Sequelae of Hypoxia and Ventilation

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The patient, a 56-year-old male veteran with a history of diabetes mellitus, hyperlipidemia, and generalized anxiety disorder, was admitted to an outside hospital for respiratory failure, cardiogenic shock, acute heart failure with bilateral interstitial infiltrate, and pulmonary edema. On arrival to the emergency department (ED), the patient was in severe respiratory distress, not oriented to place or situation, drowsy, and with limited communication capacity. Computed tomography scan of the head was not remarkable. The patient had smoked two to three packs of cigarettes per day since the early 1970s. Prior to admission, his medications included tamsulosin, albuterol, oxycodone, and alprazolam 2 mg three times per day. The alprazolam had been prescribed by the patient's primary care physician for at least the past 10 years for anxiety. His troponin level was slightly elevated, suggesting comorbid myocardial ischemic injury. He was intubated and mechanically vented with extubation 2 days later. No paranoia was noted on extubation.

Collateral information from his daughter revealed that the patient had good relationships with his children and no known history of depression, psychosis, psychiatric hospitalizations, alcohol, or illicit substance use for the past 3 decades. He had no significant psychiatric history. The patient has lived alone since the death of his mother 12 years ago. His daughter reported that she and her sister were in touch with him by occasional visits and daily by telephone calls.

The patient's hospital medications included intravenous meropenem, azithromycin, furosemide, nicotine patch, and alprazolam 0.25 mg three times per day. On hospital day 4, he started saying that the hospital staff was spying on him and that he was fearful that staff members would kill him. He refused further treatment, and he and his family requested that he be transferred to the Veterans Affairs (VA) Hospital where he normally received his health care, "for better management." Upon transfer, the patient was fully alert and oriented. The ED physician at the VA hospital noted that the patient still had paranoid ideations about the prior hospital staff. On hospital day 5, the patient asked to leave the VA hospital because he was having continuing paranoid thoughts about the VA nursing staff and physicians. He claimed that they were conspiring against him and watching him by camera. He refused all medications. The Psychiatry Consult Liaison Service (CLS) was called.

On CLS examination, the patient was alert and oriented to time, place, person, date, month, year, name of

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the president, and knew why he was in the hospital. Temperature was normal but blood pressure (148/102 mm Hg), pulse (93 beats per minute), and respirations (22 breaths per minute) were elevated, suggesting anxiety. He denied any pain. A chest X-ray was normal, with pulse oximetry showing oxygen saturation >95%. His laboratory tests were all normal, including complete blood count, basic metabolic panel, thyroid-stimulating hormone, vitamin B-12, folate, and urinalysis. He was dressed appropriately, looked his stated age, and established good eye-to-eye contact. However, he was not cooperative throughout the interview, revealing minimal information and at times becoming agitated. Although he denied any hallucinations, he reported that the treatment team was conspiring against him and wanted to harm him. He refused to provide any specific details. There was mild psychomotor agitation. Speech showed normal volume, rate, and prosody without word-finding difficulties. The patient's mood was "why would I tell you?" Affect was agitated, guarded, and with a reluctance to share information. Thought processes contained paranoid delusions but were goal-directed. Thought content contained no suicidal or homicidal ideations, plan, or content. There was no evidence of obsessions, circumstantiality, tangentiality, thought blocking, insertion, withdrawal, or thought broadcasting.

The patient did cooperate with several components of the cognitive and function assessment. His immediate, recent, and remote memory were intact. Attention and concentration were excellent, with a flawless performance of the serial 7s exam. Clock draw test was normal, as was his drawing of two intersecting pentagons. His insight and judgment were poor. The consult team suggested haloperidol 0.5 mg twice per day and 0.25 mg as needed as well as continuation of alprazolam 0.25 mg twice per day in accord with the medical team's decision to decrease the dose.

On hospital night 5, a temporary detention order was obtained by the medicine team as the patient became agitated and called 911. He requested that the police come to the VA to help him get out of the hospital. On hospital day 6, the patient continued to have delusions of persecution in the presence of full consciousness, attention, and orientation. Hospital day 7 found the patient alert and oriented, with attention and concentration well sustained. However, he was experiencing paranoid ideations that "family members and staff are talking badly about me." Consequently, the haloperidol was increased to 1 mg twice per day. On the same day, neurology consult found the patient to be oriented to date, day of the week, month, year, and location. The patient revealed no memory deficits and was pleasant and cooperative. He has insight into his medical conditions but no insight into his referential and paranoid delusions. The neurologist had no recommendations.

On hospital day 8, the patient demonstrated no paranoia, hallucinations, depression, or anxiety. He was discharged home on haloperidol 1 mg twice per day. At a 6-month follow-up, the patient revealed no residual psychiatric symptoms from his hospitalization. The haloperidol was discontinued.

DIAGNOSIS

Intensive Care Unit Psychosis and Delirium

DISCUSSION

The initial differential diagnosis was very broad and included the following: benzodiazepine withdrawal; benzodiazepine-induced psychosis; drug-induced psychosis; brief psychotic disorder; psychosis due to general medical condition (hypoxic brain injury); and intensive care unit (ICU) psychosis. Medical literature was not found to support benzodiazepine-induced psychosis. A reduction of alprazolam from 6 mg/day to 0.75 mg may induce grand mal seizure; however, there was no mention of a seizure during the first hospitalization. No evidence in the literature could be found to suggest a meropenem-induced or azithromycin-induced psychosis. The differential diagnoses were thus reduced to psychotic disorder due to another medical condition,[1] brief psychosis, and ICU psychosis (a form of delirium).

In this case study, hospital records document that when the patient was in respiratory failure and on a ventilator, he was delirious. Delirium must be considered as the most probable syndrome underlying the post-ventilator psychosis; however, there were no disturbances of consciousness with reduced ability to focus or to sustain or shift attention following extubation. There

was no evidence to support the diagnosis of a preexisting psychiatric disorder. The predominant post-ventilator symptoms were limited to paranoia symptoms, except for impaired executive functioning. There was no change in cognition or development of perceptual disturbances that could not better be accounted for by a preexisting, existing, or evolving dementia. As delirium represents an acute alteration in mental status due to a medical condition (such as infection, hypoxia, or a medication adverse effect), it is probable that despite the resolution of his cognitive symptoms after extubation, paranoia was a residual manifestation of delirium.

In patients with delirium, there are often notable pathophysiologic alterations. Neurochemical changes include decreased acetylcholinesterase, 5-hydroxytriptamine, norepinephrine, and gamma-aminobutyric acid. There may be increased dopamine (DA), glutamate, and cytokines. Significant amounts of DA are released and there is a failure of adequate DA reuptake. The influx of calcium ions stimulates the activity of tyrosine hydroxylase[2] and decreases adenosine-5'-triphosphate and toxic metabolites, inhibiting catechol-o-methyltransferase.[3] The cellular signaling hypothesis suggests that disturbances in intra-neuronal signal transduction affect neurotransmitter synthesis and release. These and other pathophysiologic alteration theories are complementary rather than competing. Data suggest that depletion of DA by alpha methylparatyrosine may protect neurons against hypoxic stress and injury.[4,5] Similarly, DA blockade can be used to reduce hypoxic damage in the hippocampus.[6] DA-2 antagonist agents also enhance acetylcholinesterase release, which may be an additional mechanism that assists in alleviating the symptoms of delirium.[7,8] It can be hypothesized that in delirium while on the ventilator, the patient in this case developed a hyper-dopaminergic state that resolved gradually after he was extubated.

Cognitive impairment, confusional states, and delirium can occur in mild sustained hypoxia.

A study conducted at a teaching hospital suggested that once delirium occurs, only about 4% of patients experience full resolution of symptoms before discharge from the hospital. In the same study, it was not until 6 months after hospital discharge that an additional 40% of patients experienced full resolution of symptoms.[9] Between 50% and 80% percent of ICU patients develop long-term cognitive impairment,[10] and approximately 30% develop clinical depression. It has been reported that 15%-40% percent of patients develop posttraumatic stress disorder (PTSD).[11]

There are several clinical syndromes that follow cerebral hypoxia and anoxia.[12] Cognitive impairment, confusional states, and delirium can occur in mild sustained hypoxia. Brief anoxic-ischemic events include syncope and abortive or actual generalized seizure activity. Sustained severe hypoxia may result in coma with residual neurological deficits leading to dementia, a vegetative state, or brain death. Other sustained severe hypoxia sequelae include seizure activity, and watershed infarction of the cerebrum, cerebellum, and spinal cord, in addition to infarction distal to a preexisting arterial stenosis or occlusion and postanoxic demyelination. Delayed postanoxic encephalopathy is a rare condition that presents after apparent recovery from acute cerebral anoxia. It appears within 1 to 3 weeks after anoxia and may lead to cognitive, neuropsychiatric, motor, and extrapyramidal abnormalities. At onset, the patient shows apathy, confusion, attention and memory deficits, irritability, and aggressiveness. This may be followed by altered gait, spasticity, and extrapyramidal manifestations, which in some cases may eventually lead to coma or death.[13-15] In the present case, the veteran has not exhibited any of these short-term or long-term negative sequelae 6 months after hospital discharge.

In the present case, although the patient's sensorium was clear, it is interesting that in the realm of cognitive functioning, his executive functioning (insight/judgment) was the one area to be noted deficient. It has been reported that the frontal lobes (neocortex) are sensitive to decreased perfusion, being physiologically distant from the heart. There is likely a relationship between frontal lobe dysfunction (impaired insight/judgment/reality testing) and development of paranoid delusions. For example, a study of Alzheimer patients found that decreased me-

tabolism in the frontal lobes was associated with an increased risk of delusions.[16] Devinsky[17] proposed a dual mechanism for the delusional misidentification syndromes. The mechanism involves the negative effects of right hemisphere and frontal lobe dysfunction (eg, trauma, hypoxia) accompanied by compensation from an intact left hemisphere. The left hemisphere attempts to interpret the altered right hemisphere and frontal lobe attachment of impaired emotional valence and familiarity to stimuli with extraordinary explanations of these abnormal events, leading to delusional symptoms. Hence, it is the left hemisphere that is deluded by the reaction of trauma and/or hypoxia in the right hemisphere and frontal lobe.[17]

A common phenomenon in the ICU is ICU psychosis, also called ICU delirium. This occurs when patients in an ICU or similar setting experience a cluster of serious psychiatric symptoms. The ICU environmental causes are numerous. Patient stress may be increased in the ICU as they may feel a loss of control of their life. The ICU may have constant light levels that disrupt patient biorhythms so there is no awareness of day or night. Disorientation occurs with the patient's loss of time and date. A patient may have sensory deprivation by virtue of being in a room that often has no windows, and is often without family, friends, or familiar surroundings. The noise of monitoring devices can be disturbing and create sensory overload. The constant disturbance and noise associated with the hospital staff coming at all hours to check vital signs and to give medications may also contribute to sleep disturbance and sleep deprivation.[18] There are multiple possible medical causes of ICU delirium. Origins of delirium may include inadequately controlled pain, heart failure, dehydration, unrecognized infection, metabolic disturbances, and cumulative analgesia. Commonly seen symptoms are altered state of consciousness, disorientation, agitation, anxiety, auditory hallucinations, and delusions. The level of consciousness may include aggressive or passive behavior periods. The latter are often observed by the nursing staff and not by the treatment team.[19]

It is most important to have a consistent, multidisciplinary clinical team and to minimize relocation in the hospital.

How can ICU psychosis and/or delirium be prevented? A landmark study by Inouye et al.[20] in 1999 reported six interventions that reduced delirium from 15% to 9.9%. In July 2012, the National Institute for Health and Clinical Excellence[21] included 13 recommendations for preventing delirium by 33% in at-risk patients. It is most important to have a consistent, multidisciplinary clinical team and to minimize relocation in the hospital. Other strategies include avoiding catheterization and treatment of dehydration, constipation, hypoxemia, infections, pain, and malnutrition. Many other strategies have been reported: minimizing polypharmacy; addressing poor nutrition and sensory impairment (eg, vision, hearing); promoting sleep hygiene (eg, lower lights, television off, pagers on vibrate, avoid waking patient for vital signs); coordinating lighting with the local day-night cycle; using orientation strategies (clock, calendar that patient can see); and, stimulating cognition three times each day (word games, structured reminiscences).[20-23]

The barriers to delirium and ICU psychosis are substantial. The primary barrier is the failure to identify at-risk patients on hospital admission.[24] There is often insufficient time to perform a thorough delirium-risk screen. Hospital staffs are frequently inadequately trained in the prevention and identification of delirium. Removing glasses and hearing aids from patients promotes sensory deprivation. Frequent moves within the hospital reduce continuity of care.[22,23]

According to the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (*DSM-5*)[1] criteria, the diagnosis of psychotic disorder due to another medical condition may be supported by the following: prominent hallucinations or delusions; evidence from the history, physical examination, and/or laboratory findings that the disturbance was the direct physiological consequence of a general medical condition (respiratory failure, cardiogenic shock, acute heart failure with bilateral interstitial infiltrate and pulmonary edema); the disturbance was not better accounted for by another mental disorder (eg, brief psychosis, benzodiazepine withdrawal); and the disturbance did not occur exclusively during the course of a delirium.

In this case, all the patient's sensorium was essentially clear, with executive functioning being the one cognitive deficit that was impaired. The coding would be based on the predominant symptoms of the psychotic disorder due to another medical condition (283.00): 293.81 with delusions; or 293.82 with hallucinations. The name of the general medical condition would be listed before the psychiatric diagnosis.

CONCLUSIONS

Delirium following cerebral hypoxia is commonly seen on the medical and surgical services. Psychotic symptoms often appear as a component of delirium. Diagnostically, in the presence of a recent significant cerebral hypoxic injury that resolved within 1 to 6 days after 2 days of ICU ventilation, and the absence of any past psychiatric or family history, diagnosis of a brief psychotic disorder can be ruled out. In the case presented here, the most probable pivotal precipitants were the medical conditions leading to the hypoxia and the need for ventilation: respiratory failure; cardiogenic shock; acute heart failure with bilateral interstitial infiltrate; and pulmonary edema. To the best of our knowledge, psychosis in the form of paranoid delusions and referential delusions based on the patient's paranoia and the assumption that people were talking about him presenting as postsequelae signs of cerebral hypoxia following an episode of delirium, with a clear sensorium is an uncommon phenomenon in the English medical literature.

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