MANAGEMENT OF MAJOR DEPRESSION FOLLOWING VASOCONSTRICTIVE STROKE DUE TO SEROTONERGIC MEDICATIONS: A CASE REPORT

Rafael Tamargo MD MBA[1] & Robin Valpey MD[1]
[1]*University of Pittsburgh Medical Center, Western Psychiatric Hospital*

Background

Reversible cerebral vasoconstriction syndrome (RCVS) is an uncommon form of stroke caused by temporary dysregulation of cerebrovascular tone. Annual incidence is estimated to be 2.7 cases per million adults based on hospital admission data (Magid-Bernstein, 2021). Women are more frequently affected than men. Symptoms include severe, recurrent headaches, with or without focal neurological findings. Onset is often acute, with thunderclap headache. Radiography reveals diffuse segmental vasospasm of cerebral arteries that peaks 2-3 weeks after symptom onset and resolves spontaneously within 3 months. Diagnosis is confirmed by cerebral angiogram showing a "string of beads" pattern on one or more cerebral arteries, but patients with typical clinical features and absence of other potential causes should be treated as having probable RCVS, even without angiographic confirmation. (Ducros, 2012).

RCVS can occur spontaneously, but the majority of cases are linked to vasoactive drugs. Antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs) and selective noradrenergic reuptake inhibitors (SNRIs) are among the most common causes of RCVS (Ducros, 2012). RCVS can occur at any point in treatment. Other possible causes include illicit drugs such as cannabis, cocaine, and amphetamines; alpha-sympathomimetics; and triptans. RCVS can spontaneously occur post-partum.

Management includes discontinuation and indefinite avoidance of vasoactive drugs due to risk of recurrence. RCVS is self-limiting and treatment is often symptomatic, including rest and limiting activities that could increase intracranial pressure. More severe cases may require analgesics, antiepileptics, blood pressure control, and intensive care unit admission. Nimodipine, verapamil, and magnesium sulfate have been used to treat radiographically-confirmed vasospasm. No randomized controlled trials exist to guide treatment. 99% of patients survive and the rate of recurrence is unknown (Ducros, 2012).

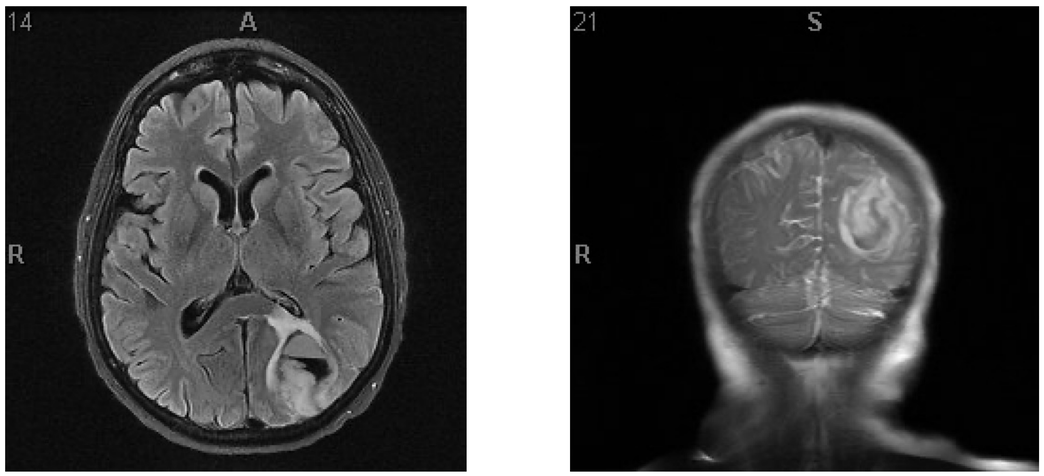

Figure 1. Transverse (left) and coronal (right) MRI images showing patient's left parietal subarachnoid hemorrhage due to RCVS.

Initial Presentation

We present a 53-year-old female with past medical history of serous ovarian cancer diagnosed March 2020, who developed left parietal and right frontal subarachnoid hemorrhages (**Figure 1**) on June 4, 2020. She has psychiatric history of MDD, GAD, and alcohol use disorder in sustained remission. She was referred to the outpatient psycho-oncology clinic for management of depression following strokes.

Neurology was consulted at the time of her strokes. In the absence of other apparent risk factors or precipitating events, her strokes were deemed to be caused by RCVS. They suspected vasospasm secondary to serotonergic medications, specifically duloxetine 30 mg daily and bupropion XL 150 mg daily, which she was prescribed for MDD. Inpatient CL Psychiatry was consulted soon after and discontinued duloxetine and bupropion. She had obtained a medical cannabis card and was similarly advised to stop using cannabis due to potential serotonergic effects. Quetiapine 25 mg nightly was started later in admission by her primary medicine team for anxiety.

Upon initial evaluation in the outpatient psycho-oncology clinic, the patient reported side effects of weight gain and night sweats since starting quetiapine. She had briefly stopped taking it as an outpatient, but developed irritability, angry outbursts, tearfulness, and restless sleep within a week. She restarted quetiapine and side effects recurred. She requested an alternative medication for mood due to the above side effects. She denied SI, HI, AVH. She denied significant anxious symptoms or panic attacks. She denied history suggestive of mania, psychosis, or OCD. She endorsed history of trauma related to her sister's suicide when the patient was in her early 30s. She denied, however, current episodes of reexperiencing, hypervigilance, hyperarousal, or avoidance related to this.

She additionally stated goal of reducing controlled substances prescribed for anxiety and pain secondary to cancer, given her history of alcohol use disorder. She was prescribed clonazepam 0.5 mg night plus three times daily as needed for anxiety. She was also prescribed oxycodone 5 mg daily for pain, and tramadol 50 mg twice daily as needed for pain. She denied misuse of these medications and denied cravings between doses. Her goal was to reduce clonazepam use to as-needed only, and to discontinue oxycodone.

She reported history of one inpatient psychiatric hospitalization in her early 30s for depression following the death of her sister by suicide. She had no history of suicide attempts herself. Other medication trials for mood included fluoxetine (up to 80 mg daily), escitalopram (up to 40 mg daily), buspirone, venlafaxine, paroxetine, and alprazolam. Past treatment for alcohol use included one inpatient rehabilitation and two outpatient rehabilitation clinics. Last drink was 5 years prior. She denied history of complicated withdrawal and denied other substances. She denied other family psychiatric history. She was married with three grown children and had worked as a pharmacist prior to her cancer diagnosis but had since been on medical leave.

Treatment Course

Following initial outpatient evaluation, the patient was diagnosed with MDD, recurrent episode, moderate; GAD, and alcohol use disorder in sustained remission. Differential diagnosis included adjustment disorder, substance-induced depression and anxiety, and post-stroke depression. Quetiapine was discontinued. Mirtazapine 15 mg nightly was started due to relatively low serotonergic activity and absence of case reports of RCVS secondary to mirtazapine after literature review. Clonazepam was reduced to three times daily as needed. She was referred for Supportive Psychotherapy.

At six-week follow-up she reported improved mood with mirtazapine but had increased hunger and weight gain. Dose was decreased to 7.5 mg nightly. She called a week later, reporting worse mood, notably after surgery for tumor resection, and dose was increased to 11.25 mg nightly.

One month later, she began chemotherapy and mood declined again, with low mood, anxiety, insomnia, and frequent crying. She declined mirtazapine increase due to concern for side effects, so aripiprazole 5 mg daily was added for augmentation.

Aripiprazole was titrated to 10 mg nightly over the next 4 months, but she developed akathisia at higher doses. Mirtazapine was reduced to 7.5 mg nightly due to complaints of morning sedation. Depressive symptoms persisted. With limited non-serotonergic options, liothyronine 25 mcg daily was started. At four-week follow-up she reported significant improvement in mood, with increased energy and activity level that began two weeks after starting liothyronine. Clonazepam was eventually discontinued after 6-month taper, and oxycodone was reduced to as-needed only.

Depression remained in remission for four months but recurred, at which time she was referred for transcranial magnetic stimulation (TMS). She completed 36 sessions, with improvement in mood that has remained stable.

Discussion

RCVS is a rare but serious side effect of serotonergic and noradrenergic medications, both of which are routinely prescribed by psychiatrists. Management of mood disorders following RCVS poses a significant clinical challenge given the dearth of non-serotonergic and -noradrenergic medications available to treat such conditions. We present successful treatment of MDD and GAD despite the clinical limitations posed by RCVS as a guide for CL psychiatrists facing similar management challenges.

There are few options for treating depression after eliminating serotonergic and noradrenergic drugs. Mirtazapine, atypical antipsychotics, lithium, liothyronine, and interventional options such as ECT and TMS are among the few remaining options, although further investigation is needed to determine whether ECT could cause unsafe increased in intracranial pressure. Some of these were used to various degrees of effect in the patient presented. Her limited response to and/or side effects with the above options posed a persistent clinical challenge.

We additionally emphasize the importance of integrating within the medical community, as coordination with both oncology and neurology was imperative for optimal management of this case. CL Psychiatrists should coordinate removal of potential offending agents with Neurology to prevent relapse of psychiatric symptoms, while further psychiatric and oncologic treatments should be jointly agreed upon to reduce the risk of RCVS recurring.

References:
1. Ducros, A. (2012). Reversible cerebral vasoconstriction syndrome. The Lancet Neurology, 11(10), 906-917.
2. Magid-Bernstein J, Omran SS, Parikh NS, Merkler AE, Navi B, Kamel H. RCVS: Symptoms, Incidence, and Resource Utilization in a Population-Based US Cohort. Neurology. 2021 May 28;97(3):e248–53. doi: 10.1212/WNL.0000000000012223. Epub ahead of print. PMID: 34050007; PMCID: PMC8302148.