, at which point he was able to communicate verbally, follow simple instructions, initiate bowel movements, and display less agitation and aggression. Physically, he was still dependent for mobility, but showed greater motor control of his right upper extremity with some participation in basic components of activities of daily living.

Following discharge, he continued to make functional progress while remaining on lamotrigine 200 mg BID. Twenty months after injury he was admitted to the neurobehavioral unit for a comprehensive assessment and rehabilitation. At that time, he was able to engage in conversation, voluntarily move both arms and self-propel his wheelchair. A neuropsychological assessment was completed between 22 and 23 months post-injury which indicated a DSM-5 diagnosis of Major Neurocognitive Disorder due to traumatic brain injury, with behavioural disturbance (affective lability). He had relative strengths within the verbal domain including vocabulary, verbal fluency and immediate memory for simple verbal information as well as emotionally salient information (while this is typical for all individuals, it appeared more drastic in light of his lower memory capacity). He continued to have significant cognitive deficits in attention, processing speed, working memory, executive functioning, and emotional regulation as well as left homonymous visual field loss. Behaviorally, he was generally positive although he continued to have emotional outbursts when overwhelmed or frustrated. In general, the patient had limited insight into his difficulties, although there were signs of improvement in his level of insight over the course of this admission. He gradually became faster at independently recognizing his outbursts as inappropriate and would apologize without being prompted. In addition, over time he was able to learn the types of responses that he should inhibit and was able to successfully do so in some situations. Physically, by the end of this admission he was able to complete pivot transfers and ambulate short-distances with a rollator walker and minimal assistance

The patient's timeline since his brain injury is summarized in Fig. 2.

3. Discussion and conclusion

In summary, we observed a striking and relatively rapid response to lamotrigine in this patient with severe TBI when he appeared to have reached a plateau in cognitive function five months after injury. Later decrease of the dose of lamotrigine in an attempt to reduce his inappropriate behavior was associated with worsened cognitive status. Prior to the lamotrigine trial, he was refractory to other neuro-stimulants.

To our knowledge, only one case study of lamotrigine on cognitive status for patients with severe ABI exists, in which the authors reported 13 patients that benefited cognitively from the switch of AEDs (phenobarbital, phenytoin and/or carbamazepine) to lamotrigine, and demonstrated improved functional outcomes in rehabilitation, as more of these patients were able to be discharged to the community rather than to a nursing home [17]. The replaced AEDs in their study are known to have worse cognitive adverse effects than lamotrigine, levetiracetam and other newer medications [1]. While the clinical improvement of their patients could be explained, at least partially, by less adverse effects of lamotrigine compared to those older AEDs, our patient was using levetiracetam, which has no significantly negative effect on cognition [1]. Interestingly, our patient started to respond to lamotrigine even before levetiracetam was tapered, with significant improvement in terms of his level of arousal and functional abilities. Therefore, this case report serves as more substantive evidence that lamotrigine may be cognitively beneficial for patients with severe ABI.

Another question is whether lamotrigine provided a better control of seizure activity and thus led to improved cognitive status, for which Showalter and Kimmel (2000) did not provide an answer in their study. As discussed earlier, our patient was using high dose levetiracetam and had two EEG studies that did not detect epileptiform abnormality shortly before his admission to the rehabilitation unit. Thus, non-convulsive status epilepticus was ruled out as the cause of his low level of cognition, although occasional clinical or subclinical seizures could not be excluded. The neurostimulant amantadine could have caused focal impaired awareness seizures that manifested as zoning out episodes with epileptiform findings on EEG, resulting in a reduced level of functioning. Discontinuation of amantadine eliminated the episodic zoning out and led to a gradual return to his functional baseline, which preceded the lamotrigine trial. Later on, levetiracetam was tapered off during the time that lamotrigine was titrated up, and did not lead to any setbacks of his cognitive progress. Taken together, though it cannot be completely excluded, we believe that his low cognitive status prior to lamotrigine use was less likely to be predominantly due to uncontrolled seizures, and thus also less likely to have specifically been only the anti-epileptic effects of lamotrigine that allowed the patient to improve his functioning.

In contrast to its widely accepted antiepileptic and mood stabilising properties, the cognitive effect of lamotrigine has been minimally explored [14]. In patients with bipolar disorder, lamotrigine was observed to improve their working memory, verbal memory and executive function [7,13], and enhance cortical function within neural circuits involved in working memory and emotional processing on functional MRI [5]. Moreover, lamotrigine was shown to slightly improve attentional processes in patients with focal epilepsy based on EEG data [9]. Interestingly, healthy adults using lamotrigine showed statistically better performance on reading speed on neuropsychological testing compared to that in a drug-free condition [10]. In addition, the protective effects of lamotrigine on cognition after cerebral ischemia was demonstrated in an animal study, possibly via inhibition of β-amyloid accumulation and tau hyperphosphorylation in the hippocampus [6]. The current case report adds evidence towards the potential cognition-enhancing effect of lamotrigine in patients with severe ABI.

The mechanism of action of lamotrigine during in vitro pharmacological studies demonstrated its properties of inhibiting voltage-gated sodium and calcium channels, thereby modulating presynaptic transmission of glutamate [13,14]. Further research is warranted to clarify the mechanism underlying the observed potential beneficial effect of lamotrigine on cognition.

There is one case report of lamotrigine leading to a decrease in aggression and agitation in a patient with severe TBI [12], which is notably in contrast to the increase in aggression noted in our patient when he was improving in cognitive status. Of note, the patient in that case had presented with behavioral disturbance before the use of lamotrigine, whereas our patient was in a minimally conscious state prior to the trial of lamotrigine. Thus, our patient's disinhibited behavior with verbal aggression was likely a part of the natural recovery from severe brain injury rather than the adverse effects of lamotrigine.

A possible confounding factor and limitation of this study was the switch of baclofen to dantrolene for spasticity management, which may have slightly, if any, helped his overall functional improvement, given baclofen's possible adverse effects including proconvulsive action and dantrolene's possible protective properties. That being said, the patient continued to improve after baclofen (peak dose 15 mg TID) was discontinued, and dantrolene's potential cognitive effect has only been demonstrated in animal models with inconsistent reports [8]. Similarly, he was trialled with intrathecal baclofen injection (100mcg) on the same day that he began saying sentences, but as he had no significant improvement in spasticity with this, intrathecal baclofen pump was not considered. Neither did that intrathecal baclofen administration worsen nor its withdrawal improve his cognition acutely, making baclofen's taper less likely to be the cause for his improvement. Given that all of the medication changes and their potential confounding effects have been taken into consideration as discussed above, lamotrigine appears to be the major cause of our patient's improvement in cognitive status. However, it is difficult to generalize these findings to the ABI population. First, the mechanism, location, and severity of brain injury vary from patient to patient. Second, complications following brain injury also affect functional outcome. Third, most patients with severe brain injury require medication to manage multiple symptoms and

complications such as sleep disturbance, spasticity and pain, all of which may further impact cognitive functioning. As a result, all of these contributing factors need to be taken into account when considering the generalizability of these findings.

In conclusion, this case study indicates that lamotrigine may be a useful medical therapy in patients with severe ABI, particularly for those requiring seizure prophylaxis. Lamotrigine appears to have potential cognitive benefits independent of its antiepileptic properties. Given the sparse evidence in the area, this case study highlights the need for future research that focuses on neuropharmacology for severe ABI populations where lamotrigine may be a viable option.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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