Schizophrenia-Associated Idiopathic Unconjugated Hyperbilirubinemia (Gilbert's Syndrome)

Tsuyoshi Miyaoka, M.D.; Haruo Seno, M.D.; Motoi Itoga, M.D.; Masaaki Iijima, M.D.; Takuji Inagaki, M.D.; and Jun Horiguchi, M.D.

Background: Idiopathic unconjugated hyperbilirubinemia (Gilbert's syndrome) is a benign hyperbilirubinemia found in the general population. There has been only 1 previous report of Gilbert's syndrome occurring in schizophrenic patients. The present study was conducted to determine the frequency of Gilbert's syndrome in schizophrenic patients relative to patients with other psychiatric disorders.

Method: Plasma bilirubin concentrations of every patient admitted to the psychiatric hospital during a 3-year period were collected, and patients were examined to exclude all other causes of hyperbilirubinemia. In addition, the psychiatric symptoms of schizophrenic patients (ICD-10 criteria) with hyperbilirubinemia were evaluated by the Positive and Negative Syndrome Scale (PANSS).

Results: Schizophrenic patients showed a significantly higher incidence of hyperbilirubinemia ($p < .05$) relative to patients suffering from other psychiatric disorders, and schizophrenic patients with hyperbilirubinemia showed significantly higher scores on the positive and general psychiatric subscales of the PANSS ($p < .0001$) than patients without hyperbilirubinemia.

Conclusion: The apparently higher frequency of Gilbert's syndrome in schizophrenic patients may reflect a relationship between hyperbilirubinemia and schizophrenic psychosis. Hypothetical explanations, such as a possible genetic disposition for Gilbert's syndrome, an increased vulnerability of red cell membranes, and the role of estrogens in schizophrenic patients, are discussed.

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Reprint requests to: Tsuyoshi Miyaoka, M.D., Department of Psychiatry, Shimane Medical University, 89-1 Enyacho, Izumo 693-8501, Japan.

Idiopathic unconjugated hyperbilirubinemia (Gilbert's syndrome) is a relatively common congenital hyperbilirubinemia occurring in 3% to 7% of the population.[1–3] In Japan, the prevalence of this syndrome is 2.4% (3.3% in men, 1.6% in women) in general healthy populations.[4] The condition was first described in 1901[5]; since then, it has been recognized as a benign familial condition in which hyperbilirubinemia occurs in the absence of structural liver disease or hemolysis and the plasma concentration of conjugated bilirubin is normal. This benign but chronic disorder encompasses a heterogeneous group of biochemical defects. The precise mode of inheritance is still unclear, and this syndrome occurs sporadically in many cases.[6]

Recently, it was reported that schizophrenic individuals showed a significantly higher frequency of hyperbilirubinemia relative to patients suffering from other psychiatric disorders and the general healthy population.[7] We also have observed that patients suffering from schizophrenia frequently presented with an increased plasma bilirubin concentration when admitted to the hospital.[8] To determine whether the frequency of Gilbert's syndrome in schizophrenic patients is higher than in other populations, the plasma bilirubin concentration of every patient admitted over a period of 3 years was recorded for further evaluation of this phenomenon.

METHOD

Plasma bilirubin concentration data were collected from 290 consecutive patients admitted to the Department of Psychiatry at the Shimane Medical University (Izumo, Japan) over a period of 3 years. Written informed consent was obtained from all subjects after the procedures had been fully explained. To determine total and direct bilirubin levels, a standard method based on the bilirubin oxidase method[9] was used (Nescoat VL kit, Nippon Shoji Co., Osaka, Japan). The upper limit of normal for total serum bilirubin level with this method was 1.2 mg/dL. To avoid artifact and to control precision, a standard reagent was used. Unconjugated (indirect) bilirubin level was estimated on the basis of the difference

Table 1. Hyperbilirubinemia in Various Subjects

Group	Subjects Total N (M/F)	Subjects With Hyperbilirubinemia Total N (M/F)	%	p Value (vs Schizophrenia)[a]
All patients	290 (133/157)	26 (14/12)	9.0	...
Schizophrenia	97 (45/52)	20 (12/8)	20.6	...
Affective psychosis	145 (71/74)	4 (1/3)	2.8	< .0001
Mania	31 (13/18)	1 (0/1)	3.2	.0457
Depression	114 (58/ 56)	3 (1/2)	2.6	< .0001
Neurosis/personality disorder	48 (17/31)	2 (1/1)	4.2	.0186

[a]Percentages compared using chi-square test with Yates continuity correlation.

between total bilirubin level and direct (conjugated) bilirubin level.

Patients with a hyperbilirubinemia of ≥ 1.3 mg/dL and normal plasma aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase (GGT), and alkaline phosphatase (ALP) concentrations were included in the present study. The plasma bilirubin concentration was usually measured on the first morning after admission to the hospital. It was continuously reevaluated in most patients until the bilirubin level was within a normal range.

According to their psychiatric diagnoses (ICD-10),[10] the patients were subdivided into 3 groups: schizophrenia, affective psychosis (mania, depression), and neurosis/personality disorders. ICD-10 diagnoses were established in all patients by well-trained psychiatrists using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN).[11] The group with schizophrenia included 97 patients with a mean ± SD age of 39.1 ± 1.3 years; the group with affective psychosis, 145 patients with a mean ± SD age of 47.7 ± 1.3 years; and the group with neurosis/personality disorders, 48 patients with a mean ± SD age of 42.8 ± 3.0 years. No significant differences in sex were found among these groups (chi-square test), but significant differences in age existed between the schizophrenia and affective psychosis groups (39.1 vs. 47.7 years; $p < .0001$, analysis of variance [ANOVA] with post hoc Bonferroni tests) and between the neurosis/personality disorder and affective psychosis groups (42.8 vs. 47.7 years; $p = .037$, ANOVA with post hoc Bonferroni tests). However, no significant differences in age were found between the schizophrenia and neurosis/personality disorder groups (39.1 vs. 42.8 years; $p = .262$, ANOVA with post hoc Bonferroni tests). Patients with a diagnosis of alcohol abuse or dependence, drug abuse or dependence, liver disease, or overt signs of hemolysis were excluded. During hospitalization, the psychopharmacologic treatment of schizophrenic patients consisted of butyrophenones and/or phenothiazines and/or thioxanthenes. Manic patients received almost identical antipsychotic medication (butyrophenones and/or phenothiazines). Twenty of these patients were additionally treated with lithium. Depressed patients were treated with tricyclic or tetracyclic antidepressants.

All schizophrenic patients were examined by 3 well-trained psychiatrists using the Positive and Negative Syndrome Scale (PANSS).[12] The PANSS was developed by Kay et al.[12] to evaluate positive and negative schizophrenic symptoms and syndromes. Interrater reliability determined prior to the study ranged from .79 to .84 for total PANSS scores.

Statistical analysis was performed by ANOVA with post hoc Bonferroni tests, a paired t test, an unpaired t test, the chi-square test (with Yates continuity correlation), and the Fisher exact probability test.

RESULTS

A total of 9.0% of the psychiatric patients had elevated plasma bilirubin levels. In all schizophrenic patients with hyperbilirubinemia, conjugated and unconjugated bilirubin were differentiated. Unconjugated bilirubin was increased in all schizophrenic patients, whereas conjugated bilirubin was nearly within the normal range (data not shown). Schizophrenic patients showed a significantly higher incidence of hyperbilirubinemia than all the other diagnostic groups (chi-square test; Table 1). Significant differences were found between patients with schizophrenia and affective psychosis ($\chi^2 = 18.8$, $p < .0001$), between those with schizophrenia and mania ($\chi^2 = 3.991$, $p < .0457$), between those with schizophrenia and depression ($\chi^2 = 15.66$, $p < .0001$), and between those with schizophrenia and neurosis/personality disorders ($\chi^2 = 5.543$, $p < .0186$). The mean ± SD plasma bilirubin level of schizophrenic patients with hyperbilirubinemia was 2.05 ± 0.15 mg/dL. During hospitalization, hyperbilirubinemia decreased in 80% (N = 16), fluctuated in 20% (N = 4), and increased in 0% (N = 0) of the 20 patients receiving antipsychotic treatment. Of the schizophrenic patients with hyperbilirubinemia, 45% (N = 9) had been drug-free for at least 6 to 8 weeks prior to their admission. Statistically, the schizophrenic patients with hyperbilirubinemia showed a significant decrease in plasma bilirubin concentration during the course of the neuroleptic treatment (mean ± SD = 2.05 ± 0.15 vs. 0.97 ± 0.12 mg/dL; $t = 7.702$, $p < .0001$). No significant differences were found between the plasma bilirubin levels of schizophrenic patients with hyperbilirubinemia who were pretreated with neuroleptics (mean ± SD = 1.92 ± 0.19 mg/dL) and those of schizophrenic patients who were not pretreated (mean ± SD = 2.20 ± 0.25 mg/dL).

Thirty-one manic patients, receiving neuroleptic therapy almost identical to that of the schizophrenic patients, mostly in even higher doses, showed no higher rate of hyperbilirubinemia compared with the general population. The plasma bilirubin level of the 1 manic patient with hyperbilirubinemia (a 51-year-old woman) was

Table 2. Comparison of Positive and Negative Syndrome Scale (PANSS) Scores Between Schizophrenics With and Without Hyperbilirubinemia

	With Hyperbilirubinemia (N = 20)		Without Hyperbilirubinemia (N = 77)		
PANSS Item	Mean	SD	Mean	SD	p Value[a]
Positive syndrome subscale (7 items)	40.6	1.1	29.0	0.7	< .0001
Negative syndrome subscale (7 items)	29.3	1.3	27.7	0.8	.3501
General scores (16 items)	77.6	2.8	58.6	1.0	< .0001

[a]Comparisons made using unpaired t test.

1.30 mg/dL. In the group of depressed patients (1 man and 2 women), 2.6% showed hyperbilirubinemia. The mean ± SD plasma level of elevated bilirubin for depressed patients was 1.57 ± 0.21 mg/dL, and the mean ± SD age was 37.7 ± 3.0 years.

Next, we evaluated the psychiatric symptoms of schizophrenic patients with hyperbilirubinemia using the PANSS. As shown in Table 2, positive PANSS scores differed significantly between schizophrenic patients with and without hyperbilirubinemia ($t = 8.057$, $p < .0001$). Similarly, a significant difference was found between schizophrenic patients with and without hyperbilirubinemia on the general scores of the PANSS. However, no difference was found between schizophrenic subjects with and without hyperbilirubinemia on the negative symptom subscale.

DISCUSSION

As observed, 20.6% of the schizophrenic patients presented with mild hyperbilirubinemia. This is far higher than the average of the general population (2.4%–7.0%[1–4]) and significantly higher than that found among the remaining psychiatric disorders in this study (2.6%–4.2%). Aside from the patients diagnosed as schizophrenic, the proportion of the 193 patients presenting with hyperbilirubinemia was 3.1%. This coincides with the proportion of patients with chronic, unconjugated hyperbilirubinemia in Japan.[4] The predominance of males with Gilbert's syndrome has previously been reported. The incidence of hyperbilirubinemia in schizophrenic men was 1.5 times higher than in women, but without a significant difference ($p = .3870$, $\chi^2 = 0.748$). There was a significant difference in age between patients with schizophrenia and affective psychosis. However, it seems that the difference in the mean ages had no effect on the difference in frequencies of hyperbilirubinemia with schizophrenia and affective psychosis because Gilbert's syndrome was observed widely in every age group,[4] and there was a significant difference in frequencies of hyperbilirubinemia between schizophrenics and patients with neurosis/personality disorder, despite the lack of differences between the mean ages of both.

Interestingly, schizophrenic patients with hyperbilirubinemia in this study showed higher scores on the positive and general subscales of PANSS than patients without hyperbilirubinemia, although there were no differences in scores on the negative subscale. Thus, schizophrenic patients with hyperbilirubinemia tended to show acute psychiatric symptoms of greater severity. From the viewpoint of heterogeneity of schizophrenia, there may be an acute and severe subtype of schizophrenia with hyperbilirubinemia. It is also possible that a higher concentration of bilirubin in serum affects psychiatric symptoms.

It is known that psychopharmacologic medication as well as stress or fasting can provoke hyperbilirubinemia and should be taken into consideration. Neuroleptics and antidepressant drugs can cause hepatotoxicity by 2 different mechanisms: (1) non–dose-related allergic reactions (with or without icterus) accompanied by fever, rash, eosinophilia, and an increase of conjugated bilirubin, liver enzymes, and ALP[13]; and (2) dose-related minor abnormalities in liver function with a slight increase of concentrations of liver enzymes and conjugated bilirubin.[13] The high ratio of hyperbilirubinemia in schizophrenic patients does not seem to be due to hepatotoxic side effects of neuroleptics. First, patients with increased concentrations of aspartate aminotransferase, alanine aminotransferase, GGT, and ALP had been excluded. Second, hyperbilirubinemia tended to decrease in most patients during neuroleptic treatment. Since 45% of the admitted schizophrenic patients showing hyperbilirubinemia (9 patients) had not been treated with neuroleptics or other psychotropic drugs in the 6 to 8 weeks prior to hospitalization, it is not possible that the increased plasma bilirubin level was due to neuroleptic medication. Furthermore, when conjugated and unconjugated bilirubin of all schizophrenic patients were differentiated, unconjugated bilirubin was elevated in all of them (data not shown). In drug-induced hyperbilirubinemia, one would expect an increased range of conjugated bilirubin levels.[14]

The group of 31 manic patients received almost the same neuroleptic medication as the schizophrenic patients (butyrophenones and/or phenothiazines and often in higher doses), yet they showed no increased hyperbilirubinemia rate. Stress and fasting are well-known contributors to elevated plasma bilirubin levels in patients with Gilbert's syndrome.[15] As a result of their psychiatric disorders, both schizophrenic and manic depressive patients may show a lack of food intake. On the other hand, admittance to the hospital may provoke stress in some patients and therefore indirectly increase their plasma bilirubin levels. Since, however, these factors are relevant for all psychiatric patients included in the present study, they cannot be considered responsible for the differences in the hyperbilirubinemia rates between schizophrenia and the

other psychiatric disorders. Recently, we reported 3 cases in which the exacerbation and remission of hyperbilirubinemia closely correlated with the psychosis of schizophrenia.[8] Thus, hyperbilirubinemia may be a state marker for schizophrenic decompensation related to some peculiarity of stress due to schizophrenia.

Until now, whether stress and fasting can provoke hyperbilirubinemia in persons who have no genetic disposition for Gilbert's syndrome had not been clarified. This leads to the question of whether a genetic disposition for Gilbert's syndrome or especially the risk of a deficiency in glucuronyl transferase activity may be elevated in schizophrenic patients. On the other hand, hemolysis can cause an increase in plasma bilirubin levels. Some schizophrenic patients are known to show altered red blood cell membranes,[16] which, in turn, might cause an elevated plasma bilirubin concentration. Treatment with neuroleptics seems to normalize the phospholipid alterations of the red cell membrane in schizophrenic patients.[17] In addition, estrogens provide protection against hyperbilirubinemia, especially Gilbert's syndrome[18,19]; influence dopamine metabolism[20]; and are thought to play a protective role in the onset of schizophrenia.[20,21] These possible explanations of the described phenomenon of mild hyperbilirubinemia in schizophrenic patients should be considered for further investigation.

Recently, it was reported that schizophrenic patients showed a significantly higher incidence of hyperbilirubinemia than patients suffering from other psychiatric disorders,[7] but there have been no other reports of this phenomenon. We think that this phenomenon was possibly not followed up because only a slight increase in plasma bilirubin levels—which, in the present sample, had decreased in most cases to a normal range at reevaluation—can be observed in most schizophrenic patients with hyperbilirubinemia. Our findings should provoke further prospective and laboratory studies on hyperbilirubinemia in schizophrenic patients to evaluate this long-standing phenomenon.

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