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LETTER TO THE EDITOR

UGT1A1 mutations and psychoses: towards understanding the relationship with unconjugated bilirubin

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To the Editor:

We read with great interest the recent systematic review in your journal, which gathers the studies on the relationship between unconjugated bilirubin (UCB) and schizophrenia.[1] The authors, based on the articles they cited, support the existence of a correlation between UCB and schizophrenia, but point out that the relationship between the two is not clear. Indeed, it is uncertain whether there is a direct or inverse relation between serum UCB levels and the incidence of schizophrenia, because a discrepancy exists in the literature: some studies claim an increased incidence of schizophrenia with higher levels of UCB, others with lower levels. Moreover, some studies reveal a reduction in plasma UCB levels after treatment; others report even a correlation with symptomatic scales. The authors conclude that, given the complex nature of schizophrenia, the association might be multifactorial and nonlinear, with UCB and the pathophysiology of schizophrenia being mutually influenced by each other. This hypothesis is based on the complex role of UCB in antioxidant and inflammatory responses. In fact, UCB has been associated with *in vitro* and *in vivo* neurotoxicity, and the threshold above which UCB starts to miss its favorable antioxidant effects seems to be fairly small. Ultimately, the core of the problem could be an impairment in the inflammatory mechanisms in the brain. If plasma UCB levels were too high, it would directly cause neuroinflammation, reactive oxygen species (ROS) production, and cell apoptosis; if it were too low, nevertheless, it could weaken the antioxidative defenses and also result in increased inflammation and ROS levels. Thus, the authors conclude that schizophrenia is the cause and effect of fluctuations in UCB levels and vice versa, creating a vicious circle that would sustain the symptoms of schizophrenia. Moreover, extending the role of UCB in different stages of the progression of schizophrenia, schizoaffective disorders, and bipolar disorder, one hypothesis is that these could be different points of the same pathological spectrum. A thine criticism to this review is the small space dedicated to the possible genetic implications. Interestingly, homozygotic recessive-jaundiced animal models (Gunn rats), presenting schizophrenia-like behavior, have a congenital deficiency of the bilirubin liver conjugating enzyme, UGT1A1. Gunn rat is also a molecular and metabolic model of Crigler-Najjar syndrome type 1 (CN1), consistently exhibiting acute central nervous system dysfunction and kernicterus.

We have the opportunity to deepen the discussion and support this vision of the pathological spectrum of psychoses providing the genetic aspect as a possible explanation, thanks to two patients of ours. We present B (39 years old) and her mother, R (69 years old), affected by mental illness at different degrees. B, a unique daughter, was diagnosed with CN2 when she was a child, because of the jaundice and total serum bilirubin level of 17.0 mg/dL. Although initially very effective, phenobarbital and phototherapy (12 h/d) are socially inconvenient and become less efficient in the older age. For this reason, she had orthotopic liver transplantation (OLT) at the age of 15, resulting in lifelong immunosuppressive therapy with cyclosporine. However, B was proficient at school, with no learning problems or specific disabilities. Four years after OLT, the first manic episode occurred, introduced by insomnia and physical health concerns. B showed euphoria, ideas of reference, high anxiety, and disorganized behavior. In the following 13 years, she had further three hospitalizations in psychiatry

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ward and two emergency room accesses because of manic episodes, with similar pre-existing stressful events and clinical features, with some inter-episodes of depressed mood phases, probably enhanced by psychotropic drugs, too. At her last hospitalization, the diagnosis was confirmed with SCID-I interview, as "bipolar I disorder, most recent episode manic, severe with mood-incongruent psychotic features." During this hospitalization, risperidone was shifted to olanzapine, plus citalopram. Positive and Negative Syndrome Scale (PANSS) was administered during hospitalization giving the following results: positive symptomatology 15/49, negative symptomatology 9/49, general psychopathology 28/112, total score 52. After discharge, B showed clinical stability and went on with medication prescribed by the outpatient service. Meanwhile, she got married and asked for genetic testing and preconception counseling for a reproductive risk of CN2. It is well known that mutations in the *UGT1A1* gene, causing an absence or severe reduction in UGT1A1 enzymatic activity, can result, respectively, in CN1 and CN2.[2] Moreover, it has been shown that CN2 is a far less severe condition than CN1, due to residual bilirubin glucuronidating activity. Because mild hyperbilirubinemia is often found among the relatives of patients with CN, some have postulated that Gilbert's syndrome (GS) represents a heterozygous form of CN. However, many carriers of CN do not have hyperbilirubinemia. Indeed, this condition is mostly caused by $A(TA)_7TAA$ polymorphism in the promoter region, resulting in a reduced expression of the structurally normal enzyme.[3] A genetic analysis by direct sequencing of all coding exons and relative splicing regions of the *UGT1A1* gene evidenced two missense mutations in heterozygous state in B: one, p.R336W, previously described in CN1 patients[4]; the other, p.G377V, previously described in CN2 patients.[5] Besides, B showed homozygosity for the normal promoter TA_6/TA_6 allele. Therefore, our patient is a compound heterozygote, compared with another patient previously described (CN2-6),[2] but unfortunately, there are no descriptions of the phenotype.

We met B's mother, R, when she was a 69-year-old retired factory worker, untidy, and overweight. R suffered from schizophrenia, "catatonic type, episodic with inter-episode residual symptoms, with prominent negative symptoms," firstly diagnosed in 1980 when she was pregnant with B, and confirmed by us with SCID-I interview during her last admission. PANSS was administered and provided the following results: positive symptomatology 18/49, negative symptomatology 35/49, general psychopathology 62/112, total score 115. Going back to R's past, in 1974 she experienced a poorly described psychotic onset, following a traumatic sexual abuse life event and characterized by persecutory ideation, mutism, flat affect, abulia, and apathy with auditory hallucinations. Though medicated with haloperidol and amitriptyline with appropriate dosage, when she was 8 months pregnant (1980), she relapsed falling in a bad depressive state and was referred from maternal care to outpatient psychiatric care. Psychotropic drugs were postponed after B's delivery. As much happy for the baby and as much worried about her health conditions, R will have a hard life for her mental illness and B's physical and psychic concerns. Their relationship has been very strong, and clinicians observed that B became as far independent as much R fell in psychotic episodes. From 1980 to 1988, she was in good health with some episodes of mutism and negativism, being on maintenance therapy. In 1988, another psychotic episode was mentioned and was treated with haloperidol, thioridazine, and monthly fluphenazine depot. Simultaneously with B's OLT, she had a depressive episode; so neuroleptic treatment was withdrawn and antidepressant (citalopram 50 mg/d) was started. In 2000, B had a psychotic episode; and R, a depressive one. Finally, she was hospitalized in 2013 because of dyskinesia and tremors related to second-generation antipsychotic drugs. She appeared frumpy, with depressed mood and acritical about her condition. Paliperidone and tetrabenazine were withdrawn; she started a new treatment with clozapine 100 mg/d and hydroxyzine with clinical improvement. No genetic analysis of *UGT1A1* was conducted in R, but considering that CN is extremely rare and inherited as autosomal recessive condition, we can assume that she carries one of the two mutations of B. These data, together with the normal levels of bilirubin, support the hypothesis that R suffers from GS, distinguished by the lack of morbidity in patients and by a lower total serum bilirubin level, ranging from 1 to 6 mg/dL.[3] However, two Chinese studies reported parents with GS in CN2 patients.[6,7]

To our knowledge, this is the first work reporting on a mother and her daughter both with *UGT1A1* gene mutations and mental illnesses. In particular, the two patients showed different expressions of their psychic and physical pathologies: B, the daughter, suffering from bipolar disorder, had a severe form of CN2, leading in her childhood to OLT that prevented kernicterus; and R, the mother, suffering from catatonic schizophrenia, a more severe mental illness, just carried one missense mutation in *UGT1A1*, without expressing CN syndrome phenotypically. In B, bipolar disorder onset was at 19 years, after CN2 diagnosis, and high UCB levels already had occurred and having caused damage. As some authors affirm,[8] hyperbilirubinemia even before kernicterus has a specific pathological pathway on the brain, in particular involving basal ganglia and cerebellum, thus influencing cognition, impulse control, and executive functioning. The mother had a more severe mental illness, but no hyperbilirubinemia. We could hypothesize that high UCB levels, when B was a child, biologically predisposed to a later expression of a bipolar disorder. Stressors may have contributed to this psychopathological mechanism.

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Indeed, it is well known how liver transplant recipients have unique risk factors for perioperative and long-term psychiatric disturbances. According to some authors, 30%–40% of patients who underwent liver transplantation develop depression[9] – in some cases, posttraumatic stress disorder[10] too. Rapidly cycling bipolar II disorder has been described immediately following liver transplantation and immunosuppressant therapy, without prior depression, thus leading to the diagnosis of organic affective disorder, remitting gradually in association with a reduction in immunosuppressant treatment or, within a few days, after the early postoperative period.[11]

In conclusion, we support the vision of the pathological spectrum of psychoses,[1] providing the genetic factor as a possible interpretation key. In fact, it has been described that the mean bilirubin level of patients with schizophrenia could be in the reference interval, and the frequency of GS is significantly higher in patients with schizophrenia.[12] Accordingly, R, the mother, with normal levels of bilirubin and one missense mutation in *UGT1A1* causing GS, suffered from schizophrenia. The daughter, B, is a compound heterozygote with two missense mutations in *UGT1A1* gene associated with a severe form of CN2, with high levels of bilirubin in her childhood that may have created an irreversible susceptibility to bipolar disorder. B's medical history shows that the first psychiatric symptoms developed some years after OLT. It could be hypothesized that a previous biological damage in the brain caused by UCB, with the contribution of both biological (OLT, cyclosporine, and corticoid treatment) and psychological stressors (pregnancy seeking and genetic analysis), expressed itself openly with a bipolar disorder. Further studies are needed to investigate genotype–phenotype correlations between *UGT1A1* mutations and psychoses, following the hypothesis that UCB pathways could be involved in understanding mental illnesses.

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Disclosures

Angela Bentivegna, Jacopo Santambrogio, and Massimo Clerici do not have anything to disclose.

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