The Differential Diagnosis of Excessive Daytime Sleepiness and Cognitive Deficits in a Patient with Delirium, Schizophrenia and Possible Narcolepsy: A Case Report

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Abstract

Narcolepsy and schizophrenia are disorders which share common features of negative symptoms, excessive daytime sleepiness and cognitive deficits. Presented here is a case report of a fifty-nine year old man with a past medical history of schizophrenia who was evaluated for suspected symptoms of delirium. After an electroencephalogram was performed with surprising results, the patient's differential diagnosis included schizophrenia with comorbid narcolepsy. We present emerging evidence that excessive daytime sleepiness and attentional deficits in both narcolepsy and schizophrenia may share a common pathophysiological pathway through orexin deficiency and its effects on the dopamine system. Finally, we discuss the potential for modafinil as a treatment for excessive daytime sleepiness and attentional problems in schizophrenia and narcolepsy.

Key Words: Cognition, Schizophrenia, Sedation, Sleep, Dopamine

Introduction

The hallmarks of delirium as described by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* are a disturbance of consciousness with reduced ability to focus, sustain or shift attention. Also present is a change in cognition, such as memory deficit, disorientation or language impairment, or a perceptual disturbance. Delirium usually develops over a short period of time and fluctuates during the course of the day (1).

Schizophrenia is a chronic and serious mental disorder affecting thought, emotion, behavior and cognition. The disease has a mixture of characteristic signs and symptoms, including the positive symptoms of delusions, hallucinations, disorganized speech and grossly disorganized or catatonic behavior, and negative symptoms such as flattened affect, alogia and avolition (1). Patients with schizophrenia also have cognitive deficits, including poor attention span.

Rapid eye movement (REM) sleep onset disorders such as narcolepsy are classified as dyssomnias since they are due to abnormalities in the amount, timing and quality of sleep (1). Narcolepsy is characterized by repeated attacks of sleep, cataplexy and recurrent patterns of REM sleep during the time between sleep and wakefulness. Individuals suffering from narcolepsy experience cataplexy, recurrent REM sleep, hallucinations and excessive daytime sleepiness (EDS) (1).

We present a patient with schizophrenia and clinical symptoms that suggested a diagnosis of delirium after being struck by an automobile, resulting in intracerebral bleeds. Little improvement in supposed symptoms of delirium could only be explained after electroencephalography helped potentially clarify this diagnostic dilemma.

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Case Report

Our patient was a fifty-nine year old, African-American male who was evaluated by the Consult-Liaison (C-L) Service to distinguish delirium from schizophrenia. The patient presented to the Emergency Department after being struck by an automobile. He was thrown approximately twenty-five feet and sustained injuries that warranted admission to the Multi-Trauma Service. At admission, no past medical history, family history, social history or psychiatric history was elicited. The patient was found to have right subarachnoid and subdural hematomas, a left epidural hematoma and left temporal bone fractures. In the ambulance, his Glasgow Coma Scale (GCS) was 15, and at the hospital it was 11 (2). Neurosurgery determined his injuries to be inoperable, and supportive care was provided.

Thus, there does seem to be a common phenomenology of EDS and attentional deficits in schizophrenia, narcolepsy and hypokinetic delirium.

Shortly after admission, the patient became agitated and was medically treated with haloperidol and lorazepam, which were subsequently changed to loxapine twice daily. Collateral history from the family revealed that the patient had a twenty-five year history of paranoid schizophrenia. There was a history of noncompliance with outpatient medications, including, but not limited to, haloperidol, thiothixene, risperidone and olanzapine, as well as with therapy, with the patient last receiving treatment two years prior to this admission. He had no history of substance abuse. Due to the patient's inability to consent to any medical procedures, the C-L Service became involved in his care.

On our initial evaluation, the patient had a Richmond Agitation Sedation Scale (RASS) score varying between -1 and +1 during the course of the interview (3). He was unable to complete the "Vigilant A" section of the Confusion Assessment Method (CAM), and a clinical impression of delirium was established (4). At times he was observed performing stereotypic movements such as rubbing his forehead and picking at the tape surrounding his intravenous line. While this could be attributed to catatonic schizophrenia, these movements seemed to develop after the initiation of haloperidol and, subsequently, loxapine. The patient was not able to complete a full psychiatric assessment. Nonetheless, loxapine was discontinued, being a possible causal agent of these stereotypies. The patient was started on 5 mg olanzapine BID. Gamma glutamyl transpeptidase (GGTP) was ordered to determine recent past alcohol usage and evaluate for possible alcohol withdrawal. Ammonia level was also ordered to rule out hepatic encephalopathy as a cause of his suspected delirium. Both the GGTP and the ammonia levels were within normal limits, and a urine drug screen on admission was negative.

With continuing fluctuations in his RASS score from -1 to -3, electroencephalography (EEG) was ordered to help determine whether the patient's current state was due to delirium or his underlying psychiatric diagnosis (5). The EEG was performed, and the typical slowing usually found in patients with delirium was not appreciated (5). Rather, the patient drifted readily between alert and drowsy states, and twenty minutes into the recording entered sleep. The pattern noted during the procedure was suggestive of sleep-onset REM, inferring that the patient suffered from an undiagnosed sleep disorder, possibly narcolepsy. A multiple sleep latency test (MSLT) could have proved diagnostic, but one was not performed prior to the patient leaving our facility. Both the patient and his family denied any history of possible symptoms of narcolepsy until after his head trauma from the motor vehicle accident.

Due to the surprising result found on our patient's EEG, olanzapine was discontinued, and he was started on modafinil 200 mg PO to treat the possible narcolepsy. Olanzapine was discontinued in lieu of the less sedating ziprasidone with an antipsychotic dose of 80 mg PO BID with meals. With both medications he was more alert, more goal oriented and, though he still had difficulties with attention span, was able to sustain and focus attention to a greater degree.

Discussion

This case highlights the difficulties encountered with a clinical diagnosis of delirium in a patient with a psychotic illness. While the CAM has reported sensitivities for delirium ranging from 0.81–0.86, the reported specificities range from 0.63–1.00 (6, 7). Initially the patient seemed to have hypokinetic delirium and his motor symptoms were treated with a dose of olanzapine based on case reports indicating potential efficacy of olanzapine in the treatment of hypokinesis (8, 9). While the patient became less hypokinetic during this treatment, he was still inattentive with verbal and motor stereotypies. Ultimately, an EEG was ordered to help clarify the clinical findings, and it proved to be crucial in further developing the differential diagnosis. Despite its limitations in differentiating delirium from dementia, the EEG is useful in the uncommon situation in which one is attempting to distinguish delirium from other psychiatric states. EEG findings in delirium (not delirium tremens or benzodiazepine withdrawal) consistently show diffuse disorganization and flattening followed by reorganization at

frequencies slower than normal for that person (10). Additionally, patients with delirium may show relative slowing (i.e., reduction in specific background rhythm by 3–4 Hz) (11). Since the EEG did not demonstrate findings consistent with delirium, our new working diagnosis for the patient's symptoms of decreased alertness and inattention was narcolepsy with cognitive symptoms of schizophrenia.

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Because of the many overlapping symptoms between schizophrenia and narcolepsy, misdiagnosis between these two may be more common than with other disorders. While not pathognomonic for either illness, hallucinations occur in both schizophrenia and narcolepsy. A comparison of hallucinations in both of these illnesses has been reviewed elsewhere (12). Briefly, hallucinations that occur solely at the interface of the sleep-wake junction (and visa versa) are more consistent with narcolepsy than schizophrenia. While hallucinations are strongly associated with schizophrenia, hypnagogic or hypnopompic hallucinations may occur in 20–40% of narcolepsy patients. Of particular interest for this case report, EDS occurs in nearly 100% of narcolepsy patients, with resultant cognitive difficulties in attention and concentration, while EDS in schizophrenia is probably multifactorial (12).

We would like to briefly review the negative/cognitive symptoms in schizophrenia to understand how the aforementioned diagnostic dilemma developed. The cognitive symptoms of schizophrenia include distractibility, poor attention and the dysexecutive syndrome (13). The negative symptoms refer to flattening of affect and a reduction in emotion. Behavioral indicators are blunted affect, emotional and passive withdrawal, poor rapport, lack of spontaneity, motor retardation and disturbance of volition (13). At the core of the cognitive symptoms is a working memory deficit in which there is difficulty in maintaining items in short-term memory, which could directly or indirectly account for a wide range of cognitive symptoms. While the pathophysiology of schizophrenia continues to be evaluated, current theory posits hypodopaminergia in the prefrontal cortex to account for the cognitive and negative symptoms of schizophrenia (13). Antipsychotics, especially the conventional types, decrease dopaminergic transmission throughout the prefrontal cortex, which could accentuate cognitive and negative symptoms in our patient who has been treated with haloperidol and thiothixene.

While hypodopaminergia may have played a role in the patient's attention deficits, EDS in schizophrenia may be considered a "negative symptom," and may also be influenced by low amounts of stage 4 sleep. Previous publications have shown that persons with schizophrenia tend to display low amounts of stage 4 sleep compared with control participants. This is consistent with the findings of Orzack et al. (14) that showed decreased slow-wave sleep is associated with poor performance on a continuous performance test. In addition, increased time spent awake during the night correlates with longer reaction times on selective attention tasks in patients with schizophrenia, which may reflect reduced vigilance or increased sleepiness during neuropsychological testing. It is also noted that patients with schizophrenia exhibit frontal and dopaminergic impairments that have been linked to stage 4 deficits (15). Thus, there does seem to be a common phenomenology of EDS and attentional deficits in schizophrenia, narcolepsy and hypokinetic delirium.

Nonetheless, based on our findings, modafinil augmentation in the treatment of EDS and attentional deficits in schizophrenia may warrant larger scale trials.

This case is made more intriguing by the possibility of our patient having comorbid narcolepsy and schizophrenia, which is a rare, albeit, sporadic occurrence. Approximately ten years ago, orexin was discovered and, shortly afterwards, the core features of narcolepsy, especially EDS, were explained by a decrease in orexin cells in the lateral hypothalamus (16). Orexin has functional roles in arousal, energy homeostasis and sleep. Anatomical organization of the orexin system has indicated that orexin and dopamine intersect in certain brain sites. Both orexin inputs to the midbrain dopaminergic cell group regions and to projections to the prefrontal cortex (PFC) that receive dopamine inputs have been described, especially at the ventral tegmental area (VTA), which itself innervates the PFC. It has been proposed that orexin modulates dopaminergic transmission, especially in the PFC, a region purported to be involved in the negative and cognitive symptoms of schizophrenia. Preclinical data intimates that intra-VTA infusion of orexin improves PFC-mediated cognitive functions. Similarly, dopamine innervation of the lateral hypothalamus (LH) indicates that dopamine inputs to the LH/orexin cells may modulate orexin activity as well (17).

Theoretically, in our patient, his decreased alertness, arousal and attention span could be described in multiple

manners. Of course, a hypokinetic delirium could have explained these initial presenting symptoms. But, as his medical condition improved, his EDS and attentional deficits did not. It would be tempting to ascribe this solely as a function of schizophrenia; however, if we consider that our patient did have comorbid narcolepsy, it is conceivable that a bidirectional relationship between dopamine and orexin is at the "core" of EDS and attentional deficits. For instance, if our patient did have narcolepsy, a decrease in orexin input to both the PFC and VTA could accentuate the EDS and cognitive symptoms. Additionally, given the possible association between hypodopaminergia at the VTA and PFC, it is possible that, if there is decreased dopaminergic innervation to the LH/orexin cells, the EDS and cognitive symptoms in our patient could be explained by decreased orexin secondary to attenuated dopamine transmission. Toward that rationale, our patient's alertness, arousal and attention span did improve with modafinil, which has been reported to activate orexin neurons (17). It is possible that enhanced dopaminergic transmission in the PFC via activation of orexin neurons could improve EDS and cognitive symptoms, which may be dependent on frontal cortical dopamine innervation. However, we would like to caution this theory, since, to the best of our knowledge, the functional relationship between dopaminergic transmission and the LH/orexin region in schizophrenia has not been established. Nonetheless, based on our findings, modafinil augmentation in the treatment of EDS and attentional deficits in schizophrenia may warrant larger scale trials.

There are several limitations in this case report, some of which have already been addressed. First of all, our patient's diagnosis of narcolepsy was suggested by the EEG; however, this diagnosis can only be confirmed by MSLT (12), which was not performed on our patient. Secondly, the interaction involving orexin and dopamine transmission is in its infancy, and further research concerning orexin and schizophrenia needs to be performed. Thirdly, improvement in EDS and cognition may have occurred without medication intervention if more time were allotted for recovery from the intracerebral bleed. Finally, treatment with olanzapine, then subsequently ziprasidone, may have improved EDS and cognitive symptoms attributable solely to schizophrenia. That is, if our patient did not have narcolepsy, improvements in symptoms may have occurred as the schizophrenia was treated. Nonetheless, we do feel this case represents common phenomenology in delirium, schizophrenia and the infrequent diagnosis of narcolepsy.

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