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Title: Hepatic Encephalopathy Resulting in Mania, a Possible Role of Bilirubin and Glutamate?

Running Title: Hepatic Encephalopathy & Mania

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Key Message

Two case reports up to date suggest that hyperbilirubinemia may induce mania in patients with pre-existing vulnerability for psychiatric disorders. Pathophysiology may consist of increased glutamatergic neuronal transmission related to unconjugated bilirubin, interacting with other clinical conditions or treatment interventions that increase brain glutamate levels, such as electroconvulsive therapy.

Introduction

Mania is known to occur secondary to a range of somatic conditions and pharmacological agents, both among patients with and without pre-existing affective disorder. We present a case of first-onset mania shortly following acute liver failure due to intentional acetaminophen intoxication. Clinical case presentation combined with a literature search supports a mediating pathophysiological role for hyperbilirubinemia and subsequent excess glutamatergic neuronal transmission leading to mania.

Case Report

Patient X. is a 50-year old Caucasian woman with a history of two severe depressive episodes with psychotic features at age 40 and 48. Both episodes required hospitalization and psychopharmacological treatment, including paroxetine, venlafaxine, and quetiapine, each time resulting in complete remission of depressive symptoms. During her first depressive episode, she committed an auto-intoxication with

sedatives and with unknown suicidal intent. Family history showed bipolar disorder (BPD) type I in one first-degree relative (mother). Further medical history only consisted of a caesarean section at age 37, and the use of an oral contraceptive (desogestrel 150µg/ethinylestradiol 20µg).

She was admitted to the psychiatric ward of a tertiary psychiatric hospital with a severe depressive episode with psychotic features. Depressive symptoms included persistent depressed mood with feelings of hopelessness, anhedonia, disturbed sleep (insomnia), psychomotor agitation and anxiety, anergia, feelings of excessive and inappropriate guilt (e.g. feelings of having disappointed the treating psychiatrist by having a relapse with concomitant fear of abandonment), indecisiveness and concentration problems. She denied suicidal ideation or intent. Depressive symptoms caused her to stop work, and interfered with her social and family life.

Before admission she was treated with venlafaxine 150 mg, alprazolam slow release 0.5 mg, quetiapine slow release 300 mg, trazodone 150 mg, and zolpidem 10 mg. During the first weeks of admission, venlafaxine was increased to 225 mg, and subsequently switched to nortriptyline. At day 42, due to insufficient therapeutic response, we decided to initiate electroconvulsive therapy (ECT). ECT-anesthesia consisted of etomidate (16 mg), succinylcholine (60 mg) and 100% oxygen. A brief-pulse, constant-current device (MECTA SR1 5000Q; Lake Oswego, OR, U.S.A.) delivered the stimulus. The patient was treated twice a week with right unilateral ECT with a 0.5 ms - 50 Hz - 8 sec - 320 mC stimulus. Meanwhile, nortriptyline dose was further increased to 75 mg. Due to insufficient clinical response, electrode placement was switched to bitemporal at the 7th treatment.

After having received 19 sessions of ECT treatment without clinical remission, the patient engaged in an intentional overdose of 16 grams of acetaminophen, with unclear suicidal intent (day 106). She received oral activated charcoal, and was transferred to the emergency department. Glasgow Coma Scale and liver tests at admission were normal with a total bilirubin of 0,45 mg/dL, an unconjugated

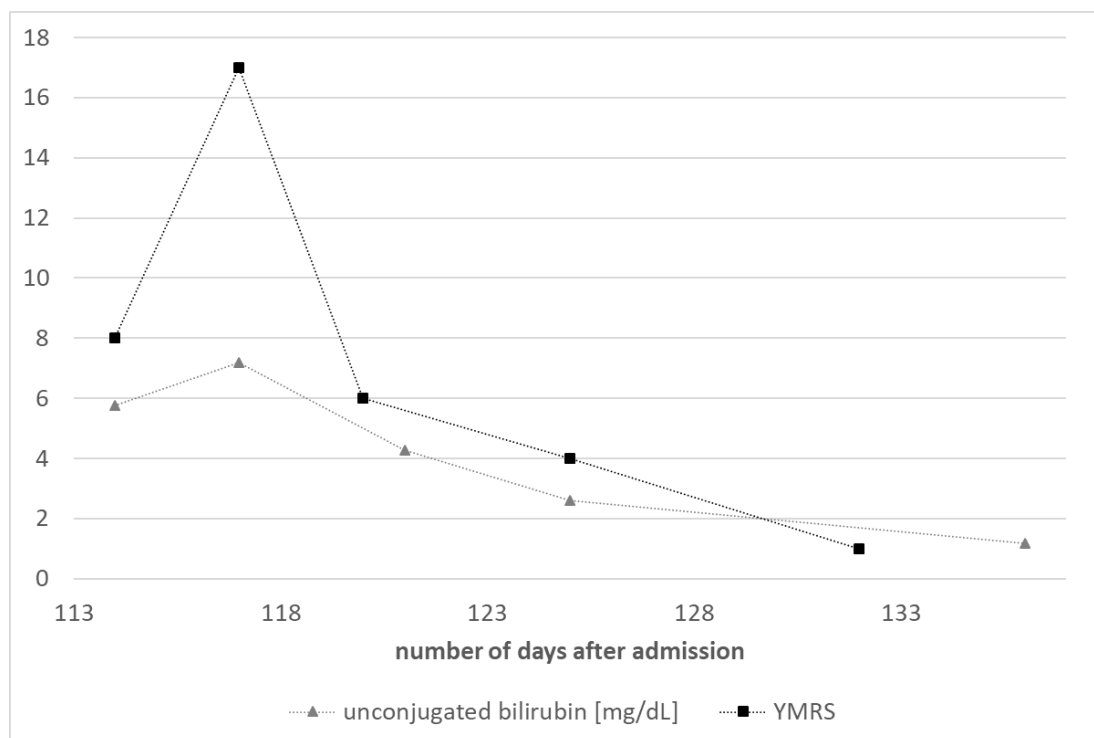
bilirubin (UCB) of 0,18 mg/dL and normal levels of aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (γ -GT), albumin, prothrombin time (PT), and activated partial thromboplastin time (aPTT). Acetaminophen serum levels 4 hours after ingestion were moderately elevated (56 mg/L), not requiring the administration of N-acetylcysteine (NAC). After a short observation, the patient was transferred back to the psychiatric ward. On day 108, she received the next ECT session as scheduled.

On day 109 (approximately 72 hours after acetaminophen ingestion), a control blood sample showed a substantial elevation of AST (8,324 U/L), ALT (10,236 U/L), total bilirubin (6.44 mg/dL), and γ -GT (355 U/L), suggestive for Stage III acetaminophen-induced hepatotoxicity. The patient was transferred to a high-care emergency unit, where she soon developed a mild flapping tremor, motor lag and jaundice. NAC treatment was initiated (350 mg/hour), associated with a proton-pump inhibitor (pantoprazole 20 mg) to prevent stress ulcers. Ammonia peaked on day 110 (118 μ mol/L). She developed signs of hepatic encephalopathy, including somnolence and a decreased sense of orientation, for which lactulose was administered. Initial intravenous infusion with glucose resulted in a mild hypokalemia, for which she received potassium replacement therapy (10 mg daily). Psychopharmacological treatment and ECT were stopped. During the following days, the patient was monitored at the medium care unit, and preparatory procedures for liver transplantation were conducted. The clinical course was favorable, however, with an expected full recuperation of liver function over the following weeks.

On day 114, the patient was transferred back to the psychiatric ward. Upon arrival she showed irritability and increased talkativeness. She scored 8 points on the Young Mania Rating Scale (YMRS). There were no indications of persistent encephalopathy: consciousness was clear at all times, and there were no signs of disorientation or cognitive impairment. Total bilirubin peaked on day 117 (eleven days after intoxication) with a total bilirubin of 8.75 mg/dL (UCB 7.20 mg/dL). The patient showed

decreased need for sleep, talkativeness with associative thinking, an increase in goal-directed activity, and psychomotor agitation. She engaged in a romantic relationship, and was preoccupied with making plans for the future. YMRS-score increased to 17 points, consolidating a clinical diagnosis of mania. Due to risk for relapse hepatotoxicity, no pharmacological treatment was possible. During the following two weeks, the patient's manic symptoms gradually decreased. Liver tests normalized at day 136. At that point, there were no longer clinical arguments for mania (YMRS=1). A few days after complete normalization of total bilirubin < 1,18 mg/dL, the patient relapsed into a major depressive episode with psychotic features. The therapeutic plan was changed to initiation of Lithium-carbonate, Fluoxetine 20mg and Olanzapine 5mg.

Figure 1: Serum levels of unconjugated bilirubin and Young Mania Rating Scale (YMRS) scores over the course of 30 days after intoxication with acetaminophen (day 114).



Discussion

Figure 1 shows UCB levels and YMRS scores during a one-month follow-up period after the acetaminophen overdose. The co-evolution in time of increased serum levels of UCB with the emergence of manic symptoms is striking, and suggests a possible role of UCB in the pathophysiology of mania. One previous case report observed a link between increased UCB levels following a fulminant post-transfusion hepatitis B and encephalopathy evolving into a manic syndrome ¹. Interestingly, the 60-year old female patient described by Müller et al. ¹ had no previous psychiatric history, but did have one sibling who experienced an isolated psychotic episode. This patient developed a “*paranoid-hallucinatory syndrome*” with concentration and memory deficits (no somnolence), restlessness, agitation, and anxiety, co-occurring with only mildly elevated ammonium levels (49 µmol/L) but substantially elevated UCB levels (up to 31 mg/dL). This was followed by an “*increasing manic syndrome*”, including euphoria, increased drive, loss of criticism, and reduced need for sleep, responsive to haloperidol 5 mg, and co-occurring with decreasing levels of liver enzymes and UCB, similar to our observations.

Evidence from the literature supports the hypothesis of UCB leading to excess glutamatergic transmission, subsequently resulting into a manic episode. UCB is a lipophilic molecule that readily traverses the blood-brain barrier, where it exerts a neurotoxic effect through oxidative stress, cytokine release, and damage to plasma membranes and mitochondria. Specifically, it has been shown that reuptake of glutamate, an excitatory neurotransmitter, by astrocytes exposed to UCB is impaired, resulting in an increase of extracellular concentrations of glutamate, overstimulation of neurotransmitter receptors and excitotoxicity ². Apart from noradrenalin and dopamine, increasing evidence suggests that glutamate plays a role in the pathophysiology of mania in bipolar disorder (BPD), with increased glutamate and glutamine levels (Glx) being the most consistent neurochemical alteration reported ³. In line with these findings, a range of new molecules that act on the glutamate and GABA neurotransmitter systems are being studied as potential pharmacological agents for BPD (e.g.,

ketamine, esketamine, lanicemine, traxoprodil, among others) ⁴. With regard to our case history, it is also important to point out that ECT is known to upregulate brain glutamate receptor units ⁵, which lends to the hypothesis that the ECT treatment delivered to our patient may have interacted with hyperbilirubinemia to increase glutamatergic transmission above a critical threshold.

In contrast to the Müller et al. case, several elements in our case report do suggest a final diagnosis of BPD. Key characteristics include the presence of a family history of BPD, several past episodes of severe depression with psychotic symptoms requiring hospitalization, a recent history of treatment-resistant depression, and finally, the occurrence of a secondary manic syndrome. It remains unclear to what extent hyperbilirubinemia could be a sufficient solitary cause for secondary mania. The fact that co-occurrence of mania and hyperbilirubinemia seems to be a rarely observed event, suggests that excess bilirubin levels only lead to mania in patients with a pre-existing increased vulnerability. It is therefore striking that the patient observed by Müller et al. only has a family history of psychosis, without any personal history of psychiatric disorder or other risk factors for mental illness.

Our case report points to the need for increased vigilance among general hospital clinicians and consultation-liaison psychiatrists with regard to the potential onset of mania related to hyperbilirubinemia. This may be particularly relevant when considering psychiatric patients, among which acetaminophen intoxication is a common cause for hepatic failure and encephalopathy, and among which other pre-existing vulnerabilities for heightened brain glutamatergic activity may exist, including a suspected or known diagnosis of BPD or treatment with ECT.

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