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Usefulness of vortioxetine noted in depression secondary to hypoxic brain injury and residual cognitive deficits

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***Abstract*:** We report on our experience of treating depression secondary to hypoxic brain injury with the antidepressant vortioxetine to share in the growing body of evidence. Our patient was referred to a community mental health team with depression, amotivation and memory difficulties following a myocardial infarction and cardiac arrest 2 years prior. Regardless of motor recovery, major cognitive deficits remained; however, neurorehabilitation was impossible due to severe depression. We tried vortioxetine in the light of two failed antidepressants and saw a remarkable improvement in mood, motivation and engagement.

Keywords: vortioxetine, hypoxic (anoxic) brain injury, depression, cognition

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Introduction

Sudden cardiac arrest is a serious condition in which the resulting circulatory failure can lead to hypoxic (anoxic) brain injury. Survivors with subsequent anoxic brain injury experience more psychosocial difficulties, which could be attributed to neuropsychological, social and psychological factors.[1] With much improvement in cardiopulmonary mortality, we are seeing a greater population surviving with the said effects and there is little concrete treatment. In a patient referred to a community mental health team (CMHT) with depression, amotivation and memory difficulties following a myocardial infarction and cardiac arrest 2 years prior, we tried vortioxetine in the light of two failed antidepressants.

Case outline

Mr. X, a 57-year-old male, was referred to the CMHT in 2018 by his general practitioner (GP) for depression, amotivation, memory difficulties (anterograde and retrograde amnesia) with short-term memory difficulties following a cardiac arrest 2 years ago.

Chain of events

Mr. X was abroad having taken a long, emergency flight in 2016 to visit his sick mother. He was found collapsed at his accommodation and a 15-min delay in accessing medical help was noted. He was given cardiopulmonary resuscitation, two direct current cardioversion shocks and thrombolysis for an anterior wall myocardial infarction. He was placed on mechanical ventilation for 2 days and spent 1 month in the intensive care unit. Initially, he was paraplegic and unable to speak but made a promising recovery of motor skills and was returned to the United Kingdom (UK) after several months.

Severe cognitive deficits were noted, necessitating 24-h supervision. Mr. X was referred to neuropsychiatry inpatient where he was admitted for 3 months. citalopram was tried, with some initial benefit, the dose titrated to 40 mg. modafinil also was tried but discontinued because it increased confusion.

Mr. X was referred for specialist neurorehabilitation in a vocational rehabilitation programme, and to Headway for his severe cognitive deficits. He struggled to adjust to the change in life and was noted to be severely depressed; hence, rehabilitation could not be initiated. The antidepressant was changed to mirtazapine and he was discharged to the GP with advice to seek support on treating his depression. A minimal support care package was provided, which he did not use.

Patient background and premorbid functioning

Mr. X is a qualified doctor. Prior to his cardiac arrest he was said to be very active and enjoyed a wide range of outdoor activities as well maintaining an active family and social life. Mr. X has type 2 diabetes mellitus (diet control). He was previously only on aspirin 75 mg, bisoprolol 2.5 mg, lansoprazole 30 mg and ezetimibe 10 mg.

Our Assessment

When we saw Mr. X in CMHT he described his mood as 'very depressed'. A collateral history from his wife revealed that he had lost interest in TV, books and his friends. She described him as a 'changed person'. Mr. X would struggle to find words at times during conversation. However, he would often cope because of his excellent premorbid vocabulary. He was spending an excessive amount of time confining himself to his bed but reported not sleeping. He was able to make a cup of tea for himself if the ingredients were laid out on the counter but was increasingly avoiding participating in any household work. According to his wife, Mr. X struggled with memory and could not remember local routes, needing someone to accompany him outside. No psychotic features were noted, and Mr. X denied thoughts to harm himself or others. Mr. X was provided a high level of support from the family with some carer input.

Investigations

1. Magnetic resonance imaging Head (March 2017 and April 2018): mild atrophy of frontal, parietal and temporal lobes was visualised, which was in excess to the patient's age.
2. Addenbrooke's Cognitive Examination (ACE III) total score 60/100. Attention = 14/18, Memory = 9/26, Fluency = 4/14, Language = 17/26, Visuospatial = 16/16. Preservation of mild degree and difficulty in retaining information for the tasks was noted.
3. Activity of daily living report from neurorehabilitation centre: Severe cognitive deficits, including higher level language difficulties and severe verbal and visual memory impairment, required supervision, with extremely limited engagement in meaningful activities and depression.
4. Blood tests showed mild thyroid dysfunction and raised cholesterol. Started on levothyroxine 50 microgram and rosuvastatin 10 mg by the GP.

Management

Pharmacological

- Having seen no effect on mood even after the maximum dose of mirtazapine, antidepressant was changed to vortioxetine. Starting with 5 mg orally in the morning after food, with the dose increased to 10 mg and subsequently to 15 mg and 20 mg. Side effects were discussed. Nausea was reported as the most common side effect. The patient reported mild nausea, which settled down after 2 weeks.

Psychological

- Treatment was delivered utilising a family therapy model, with eight support sessions provided at the patient's home.

Occupational health

- The occupational therapist (OT) lead provided one-to-one support to encourage and take Mr. X out of the house and engage in daily life. Our team also liaised with social services to enhance the social care package.

Outcome

Mr. X has shown a significant improvement in mood with vortioxetine. Remarkable changes were seen within 3 months at a dose of 15 mg wherein he was alert, motivated to attend the gym and openly discussed his low mood. This enabled him to engage in psychological therapies and to express his distress with the changes in his life. It allowed his family to understand Mr. X's difficulties and hence led to greater family support. He is also now able to participate in OT activities and venture out of his house. There was no shift in cognitive deficits and he continues to need intense support. He can manage his personal care but still needs prompting. However, he is now ready to be transferred back to the specialist neurorehabilitation unit.

Current literature

Depression and mood disorders are known secondary complications following hypoxic brain injury. In terms of pathology, Zhao *et al.* have investigated the mechanism of hypoxic brain injury and relation to mood disorders.[2] The brain is highly sensitive to oxygen concentration in arterial blood; hence, any condition that affects the airflow and or blood perfusion might alter neuronal function, leading to cell injury and death.

Spatial memory and learning deficits secondary to long term intermittent hypoxia, in conditions like obstructive sleep apnoea, are noted to be associated with an increase in oxidative stress especially in the hippocampus, which is involved in cognitions and memory. Oxidative stress, inflammation, apoptosis and excitotoxicity were implicated as primary mechanisms for hypoxic brain injury, and hence affect neuronal plasticity. The hippocampus, frontal cortex, amygdala, insula, anterior cingulate, fornix, mammillary bodies and the cerebellum, structures that are also known to be disrupted in depression, are all noted to be impaired during and after sleep-disordered breathing. Hypoxia-induced brain injury has been known to bring about changes in behaviour regulation and thinking. This is due to the changes in the prefrontal cortex, which mediates cognition as well as affection. Hypoxia disrupts the prefrontal-hippocampal networks that play a role in thinking and behaviour.[3] Studies have shown prefrontal cortex deficits present with inattention, hyperactivity and impulsiveness as well as personality changes.[2]

Another region of the brain to consider carefully is the amygdala, which has important functions in the regulation of emotions as well as learning and attention. The key components of bipolar disorder have been shown to manifest following amygdala disturbance.[4] It has been suggested that hypoxic ischemia and subsequent axonal degeneration in the amygdala might be of significance in the development of depression.[5]

Patients with sudden cardiac arrest are noted to have impairment of visual motor skills, short term visual memory, concentration and visual motor coordination. Impairment of memory trace storage and recall after delay was more prominent in patients suffering sudden cardiac arrest as compared with patients with myocardial infarction without sudden cardiac arrest or healthy controls,[6–8] emphasising that the sudden lack of oxygenated circulation and consequent hypoxic damage has greater impact.

Unfortunately, even with detailed information on the pathology there is little guidance on targeted treatments on mood disorders secondary to hypoxic injury. vortioxetine received United States Food and Drug Administration approval for the treatment of major depressive disorder in 2013. vortioxetine is classified as a selective serotonin reuptake inhibitor; however, it has a mixed multimodal function.[9,10] Vortioxetine effects serotonergic neurotransmission through a number of mechanisms. It is an antagonist at SERT (serotonin receptor) as well as at 5-HT3 and 5-HT7 receptors. It is a near full agonist at 5-HT1A receptor and a partial agonist at 5-HT1B receptor. Vortioxetine has a multimodal activity because it has three modes of action: (a) inhibition of SERT, (b) acting on G-protein-coupled receptors, and (c) inhibition of ligand gated ion channel at 5-HT3 receptor.[11] Inhibition of the 5-HT3 receptor is known to increase serotonin levels in both the frontal cortex and ventral hippocampus; subsequently, it should be noted that vortioxetine displays a particularly high affinity for SERT and 5-HT3 receptors.[12]

Hypoxia induces depression through a number of aforementioned mechanisms, which include oxidative stress and cell apoptosis, as well as the upregulation of proinflammatory cytokines such as tumour necrosis factor alpha (TNF-a) and interleukin (IL)-6. Transforming growth factor beta 1 (TGF-β1) is an anti-inflammatory cytokine with a well-documented neuroprotective profile in acute ischemia.[13]

In rat models, it was found that the TGF-β1-mediated SMAD3 signalling pathway was upregulated following the onset of ischemic stroke. It is hypothesised that expression of Bcl-2 *via* SMAD3 may prevent apoptosis of neurons following ischemic injury.[14] A recent study by Torrisi *et al.* found that in animal models treatment with fluoxetine and vortioxetine reduced the depression phenotype as well as prevented cognitive decline.[15] They found that both anti-depressants increased the level of TGF-β1 in the hippocampus. Interestingly, the study showed that vortioxetine was able to completely rescue hippocampal TGF-β1 levels at half the dose of fluoxetine, suggesting that vortioxetine may play a more potent role in harnessing the anti-inflammatory neuroprotection provided by TGF-β1.[15] It must be noted that the study examined the role of antidepressants in Alzheimer's Disease models and further studies should be conducted in animal models of cerebral ischemia to examine the efficacy of vortioxetine in hypoxia-induced depression due to increased expression of TGF-β1. Furthermore, there has been research examining the use of various antidepressants to treat depression induced by lipopolysaccharide; a recent study found that vortioxetine had a unique ability to decrease expression of pro-inflammatory

nuclear factor kappa B (NF-κB) p65 in the hippocampus and increase the expression of anti-inflammatory cytokine IL-4 in the striatum and the hypothalamus.[16]

We cannot be certain of how vortioxetine mediates cognition in depressed patients, but the combination of 5-HT3 and 5-HT7 receptor antagonism (involved in regulation of cognitive function) and TGF-β1 neuroprotection is a promising avenue for further research. In rat models, *in vitro* studies have shown increased synaptic transmission and plasticity in the hippocampus following vortioxetine use.[17]

Perhaps its success in managing depression secondary to hypoxic brain injury with Mr. X is related to the additional immunomodulatory (antioxidant and anti-inflammatory) effects.[18] Neuronal damage secondary to soluble inflammatory molecules such as cytokines, chemokines, reactive oxygen and nitrogen species is noted as a major mediator of neuronal injury in neonatal hypoxia-ischemia.[19] Cytokines play an important role in pro-inflammatory responses in depression *via* effects on the hippocampus.[20]

Implications for clinical care

The implications of our experience are pertinent with the rising success of cardiopulmonary resuscitation and a greater number of survivals with sustained periods of cerebral hypoxia. Clinicians need to be well-equipped in managing the long-term sequelae, including depression.

Vortioxetine is a relatively new antidepressant with a multimodal mechanism of action and a yet to be fully determined function on cognition. Our novel approach with Mr. X contributes towards a growing evidence base for the use of vortioxetine. As an antidepressant, its main function is not on cognition; however, there is emerging evidence on its dual affects. Furthermore, the improvement in the mood and motivation of patients can unlock the full potential of neurorehabilitation, forming a true holistic care plan.

The main query that arises from our experience is why was vortioxetine successful when two other antidepressants had failed previously? We can only hypothesise that vortioxetine had the greatest impact on increasing neurotransmitter levels and activity in areas that correlate to areas affected in hypoxic brain injury. Is this a cause and effect relationship? That is a question we would like to pose for further research: the mechanism of specificity and effectiveness of antidepressants in mood disorders secondary to hypoxic brain injury.

Conflict of interest statement

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