Psychiatr Q (2010) 81:73–79
DOI 10.1007/s11126-009-9120-8

CASE REPORT

Post Stroke Depression: Treatments and Complications in a Young Adult

Vincent F. Capaldi II · Gary H. Wynn

Published online: 24 December 2009

Abstract Post-stroke depression has been noted to be one of the most frequent complications of stroke with an estimated prevalence of as high as 80%. However, the incidence of stroke in the young is extremely low and evidence based therapy for this complication is quite limited. The case of a 28-year-old woman who experienced a basilar artery vasospasmic stroke resulting in anoxic brain injury to the midbrain and paramedian thalamus is presented, along with a literature review of psychiatric complications of this injury to include post-stroke depression (PSD). Therapeutic modalities such as TCAs, SSRIs, atypical antipsychotics and stimulant medications are also reviewed as these medications may aid in the treatment of such patients but may also contribute to psychiatric sequelae.

Keywords Post stroke depression · Brainstem stroke · Migrainous vasospasm · TCA · SSRI · Methylphenidate · Aripiprazole · Suicidality

Introduction

The incidence of basilar artery stroke is extremely rare and deadly. In western nations the incidence has been reported at <5% [1]. Mortality rates for basilar artery infarcts have been reported between 75 and 90% [2–4]. Patients surviving these events have potentially significant physiologic and psychiatric complications. Psychiatric complications include such maladies as post-stroke depression [5], anxiety [6], psychosis and PTSD [7].

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

V. F. Capaldi II (✉) · G. H. Wynn
Department of Psychiatry, Walter Reed Army Medical Center, 6900 Georgia Avenue, Washington, DC 20307-5001, USA
e-mail: vin@capaldi.org

V. F. Capaldi II · G. H. Wynn
Uniformed Services University of the Health Sciences F. Edward Hebert School of Medicine, Bethesda, MD, USA

The prevalence of post-stroke depression has been reported as high as 80% depending on the research tool used in the study [8]. Predictors in the development of post-stroke depression in first stroke patients include crying behaviors soon after stroke, a younger age, and severe disability [8]. This case highlights the risks and benefits of treating post-stroke depression with SSRIs, TCAs, atypical antipsychotics and stimulant medications. In this case report we focus on the evidence and rational for selection of pharmacologic treatments of post-stroke depression in the young. To our knowledge, this is the first published case report of the treatment of post-stroke depression in the young adult.

In this submission, we report a case of a 28 year old female with no significant psychiatric history who presents with post-stroke depression after suffering a basilar artery vasospasmic stroke.

Case Report

"Ms. K.", a 28 year old female with past medical history significant for migraine headaches, presented with symptoms of headache, numbness and generalized weakness in the context of recent extended airplane flight, high altitude exertion, OCP use and anemia. The patient presented to a local emergency room after hiking a mountain, approximately 3800 m above sea level outside the US, with a worsening headache for over 24 h that was not responsive to OTC pain medications. She also experienced decreased sensation over her entire body, ataxia, dysarthria and right upper extremity weakness. The patient initially underwent treatment for presumed altitude sickness. Her immediate therapies included oxygen and diamox. She experienced no improvement with these therapies.

Within hours of presentation at the local emergency department, the patient was transported to a higher level of care because of worsening mental status. A head CT was obtained in the local hospital. According to reports, the head CT was read as within normal limits. She was started on ceftriaxone and vancomycin for presumed bacterial meningitis. A lumbar puncture was performed and found to be inconsistent with bacterial meningitis although viral encephalitis remained in the differential. She was subsequently transported to the general hospital in country for more definitive care. Upon arrival the patient was noted to be bradycardic and apneic necessitating intubation.

While intubated, an MRI was conducted and revealed bilateral brainstem stroke in the territory of the basilar artery with evidence of infarct more prominent on the left side. The patient remained intubated for approximately 48 h. Upon extubation it was found that the patient's deficits were consistent with anoxic injury to the midbrain and paramedian thalamus. This localization was confirmed with radiographic findings. Local physicians hypothesized that her stroke was secondary to migrainous vasospasm given the onset of neurologic symptoms and no evidence of obstructive lesion noted in the basilar artery. A transthoracic echocardiogram, EEG and carotid ultrasound were performed in country and found to be normal. The patient was stabilized in the intensive care unit and transported to Walter Reed Army Medical Center in Washington, DC.

On admission to Walter Reed Army Medical Center (WRAMC) the patient was able to follow commands but had significant neurologic deficits including 4/5 weakness of the RUE, right-sided hyporeflexia, dysconjugate gaze, right sided facial droop and expressive aphasia. During her stay the patient had several complications to include ventilator associated pneumonia, fever of unknown origin and both oral and vaginal candidiasis. The patient underwent multiple modified barium swallow studies because of concerns for liquid and solid aspiration. After several evaluations, a PEG tube was inserted due to aspiration

concerns secondary to likely bulbar dysfunction. The patient was also noted to have marked difficulty in completing rehabilitation exercises. She was reported to have trouble maintaining concentration on tasks and was noted to fall asleep during sessions.

Modafinil was added to the patient's medication regimen to target symptoms of daytime somnolence, anhedonia and impaired concentration. On this medication, the patient made significant improvements in her level of consciousness and ability to participate in rehabilitation activities. With significant improvement in target symptoms, the patient was transferred to a Veterans Affairs (VA) Hospital for continued physical therapy and rehabilitation. While at that hospital, modafinil was discontinued and methylphenidate was started. According to reports, stimulant medication was changed because of decreased efficacy in treating target symptoms particularly with regard to daytime somnolence.

Shortly after changing her stimulant medications, the patient began endorsing symptoms of post stroke depression. Her depressive symptoms included depressed mood, anhedonia, irritability, feelings of worthlessness and suicidal ideation. The patient stated that she felt as though she was in a dream and that she would only be woken from the dream if she experienced some trauma such as being killed or violently assaulted. During her stay the patient attempted to bite staff during evaluations and rehabilitation activities. Sertraline was started to target depressive symptoms including depressed mood, anhedonia, decreased concentration, appetite, energy and suicidal ideation. The patient remained at the VA Medical Center for approximately 1 month before returning to WRAMC. She was transferred to psychiatry at WRAMC because of increased aggression toward staff, non-compliance with rehabilitative treatment, mood lability and suicidal ideation.

On admission, methylphenidate 5 mg twice daily was discontinued. It was hypothesized that the stimulant medication, methylphenidate, may have contributed to increased irritability and aggressive behaviors. The atypical antipsychotic medication, aripiprazole was started to further control target symptoms of irritability and aggressive behaviors. The medication was titrated up to a dose of 10 mg daily. After the stimulant was discontinued and aripiprazole was added, the patient had fewer episodes of aggression and mood lability. Approximately 1 week later, modafinil was started and tapered up to 200 mg daily because the patient was having difficulty maintaining her concentration during rehabilitation exercises. With the change from methylphenidate to modafinil, the patient was noted to have no agressive behavior and was compliant with rehabilitation therapy. The patient was then transferred back to the VA Medical Center for continued care and therapy.

Discussion

Bio-Psycho-Social Formulation of Post-Stroke Depression

Biologically, the neuropsychiatric underpinnings of post-stroke depression have not been conclusively elucidated in extant literature. As stroke complications primarily afflict elderly patients, post-stroke depression has been generally studied in geriatric populations. Early hypotheses posit that ischemic insults to neural circuits of mood regulation, specifically frontal sub-cortical circuits result in depletion of biogenic amines and contribute to symptoms of depression [9, 10]. It has also been hypothesized that left frontal lesions are generally associated with depressive symptoms, however no research to date has definitively linked areas of brain stem infarct to depressive symptoms [11]. There have been multiple studies attempting localize a lesion that might be consistent with PSD, however recent literature suggests against discrete localization [12, 13].

Another potential explanation of this patient's symptoms include emotional lability secondary to a Pseudobulbar affect (PBA). The prevalence of PBA after stroke has been reported as high as 34% [14]. As would be expected, studies investigating the prevalence of PBA post stroke have mainly focused on the following three areas: geriatric populations, patients having a history of prior stroke, and strokes involving the internal capsule and basal ganglia [15]. There appears to be a strong association between the development of PSD and PBA. Evidence suggests that patients with PBA tend to have more severe depressive symptoms compared to patients without comorbid PBA [14, 16].

Unlike depression, there are no FDA approved medications for the treatment of PBA. Expert opinion and several studies suggest the initial treatment of PBA and PSD are quite similar. SSRIs and TCA have been shown in several case reports and small trials to be effective in the treatment of PBA [15, 17]. Therapies in the treatment of PBA have indicated a rapid improvement of symptoms with the administration of medications. Some studies have shown an improvement as early as 3–5 days after starting therapy [18]. The rapidity of symptom improvement has not been replicated in the treatment of PSD. The patient presented in this case did not have rapid resolution of symptoms with the addition of an SSRI which would suggest that her symptoms were more consistent with PSD, although components of PBA may have exacerbated her depressive symptoms. Other medications studied as treatments for PBA may prove to be useful in the treatment of post stroke depression including the dopaminergic agents levodopa, amantidine and dextromethorphan [19–21].

Psychosocially, one might hypothesize post-stroke physical disabilities could underlie neurovegetative symptoms, however research shows comparatively increased depressive symptoms in stroke patients over age matched controls contending with similar physiologic disabilities [22]. In patients who develop PSD, the severity of the diagnosis and course of treatment has been correlated with the degree of physiologic disability. Thus, while physical disability may not directly contribute to the development of post-stroke depression, the severity of illness may worsen its course as an additional stressor. It is generally accepted that the underlying causes of PSD are multifactorial including the biological insults compounded by the psychosocial impact of disability.

Treatment of Post-Stroke Depression

A number of SSRIs have been studied regarding efficacy in the treatment of post-stroke depression. Most SSRIs have demonstrated minimal efficacy in the treatment of PSD supporting the hypothesis of PSD as uniquely different from Major Depressive Disorder (MDD). As noted above, the presentation of symptoms in PSD may vary depending on the areas of the brain affected. Thus medication clinical trials in humans are confounded by the differences in the underlying disease presenting as PSD. In two double blind, placebo controlled studies sertraline was no better than placebo in treatment or prevention of PSD [23, 24]. Of the SSRIs studied in the treatment of this illness, citalopram has been shown to have the most benefit in the treatment of PSD demonstrated by symptom reduction on the Beck Depression Inventory Scale [25, 26]. TCAs should also be considered in the treatment of PSD. In 2000, a double-blind, randomized, placebo control trial by Robinson et al., demonstrated a significant decrease in Hamilton Depression Scale (HAM-D) scores in patients treated with 12 weeks of nortriptyline when compared with fluoxetine and placebo treated groups [27]. Further, patients treated with nortriptyline also showed a decrease in anxiety symptoms and improved recovery of activities of daily living [27]. Although our patient would meet strict inclusion criteria for the studies cited in this report, it is important

to be mindful of applicability to young patients as most studies reported a subject mean age greater than 65 years old and did not control for the distribution of anoxic brain injury between patients. In our patient it was difficult to assess whether the increased irritability and mood lability was secondary to underlying PSD, a side effect of stimulant medications or a function of disinhibition from her original stroke. Sertraline was continued in light of her depressive symptoms despite the equivocal evidence for benefit in PSD [28].

In conjunction with treatment for her depressive symptoms, this patient was placed on aripiprazole to target symptoms of mood lability and aggressive behavior. Aripiprazole was chosen because of its high affinity for D2 receptor sites and particularly its cortical dopamine agonism in the area of the ventral striatum pathway targeting symptoms of psychosis and irritability associated with PSD [29]. The patient had a positive response with significant reduction in aggression as noted by staff and family. Atypical antipsychotic medications are associated with increased risk of stroke [30], though the mechanism of this adverse reaction is not fully understood. While there are significant risks in long term continuation of this medication, this patient likely experienced a stroke secondary to vasospasm after a unique set of circumstances including anemia and high altitude exertion. Studies demonstrating the association between atypical antipsychotics and increased risk for stroke have been focused on elderly populations with prolonged antipsychotic use. This patient may not be at increased risk for stroke associated with atypical antipsychotic use compared to a normal age matched control given the context of her stroke in the setting of unique and time limited factors. In general, providers should counsel patients on the risks of smoking and the use of OCPs while on atypical antipsychotics as they may compound the risk of stroke.

The significant irritability and mood lability in this patient may be a manifestation of PSD. There is limited clinical research using mood stabilizers in post-stroke patients exhibiting increased mood lability and irritability. Yan et al. demonstrated that the mood stabilizer lithium might aid in the reduction in behavioral disturbances in rats post stroke and reported lithium as protective for ischemia–reperfusion injury resulting in improved grooming, spatial learning and memory ability [22, 23]. Histologically, rats that were treated with lithium prior to CVA had decreased cell death in the hippocamal CA1 region [23]. Other studies have suggested that lithium may stimulate hippocampal neurogenesis via the extracellular signal-regulated kinase pathway [31]. To our knowledge, there have been no human trials investigating the use of lithium in post stroke patients.

Stimulant medications may also prove useful in the treatment of PSD and fatigue after stroke. Methylphenidate has been shown to lower HAM-D scores in a randomized controlled trial of PSD patients [32]. Modafinil has also been studied in the treatment of post stroke fatigue but there is no evidence-based research to guide its use in the treatment of PSD [33]. Although the exact mechanism of action for modafinil is not entirely understood, it differs from the mechanism of action of amphetamines. Preclinical evidence suggests that modafinil decreases GABA activity in the area of the ascending reticular activating system thus promoting arousal [34]. Stimulant medications have been associated with increased ability to participate in physical therapy after a stroke [35]. While providing the benefit of increased energy and decreased perceived disability, some stimulant medications such as methylphenidate carry a side effect profile that may actually worsen the patient's ability to participate in therapy [36]. Modafinil was chosen for this patient because it lacks the peripheral sympathomimetic effects that are associated with methylphenidate use and is generally not associated with aggressive behavior. Side effects of stimulant medications include rare instances of mania, psychosis, suicidal ideation, depression and stroke. Considerable caution should be exercised when weighing the risks and the benefits of

stimulant use in post-stroke patients as patients might be exquisitely sensitive to side effects of these medications.

Conclusion

PSD is a common disorder in the uncommon event of stroke in the young. The biologic mechanism and evidence based guidance in the treatment of this disorder is inconclusive at this time. In this case, Ms. K appears to have benefited from the addition of the atypical antipsychotic agent, aripiprazole, and a change in her prescribed stimulant from methylphenidate to modafinil. The mood lability, aggression and irritability of this patient may have been a product of her PSD or a side effect of her prescribed stimulant medication. She had a notable reduction the target symptoms of mood lability, aggression and irritability after changing and adjusting these medications. In addition to stimulating wakefulness in this patient, the combination of aripiprazole and modafinil may have also provided adjunctive treatment for her depressive symptoms. Further research in this area is needed to aid clinicians in the choice and dosage of psychotropic medications including TCA, SSRI, antipsychotic and stimulant medications based on the localization of brain injury and target symptoms in post-stroke patients.

References

1. Marini C, Totaro R, De Santis F, Ciancarelli I, Baldassarre M, Carolei A: Stroke in young adults in the community-based L'aquila registry: Incidence and prognosis. Stroke 32:52–56, 2001
2. Yu W, Binder D, Foster-Barber A, Malek R, Smith WS, Higashida RT: Endovascular embolectomy of acute basilar artery occlusion. Neurology 61:1421–1423, 2003
3. Piechowski-Jozwiak B, Bogousslavsky J: Basilar occlusive disease: The descent of the feared foe? Archives of Neurology 61:471–472, 2004
4. Caplan LR: Bilateral distal vertebral artery occlusion. Neurology 33:552–558, 1983
5. Morris PL, Robinson RG, Raphael B: Prevalence and course of depressive disorders in hospitalized stroke patients. International Journal of Psychiatry in Medicine 20:349–364, 1990
6. Castillo CS, Schultz SK, Robinson RG: Clinical correlates of early-onset and late-onset poststroke generalized anxiety. American Journal of Psychiatry 152:1174–1179, 1995
7. Chemerinski E, Levine SR: Neuropsychiatric disorders following vascular brain injury. Mount Sinai Journal of Medicine 73:1006–1014, 2006
8. Carota A, Berney A, Aybek S, et al.: A prospective study of predictors of poststroke depression. Neurology 64:428–433, 2005
9. Robinson RG: Vascular depression and poststroke depression: Where do we go from here? American Journal of Geriatric Psychiatry 13:85–87, 2005
10. Dieguez S, Staub F, Bruggimann L, Bogousslavsky J: Is poststroke depression a vascular depression? Journal of the Neurological Sciences 226:53–58, 2004
11. Robinson RG, Lipsey JR, Bolla-Wilson K, et al.: Mood disorders in left-handed stroke patients. American Journal of Psychiatry 142:1424–1429, 1985
12. Carson AJ, MacHale S, Allen K, et al.: Depression after stroke and lesion location: A systematic review. Lancet 356:122–126, 2000
13. Bozikas VP, Gold G, Kovari E, et al.: Pathological correlates of poststroke depression in elderly patients. American Journal of Geriatric Psychiatry 13:166–169, 2005
14. House A, Dennis M, Molyneux A, Warlow C, Hawton K: Emotionalism after stroke. BMJ 298: 991–994, 1989
15. Schiffer R, Pope LE: Review of pseudobulbar affect including a novel and potential therapy. Journal of Neuropsychiatry and Clinical Neurosciences 17:447–454, 2005
16. Ross ED, Stewart RS: Pathological display of affect in patients with depression and right frontal brain damage. An alternative mechanism. The Journal of Nervous and Mental Disease 175:165–172, 1987

17. Okun MS, Riestra AR, Nadeau SE: Treatment of ballism and pseudobulbar affect with sertraline. Archives of Neurology 58:1682–1684, 2001
18. Surridge D: An investigation into some psychiatric aspects of multiple sclerosis. British Journal of Psychiatry 115:749–764, 1969
19. Udaka F, Yamao S, Nagata H, Nakamura S, Kameyama M: Pathologic laughing and crying treated with levodopa. Archives of Neurology 41:1095–1096, 1984
20. Wolf JK, Santana HB, Thorpy M: Treatment of "emotional incontinence" with levodopa. Neurology 29:1435–1436, 1979
21. Tortella FC, Pellicano M, Bowery NG: Dextromethorphan and neuromodulation: Old drug coughs up new activities. Trends in Pharmacological Sciences 10:501–507, 1989
22. Whyte EM, Mulsant BH: Post stroke depression: Epidemiology, pathophysiology, and biological treatment. Biological Psychiatry 52:253–264, 2002
23. Murray V, von Arbin M, Bartfai A, et al.: Double-blind comparison of sertraline and placebo in stroke patients with minor depression and less severe major depression. Journal of Clinical Psychiatry 66: 708–716, 2005
24. Rasmussen A, Lunde M, Poulsen DL, Sorensen K, Qvitzau S, Bech P: A double-blind, placebo-controlled study of sertraline in the prevention of depression in stroke patients. Psychosomatics 44: 216–221, 2003
25. Andersen G, Vestergaard K, Lauritzen L: Effective treatment of poststroke depression with the selective serotonin reuptake inhibitor citalopram. Stroke 25:1099–1104, 1994
26. Rampello L, Chiechio S, Nicoletti G, et al.: Prediction of the response to citalopram and reboxetine in post-stroke depressed patients. Psychopharmacology (Berlin) 173:73–76, 2004
27. Robinson RG, Schultz SK, Castillo C, et al. Nortriptyline versus fluoxetine in the treatment of depression and in short-term recovery after stroke: A placebo-controlled, double-blind study. American Journal of Psychiatry 157:351–359, 2000
28. Tharwani HM, Yerramsetty P, Mannelli P, Patkar A, Masand P: Recent advances in poststroke depression. Current Psychiatry Report 9:225–231, 2007
29. Mamo D, Graff A, Mizrahi R, Shammi CM, Romeyer F, Kapur S: Differential effects of aripiprazole on D(2), 5-HT(2), and 5-HT(1A) receptor occupancy in patients with schizophrenia: A triple tracer PET study. American Journal of Psychiatry 164:1411–1413, 2007
30. Douglas IJ, Smeeth L: Exposure to antipsychotics and risk of stroke: Self controlled case series study. BMJ 337:a1227, 2008
31. Yan XB, Hou HL, Wu LM, Liu J, Zhou JN: Lithium regulates hippocampal neurogenesis by ERK pathway and facilitates recovery of spatial learning and memory in rats after transient global cerebral ischemia. Neuropharmacology 53:487–495, 2007
32. Grade C, Redford B, Chrostowski J, Toussaint L, Blackwell B: Methylphenidate in early poststroke recovery: A double-blind, placebo-controlled study. Archives of Physical Medicine and Rehabilitation 79:1047–1050, 1998
33. Annoni JM, Staub F, Bogousslavsky J, Brioschi A: Frequency, characterisation and therapies of fatigue after stroke. Neurological Sciences 29(Suppl 2):S244, 2008
34. Qureshi A, Lee-Chiong T Jr: Medications and their effects on sleep. Medical Clinics of North America 88:751–766, 2004
35. Walker-Batson D, Smith P, Curtis S, Unwin H, Greenlee R: Amphetamine paired with physical therapy accelerates motor recovery after stroke. further evidence. Stroke 26:2254–2259, 1995
36. Lazarus LW, Winemiller DR, Lingam VR, et al. Efficacy and side effects of methylphenidate for poststroke depression. Journal of Clinical Psychiatry 53:447–449, 1992

Author Biographies

Vincent F. Capaldi, II, ScM, MD is a 3rd year resident specializing in Internal Medicine and Psychiatry at Walter Reed Army Medical Center in Washington, DC. Dr. Capaldi is a graduate of Brown University School of Medicine and Brown University's Graduate School, holding a master's degree in psychology.

Gary H. Wynn, MD is a graduate of West Point and the Uniformed Services University for the Health Sciences. He is currently a research psychiatrist at the Walter Reed Army Institute of Research in Silver Spring, MD and he has previously published on topics to include drug interactions, psychopharmacology, and PTSD.