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Primary versus secondary psychosis in a patient with congenital liver disease

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SUMMARY

In this article we report the case of a man with congenital liver disease who later developed psychotic illness and was diagnosed with schizophrenia. We illustrate how decompensation in liver function was associated with the exacerbation of psychotic symptoms. We discuss differential diagnostic challenges, and the possible overlapping neuropathology in these two conditions that may converge on glutamate/N-methyl-D-aspartate dysfunction. This patient's case underscores the need for further research to elucidate the possible underlying mechanisms linking congenital liver disease and psychosis.

BACKGROUND

Schizophrenia is a chronic, disabling mental disorder that affects 0.5%–1% of the population worldwide that commonly presents in late adolescence and early adulthood. It is characterised clinically by positive symptoms (delusions, hallucinations and thought disorder), negative symptoms (ie, social withdrawal, poverty of speech and anhedonia) and cognitive deficits (ie, attention, working memory and executive function).

Schizophrenia is associated with various neuroanatomical and structural brain abnormalities. For decades, the dopamine hypothesis has been the leading theory used to explain the mechanism of the clinical manifestations of schizophrenia symptoms. Over the past 20 years, however, there has been a confluence of evidence pointing to alterations in excitatory signalling, particularly involving hypofunction of the N-methyl-D-aspartate receptor (NMDAR), as a key contributor to the schizophrenia disease process.[1–5]

Hepatic encephalopathy (HE) is a neurological disorder that occurs as a result of liver dysfunction, particularly in cases of cirrhosis. Advanced liver disease and portosystemic shunting do not just affect the liver; they notably impact brain function, causing behavioural, cognitive and motor impairments known as portosystemic encephalopathy, now part of HE.[6]

The neuropsychiatric symptoms of HE can include depression, mania, hallucinations and delusions.[7 8] Many of these neuropsychiatric alterations are the consequence of altered neurotransmission. Hyperammonaemia is a main contributor to the alterations in neurotransmission and neurological functions in HE. However, there exists conflicting evidence regarding its utility in monitoring treatment response and predicting prognosis for patients with HE. It is evident that blood ammonia levels correlate with the severity of HE. Nonetheless, elevated ammonia levels can persist even after clinical resolution of HE. Furthermore, the association between ammonia lowering and clinical treatment response is inconsistent, and ammonia levels are not routinely used for therapeutic monitoring. Recent studies have hinted at a prognostic significance of ammonia in patients with overt HE.[9]

Both glutamatergic and GABAergic neurotransmission are altered in animal models of HE. Other models of acute liver failure have noted increased NMDA-displaceable glutamate binding in the cerebral cortex and hippocampus.[10–12]

Considering findings that have traced alterations of the same neurotransmitter systems in both schizophrenia and HE, there might be room to consider an association of cirrhosis in causation and exacerbation of schizophrenia in a patient diagnosed with both disorders.

In this case report, we describe the clinical history of a man with chronic liver disease who later developed psychotic illness and was diagnosed with schizophrenia. We illustrate how decompensated cirrhosis was associated with the exacerbation of psychotic symptoms, and we discuss differential diagnostic challenges as well as possible unifying neuropathogenic mechanisms.

CASE PRESENTATION

The patient is a male in his mid-20s with a history of early-onset cirrhosis secondary to congenital biliary atresia, and Kasai procedure at the age of 2 weeks. From childhood, the patient has been treated with lactulose, rifaximin and propranolol for chronic liver cirrhosis. Four years prior to recent presentation, he experienced his first psychotic episode which was concurrent with decompensated cirrhosis and high ammonia level in the context of liver medication non-adherence. Notably, the patient's cognitive development and educational milestones were reportedly within normal limits up to his 20s. Also, there was no personal or family history of psychiatric symptoms and no history of alcohol or drug use. After an extended period of medical and psychiatric hospitalisation, a diagnosis of schizophrenia was established, leading to the initiation of antipsychotic treatment with paliperidone. Concurrently, his HE medications were restarted and his mental status and ammonia levels improved.

Following several months of antipsychotic treatment, the patient was gradually tapered off of medication. Remarkably, after discontinuation, the patient displayed no discernible signs of psychotic illness, until he again experienced decompensation

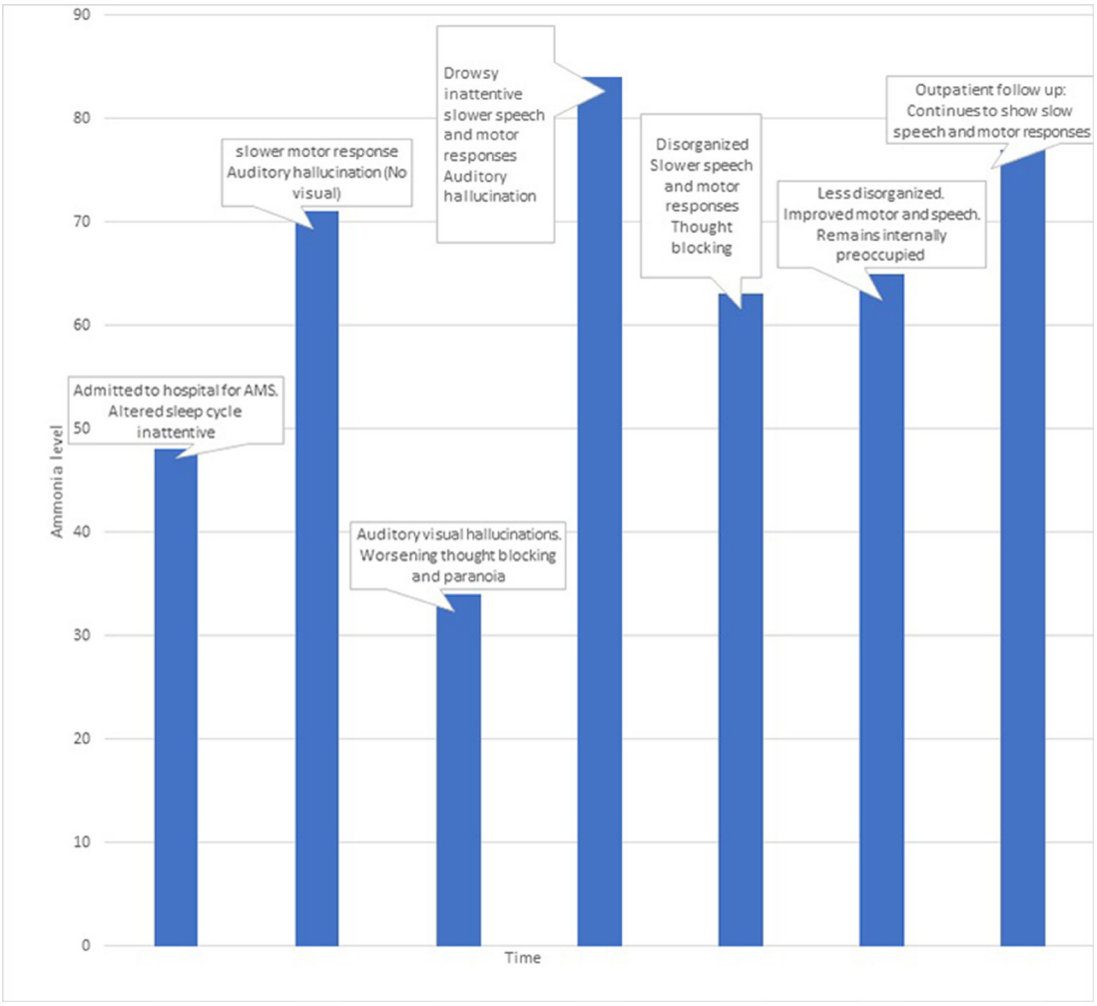

Figure 1 Summary of fluctuations in patient's mental status and corresponding ammonia level. AMS: Altered Mental Status

of cirrhosis. In fact, this occurred several times, where psychotic exacerbations and psychiatric hospitalisations were preceded by decompensated cirrhosis.

On his initial evaluation in our emergency department, the patient presented with disorientation, confusion, psychomotor slowing and jaundice following several days of medication non-adherence. Additionally, the ammonia level was measured at 48 µmol/L (Model for End-Stage Liver Disease (MELD) score: 17). He was admitted for acute medical care with consultation from the hepatology, neurology and psychiatry specialists. On initial psychiatric evaluation, the patient exhibited pronounced disorganisation both in the thought process as well as psychomotor agitation, posturing and moving his arms in bizarre ways and appearing internally preoccupied. During the course of hospitalisation, the patient displayed fluctuating mental status, elevated ammonia levels, cognitive impairment, as well as auditory and visual hallucinations (figure 1). The initial head CT scan and MRI showed no abnormalities while the ammonia level remained consistently elevated and fluctuating.

DIFFERENTIAL DIAGNOSIS

This case illustrates the complexity of making a definitive diagnosis of schizophrenia spectrum illness in a patient with lifelong liver disease who manifests psychotic symptoms, particularly during episodes of decompensated cirrhosis.

The convergence of symptoms and the intricate interplays between schizophrenia and advanced liver disease in this patient necessitate careful consideration of both diagnostic and treatment strategies. While in this patient age of onset and symptoms of thought disorganisation, hallucinations and delusions are consistent with schizophrenia, a diagnosis of schizophrenia is predicated on a lack of other potential causes of mental status change. In this case, strong indicators of delirium or HE rather than decompensation of a primary psychiatric disorder include abrupt and profound alterations in mental status, an underlying medical condition, visual hallucinations, fluctuating consciousness and the sudden onset of psychiatric symptoms during exacerbation of underlying medical illness—all of which were observed in our patient (see table 1).

Notably, on interviewing the patient and family, he had not shown any prodromal symptoms of schizophrenia. He exhibited a pattern where exacerbation of psychotic symptoms corresponded with episodes of decompensated cirrhosis. Atypicality of psychotic symptoms, fluctuation in the content of delusions and auditory hallucinations, the presence of visual hallucination, as well as varying associated distress level, may be useful in distinguishing exacerbations of a primary psychotic illness from secondary psychosis. Remarkably, there are periods of stability in mental status, off medication, as long as he maintained stable liver function.

Table 1 Signs and symptoms supporting the diagnosis of primary psychosis versus encephalopathy

Signs and symptoms supporting the diagnosis of primary psychosis	Signs and symptoms supporting the diagnosis of encephalopathy
Age of onset	Confusion at initial presentation
Frequent auditory hallucinations and paranoia	Disorientation at initial presentation
Disorganised thought and behaviour	History of cirrhosis and signs and symptoms of acute decompensated liver function
Persistence of psychotic symptoms during the course of hospitalisation, despite effective treatment for encephalopathy	Frequent visual hallucinations
During the course of hospitalisation, improvement of attention, orientation, memory and other neurologic symptoms were not accompanied by reduction of psychotic symptoms	Variable degree of paranoia and delusional thinking
	Slowed speech and motor function, asterixis, jaundice at initial presentation
	Lack of family history
	Lack of prodromal symptoms

However, during the course of hospitalisation, despite effective treatment for acute HE and improvement of hepatic function, the patient continued to exhibit psychotic symptoms. While the improvement in attention, orientation and memory suggests a partial response to treatment, the persistence of psychosis raises questions regarding its primary origin and the role of liver decompression in exacerbating psychiatric symptoms.

TREATMENT

During the present medical admission, lactulose was increased to 20 mL four times daily and rifaximin was continued. Paliperidone was restarted by the psychiatry team at 3 mg and gradually increased to 9 mg daily. The rationale to start paliperidone over other antipsychotics is that this second-generation antipsychotic, the primary active metabolite of risperidone, is metabolised and excreted solely by the kidney. No dosage adjustment is required for hepatic impairment. Moreover, studies have shown switching risperidone to paliperidone yields improvement of liver enzymes during drug-induced hepatitis or liver cirrhosis.[13 14] However, it is important to mention that long-term treatment with paliperidone, like other second-generation antipsychotic medications, carries the risk of metabolic side effects and subsequent non-alcoholic fatty liver disease, now referred to as metabolic dysfunction-associated steatotic liver disease which may adversely affect outcomes in patients with cirrhosis.[15]

After 8 days of management on the medical service, his hepatic function improved, ammonia level decreased, but psychosis persisted, necessitating transfer to inpatient psychiatry.

While in the psychiatric unit, his psychotic symptoms gradually abated. Despite the notable reduction in psychotic symptoms, some negative symptoms (blunted affect, psychomotor slowing) and cognitive impairment (inattention, executive dysfunction) persisted. Due to the patient's extensive history of medication non-adherence, a collaborative decision was reached between the patient and the treatment team to transition the patient to a long-acting injectable antipsychotic (paliperidone palmitate, maintenance dose of 78 mg every 4 weeks), with close outpatient follow-up and collaboration between psychiatry and hepatology services.

OUTCOME AND FOLLOW-UP

Approximately 1 year following the patient's last psychiatric hospitalisation, he underwent a liver transplantation. After

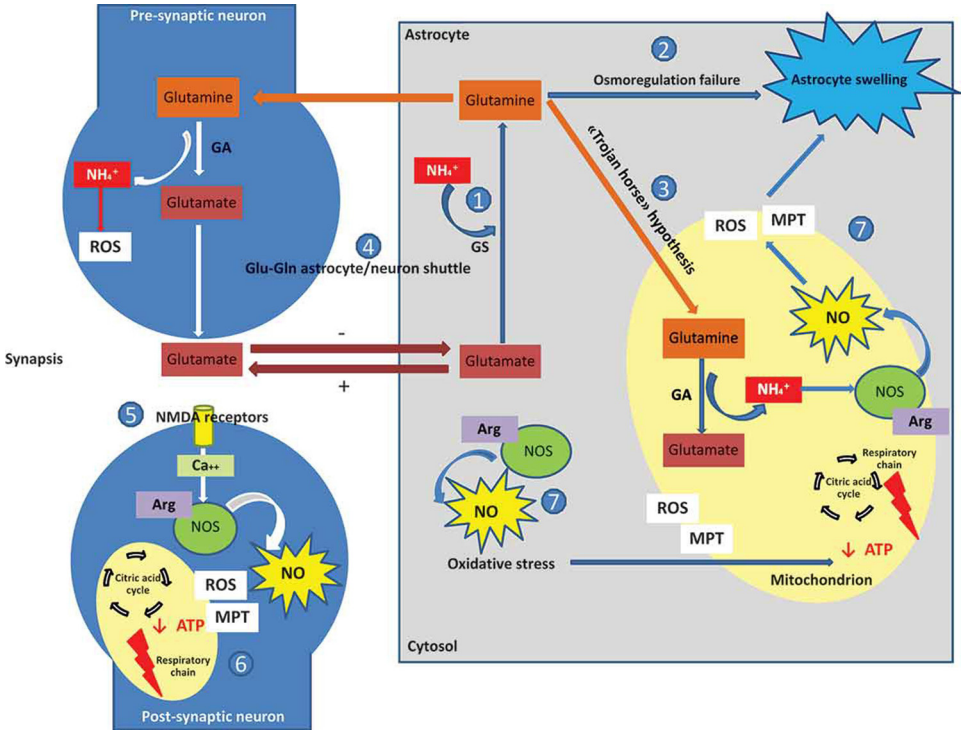

Figure 2 Schematic representation of the main mechanisms of ammonia neurotoxicity. This figure illustrates how ammonia toxicity in the brain is tightly connected to Gln metabolism in astrocytes. Adopted from Maines *et al*.[22]

transplant, he went on immunosuppressant medication (tacrolimus, prednisone and mycophenolate), along with Infectious disease prophylaxis (acyclovir, trimethoprim/sulfamethoxazole). He was maintained on paliperidone palmitate 78 mg monthly and to date has not had any further psychotic exacerbations or subsequent hospitalisations. He does, however, continue to have psychomotor slowing, constricted affect and concrete thinking.

DISCUSSION

This case illustrates the complexity of making a definitive diagnosis of schizophrenia spectrum illness in a patient with lifelong liver disease who manifests psychotic symptoms, particularly during episodes of decompensated cirrhosis. Whether he has schizophrenia, HE or some combination of the two may be impossible to determine, however, the latter seems most likely. In this case, it seems prudent to discuss potential overlapping neuropathophysiological mechanisms that may have contributed to the causation and exacerbation of psychotic symptoms in this patient.

In schizophrenia, long-term disability is primarily caused by negative and cognitive symptoms. These are linked to pervasive cortical pathology and are unlikely to be simply the consequence of dopamine dysfunction.[16–18] Over the past quarter century, ample evidence from various sources has supported the role of glutamatergic dysregulation in the pathophysiology of schizophrenia.[4] The glutamate theory of psychosis posits that the NMDA subtype of glutamate receptors is hypofunctional at critical synapses of prefrontal cortex. NMDA hypo-functioning has downstream effects on the GABA neurotransmitter as well.[5]

One leading hypothesis is that the pathophysiology of schizophrenia has a neurodevelopmental component.[19 20] Development during adolescence is a dynamic period marked by extensive functional and neuroanatomical changes such as fine-tuning of excitatory, inhibitory and monoaminergic neurotransmitter systems, stabilisation of synapses to increase the efficiency of neural function and diminish redundancy, and beginning of integration between late maturing and early maturing brain structures.[21] Therefore, imbalances or changes in timing of these developmental processes clearly increase the risk for psychiatric disorders.

Disruption of NMDA glutamate functioning is not limited to schizophrenia. Neurodegenerative abnormalities in Alzheimer and other dementias are found to cause NMDA glutamate alteration. Also, NMDAR blocking action is responsible for dissociative anaesthetic effects. Glutamate dysfunction can cause positive, negative and cognitive symptoms in various disorders such as delirium and HE.[5]

HE is a major neuropsychiatric disorder occurring in patients with severe liver disease. Although hyperammonaemia is a main contributor to the alterations in neurotransmission and in neurological functions in HE, there is increasing evidence that alterations of glutamatergic function are implicated in the pathogenesis of central nervous system consequences of acute liver failure.[8–10]

To understandthe role of glutamatergic pathway in HE, it is important to note that the urea cycle does not exist in brain and that ammonia detoxification relies on glutamine synthesis by astrocytes. Ammonia exposure alters the Glu-Gln shuttle between astrocytes and neurons, raising extracellular glutamate levels. Elevated glutamate stimulates neurons excessively through NMDARs (figure 2).[22] Furthermore, studies have found a good correlation between cerebral glutamine concentration and the severity of psychoneurological signs and intracranial pressure measurements in cirrhotic patients with hyperammonaemia.[23]

Studies on rats has shown acute ammonia toxicity causes activation of NMDARs whereas chronic moderate hyperammonaemia prevents this effect. These results indicate that long-term exposure of neurons with moderate hyperammonaemia induces NMDAR hypofunction, sharing a mechanism implicated in the manifestation of negative and cognitive symptoms of schizophrenia.[24] Improvement of acute HE in rats by memantine (a non-competitive NMDAR antagonist) further indicates the involvement of NMDA-receptor alteration in the pathogenesis of HE. Moreover, models of acute liver failure have noted increased NMDA-displaceable glutamate binding in the cerebral cortex and hippocampus[10–12] which again overlaps with the neuropathology involved in schizophrenia.

Summary points

- Considering findings that have traced alterations of the same neurotransmitter systems in both schizophrenia and HE, there might be room to consider an association of cirrhosis in causation and exacerbation of schizophrenia in a patient diagnosed with both disorders.
- In this specific case study, prolonged neuronal exposure to hyperammonaemia could have compromised NMDAR function, resembling traits observed in schizophrenia or, perhaps, triggered and exacerbated an underlying diathesis for schizophrenia illness.
- In this patient, it is clear that episodes of psychotic decompensation correlated with medication non-adherence and decompensated cirrhosis, fluctuating mental states and varying ammonia levels, complicating definitive diagnosis. Thus, aggressive concurrent treatment of both the liver dysfunction and psychotic symptoms was assumed to be necessary to maintain stability. Furthermore, ongoing adherence to medication and close care coordination between psychiatry and hepatology is essential.
- Regardless of aetiology, this patient benefits from continued treatment with antipsychotic medication. However, consideration of the potential negative impact of metabolic side effects on the prognosis of cirrhosis and, more significantly, on the prognosis of liver transplant is crucial. Monitoring and management of metabolic parameters should be prioritised in this population to optimise both liver disease management and transplant outcomes. For this patient, only time will tell whether or not his liver transplantation will ameliorate the need for chronic antipsychotic medication. However, any effort to taper off antipsychotic medication should be conducted with close monitoring.

Patient's perspective

Patient's and mother's perspectives:

Patient: 'I think all my psychiatric symptoms were due to my physical condition. I do not believe I have schizophrenia. Antipsychotics have not helped me and I would like to go off of antipsychotic medication.'

Mother: 'I think his liver condition has changed his brain. Whether its schizophrenia or not, medication has helped him. After liver transplant, he has been doing relatively better cognitively and socially. He has had no other psychotic symptoms since his last psychiatric hospitalization and the initiation of the long-acting injectable antipsychotic.'

Learning points

- Emerging evidence highlights the pivotal role of glutamatergic dysfunction in the neuropathophysiology of both schizophrenia and acute liver failure. The brain's reliance on glutamate for urea detoxification, due to the absence of a urea cycle, leads to elevated extracellular glutamate levels in the presence of increased urea concentrations.
- Chronic exposure to ammonia triggers N-methyl-D-aspartate receptor hypofunctioning, mirroring mechanisms seen in neurodevelopmental disorders like schizophrenia, often influenced by developmental imbalances during adolescence.
- Further research is needed to elucidate possible underlying mechanisms linking congenital liver disease and psychosis that may be targeted in future therapeutic innovations.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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