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Gilbert's syndrome and schizophrenia

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Gilbert's syndrome (idiopathic unconjugated hyperbilirubinemia) is a benign hyperbilirubinemia found in the general population. We report one case in which the exacerbation and remission of hyperbilirubinemia closely correlated with the psychosis of schizophrenia. Some studies have reported that schizophrenic individuals had a significantly higher frequency of hyperbilirubinemia than patients suffering from other psychiatric disorders and the general healthy population. Stress and fasting are well-known contributors to elevated plasma bilirubin levels in patients with Gilbert's syndrome. A 38 year old woman inpatient with acute schizophrenic symptoms had a bilirubin plasma level of 2.7 mg/dl. She was treated with risperidone that produced no adverse effects on hepatic function. Schizophrenic symptoms improved and a decrease in bilirubin plasma concentration was observed.

Palabras clave:
Schizophrenia. Psychosis. Unconjugated hyperbilirubinemia. Gilbert's syndrome. Risperidone.

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Enfermedad de Gilbert y esquizofrenia

La enfermedad de Gilbert o hiperbilirrubinemia no conjugada es un tipo de hiperbilirrubinemia benigna familiar frecuente en la población general. Presentamos un caso en el que la exacerbación y remisión de la hiperbilirrubinemia se correlacionó estrechamente con la evolución de los síntomas psicóticos. Algunos estudios han encontrado que los pacientes esquizofrénicos presentaban con mayor frecuencia hiperbilirrubinemia que otros trastornos mentales o que la población general. El estrés y el ayuno son factores que contribuyen a la elevación de los niveles de bilirrubina en sangre en los pacientes con enfermedad de Gilbert. La paciente era una mujer de 38 años hospitalizada por clínica psicótica aguda que presentaba una bilirrubina total de 2,7 mg/dl. En el tratamiento se utilizó risperidona, mejorando los síntomas psicóticos y observándose un descenso de los niveles de bilirrubina en sangre sin afectarse la función hepática.

Palabras clave:
Esquizofrenia. Psicosis. Hiperbilirrubinemia no conjugada. Enfermedad de Gilbert. Risperidona.

INTRODUCTION

Gilbert's syndrome is a chronic and benign hyperbilirubinemia that affects 3 %-7 % of the general population[1]. It has been called by different names, all descriptive, such as icterus intermittent juvenilis, mild chronic hyperbilirubinemia, familial non-hemolytic-non-obstructive jaundice; constitutional liver dysfunction, unconjugated benign bilirubinemia. It was described in 1901 as a familial benign disease that occurs with hyperbilirubinemia in absence of hepatic structural alterations or hemolysis. This disorder involves a heterogeneous group of biochemical defects that seem to be related with decreased activity of the enzyme that favors bilirubin conjugation (glucuronosyltransferase), or, in a smaller proportion, to a decrease in hepatic uptake of bilirubin. There are some hereditary factors that are not very well known. These increase the risk of the disorder through a defect in the expression of the UGT1 gene[2], although there are some cases of subjects without family background who suffer the disorder. It is more frequent in men. Individuals affected generally do no have jaundice. However, this appears in conditions of excessive effort, stress, fasting or infections. Jaundice is clear when serum bilirubin reaches levels equal to or greater than 2.5 mg/dl[3]. However, it has not been clarified up to now if stress or fasting may cause hyperbilirubinemia in persons without genetic predisposition to Gilbert's disorder. Diagnosis is made by provocation tests, such as fasting (for example, with a 400 calorie diet during 48 hours) or with the administration of phenobarbital which, in Gilbert's disorder, respectively causes an increase and decrease in unconjugated bilirubin levels in blood.

Some schizophrenic patients may have alterations in the red blood cell membranes, which may cause an increase in

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bilirubin plasma concentrations[4]. It seems that treatment with antipsychotic drugs may normalize phospholipidic alterations of the red blood cell membrane in schizophrenic patients[5].

CLINICAL CASE

This is a case of a 38 year old woman from Slovakia who has lived in our country since 11 years ago. She is married and the mother of a 10 year old boy. She works as a translator. She was admitted to the psychiatric unit from the emergency service where she was brought by the Police with court authorization for involuntary hospitalization due to the behavior disorders of the patient. These disorders had caused a significant deterioration in her usual functioning, noticeably interfering in her family life. The psychopathological examination showed acute psychotic symptoms with delusional ideas of harm, numerous delusional interpretations of reality, auditory hallucinations and null awareness of disease. She reports no drug allergies or somatic diseases of interest. She denies toxic consumption (cocaine, opiates and cannabis were negative in urine on admission). She reported background of bulimic behaviors in adolescence that led to psychoanalytic treatment in her country, but she never had been hospitalized in any psychiatric unit. There was no familial psychiatric background.

On admission, jaundice aspect stood out. Thus, consultation was requested with the internal medicine service. In the blood biochemistry, they detected bilirubin of 2.7 mg/dl with normal hepatic function and direct bilirubin of 0.6 mg/dl. The remaining complementary tests requested were normal, including the cranial CT scan (computed axial tomography). The picture fit in with Gilbert's disorder, in which, after a detailed anamnesis, the hyperbilirubinemia seemed to be related with a diet to lose weight based on sage that the patient had begun a few weeks before her admission.

Treatment was initiated with 3 mg of risperidone and 1.5 mg of clonazepam. Coinciding with the improvement of the psychotic symptoms and normalization in food intake, her bilirubin levels also decreased. No side effects with the psychopharmacological treatment or hepatic function alterations were observed.

DISCUSSION

There are few studies on the relationship between hyperbilirubinemia and mental diseases (table 1). Muller et al.[6] conducted a retrospective study on plasma bilirubin levels on admission of 892 psychiatric patients. They excluded those who had hepatic disorders, substance abuse, hemolysis or increased hepatic enzymes. They observed that schizophrenia patients had a significantly higher incidence of hyperbilirubinemia than patients with other mental disorders. In addition, they assessed the stress that could be cause by the hospitalization and the fasting periods frequently occurring in these patients coinciding with acute psychotic decompensation episodes as possible factors related with hyperbilirubinemia in psychiatric patients. However, this hypothesis did not explain the greater incidence in patients with schizophrenia versus those with other psychiatric conditions. They suggested that hyperbilirubinemia did not seem to be due to hepatotoxic effects of antipsychotic drugs. They based this on, in the first place, that the bilirubin levels tended to decrease in most of the patients during the antipsychotic treatment and, in the second place, on the fact that when hyperbilirubinemia is produced by drugs, what was to be expected was that the increase would occur at the cost of the direct or conjugated bilirubin[7] and not at the cost of the indirect one as occurred in these patients.

Miyaoka et al.[8] observed that schizophrenic patients with hyperbilirubinemia tended to have more serious acute psychotic symptoms. This posed a possible relationship between high bilirubin plasma concentrations and the seriousness of psychotic symptoms.

Toxicity related with genetic deficiencies in glucoronosyltransferase is known in the case of antipsychotics as phenotiazines or tricyclic antidepressives. Thus, they are generally avoided in patients with hepatic disorders[9]. However, Durst et al.[10] reported the absence of side effects or hepatic func-

Table 1 Previous studies on hyperbilirubinemia and schizophrenia

Studies	N	Total patients with hyperbilirubinemia	Hyperbilirubinemia in patients			
			Mania	Depression	Neurosis/PD	Schizophrenia
Müller et al. (1991)	892	11 %	9.2 %	6.1 %	9.3 %	25.4 %
Miyaoka et al. (2000)	290	9 %	3.2 %	2.6 %	4.2 %	20.6 %

PD: personality disorders.

tion disorders in patients treated with phenothiazine antipsychotics and tricyclic antidepressants.

Two different mechanisms that seem to be involved in hepatotoxicity produced by antipsychotics have been described[11]. The first one would consist in allergic reactions that have no relationship with the drug dose used and that may occur with or without jaundice accompanied by fever, skin rash, eosinophilia and increased conjugated bilirubin, hepatic enzymes and alkaline phosphatase. In the second mechanism, there may be increases of hepatic enzymes and conjugated bilirubin, however the hepatic function disorders are related with the dose used in this case.

Regarding atypical antipsychotics, there is a case published on a patient with Gilbert's disorder and schizophrenia who had side effect on the sixth day of treatment with 10 mg of olanzapine. Mutism and absence of response to stimuli appeared[12]. Presence of mutism has also been described in cases of overdose with olanzapine[13]. It seems that patients with glucuronosyltransferase alterations may have toxicity symptoms at therapeutic doses since olanzapine is metabolized in the liver through the reaction of glucuronization.

We have only found one previous article that reports on three cases in which the exacerbation and remission of hyperbilirubinemia had a parallel course to the psychotic symptoms[14]. In these cases, the authors presented the possibility that the hyperbilirubinemia could be a marker of the status for psychotic decompensation related with a specific form of stress due to schizophrenia.

The interest of the case is found in the fact that coexistence of Gilbert's Syndrome and schizophrenia does not seem to be a casual and isolated fact but rather a relatively frequent phenomenon after having made a review of the existing literature. Some authors have tried to explain the presence of hyperbilirubinemia in patients with acute psychotic symptoms as a possible marker of psychotic decompensations or as an indicator of the seriousness of psychotic symptoms, but these findings still have not been studied sufficiently.

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