A Case of Recurrent Psychosis during Sickle Cell Disease Crisis Treated Successfully with Ziprasidone

David R. Spiegel [1], Cory Messerschmidt [1], Jerry Morewitz [1], Morakinyo Akintola [1]

Abstract

We present and follow a series of three consecutive hospitalizations of a 36-year-old, African-American male with sickle cell anemia disease who presented with sickle cell crises and a new onset psychotic episode. After multiple hospitalizations for prior episodes of sickle cell crisis-induced pain, treated with rehydration, blood transfusions, and opiate medication, this hospitalization was the first time he developed psychosis. As such, we discuss the differential diagnosis of the latter, and effective adjunctive treatment with ziprasidone.

Key Words: Sickle Cell Disease, Psychoses, Silent Infarcts, Ziprasidone

Introduction

Sickle cell disease is a genetic disorder with a multitude of complications. Children with sickle cell disease (SCD) have a high rate of overt strokes and silent cerebral infarcts. Overt strokes have been reported to occur in 11% of patients with homozygous hemoglobin sickle cell anemia before age 20. One study reports that progressive cerebral infarcts occurred in 45% of children while receiving chronic blood transfusion therapy; 7% and 11% had second overt strokes and new silent cerebral infarcts, respectively. The authors concluded that children with SCD and overt strokes, receiving regular blood transfusion therapy, experience silent cerebral infarcts at a higher rate than previously recognized (1).

[1]*Department of Psychiatry and Behavioral Sciences, Eastern Virginia Medical School, Norfolk, Virginia*

Address for correspondence: Dr. David R. Spiegel, Eastern Virginia Medical School, Department of Psychiatry and Behavioral Sciences, 825 Fairfax Avenue, Norfolk, Virginia 23507
Phone: 757-446-5888; E-mail: spiegedr@evms.edu

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One aspect of the disease that has undergone relatively limited investigation is the neuropsychiatric sequelae, which can present as neurocognitive dysfunction, anxiety and/or depression, and even psychotic phenomenology (2). Psychotic features characterized by delusions and visual hallucinations, as well as associated aggressive behaviors, have all been associated with sickle cell crisis (3-5). We present and follow a series of three consecutive hospitalizations of a 36-year-old, African-American male with sickle cell anemia who presented with sickle cell crises and a new onset psychotic episode.

Case Presentation

Our patient was a 36-year-old, African-American male with a history of sickle cell anemia disease, admitted to our hospital for sickle cell pain crisis. Four weeks into his admission, our psychiatry consultation service was asked to assist in the evaluation of an abrupt change in the patient's mental status. In the year prior to admission, he had been admitted and treated eight times for sickle cell pain crises without evidence of any psychotic symptomatology. The initial hospital course of this current admission was standard protocol: he received opiates for pain control and intravenous fluids.

Specifically, medications during this hospitalization included patient controlled administered (PCA) hydromorphone (HM) and morphine sulfate (MS) 60 mg po tid. Twenty-five days into admission, staff first noticed an abrupt change in the patient's behavior. He began endorsing auditory hallucinations, claiming to hear voices talking about him. The patient also expressed paranoid thoughts, believing that hospital staff and other patients were laughing at him and began to exhibit new religious delusional ideas. Over the next day, the patient continued to exhibit increasingly odd behaviors and "incessant prayer," at which time we were consulted.

Psychotic features characterized by delusions and visual hallucinations, as well as associated aggressive behaviors, have all been associated with sickle cell crisis.

Our patient reports that he has had transfusion therapy throughout his life. He has had a history of iron overload, including a ferritin level on this admission which was elevated at 1,307 ng/mL. Additionally, he has a history of multiple transient ischemic attacks and "one stroke." He denies a prior history of (or symptoms to support) acute chest syndrome. He has, however, had multiple episodes of sickle cell crises that initially involved treatment in the intensive care unit, including his most recent admission prior to the "index admission" described.

On our initial interview, the patient denied any personal or family psychiatric history, although he did state that in his early teens he engaged in one episode of self-mutilating behavior, not associated with any mood symptoms. He was found to be in hospital gown, appearing younger than his stated age. He engaged with the interviewer in an intense, guarded and, at times, overtly paranoid manner. His mood was irritable, while his affective range was constricted. His speech was tangential, with significant use of metaphors. He also exhibited paranoid delusions and auditory hallucinations, stating that God was speaking to him. He was oriented to person, place, and time, and was without fluctuation in his level of alertness. Evaluation on the Confusion Assessment Method (CAM) (6) screening protocol was unremarkable for delirium. The patient denied using alcohol or illicit drugs as well as over-the-counter and herbal medications. While he had home prescriptions for opiates, the patient indicated that he had not been taking them. He denied any previous personal/family psychiatric history.

On physical examination, no focal neurological deficits were noted. His oxygen saturations at the time of our consultation evaluation were fluctuating, dropping to low 90%/high 80% when off of the oxygen nasal cannula. Otherwise, he remained afebrile and normotensive. His hemoglobin and hematocrit were stable at 6.8 g/dL and 18.3 g/dL respectively. Prior records indicated that he had a baseline hemoglobin of 7.1 g/dL. Complete metabolic profile was unremarkable. On admission, blood alcohol and urine drug screen (UDS) were both negative. Electroencephalogram was within normal limits and noncontrast Magnetic Resonance Imaging (MRI) of the head showed cortical atrophy and benign dural calcification without acute areas of ischemia or hemorrhage, but with frontal and parietal lobe white matter disease. Our patient did have a magnetic resonance imaging of the head from an admission approximately one year prior to this admission, showing only a benign dural calcification with no significant parenchymal abnormalities or gross hemorrhage. There was significantly less white matter disease noted on this MRI. Transcranial ultrasound showed patent basal-cerebral arteries with no significant elevation in mean velocities.

We initiated treatment with ziprasidone 10 mg IM tid. Concomitantly, his morphine sulfate was decreased from 60 mg po tid to 30 mg po tid and hydromorphone discontinued. After two days, his psychosis resolved and we discontinued ziprasidone. He was discharged the next day without clinical symptoms of psychosis being noted.

Unfortunately, within two weeks of discharge, the patient was readmitted to our hospital in another sickle cell crisis. Initial work-up and treatment was similar to the previous admission described, but on this admission his hemoglobin was 4.7 g/dL and, on hospital day two, 2.5 units of packed red blood cells, via transfusion, were administered. Medications during this admission included PCA HM and MS at his outpatient dosage of 30 mg po tid.

On day six of the patient's admission, it was again reported that the patient had developed an "altered mental status" and the psychiatry service was re-consulted. At this point, the patient's most recent hematocrit was 18.5 g/dL, while his hemoglobin was 6.5 g/dL. It was noted that both were improvements on his levels over the previous two days. Our initial psychiatric interview revealed a patient who displayed persecutory delusions but there was no evidence of any auditory hallucinations. Again, our patient's speech was tangential, with significant utilization of metaphors, which made his speech difficult to understand. However, he did not display waxing/waning levels of alertness, and the CAM was again scored as negative for delirium. MRI of the head was unchanged from the prior admission and blood alcohol and UDS were again negative. Based upon our previous experience with this patient, we re-initiated treatment with ziprasidone 10 mg IM tid along with tapering of opiate pain analgesics. Four days later, his psychotic symptoms remitted

and we were again able to stop ziprasidone on the day before discharge, without apparent sequellae.

Interestingly, the patient was readmitted three days later for another sickle cell pain crisis with complaints of severe pain in his right shoulder and knee. Patient's pain was treated with similar opiates and transfusion. Due to his acute psychotic episodes during his previous two admissions, while perhaps atypical, we prophylactically initiated treatment with ziprasidone 80 mg po tid with meals on day three of this admission. The patient endured a fluctuating pain crisis, but was eventually discharged home on day 16 of this admission without developing psychosis and without post-discharge use of ziprasidone.

Notably, after each hospitalization was completed, our patient had no psychotic symptoms, even without ziprasidone.

Discussion

There is a paucity of reports in the literature of transient psychotic episodes in sickle cell patients experiencing a pain crisis, as well as a lack of a clear understanding of the etiology of the manifesting psychosis. Nonetheless, the presence of psychotic features in patients with sickle cell disease has been documented in a few case reports. These patients have presented with visual hallucinations and delusions (7, 8) and severe agitation (5). Statius van Eps et al. (5) reported transient psychosis in a patient with sickle cell hemoglobin C (Hb SC) experiencing an acute thrombotic crisis primarily in the brain. It has also been suggested that there is a correlation between acute sickle cell disease complications and the severity of psychotic symptoms (4).

The differential for acute psychosis in our patient included several possibilities: psychosis secondary to general medical condition (sickle cell disease), substance-induced psychotic disorder, and idiopathic psychiatric illness. We examine each in more detail below.

Psychosis Secondary to General Medical Condition—Sickle Cell Disease: Hypoxia

During a sickle cell crisis, red blood cell deformation results in an inability to adequately carry oxygen to the body's tissues. As a result, sickle cell crises lead to significant anemia and disturbances in tissue oxygenation. This associated hypoxia results in problems with cerebral oxygenation and perfusion, a phenomenon known as anemic anoxia. Sickle cell patients are chronically hypoxic and, during a crisis, this exacerbation of hypoxia can lead to hypoperfusion and altered mental status (9). Furthermore, it has been shown that cerebral hypoxia is a metabolic risk factor for psychosis (10, 11). Therefore, sickle cell crises causing cerebral hypoxia remain a possible etiology for acute psychosis.

Acute chest syndrome (ACS) is the presence of a new pulmonary infiltrate in combination with fever or respiratory symptoms in a patient with sickle cell disease. Severe hypoxia has been reported to occur in up to 18% of sickle cell adults tested and could not be predicted by examination or laboratory findings. Thus, while ACS need be considered in the differential diagnosis of hypoxia in sickle cell disease, our patient did not have any history, physical examination, or imaging findings consistent with this condition (12).

Furthermore, it has been shown that cerebral hypoxia is a metabolic risk factor for psychosis. Therefore, sickle cell crises causing cerebral hypoxia remain a possible etiology for acute psychosis.

Additionally, in adult sickle cell anemia patients, pulmonary hypertension can cause hypoxia and is emerging as a major risk factor for death (13). Nonetheless, our patient did not have this condition. Finally, while sickle cell disease is associated with an increased incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE), which can contribute to hypoxia, as well as mortality (14), our patient did not have symptoms of either DVT or PE, although peripheral vascular studies and a ventilation/perfusion scan were not performed.

Our patient exhibited a fluctuating level of oxygen saturation throughout the hospitalization, with saturations down to 88% recorded in the days prior to the onset of psychosis. He had been supplemented with oxygen canula during his stay, but had not used it consistently. Given the duration of his crisis and oxygen requirement, it is plausible that prolonged, low-grade hypoxia could have contributed to the development of this patient's psychotic symptomatology. Supplemental oxygen administered more consistently might have precluded the development of, or, alternatively, assisted in, the ultimate resolution of the patient's psychotic symptoms.

Psychosis Secondary to General Medical Condition—Sickle Cell Disease: Infarction

Deformation of red blood cells during sickle cell crises leads to vaso-occlusive crises throughout the body. When such occlusion occurs in the cerebral vasculature, Transient Ischemic Attacks and cerebrovascular accidents can result. Not surprisingly, sickle cell patients are at increased risk for stroke, especially during sickle cell crises (15). Although strokes typically happen more often in children, it still re-

mains the leading cause of death in adults with sickle cell disease (16). Overall calculated incidence of first overt infarction in hemoglobin sickle cell anemia patients by age 20 years is 11% and by age 45 years 24%. The highest frequency occurs in children aged two through five years, followed by those aged six to nine years; however, a second peak is observed in adults greater than 20 years of age. Using definitive neuroimaging techniques based on the presence of areas of cerebral atrophy or old infarcts in the border zone regions, these patients may have "silent" stroke (incomplete infarctions) before overt clinical stroke becomes apparent (17).

Stroke can cause psychosis depending on the region of the brain that is rendered ischemic. There are multiple case reports in the literature of stroke-related psychosis (18, 19). These infarcts are often identifiable on MRI. However, small infarcts can go unnoticed on imaging. Furthermore, if there is transient ischemia with recovery, there is less likelihood of findings on neuroimaging.

Thus, cerebrovascular occlusion during sickle cell crises remains another possible etiologic contributant of the acute psychosis seen in our patient.

In our patient's case, MRI of the brain showed no evidence of acute cortical infarction, but did demonstrate white matter disease of the frontal and parietal lobes. The neurochemical basis of psychosis has been proposed as a dysfunction of the corticostriatal pathways with negative feedback disinhibition of the thalamus with resultant sensory flooding, which leads to the perception of psychosis in susceptible patients. Our patient's frontal white matter disease could interfere in these corticostriatal pathways, possibly resulting in psychoses (20). White matter disease can also cause hypoperfusion in the frontal-subcortical circuit components by interfering in neural signaling of the mesocorticolimbic dopaminergic system, which has also been reported to precipitate psychosis (21).

We posit that small, incomplete ("silent")—or even recent—infarcts might not be visible on MRI at the time(s) of neuroimaging; however, in patients with silent cerebral infarctions, it is not unusual for only white matter lesions to be demonstrated on MRI (22). While there is a relative dearth of literature demonstrating direct causality of silent infarcts to development of psychosis, we are not the first to postulate this relationship (5, 23, 24). For instance, Nagaratnam and Pathma-Nathan described a number of psychiatric and behavioral symptoms in relation to silent cerebral infarction, including delusions (23). Additionally, transient occlusions, such as Transient Ischemic Attack, remain an additional possibility and would accordingly have negative specific MRI findings. Thus, cerebrovascular occlusion during sickle cell crises remains another possible etiologic contributant of the acute psychosis seen in our patient.

Substance-Induced Psychotic Disorder

Opiate analgesics are a cornerstone of pain management for sickle cell patients and many patients require opiates as outpatients for chronic pain management, as well as increased amounts during hospitalization for sickle cell crisis. However, in spite of a lack of controlled research support, anecdotal reports have noted that selected opioid medications (such as morphine, meperidine, oxycodone), as well as opioid analgesics as a group, can be associated with a neurotoxic syndrome (25-28). The development of such a syndrome, potentially consisting of various neurocognitive deficits, hallucinosis, delirium, and/or other effects, appears to be more likely in the setting of dehydration, higher opioid dosages, and relatively longer periods of use (25-28). Our patient was receiving substantial daily doses of opiates (PCA hydromorphone and morphine sulfate) during the first two hospitalizations described and resolution of his psychotic symptoms appeared to occur with the tapering of his opioid analgesic to his outpatient dosage level, as well as the addition of ziprasidone and other supportive interventions. This suggests that higher doses of opioid analgesia may have played a contributory, though not exclusive, role in this patient's psychotic clinical presentation.

Idiopathic Psychiatric Illness

Our patient denied any personal or family psychiatric history, although did state in his early teens he engaged in one episode of self-mutilating behavior, not associated with any mood symptoms. Thus, it is possible that he could have had a "substrate" for new onset psychosis, given a possible cerebrovascular precipitant.

Limitations

Our case report does have certain limitations, including the fact that definitive etiology of our patient's psychotic episode could be due to any one or combination of the aforementioned factors. Regardless, recent data about first time cerebrovascular events occurring in sickle cell patients in their 20–30s (17), combined with these patients appearing to have a decreased cerebral vascular reserve (and state of chronic cerebral ischemia) (29), may intimate cerebrovascular origins as the pathogenesis of psychotic symptomatology. Thus, either individually or in combination, our patient's thrombolytic crisis, anemia, opiate utilization and/or hypoxia could have contributed in varying degrees to the patient's

development of psychosis. Additionally, despite performing EEG, MRI and the CAM protocol, other instruments to assess psychiatric symptoms could have been employed. Moreover, follow-up is relatively short.

This suggests that higher doses of opioid analgesia may have played a contributory, though not exclusive, role in this patient's psychotic clinical presentation.

While larger randomized studies would be more conclusive, our case does support the use of ziprasidone as an effective adjunctive therapy for treating acute psychoses occurring during sickle cell crises until other causal factors can be elucidated and managed.

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