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Case Report and Literature Review

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The combination of citalopram and rivastigmine in the treatment of mood disorder and cognitive Impairment due to cerebrovascular disease: a case report and literature review

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Abstract

Background: Although common, mood disorder due to cerebrovascular disease is rarely diagnosed by general practitioners, despite this condition being associated with poor health outcomes and increased mortality risk in the elderly.

Methods: In this case report, we sought to characterize the clinical course of a 67-year-old man with mood symptoms associated with cerebrovascular disease, treated with a combination of the selective serotonin reuptake inhibitor (SSRI) citalopram and rivastigmine, an acetylcholinesterase inhibitor (AChEI). We then provide a brief literature review on the treatment of vascular behavioral impairment.

The patient was initially evaluated in a psychiatric outpatient clinic, accompanied He was admitted at a clinical hospital due his emotional state and to co-morbidities, when he received psychiatric, neurologic and general medical evaluations.

Results: Following a diagnosis of a mood disorder with associated cognitive symptoms, treatment was started, combining psychotherapy and citalopram, leading to a partial response. A series of adjuctive antidepressants were added, each quickly discontinued after the patient developed various adverse effects. Given both cognitive and mood residual symptoms, rivastigmine was added to citalopram, and the combination resulted marked improvement in depression, with reduction from 23 to 7 points on the Hamilton Depressive Scale (HAM-D), and improved cognition, reflected in an increase from 25 to 28 points in the Mini-Mental State Examination (MMSE) score. The patient was followed annually for six years with both clinical and cognitive evaluations, and at the end of this time he died after a stroke and brief period of significant clinical and cognitive decline. At the time of his last psychiatric evaluation, a few months prior to his death, the patient met criteria for vascular dementia.

Conclusion: In this single case report, we highlight important features of the treatment of mood disorder and cognitive due to cerebrovascular disease. A brief review of literature found studies demonstrating improvement of vascular behavioral cognitive impairment, after treatment with the combination of association of SSRIs and AChEIs. These studies point to the need for randomized controlled trials of combination treatment for this condition.

Introduction

Mood symptoms are very common in the elderly and are a frequent cause of emotional distress and decreased quality of life [1]. Depressive episodes occurring later in life are frequently related to poor treatment response and poor prognosis, the latter of which may be due to associated cognitive deficits and development of dementia in some patients [2]. The familial risk for depression declines with aging, and late-onset disorders may result from diseases whose incidence increases with the aging process, such as cerebrovascular and neurodegenerative diseases [3]. Late-onset depression is generally secondary to subtle brain-vascular changes due to atherosclerosis ("atherosclerotic depression"), with risk factors such as high blood pressure (hypertension), diabetes mellitus (DM) and dyslipidemia [4].

Recent studies reveal that severe atherosclerosis was associated with the high prevalence of mood disorder and cognitive impairment, and strongly correlated with severe coronary artery disease and aortic calcification [5]. It is important to note that the evaluation and diagnosis of depression in patients with vascular brain injury is often difficult, as these individuals may experience language or memory deficits and altered level of consciousness, limiting the patient's ability to provide a reliable self-report of and hindering the clinician's ability to establish effective communication [5].

Herein we present a follow-up to a case report that was published previously [6], of an older patient with mood symptoms that were difficult to control. The challenge with the patients was to find an optimal treatment that would bring about remission. With a six-year follow-up, we describe the clinical course for this patient and then provide a brief review of relevant literature.

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The patient and his family signed an informed consent and they are aware of this scientific publication.

Case report

The patient was a 67-year-old white man, with six and a half years of schooling, married for the second time. He was brought by his wife to an outpatient psychiatric clinic for an evaluation, who described a gradual worsening of anhedonia and irritability over the prior two years, accompanied by insomnia and decreased appetite, and what he called "job widowhood", due to retirement four years previously. The patient had experienced a prior "depressive" episode 17 years ago, after the death of his first wife, in which he experienced sadness, tearfulness and discouragement. He was prescribed tricyclic antidepressant, but because of a good response, he discontinued the medication after 30 days, ascribing his improving to emergence from a period of mourning.

The patient had a significant medical history. Twenty years prior, he was diagnosed with hypertension, rheumatic aortic valvular disease, atherosclerosis, and DM. He has a family history significant for depression and cardiovascular disease. His recent medication list included carvedilol 1.25mg/MID, glibenclamide 5mg/MID, losartan 50mg/MID, metformin 850mg/BID, simvastatin 20mg/MID, acetyl salicylic acid 100mg/MID, nitrate 20mg/MID, and furosemide 40mg/MID. Given the patient's numerous medical issues, he was admitted to a general medical inpatient service in order to comprehensively diagnose and manage his complex condition.

At this initial inpatient evaluation, he demonstrated apathy, psychomotor slowing and lack of insight, but intact consciousness, alertness and orientation (time and visual-spatial orientation). In addition, his logical reasoning and memory were preserved, and he showed no decrease of consciousness. The physical exam was largely unremarkable, and his neurological exam showed no focal signs. Laboratory tests were normal, and an electrocardiogram showed coronary insufficiency and left ventricular hypertrophy. Echocardiography showed double rheumatic aortic injury, rheumatic mitral insufficiency, and mild increase of left ventricle, but with normal systolic function.

A brain magnetic resonance imaging scan showed signs of atrophy in the right frontal and temporal lobes, with minor thinning myelin areas (Figure 1), and a right sequela of a lacunar ischemic lesion (Figure 2). Cardiac catheterization revealed significant arterial coronary injury. Due to the severity of his clinical condition, the patient underwent a heart bypass surgery and aortic valvuloplasty.

Two weeks after the surgery, because the patient continued to display significant anhedonia, he underwent a thorough clinical and laboratory evaluation to rule out post-operative systemic or metabolic events (delirium, drug reaction, pain, symptoms due to being bedridden). With a negative work-up, his symptoms were deemed to be consistent with a moderate major depressive episode. The Hamilton Depression Rating Scale (HAM-D) scored 23 points; the Mini-Mental State Examination (MMSE) scored 28 points and Cambridge Cognitive Test (CAMCOG) score was 97. The patient showed errors in copying of pentagons (he drew a pentagon with a square) and clock drawing (improper placement of numbers and incorrect time), and poor reproduction of the Rey-Osterrieth Complex Figure. Regarding daily living activities, the patient reported social isolation, abandonment of leisure activities, and decreased interest in new friendships.

Depression treatment included psychotherapy and the antidepressant citalopram, which was started at a daily dose of 10mg, and increased to 20 mg daily after one week. After eight weeks of treatment, there was partial remission of symptoms, and citalopram was increased to 40mg daily. Because of ongoing apathy, bupropion 75mg daily was added to the regimen, but then discontinued because of increased blood pressure.

Over the subsequent eight weeks, the patient was clinically stable, but still had quite significant residual depressive symptoms (irritability, anhedonia, apathy and insomnia). As a result, nortriptyline was added at a dose of 10mg daily, but the patient experienced autonomic dysfunction (bradycardia and low blood pressure), so the cardiologist strongly argued against trials of other antidepressants and in favor of continued citalopram monotherapy.

Following another 26 weeks, the patient showed mild improvement, still with residual depressive symptoms and a cognitive decline with an MMSE score of 24/30 (with errors in orientation and memory). In addition to citalopram, which was maintained at a daily dose of 40mg (with no QTc prolongation found), and taking into account the cognitive decline, treatment with rivastigmine was started at a dose of with 1.5mg twice daily/BID. This was titrated over four weeks to a dose of 6mg twice daily with the patient experiencing no significant adverse effects. At the end of the 12th week of rivastigmine treatment, the patient had a profound improvement in depressive symptoms, and most notably had a complete remission of insomnia and anhedonia. The HAM-D score was 7, and his cognition improved, reflected in an MMSE score of 27/30.

Even does not having a systematic neuropsychological test, during the months before his death, the patient presented with symptoms consistent with vascular dementia, according to his last psychiatric evaluation.

Discussion

We present the case of a 67-year-old man with mood and cognitive symptoms in the text of diabetes, hypertension and coronary heart disease. He was initially diagnosed with a major depressive episode and secondary cognitive symptoms. He was treated with citalopram augmented with a series of antidepressants, the latter causing serious adverse effects without improving symptoms.

The slight improvement in cognitive function after combination treatment with citalopram and rivastigmine that resulted in remission of mood symptoms reinforces the diagnosis of mood disorder due to cerebrovascular disease. After initial evaluation, we considered an alternate diagnosis of vascular mild cognitive impairment with associated depressive symptoms. While there was no subjective cognitive complaint, a primary cognitive disorder was high among the differential diagnosis, and as such pointed to the need for careful follow-up of the patient.

Follow-up

Due to his severe and acute valvular disease and cardiomyopathy, the patient underwent surgery. As the patient's mood symptoms remitted with combination citalopram with rivastigmine, we followed the patient each year for five more years, at which time he died following a stroke. While the family did not consent to brain autopsy, his "*causa mortis*" corroborated our hypothesis a vascular etiology for his depression, supported by key clinical factors such as the late-age onset of depression, presence of cerebrovascular risk factors, and presence of cognitive impairment.

The patient's mood and cognitive symptoms remained improved. His social functioning also improved, and he re-engaged with his friends and leisure activities.

Literature Review

Similar to vascular dementia, mood disorder and cognitive impairment due to cerebrovascular disease is associated with a variety of cerebrovascular risk factors, especially those related to stroke and coronary heart disease, i.e., hypertension and dyslipidemia. In addition, elderly patients with so called "vascular depression" often have cognitive impairment, with characteristic changes in information processing speed, visual-spatial disorientation, and executive dysfunction, which are associated with impaired activities of daily living and functional impairment that may persist even after remission of the mood symptoms [7].

In our patient, the persistence of cognitive deficits and mood symptoms led to augmentation of an antidepressant with a cholinesterase inhibitor. Some studies have shown that the cholinesterase inhibitors rivastigmine, donepezil and galantamine may improve cognitive, psychiatric and behavioral symptoms in Alzheimer's Disease (AD) patients [8]. The serotonin-dopamine hypothesis related to development of mood symptoms in these patients was supported by a study suggesting a positive effect of donepezil and galantamine on striatal dopamine levels in mice [9]. Neuropsychiatric symptoms present in AD patients, specifically anxiety and depression, are often described as secondary to a dysfunction in these neurotransmitter systems, [10] further supporting the serotonin-dopamine hypothesis. In addition, a study of depressed patients using fluoxetine, citalopram and paroxetine, suggested the possibility of "D2-like" sensitization of receptors as the main effect of antidepressant action of SSRIs in these patients [11].

There are limited data on the use of antidepressants to treat cognitive symptoms in older adults. A recent systematic literature review focused on the efficacy and safety of SSRI versus placebo treatment of cognitive decline in patients with MCI Only one study met the inclusion criteria, and it was comprised of 58 participants with MCI randomized to either fluoxetine 20mg or placebo daily for eight weeks. The authors found that cognition was significantly better in the fluoxetine group compared to placebo at the end of treatment [12].

Another study found that cholinesterase inhibitors apart from effects on cognition, could improve apathy, irritability, psychosis, depression, mania, tics, and delirium, associated with dementia [13].

In a placebo-controlled study, the combination of sertraline and donepezil led to a reduction of mood symptoms in patients with moderate to severe possible or probable AD [14]. In a meta-analysis of controlled clinical trials, the use of rivastigmine, at the dose of 6-12mg/day, provided improvement and/or prevention of behavioral changes in patients with mild to moderate AD [15].

In a recent double blind randomized clinical trial, the authors followed 186 probable AD patients divided in two groups, 92 taking citalopram 30 mg daily and 94 taking placebo, with each group also receiving a standardized psychological intervention [16]. The authors found that the former group showed much better improvement of behavioral symptoms and caregiver distress, confirming the benefits of SSRIs in treating NPS in AD patients.

Conclusion

Although there is scant data on combining cholinesterase inhibitors and antidepressants in the treatment of older adults with mood disorder and cognitive impairment due to cerebrovascular disease, the findings support the possible therapeutic efficacy of this combination. If future studies confirm these findings, the prognosis for these patients may be more hopeful, with a reduction in the risk of progression to dementia, and improved survival of patients with serious medical comorbidities.

In the present case, we suggested that the Patient was experiencing mood disorder and cognitive impairment due to cerebrovascular disease based on presence of vascular risk factors, vascular changes on MRI, and development of vascular dementia and a occurrence of stroke shortly before his death. The case led us to examine the literature on combination treatment with an antidepressant and cholinesterase inhibitor in such patients. While we found some studies that addressed this question, it is clear that more controlled studies are needed to help guide the management of neuropsychiatric symptoms in patients with cerebrovascular disease.

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