"Depression" After Hypoxic-Ischemic Injury

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Case

Ronald is a 16-year-old male with a history of Hashimoto's thyroiditis, depression, and opioid substance use disorder as well as a history of marijuana and cocaine use, who presented with a serious drug overdose requiring hospitalization after he was found unresponsive. His pulse was detectable on initial discovery but he was noted to be cyanotic with minimal respirations and respiratory resuscitation was initiated while awaiting emergency services. On arrival, Ronald was given intranasal naloxone 2 mg with subsequent improvement in spontaneous respiration. Ronald had jerking movements concerning for seizures and required multiple doses of diazepam and subsequent intubation with etomidate. On arrival to the emergency department, Ronald had a Glasgow coma score (GCS) of 6 with sluggish but reactive pupils, and he was intubated. Initial labs indicated his serum pH was 7.14 with an elevated partial pressure of carbon dioxide (pCO2) of 74 and serum lactate of 6.2. Serum creatinine was 2.1. Seizure was suspected and he was given a loading dose of fosphenytoin. Epinephrine was initiated for hypotension with systolic blood pressures in the 80s. Urine drug screen was positive for cocaine, benzodiazepines, opioids, and cannabinoids.

Initial computed tomography (CT) scan of the head showed intact differentiation of the gray and white matter without edema or hemorrhage. Magnetic resonance imaging (MRI), shown in Figs. 4.1 and 4.2, revealed numerous foci of acute

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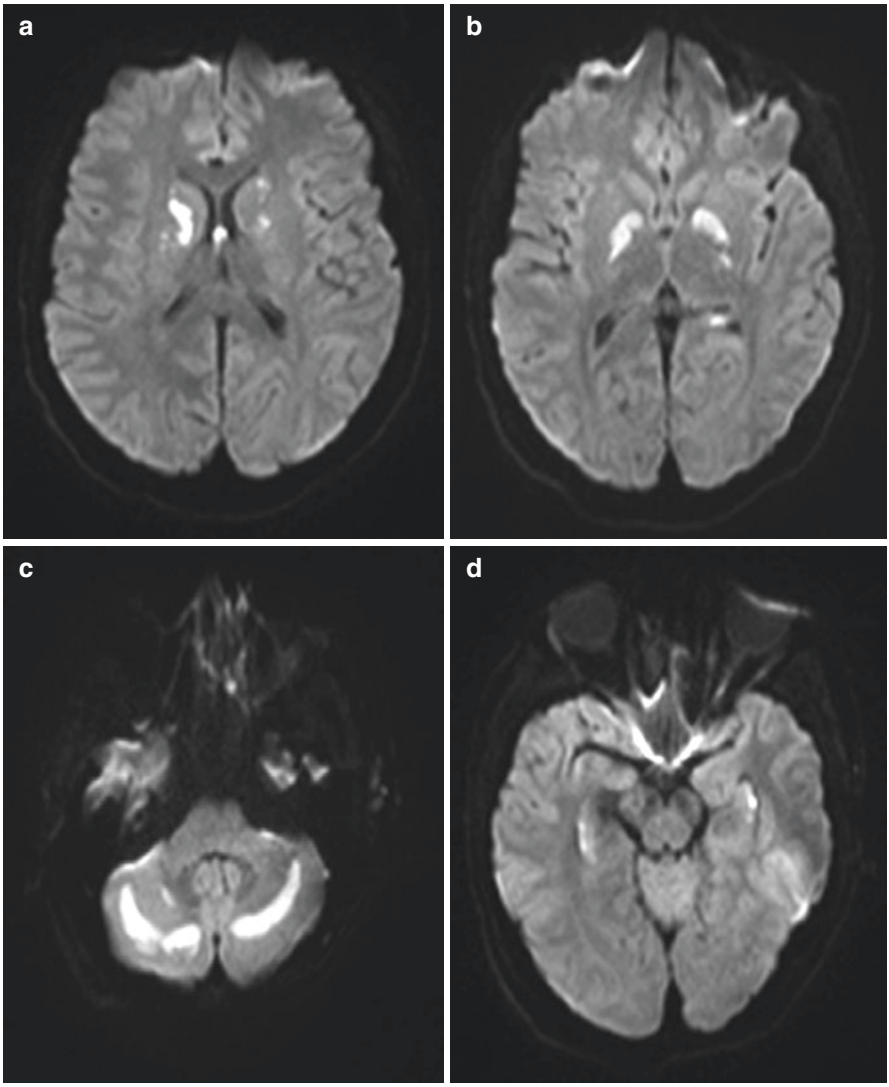

Fig. 4.1 MRI diffusion-weighted imaging (DWI) sequence demonstrates acute infarcts in the basal ganglia (**a**) and specifically in the globus pallidus bilaterally (**b**), as well as in the bilateral cerebellar hemispheres (**c**) and mesial temporal lobes (**d**)

infarction in a symmetric distribution in the bilateral basal ganglia including the caudate and globus pallidus, as well as in the bilateral cerebellar hemispheres, subcortical white matter, corticospinal tracts, and mesial temporal lobes.

Ronald's level of consciousness gradually improved. He was noted by the pediatrics team to be affectively flat and confused. Pediatric psychiatry was consulted to evaluate for possible depression and delirium. History from Ronald's family

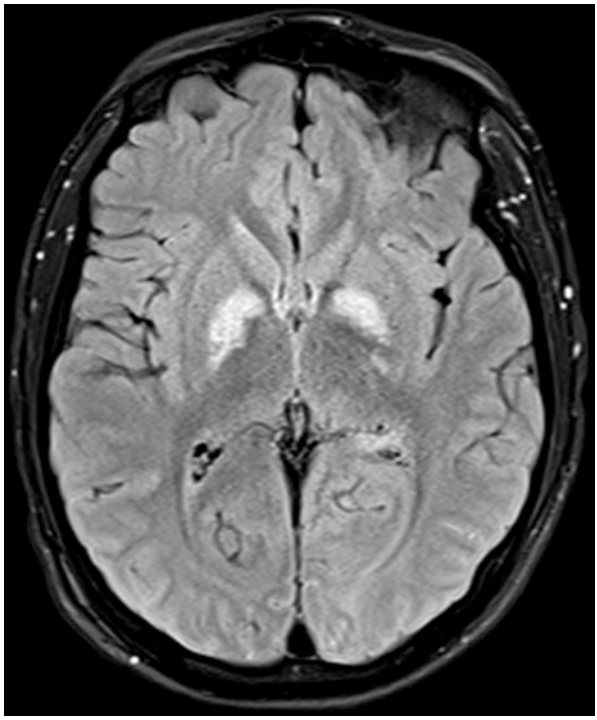

Fig. 4.2 MRI fluid-attenuated inversion recovery (FLAIR) sequence demonstrates hyperintensities in the globus pallidus bilaterally

indicated that he had a similar overdose of multiple substances (likely including cocaine, marijuana, and opioids) about 5 weeks prior to this presentation. At the time of this prior overdose, Ronald had been admitted to the inpatient pediatric psychiatry service for 3 weeks and started on citalopram, a selective serotonin reuptake inhibitor antidepressant. His family reported the medication to have been previously effective for his depression at a dose of 40 mg.

On evaluation by pediatric psychiatry, Ronald was noted to be drowsy, cognitively slowed, and disoriented to time and place. His affect was flat but he denied depressed mood. He struggled to describe or define his subjective emotional states, which was reported by his clinical team as a demonstration of alexithymia. His sleep and appetite were normal. It was recommended that his opioid analgesia be tapered, if possible, due to probable contribution to delirium. Lorazepam, prescribed to prevent benzodiazepine withdrawal, was converted to clonazepam, which was then tapered gradually. Despite persistence in affective flattening as his medical picture improved, Ronald continued to deny depressed mood and he repeatedly denied intentional overdose of substances.

Given his medical stability, he was discharged to acute inpatient rehabilitation, where he continued to improve. Pediatric neurology was consulted for abnormal movements which emerged primarily after completion of his clonazepam taper. These movements were described by the patient's family as intermittent writhing movements of the upper body and one or both arms at various times with occasional abrupt jerking movements. There were also occasional twisting movements of his

legs at night. There were no rhythmic movements that would have suggested seizures. Ronald was not bothered by these movements. His voice was quieter, and he was noted to be speaking less than his reported baseline. When ambulating, he would sometimes fall backwards.

Ronald's neurological exam was notable for flat affect with reduced facial expressivity (hypomimia), slowness of movement (bradykinesia), slowness of thought (bradyphrenia), and reduced vocal volume (hypophonia). No choreoathetotic movements were observed, but physical examination did reveal intermittent brief myoclonic jerks in the hands and arms. He was dysmetric on coordination testing, greater on the left side than on the right. Ronald's gait was noted initially to be significant for shortened steps, an anteriorly flexed posture, and a tendency toward retropulsion, and reduced arm swing bilaterally, though these features improved over his several weeks in inpatient rehabilitation. The clinical impression at that time was of a mixed movement disorder with parkinsonian features and choreoathetoid movements due to bilateral basal ganglia injury as well as a post-hypoxic myoclonus syndrome ("Lance-Adams myoclonus"). It was thought that clonazepam had likely been masking these movements prior to its taper. Neurocognitive and affective features including cognitive slowing (bradyphrenia), flat affect, and decreased spontaneous speech and behavior were also attributed primarily to the basal ganglia injury.

Given his clinical constellation of symptoms, Ronald did not appear to be demonstrating an adjustment disorder with depressed mood or major depressive disorder, but rather was exhibiting sequelae of basal ganglia injury. Dopamine replacement therapy was offered for treatment of parkinsonian cognitive and motor features but Ronald's parents opted against this. Ronald continued to improve clinically, and follow-up MRI at 1 year from the incident showed near complete resolution of the FLAIR hyperintense lesions involving the bilateral basal ganglia and cerebellar hemispheres, with only a small amount of encephalomalacia noted in the bilateral globus pallidus and caudate consistent with ischemic injury. On follow-up with his neurologist, he was noted to have some residual bradykinesia, mild hypophonia, and decreased facial expression, but he no longer had any abnormal involuntary movements.

Neuroanatomy and Pathophysiology

Hypoxic-ischemic brain injury in the setting of circulatory arrest typically produces injury in those brain areas which are most metabolically active or which exist at the border zones of cerebrovascular territories. The CA1 neurons of the hippocampus are highly vulnerable, as are the Purkinje cells of the cerebellum and pyramidal neurons in layers 3, 5, and 6 in the neocortex; the reticular neurons of the thalamus and medium-sized neurons of the striatum can also be affected [1]. While brain injuries due to purely hypoxic events are often grouped with those related to cardiac arrest for ease of discussion, pure hypoxia may induce functional neuronal changes without causing cell death, leading to better recovery potential as compared to

cardiac arrest. Pure hypoxia, which most often occurs in the setting of intoxication or obstructive airway events, tends to affect a younger population with less cerebrovascular disease on average. Perhaps even more importantly, in these cases, because circulation is preserved, nutrients and waste products can still be brought to and from the neurons, helping to maintain a more hospitable local environment than is seen after complete circulatory collapse [1]. In these cases, initial imaging may appear similar to that seen in hypoxic-ischemic injury but tends to evolve and improve over time [2].

Based on all available information, it is likely that Ronald experienced a primarily hypoxic event. The basal ganglia appear to be especially susceptible to prolonged hypoxia, with globus pallidus injury described most frequently in the setting of carbon monoxide poisoning and other substance intoxications. Clinical parkinsonism commonly follows this type of injury, with a classic "akinetic-rigid" motor syndrome described in which patients demonstrate varying degrees of bradykinesia, micrographia, axial rigidity, resting or postural tremor, and postural instability [3]. These findings may improve over time, correlating to improvement seen on neuroimaging.

The basal ganglia are suspected to be involved in regulation of mood as part of its function within the cortical-basal ganglia-thalamo-cortical loop [4]. The globus pallidus is a key part of this circuit, and its injury appears to be one of many possible ways in which depressive symptoms can occur in the context of basal ganglia injury [3]. A classic example of depressive symptomatology seen in basal ganglia injury is described in Parkinson's disease (PD). In PD, depression is suspected to occur, in part, as a result of decreased dopaminergic stimulation of the orbitofrontal prefrontal cortex which interferes with prefrontal serotonergic cortical connections. Depression in PD is associated with poor fronto-executive cognitive function and bradykinesia, bradyphrenia, hypomimia, hypophonia, and tremor. These signs and symptoms are particularly unusual to see in children and adolescents who are not taking neuroleptics. As a result, symptomatic sequelae of basal ganglia injury would likely be lower on the differential diagnosis for clinicians than they might have been in an older individual [5].

Intact anterior cingulate circuitry appears to be necessary for goal-motivated behaviors. Reduced activity in this region can contribute to diminished self-awareness, depression, motor neglect, and akinetic mutism [6]. The globus pallidus forms part of a circuit with the anterior cingulate cortex and appears to be necessary for these functions to remain intact. The neuropsychiatric presentation of bilateral pallidal lesions has been described as "psychic akinesia," marked by prominent apathy and anhedonia with limited initiation of behavior. Injury elsewhere along the circuitry functionally connected to the anterior cingulate circuit results in apathy, lack of motivation, alexithymia, and amotivation [7, 8]. Alexithymia, the inability to access or report subjective emotional experience, may develop because of an interruption in the anterior cingulate cortex, the dorsal pons, cerebellum, and left dorsolateral prefrontal cortex as well as bilateral globus pallidus injury [7, 9–11].

In addition to Ronald's basal ganglia injury, it should be noted that he had bilateral cerebellar ischemia as well. There is evidence that involvement of the cerebellar hemispheres in this case may have also possibly contributed to his affective symptoms. Patients with "cerebellar cognitive affective syndrome (CCAS)" have been described as having personality changes with affective blunting correlating with lesions involving the posterior lobe of the cerebellum and vermis [12].

This case is an excellent demonstration of how disruption in circuitry that includes the globus pallidus elicits symptoms that largely overlap with the appearance of depression but differ due to lack of subjective depressive symptoms, alexithymia, and motoric symptoms of parkinsonism. Ronald's lack of subjective expression of depressed mood, anhedonia, or other subjective symptoms that make up the diagnostic criteria for major depressive disorder provide significant evidence for this.

Treatment Strategies

Depression in the setting of parkinsonian symptoms may need to be treated differently than the other diagnoses on the differential for this patient, namely, an underlying mood disorder, adjustment disorder with depressed mood, and a substance-induced mood disorder. Levodopa and dopamine agonists, the mainstays of idiopathic Parkinson's disease treatment, can be tried for the akinetic-rigid motor syndrome but generally are not helpful [3, 13], consistent with the literature on vascular parkinsonism more generally [14]. While antidepressants continue to be recommended for management of depression in parkinsonism, the prevailing logic at this time is that, since depression is a comorbid syndrome associated with the various motor symptoms, dopamine agonists may be helpful in targeting involved mesocortical and mesolimbic pathways [13].

Specific components of this patient's syndrome may be addressed and treated individually, such as alexithymia, amotivational syndrome, and abulia. Unfortunately, alexithymia is not as easily targeted as the core major depressive symptoms may be [7]. There is no specific recommended treatment for alexithymia; however, some evidence exists for use of antidepressants, with some particular reports of benefit with venlafaxine, a dual serotonin and norepinephrine reuptake inhibitor. There are also reports of benefits from deep brain stimulation [15–17].

Neuropsychiatry Lessons

Overall, the globus pallidus is generally relatively spared in hypoxic-ischemic injury as compared to the caudate and putamen, with bilateral pallidal infarcts most commonly associated with prolonged hypoxia and intoxications such as carbon monoxide poisoning and opioid, MDMA (3,4-methylenedioxymethamphetamine), and cocaine toxicity. In addition to basal ganglia injury, bilateral acute complete

hippocampal ischemia with anterograde amnesia syndrome has also recently been reported in a number of cases of opioid overdose and is not unexpected following hypoxic injury [18].

Ronald demonstrates the classic challenge in pediatric neuropsychiatry of differentiating an underlying psychiatric condition from mood and other sequelae of an acquired brain injury. This patient's complexity and challenging premorbid history further complicated both diagnostic and treatment efforts. His case also exemplifies the extent to which sometimes symptomatic management often must diverge from classic evidence-based treatment due to a lack of data on the management of such patients.

Ronald was initially seen by pediatric psychiatry for assessment of "depression"; however, depression has manifestations that overlap with numerous specific neurological insults. Thus, if symptoms of depression are present in a brain-injured patient, it is important to investigate the location of structural damage associated with the patient's neuropsychiatric presentation in order to differentiate a primary psychiatric illness or reactive adjustment symptoms from a secondary neuropsychiatric syndrome.

Subjective feelings of depression or anhedonia are necessary for a primary psychiatric diagnosis of major depressive disorder [19]. Poststroke depression has been found to correlate with infarctions within specific substrates of the prefrontal-subcortical circuits, such as the caudate and pallidum [20]. Apathy, which can be seen both in depression and prefrontal or subcortical injury, also manifests as an observable behavioral syndrome that results in a noticeable reduction of goal directed or voluntary behaviors [21].

Common between apathy and depression are shared motivational deficits, along with lack of concern and emotional indifference [22]. However, an important distinction between apathy and depression is that those with depression are, in fact, more effortful with their voluntary actions compared to normal subjects [23, 24]. A further complication is that apathy and depression can be comorbid in brain injury due to a disruption in frontal-subcortical circuits.

Regarding Ronald, there was high suspicion for depression based on his history of treated depression and multiple drug overdoses. However, he denied all subjective depressive symptoms and did not demonstrate any typical depressive neurovegetative changes. It was thought most likely that his "depressed" appearance represented apathy and parkinsonism related to basal ganglia injury and that these symptoms would be best targeted through dopaminergic therapies rather than antidepressants. It is evident why depressive symptoms would be of significant concern based on his history, and whether treatment would be recommended, especially based on success of his previous trial of citalopram. However, on detailed examination, despite having a depressed affect and external appearance of depression, he reported no subjective phenomenology consistent with major depressive disorder or other forms of depression.

Ronald, like many individuals with acquired brain injury that impacts frontal and subcortical circuitry, struggled both with behavioral motivation and the ability to describe his emotional states. This absolutely complicates his

diagnosis. A multidisciplinary approach, combining both a detailed neuropsychiatric evaluation and a detailed neurological examination, helped provide key data points which helped better categorize and understand the patient's unusual presentation. Crucially, the one area of his physical and mental examination that showed consistency was that he never described what is classified as classic depression, persistently presenting without any clear suicidality, appetite or sleep changes, excessive guilt, change in interest level, anhedonia, or significantly depressed mood. The energy and psychomotor changes that Ronald did experience, which can be seen in depression, were better attributable to his neurological insult.

The 1-year follow-up MRI demonstrating interval resolution of the majority of the diffusion-restricting lesions lends support to the hypothesis that Ronald experienced a purely hypoxic injury in which there was multifocal transient neuronal dysfunction which ultimately did not evolve to cell death outside of a few small areas of encephalomalacia in the basal ganglia bilaterally. With the help of the patient's supportive family, and extensive participation in physical therapy and rehabilitation, he continues to show much improvement in many areas.

Clinical Pearls

- Bilateral globus pallidus injury is a rare effect of opioid overdose that can mimic signs of depressive syndromes but that lacks subjective depressive phenomenology and also includes symptoms of parkinsonism, apathy, and alexithymia. Bilateral hippocampal lesions from overdose of opioids can also result in an atypical anterograde amnesia syndrome [18].
- Alexithymia and depression differ symptomatically and in treatment effects. While major depression classically improves with psychotherapy and antidepressant intervention, alexithymia characteristically benefits minimally, though it may benefit from SNRI treatment or deep brain stimulation.
- In certain cases, the use of specific dopamine agonists can assist in treating depression with associated parkinsonian symptoms. Still, SSRIs are most effective in treating symptoms of depression.
- Lesions of the medial and posterior cerebellum can present with blunted affect or increased impulsivity, known as "cerebellar cognitive affective syndrome" (CCAS) [12].
- Care must be taken in the diagnosis and treatment of individuals with symptoms of a primary psychiatric illness in the presence of a known or suspected neuroanatomical lesion and must be evaluated thoroughly using a cross-disciplinary approach.

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