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Posterior Reversible Encephalopathy Syndrome Secondary to Hypertensive Encephalopathy Brought on by a MAO Inhibitor: A Case Report

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Abstract

An elderly woman was admitted to the Family Medicine inpatient service for altered mental status after being brought to the emergency room by a concerned neighbor, who had come across the patient speaking incoherently. Initial evaluation was notable for elevated blood pressures, but extensive lab testing and head computed tomographic imaging were within normal limits. However, subsequent magnetic resonance imaging showed white matter changes consistent with posterior reversible encephalopathy syndrome (PRES), a neurologic syndrome characterized by headache, altered mental status, loss of vision, and seizures as well as radiographic findings of posterior cerebral white matter edema. Multiple etiologies of PRES have been described and include hypertensive encephalopathy, immunosuppressant medications, and eclampsia. This case describes an episode of PRES secondary to hypertensive encephalopathy brought about by an inappropriate dose of a monoamine oxidase (MAO) inhibitor. The patient had significant improvement in symptoms with removal of the offending agent and control of her blood pressure. While PRES generally has a good prognosis, prompt recognition, and management are important in preventing significant disease morbidity and mortality.

Keywords

hypertension, encephalopathy, MAO inhibitor, mental status change, medication effect, primary care

Case Presentation

A 70-year-old woman was brought to the emergency room after being found wandering around her neighborhood speaking incoherently. She was brought by a neighbor who reported a normal conversation with the patient just a few days prior. The patient's past medical history was significant for avoidant personality disorder, dysthymia, and binge eating disorder treated with phenelzine and topiramate under the care of a community psychiatrist. The patient lived independently and had no history of witnessed psychosis, hallucinations, or manic symptoms. Additional history included essential hypertension for which the patient was taking lisinopril 5 mg daily and NYHA (New York Heart Association) class I heart failure for which she was taking carvedilol 25 mg twice daily. Of note, the patient had recently seen her outpatient provider within a week prior to her presentation for a presurgical exam for a planned knee replacement. Surgery was postponed due to elevated systolic blood pressure >180 mm Hg at that visit and the patient's dose of lisinopril was increased to 10 mg daily.

On arrival to the inpatient floor, the patient's blood pressure was 173/89 mm Hg, which was decreased from her initial blood pressure in the emergency department of 211/86 mm Hg. The patient's cognitive status limited taking a detailed history. She was verbose and tangential in her speech. The patient reported that she and her neighbors had been picking berries earlier in the day and her neighbor became concerned when the patient started looking for her deceased father who the patient described as "the boss." The patient endorsed seeing animals in her room as well as individuals smoking cigarettes. She denied auditory hallucinations but was noted to be responding to internal stimuli. Montreal Cognitive Assessment (MoCA) was significant for a score of 14/30. Her neurologic exam revealed no

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cranial nerve deficits and no visual field defects. She was not hyperreflexic and displayed no clonus. She was moving all limbs spontaneously and had good strength in her upper and lower extremities. There was no ataxia, but the patient did have dysmetria on finger to nose testing.

The patient's initial blood workup for her altered mental status included a complete blood count, chemistry panel, creatinine, liver function tests, B12, and thyroid function tests. Urinalysis, acetaminophen, salicylate, and ethanol levels were obtained as well as a urine drug screen, which were negative. Blood work showed no evidence of a leukocytosis or elevated inflammatory markers. Electrolytes, kidney, liver, B12, and thyroid function tests were within normal ranges. Urinalysis showed no evidence of urinary infection. A head computed tomography (CT) scan demonstrated nonacute lacunar infarcts of the bilateral basal ganglia, moderate generalized volume loss, and chronic ischemic white matter changes when compared with a head CT 10 years prior. On the general floor, the patient continued to demonstrate episodes of delirium and had hypertensive episodes greater than 180 systolic. In consultation with Neurology, a magnetic resonance imaging (MRI) was obtained which demonstrated an ill-defined T2 hyperintense signal in the right occipital cortex and subcortical white matter consistent with posterior reversible encephalopathy syndrome (PRES). A carotid ultrasound did not reveal evidence of stenosis and EEG did not reveal epileptiform activity.

Further history was obtained from patient's primary care provider, outpatient psychiatrist, and therapist. The patient's primary care physician noted no concerns regarding patient's mentation when she was seen in the outpatient setting the week prior. Her dosing of phenelzine was confirmed to be 90 mg twice daily and the patient reported taking more than this dose when she needed. The maximum recommended daily dose is 90 mg per day. Management focused on safely reducing her blood pressure as well as managing her altered mental status. The phenelzine was held, and she was treated with oral labetalol as needed for blood pressures greater than 180 mm Hg systolic and her home dose of lisinopril. Blood pressures continued to be greater than 180 mm Hg systolic and 24 hours after admission the patient became increasingly agitated and confused. Her agitation was treated with Haldol and olanzapine without significant relief. Ativan was also utilized without improvement. Unfortunately, due to significant progression of her agitation, combativeness, and development of violent behavior, she was transferred to a behavioral unit for further management. While in the behavioral unit, she responded well with quetiapine and environmental controls and was transferred back to the general floor.

The patient's blood pressure continued to be elevated with occasional systolic blood pressures greater than 160 mm Hg and diastolic blood pressures greater than 110 mm Hg. Amlodipine was added to patient's lisinopril, which was increased to 20 mg. Her blood pressures continued to improve over the course of her hospitalization. The patient's agitation slowly improved with better blood pressure control as well as quetiapine. Her mentation slowly improved over the course of her hospitalization and she was discharged to a skilled nursing facility for short-term rehab on quetiapine and advised that phenelizine be discontinued.

Discussion

Posterior reversible encephalopathy syndrome (PRES) or reversible posterior leukoencephalopathy syndrome is a syndrome of clinical findings with characteristic neuroradiographic findings that was first described by Hinchey et al[1] in a case series published in the *New England Journal of Medicine* in 1996. They reported a clinical presentation characterized by one or a combination of headache, altered mental status, vision loss, and seizures. These symptoms were found in combination with neuroradiographic findings of edema of the posterior cerebral white matter. Numerous etiologies have been reported and include use of immunosuppressant medications, hypertensive encephalopathy, and eclampsia.[1] Since the advent of selective serotonin reuptake inhibitors, other antidepressant medication classes such as monoamine oxidase inhibitors (MAO-Is) have seen a significant reduction in use, but as this case demonstrates, they remain an important cause of iatrogenic morbidity, contributing to medication-induced hypertension and hypertensive encephalopathy.

The symptomatology of this syndrome varies. A prospective and retrospective case review of patients thought to have PRES at Mayo Clinic from 2005 to 2009 and 1999 to 2005, respectively, demonstrated a significant majority (86%) of PRES patients with significant hypertension with mean systolic blood pressures of 191 mm Hg and mean diastolic blood pressures of 104 mm Hg. Renal failure was present in a little over half of patients with a mean creatinine of 2.5. Seizures were the most common presenting symptom and were present in 74% of patients. Encephalopathy was found in 28% of patients whereas headache and visual disturbances were found in 26% and 20%, respectively.[2] A similar retrospective review of likely PRES cases in New Zealand demonstrated similar symptoms with common presenting features of headache, visual disturbance, seizures, and hypertension.[3]

Currently, there are no set diagnostic criteria for making the diagnosis of PRES; however, characteristic imaging findings in the setting of the above clinical presentations are consistent with the diagnosis. While changes may be present on CT, MRI is considered the best imaging modality to capture characteristic findings.[4] Common findings on both CT and MRI are white matter edema in bilateral posterior cerebral hemispheres that spares the calcarine and paramedian

aspects of the occipital lobe.[1,2] Involvement of other brain territories including the cerebellum, brainstem, frontal lobe, and basal ganglia may also occur.[2,5,6] MRI findings include increased signal of T2-weighted imaging and as a hypointense or isointense signal on diffusion-weighted imaging with apparent diffusion coefficient maps showing increased signal.[5,7,8] In the case outlined, the patient demonstrated hyper-intensity in the right occipital cortex and subcortical white matter, which was consistent with the classic imaging findings of PRES.

The differential diagnosis in patients with suspected PRES is quite broad and includes the common diagnostic considerations in elderly individuals presenting with encephalopathy. Special attention should be given to metabolic, infectious, and cerebrovascular causes of altered mental status given the significant proportion of presentations that are secondary to these.[9] Additional considerations may include encephalitis (infectious or autoimmune), neoplastic, central nercous system vasculitis, progressive multifocal leukoencephalopathy, demyelinating syndromes, and toxic leukocoencephalopathy.[10]

The exact pathophysiology of PRES is unknown and an area of active study. Current theories primarily revolve around failure of autoregulation leading to hyper- or hypoperfusion as well as endothelial dysfunction.[10] One theory suggests that a rise in systemic blood pressure overcomes the ability of the body to autoregulate cerebral blood flow that is responsible for maintaining constant blood flow to the brain. When this occurs, hyperperfusion leads to increased pressure and subsequent leakage of fluid into the surrounding brain tissue.[11] However, this proposed mechanism does not account for episodes of PRES in which patients have been found to be normotensive or hypotensive.[12] An alternate hypothesis suggests hypoperfusion could contribute to the clinical picture if disruption in autoregulation causes resultant areas of vasoconstriction.[13,14] Endothelial dysfunction is also a theorized etiology that could occur along with the previously described theories and has been seen in cases of PRES secondary to preeclampsia or cytotoxic medications.[1] Studies of preeclamptic patients have demonstrated increased markers of endothelial cell dysfunction that appear to correlate with the degree of cerebral edema.[15,16] In addition, immunosuppressant medications often have toxic effects on cells and may damage the endothelium of vessels and thus causing leakage of fluid into the brain parenchyma.[17]

Treatment guidelines for PRES have yet to be established however current consensus regarding treatment in the case of uncontrolled hypertension focuses on reduction of blood pressure with percent goal reduction of 25%.[18] Exact antihypertensive regimens have not been established. If there is concern for a drug-related cause, then the offending medication should be discontinued. In cases of eclampsia, treatment based on guidelines for eclampsia is warranted. Seizures should be managed with antiseizure medications; however, no studies have been performed on what specific drugs should be used.[10]

Individuals who develop PRES have been shown to have favorable short- and long-term outcomes. In one cohort of patients, each patient made a full neurologic recovery in a matter of weeks.[1] A 2010 study on 25 patients demonstrated initial clinical improvement with a median short-term recovery time of 2 days with a recurrence rate of 8% during a median follow-up period of a little over 6 years.[19] Findings of PRES on imaging do not improve as quickly as clinical symptoms.[19] While the majority of individuals with PRES do recover without difficulty, persistent neurologic deficits as well as death have been reported among patients receiving intensive care unit–level cares.[20,21]

In the above case, the patient had significant clearing of her mental status with better control of her blood pressure. She was discharged from the hospital to an acute care facility where a repeat MoCA was found to be 28/30 approximately 3 weeks after discharge. Unfortunately, the patient returned to her elevated dose of phenelizine and once more presented to the emergency room approximately 2 months later with altered mentation and elevated systolic blood pressure of 170 mm Hg. Repeat head imaging included a CT scan that did not show evidence of PRES. An MRI was not obtained. Her MAO-I medication was once more reduced and the patient had subsequent improvement in her mentation.

Conclusion

Posterior reversible encephalopathy syndrome (PRES) or reversible leukoencephalopathy syndrome is a neurologic syndrome characterized by symptoms that can include headache, altered mental status, vision loss, and seizures as well as characteristic neuroimaging findings. PRES is often described in the setting of immunosuppressant medications, hypertensive encephalopathy, and eclampsia. In this case, PRES developed secondary to hypertensive encephalopathy from a combination of MAO-I overdose with phenelzine and suboptimally treated hypertension. Management consisted of holding the patient's phenelzine, hypertensive control, and quetiapine.

This case demonstrates that encephalopathy along with a subtle neurologic exam finding like dysmetria can be the clinical presentation for PRES, even without visual changes, seizures, or headache. In addition, any cause of hypertension can theoretically contribute to hypertensive encephalopathy, including uncommonly prescribed medications like phenelzine. Finally, if clinical suspicion remains high in the setting of inconsistent imaging on CT scan, clinicians ought to obtain additional imaging with MRI, which is the preferred imaging modality for capturing the radiologic findings of PRES.

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