Is bupropion useful in the treatment of post-stroke thalamic apathy? A case report and considerations

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Summary

Post-stroke apathy is considered to be one of the clinical consequences of lesions affecting the structures of the prefrontal cortex, basal ganglia, thalamus and limbic system. However, there is no current consensus on the treatment of post-stroke apathy, which mainly depends on the underlying etiology and comorbidities. A 62-year-old man, affected by hemorrhagic stroke in the left thalamus, presented with mood depression, anhedonia, hyporexia and marked apathy. The patient underwent clinical evaluation before and after receiving two different pharmacological therapies: escitalopram and bupropion. Only after treatment with the latter drug did the patient show changes: high motivation and willingness to pursue activities, greater interest in the external environment and social life activities, and an overall reduction of apathy. On the basis of our observations in this case, we hypothesize that the thalamic lesion resulted in disconnection of the fronto-striatal-thalamic circuits, and that loss of the dopaminergic striatal innervation caused the patient’s apathetic state. The resolution of the apathetic disorder may be attributable to the action of the dopaminergic drug bupropion on the mesocortical pathway.

KEY WORDS: antidepressants, apathy, bupropion, thalamic stroke.

Introduction

Post-stroke cognitive and behavioral symptoms are widely documented and depend on the type of stroke and the area of the brain affected. The most significant neuropsychiatric symptoms after stroke are depression (61%), irritability (33%), eating disturbances (33%), agitation (28%), anxiety (23%) and apathy (27%) (Sacco et al., 2013). Apathy is commonly defined as loss or reduction of motivation, emotion, interest, concern; it manifests itself as a lack of pleasure in usual interests and poor engagement with others (Sande et al., 2016). For this reason, it is often misdiagnosed as a mood disorder. In clinical practice, it has received increasing attention because of its effects on emotion, behavior and cognitive functions (Caeiro et al., 2012). Apathy, in fact, is present in various medical conditions (HIV, dementia, Parkinson’s disease and stroke) and different psychiatric disorders; in particular, it is a frequent neuropsychiatric disturbance in acute stroke, being found in 38.3% of patients (Caeiro et al., 2012). Literature evidence shows that apathy in post-stroke subjects is often associated with depression and cognitive dysfunctions, even though it may occur independently of both these conditions (Jorge et al., 2010). The presence of apathy has been consistently associated with greater functional decline (Jorge et al., 2010). After a thalamic stroke it manifests itself as poor emotional response and indifference (Sande et al., 2016), which can result in misdiagnosis and no appropriate treatment. Growing evidence indicates that psychostimulants, dopaminergics and cholinesterase inhibitors may be effective in reducing this dysfunction (Corcoran et al., 2004; Wongpakaran et al., 2006; Padala et al., 2007; Toyoda et al., 2011; Yuen et al., 2014; Lin et al., 2016; Gelderblom et al., 2017). However, there is no current consensus on the treatment of apathy, which mainly depends on the underlying etiology and comorbidities. Herein, we describe the effect of two different antidepressants on amotivational syndrome in a post-thalamic stroke patient.

Case description

A 62-year-old man affected by hemorrhagic stroke involving the left thalamic region was admitted to the Neurorehabilitation Unit of IRCCS Centro Neurolesi “Bonino Pulejo”, Messina, in February 2016, to undergo intensive rehabilitation training. Neurological examination showed a moderate to severe right hemiparesis with hyposthesia and a marked reduction of independence (Barthel Index 35/100); on cognitive evaluation, he presented reduced attentional processes, with severely impaired flow of speech and thought abilities. There were no other cognitive changes (Montreal Cognitive Assessment score = 25/30). He also displayed depressive symptoms and a marked apathetic syndrome consisting of a significant reduction of motivation and of goal-di-
rected behavior, a loss of emotional response and initiative, decreased interaction with his environment, and a reduced interest in his social life. He spent eight months at our institute receiving physiotherapy, robot assisted physical therapy and psychological support, which resulted in considerably improved motor functions. During this period, he underwent two different pharmacological therapies for his amotivational syndrome and depressive symptoms. For three months, he received the serotoninergic antidepressant escitalopram (20 mg/day), which led to a mild improvement in mood. After one month during which he received no treatment, the patient was then treated with bupropion (150 mg/day) for a further three months. We administered a specific clinical and psychometric battery to evaluate behavioral and mood changes before and after each pharmacological treatment. This battery consisted of the following tools: the Montreal Cognitive Assessment (Nasreddine et al., 2005) to assess global cognitive performances; the Barthel Index (Mahoney and Barthel, 1965) to measure functional status and autonomy in activities of daily living; the Beck Depression Inventory II (Beck et al., 1961) and the Hamilton Depression Scale (HAM-D) (Hamilton, 1960) to evaluate mood; the Apathy Evaluation Scale (AES) (Marin et al., 1991) to assess apathy symptoms, and the Toronto Alexithymia Scale (TAS-20) (Bagby et al., 1994) to measure awareness of emotions. The reliable change index (RCI) is used to evaluate whether or not a change in an individual’s score — in this case before (T0, T2) vs after (T1, T3) treatment with escitalopram and bupropion, respectively — is statistically significant (based on how reliable the measure is). RCI is defined as the change in an individual’s score divided by the standard error of the difference (SEdiff) for the test being used. The boundary value for statistical significance within the RCI is ≥ 1.96 (1.96 equates with the 95% confidence interval) (De Luca et al., 2018). As shown in Table I, at the end of the first pharmacological treatment, i.e. with the selective serotonin reuptake inhibitor (SSRI) escitalopram (T1), the patient presented a mild improvement in mood compared with the initial situation (T0), but did not manifest significant behavioral improvements (AES = T0:18, T1:18; TAS-20 = T0:73; T1:73; HAM-D = T0:10, T1:9). Following treatment with bupropion (T3), the patient showed, compared with the situation before the treatment (T2), high motivation and willingness to pursue activities, greater interest in the external environment and social life activities, and an overall reduction of apathy. Moreover, he showed an improvement of mood and increased awareness of his emotions (AES = T2:18/72, T3:48/72; TAS-20 = T2:73/100, T3:60/100; HAM-D = T2:29/25, T3:6/25). Notably, the improvement of motivation and mood benefited his cognitive and motor rehabilitation.

### Discussion

The thalamus is a central relay station that integrates different afferent impulses and transmits information from the cerebellum, brain stem and basal ganglia to the cortex. The prevalence of thalamic hemorrhage ranges from 6 to 25% of intracerebral hemorrhages (Angelelli et al., 2004). Vascular lesions affecting the thalamus may cause a variety of clinical symptoms including cognitive and behavioral deficits (Van der Werf et al., 2000; Schmahmann, 2003; Tokgoz et al., 2013). The patient reported in this case study presented a post-stroke thalamic lesion with depressive symptoms and a marked apathetic syndrome, in line with previous studies that demonstrated this association (Yuen et al., 2014). Thalamic apathy is a complex reality characterized by amotivation, inactivity and deficits in the emotional, cognitive and behavioral dimensions associated with depression (Yuen et al., 2014). In recent years, much research has focused on the association between behavioral changes and thalamic lesion sites. In particular, recent evidence indicates that behavioral patterns can be defined on the basis of lesion localization in the four main arterial thalamic territories.

### Table I - Psychometric and clinical scores before (T0, T2) and after (T1, T3) escitalopram and bupropion treatment respectively.

<table>
<thead>
<tr>
<th>Escitalopram</th>
<th>Psychometric and Clinical Battery</th>
<th>T0</th>
<th>T1</th>
<th>RCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barthel Index</td>
<td>35</td>
<td>50</td>
<td></td>
<td>2.0</td>
</tr>
<tr>
<td>MoCA</td>
<td>25</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI II</td>
<td>26</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AES</td>
<td>18</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAS-20</td>
<td>73</td>
<td>73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-D</td>
<td>15</td>
<td>11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bupropion</th>
<th>Psychometric and Clinical Battery</th>
<th>T2</th>
<th>T3</th>
<th>RCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barthel Index</td>
<td>55</td>
<td>75</td>
<td></td>
<td>2.3</td>
</tr>
<tr>
<td>MoCA</td>
<td>26</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI II</td>
<td>24</td>
<td>5</td>
<td></td>
<td>3.5</td>
</tr>
<tr>
<td>AES</td>
<td>18</td>
<td>48</td>
<td></td>
<td>3.9</td>
</tr>
<tr>
<td>TAS-20</td>
<td>73</td>
<td>60</td>
<td></td>
<td>1.9</td>
</tr>
<tr>
<td>HAM-D</td>
<td>13</td>
<td>4</td>
<td></td>
<td>2.7</td>
</tr>
</tbody>
</table>

Abbreviations: MoCA=Montreal Cognitive Assessment; BDI II=Beck Depression Inventory II; AES=Apathy Evaluation Scale; TAS-20=Toronto Alexithymia Scale; HAM-D=Hamilton Depression Scale; RCI=reliable change index.
americ territories. Accordingly, apathy, amnesia, perseverations and superimposition of unrelated information are believed to be related mainly to anterior lesions (Carrera and Bogousslavsky, 2006). However, other Authors associate apathy in acute stroke with left or bilateral thalamic lesions (Kang and Kim, 2008; Caeiro et al., 2012). A recent review by Moretti and Signori (2016) shows that bilateral lesions of the internal portion of the globus palidus, lesions of the dorsomedial portion of the prefrontal cortex, or bilateral paramedian thalamic lesions are associated with deficit of auto-activation (Moretti and Signori, 2016). In particular, they demonstrate that many patients with cerebrovascular accidents may develop an apathy syndrome known as “post-stroke apathy” and that this syndrome is more frequently present in patients with right-sided lesions in general, and specifically so in those with white matter hyperintensities within the right fronto-subcortical circuit (Moretti and Signori, 2016). Furthermore, other Authors have investigated the “apathy-related sub-network” with diffusion tensor imaging connectivity analysis, and suggested a correlation of apathy symptoms with the right precuneus, the supramarginal gyrus, the right paracentral lobule, the right thalamus, the right superior temporal gyrus, bilateral insula, right putamen, hippocampus and posterior cingulum (Yang et al., 2015).

While research on the localization of the lesions and on behavioral patterns after thalamic stroke is advancing, the treatment of apathy continues to be poorly understood, with very poor empirical data available for guidance. Several agents have been used to treat apathy with divergent results; they include amantadine, amphetamine, bromocriptine, bupropion and methylphenidate. Some studies suggest a role for noradrenergic and dopaminergic systems in the neurobiology of apathy (Padala et al., 2007), although Wongpakaran et al. (2006) recommend caution in using SSRIs in depressed elderly persons as they may worsen apathy. Escitalopram had almost no effect in our patient. Moreover, an improvement of apathy and cognitive functions in post-stroke patients has been shown after cilostazol treatment (Toyoda et al., 2011).

In recent years, some studies have described the use of bupropion, a dopamine and norepinephrine reuptake inhibitor, in the treatment of apathy following various etiologies. Lin et al. (2016) demonstrated an improvement in the apathetic syndrome in a patient with a behavioral variant of frontotemporal dementia after a 10-month period of bupropion treatment. By contrast, a multicenter, randomized, double-blind, placebo-controlled, prospective crossover trial by Gelderblom et al. (2017) showed no influence of bupropion on the severity of apathy, measured with the AES (Marin et al., 1991), in non-depressed patients with Huntington’s disease. Corcoran et al. (2004) described three patients with amotivational syndromes in which bupropion led to a behavioral improvement, suggesting that the effectiveness of the drug might due to its dopaminergic properties. Previous studies have, in fact, supported the idea that compared with other antidepressants, bupropion may increase intrasynaptic dopaminergic concentrations, because it has weak and relatively selective effects on inhibition of dopamine reuptake into neuronal terminals (Ascher et al., 1995). Therefore, one may argue that bupropion may be useful for the treatment of apathy, also because dopamine is a key neurotransmitter in reward/motivation pathways in the brain. Based on the evidence from our case, we can hypothesize that his thalamic lesion caused disconnection of the fronto-striatal-thalamic circuits, which are more frequently lesioned in patients with “post-stroke apathy” (Moretti and Signori, 2016), with loss of the dopaminergic striatal innervation. We speculate that these circuits, designed for processing gratifying responses, may have caused the apathetic state in this patient. Thus, the improvement of the apathetic disorder in this patient may have been due to the action of bupropion on dopaminergic mesocortical pathways.

In conclusion, this case report is intended to highlight how bupropion may be effective for the treatment of apathetic symptoms of organic origin, including hemorrhagic stroke. Whilst previous studies focused on the treatment of apathetic syndrome with various etiologies (such as the behavioral variant of frontotemporal dementia, Huntington’s disease, stroke in subcortical regions), this is the first time that bupropion has been used in the treatment of apathy after a thalamic stroke lesion. Given that our findings come from a single case study and are therefore insufficient to definitively demonstrate the efficacy of bupropion in post-stroke apathy, further studies on a larger and homogeneous group of patients should be encouraged, in order to confirm this promising result.

References


