

## Cholinesterase Inhibitors as a Treatment for Post-Stroke Anxiety: A Case Report

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### Background

Neuropsychiatric symptoms, such as depression, anxiety, and cognitive impairment, are common following a stroke, with depression being the most common symptom recognized [1]. In contrast to the relatively large number of studies on post-stroke depression, anxiety disorders in patients with stroke has received little attention. Yet, the prevalence of anxiety disorders with stroke is estimated between 18 and 29% [2-4]. Once present, anxiety symptoms appear to have a fairly persistent course with a strong negative impact on quality of life, impairment in activities of daily living, and social functioning [4]. Despite this, a Cochrane review reveals there are even fewer studies specifically examining the treatment of post-stroke anxiety, often leaving clinicians to extrapolate evidence from the treatment of anxiety disorders in general psychiatric populations [5].

The etiology of the development of post-stroke anxiety remains incompletely understood and is likely complex and multifactorial. However, links between anxiety and deficits cognitive function have been proposed, with reports of a high prevalence of anxiety among those diagnosed with mild cognitive impairment [6, 7]. Deficits in attention and executive functioning have been demonstrated post-stroke even in those with vascular cognitive impairment without dementia and was found to result in significant impairment in daily functioning [8]. An infarct, particularly if it is located in a strategic location, may disrupt cholinergic pathways leading to a decrease in cholinergic transmission. One study describes the proposal of a central cholinergic deficiency syndrome which is clinically characterized by loss of attention, impaired concentration, and the reduced ability to detect and select relevant stimuli, which in turn results in restlessness and anxiety [9]. A further proposed conceptualization of anxiety in those with cognitive impairments suggests that perception and appraisal of an individual's situation and environment is significantly affected by that individual's cognitive status [10]. Therefore, individuals with cognitive impairment may have an increased tendency to inaccurately interpret their environment, leading in turn, to an increase in cognitive distortions. In addition, in these individuals, cognitions relating to unpredictability and a lack of control may develop, leading to feelings of anxious apprehension. A few studies have, therefore, examined the use acetylcholinesterase inhibitors on the neuropsychiatric symptoms associated with cognitive impairment and found that anxiety is among one of

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the behavioural domains that seems to most consistently show improvement [11, 12]. However, this evidence consists mostly of open label trials and case reports.

### Case summary

Mr. DM is a 62 year old, right-handed, Caucasian male who presented to the neuropsychiatry clinic with symptoms of depression and anxiety in the context of an anterior thalamic stroke suffered three years prior to his referral to the clinic. His depressive symptoms responded to desvenlafaxine initiated by his family physician. However, his main concerns at presentation were a marked decrease in concentration since his stroke as well as an increased vulnerability to stress. He described feeling mentally fatigued and easily overwhelmed when tasks he was presented with were challenging for him. He also reported an increase in muscle tension and, in fact, during the interview, he was repeatedly closing his eyes with some tension in his face and grimacing, trying to concentrate. He also appeared to be holding his shoulders in a contracted manner. There was history of other anxiety disorders like OCD, social

phobia, agoraphobia or panic attacks. He denied any symptoms in keeping with mania or psychosis and there was no history of substance misuse.

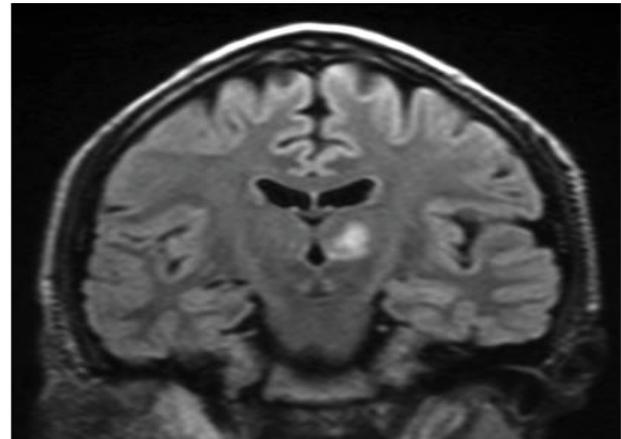
Prior to the stroke, he denied any history of psychiatric illness. He denied any major stressors in his life, describing that he was quite happy with his marriage, family life and work life and he felt quite supported. He had significant losses from 2009 to 2010, but he coped with those very well and he was relatively stable until the stroke.

He went back to work on a modified schedule part-time with a different level of demands where he was supported by a co-worker and asked only to do minor tasks. Prior to this, his work included significant multi-tasking. He described being on the phone while he was calculating and typing, responding to different stimuli at the same time, something which he felt that he not be able to do at this point. Despite having completely normal cognitive scores on screening tools like the mini-mental status examination (MMSE) [13] and Montreal Cognitive Assessment Test (MoCA) [14], we felt that Mr. DM was clearly describing difficulties in his ability to process information and we, therefore, went through a detailed inquiry about his cognitive function with the help of the Neuropsychologist associated with our clinic. He was able to give a detailed account of his day-to-day function and he did not appear to have any issue with retaining information. He reported becoming quite overwhelmed when there was a change in plans and he needed to sort out steps required to correct the directions to suit the new plans. On his own, he would find it difficult to make any decisions. His language seemed intact in comprehension and expression. We narrowed down that his primary difficulty was with information processing and handling multiple stimuli which leads to fatigue with tension headaches and a feeling of being overwhelmed. As a result of these issues, he felt more and more anxious within weeks of going back to work and few months later started feeling low in his mood.

A MRI performed shortly after his stroke revealed a normal appearance throughout with a relatively preserved hippocampal volume but unfortunately, there was evidence of a left anterior thalamic lacunar stroke, which was significant in size and was evident in few cuts (Figure 1). He did not have any other strokes or injury and there was no other white matter abnormality beyond the stroke in the thalamus.

Aside from the stroke, thought to be due to paradoxical embolism through the patent foramen ovale, Mr. DM was otherwise healthy. He had no vascular stroke risk factors on history. He received stroke prevention care from neurology and was prescribed Aspirin 81 mg as a stroke prevention strategy. There was no report of clinical evidence of stroke subsequent to the initial one and therefore no further brain imaging was done.

On initial mental status examination, Mr. DM was appropriate and pleasant. There was no focal neurological finding and he displayed a full gaze. His facial grimacing was not an involuntary movement, but rather an attempt to focus and tried to shut down stimuli to be able to think about the question he was asked. He displayed a dysthymic affect talking about how much he lost and how much he is trying to get better. He was able to appropriately



**Figure 1** A FLAIR Coronal Section from MRI of the Brain Showing Evidence of Left Anterior Thalamic Stroke. No Other Abnormalities Identified on Other Section and MRI Sequences. (FLAIR= Fluid-Attenuated Inversion Recover, the Image is Per Radiology Convention Left is Right Side of the Image).

contain his tears and was quite hopeful that he will continue to heal. We used Patient Health Questionnaire-9 as a basis for our inquiry about symptoms of depression, patient scored total of 5/27 [15]. Items that were positive are related to “loss of interest and pleasure in doing things” several days over the last 2 weeks, “feeling down, depressed or hopeless” several days over the last 2 weeks, “feeling tired or having low energy” several days over the last 2 weeks, “Trouble concentrating on things, such as reading the newspaper or watching television” more than half the days. On Generalized Anxiety Disorders-7 scale patient would score 9/21 [16]. Positive items were Feeling nervous, anxious, or on edge more than half the days over the last 2 weeks, Not being able to stop or control worrying several days over the last 2 weeks, Trouble relaxing more than half the days, Being so restless that it's hard to sit still several days over the last 2 weeks, Becoming easily annoyed or irritable more than half the days, Feeling afraid as if something awful might happen several days over the last 2 weeks.

## Management and outcome

On initial impression, we felt that Mr. DM had secondary anxiety and depression due to stroke and possible vascular cognitive impairment induced by his left anterior thalamic stroke. Given that his anxiety appeared to be related to his difficulties in concentration and information processing in environments such as his workplace that presents multiple stimuli simultaneously, and due to the strategic location of his stroke where cholinergic transmission is likely involved [17], we suggested the option of trying to enhance his information processing by using cholinesterase inhibitors. We, therefore, asked him to continue his Desvenlafaxine 50 mg daily and added donepezil, starting carefully at 2.5 mg in the morning with food. After two weeks at 2.5 mg daily, we recommended that the dose be increased to 5 mg daily.

Mr. DM was seen in follow-up three months after his initial

assessment and described that the donepezil had a significant effect on his mood, cognition, and anxiety. He reported feeling back to his baseline level of functioning, including in the workplace, stating, "I have my life back". His wife noted that she saw a big improvement in his anxiety and cognition and that this was noted by other people known to him, including his coworkers. He informed us that he was no longer having headaches related to his anxiety and his mood was described as being quite good. He had complete resolution of symptoms on the PHQ-9 and GAD-7. He denied any side effects or concerns regarding his medications and wanted to remain on the combination of desvenlafaxine and donepezil at the current doses.

## Discussion and conclusion

Neuropsychiatric symptoms as a consequence of stroke are common and important considerations in the management of cerebrovascular disease. While increased attention is being paid to the detection and management of post-stroke depression, anxiety symptoms which are often comorbid with depression, have received little focus in the literature. However, the duration of depressive symptoms and the severity of impairment in social functioning and ADLs were all found to be influenced by presence of comorbid anxiety and depression [4].

The etiology of post-stroke anxiety is still not completely understood, but in the case presented above, we hypothesized that the anxiety was driven by the strategic left thalamic stroke that likely disrupted the cholinergic transmission to the cortex via the thalamus and resulted in difficulty with information processing. We know that certain areas of the thalamus, such as the anterior thalamus and the dorso-medial nucleus of the thalamus play

important roles in information triaging from sensory input to the prefrontal cortex, which is why information-processing difficulties are quite common with such a lesion [18]. It is very common to see anxiety in the context of cognitive disorders [6, 7]. Although we cannot rule out the possibility of anxiety being also triggered directly by the disruption of serotonergic pathways, his response to donepezil suggest a role of cholinergic transmission in this syndrome. To our knowledge, this is the first published report of post-stroke anxiety improving with an acetylcholinesterase inhibitors. They have been used in Alzheimer's disease to compensate for a cholinergic deficit and have been shown to improve anxiety symptoms in those with dementia [11, 12]. Thus, it seems plausible that acetylcholinesterase inhibitors may be a possible treatment avenue to further explore in some individuals with post-stroke anxiety related to cognitive impairment. In our case, screening cognitive tools including MMSE and MoCA test were completely normal but functional inquiry by a licensed neuropsychologist with the patient and his spouse identified difficulties in information processing in real-life. These difficulties were resolved with cholinergic therapy. More detailed neuropsychological profiling of cognitive function would help delineate the relationship between different cognitive domains and anxiety symptoms but that was beyond the scope of routine clinical practice.

It is important for physicians to be aware of and enquire about the range of neuropsychiatric symptoms that may result following a stroke. More research is needed to explore the pathophysiology underlying the development of post-stroke anxiety, as well as treatments specific to this population.

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