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## Psychotic mania in glucose-6-phosphate-dehydrogenase-deficient subjects

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### Abstract

**Background:** Glucose-6-phosphate dehydrogenase (G6PD) deficiency has been associated with acute psychosis, catatonic schizophrenia, and bipolar disorders by previous inconclusive reports. A particularly disproportionate rate of enzyme deficiency was found in manic schizoaffective patients from 662 lithium patients surveyed in Sardinia. The purpose of this study was to describe clinical characteristics which may be potentially associated with G6PD deficiency.

**Methods:** Characteristics of episodes, course of illness, family pattern of illness, laboratory tests, and treatment response of 29 G6PD-deficient subjects with a Research Diagnostic Criteria diagnosis of manic schizoaffective disorder were abstracted from available records.

**Results:** The most peculiar pattern was that of acute recurrent psychotic manic episodes, mostly characterized by loosening of associations, agitation, catatonic symptoms, and/or transient confusion, concurrent hyperbilirubinemia, positive psychiatric family history, and partial response to long-term lithium treatment.

**Conclusions:** A relationship between psychiatric disorder and G6PD deficiency is to be searched in the bipolar spectrum, particularly among patients with a history of acute episodes with psychotic and/or catatonic symptoms or with transient confusion.

### Background

Glucose-6-phosphate dehydrogenase (G6PD) is a cytosolic enzyme whose main function is to produce NADPH, a key electron donor in the defense against oxidizing agents and in reductive biosynthetic reactions [1]. More than 100 missense mutations in the human X-linked gene encoding G6PD are known to date. The main clinical consequence of these mutations is an enzyme deficiency associated with acute hemolytic anemia, triggered by fava beans, drugs, and some other sources of stress [2]. G6PD deficiency has become common in many populations as a result of malaria selection and it has been estimated that 200 million people around the world are

G6PD deficient, including about 11% of Afro-Americans and 62% of Kurdish Jews. Rates in southern Sardinia range from 15 to 30% [3].

In the early 1980s, we used G6PD deficiency as a traditional X-chromosome marker in a linkage study of manic-depressive illness [4]. Subsequent to this date, we started a systematic survey of G6PD activity in outpatients admitted to our Department, which is one of the reference centers for the management of lithium and related treatments in southern Sardinia. In an account regarding 662 consecutive outpatients diagnosed according to modified Research Diagnostic Criteria (RDC), we reported excessive

**Table 1: Characteristics of 29 G6PD-deficient manic schizoaffective patients**

Gender	25 males, 4 females
Median age at onset	22 years
Median time between onset and starting lithium	5 years
Median time on lithium	6 years
Median number of manic episodes prior to lithium	2

proportions of subjects with enzyme deficiency in bipolar compared with non-bipolar subgroups [5]. The greatest contribution to the bipolar/non-bipolar distinction was provided by "atypical" disorders, such as bipolar II and manic schizoaffective disorder. The latter warranted particular attention because, while it is diagnosed in one fourth of the overall population of outpatients followed at our department, it was excessively represented in the subgroup of G6PD-deficient patients (38%), particularly in males (47%). In this report, clinical characteristics, course of illness, family pattern of illness, laboratory tests, and treatment response of G6PD-deficient subjects with a diagnosis of manic schizoaffective disorder are described. The results are discussed in the context of previous studies that had already investigated potential relationships between G6PD deficiency and psychoses [6–10].

### Methods

Out of 662 subjects from a previous study [5], 29 unrelated subjects (5 women, 24 men) were selected based on both severe G6PD deficiency and a RDC diagnosis of manic schizoaffective disorder. All subjects were patients registered at the lithium clinics, Department of Neurosciences, University of Cagliari, between 1976 and 1999 and gave informed consent to participate in the study.

Detailed information was obtained from the patient and from other available sources (such as relatives and referring clinicians) concerning demographic characteristics and lifetime medical and psychiatric history. Moreover, all available records regarding hospitalizations were examined. Family history was also systematically collected from the patient and from informative relatives.

G6PD activity was established using quantitative assays on erythrocytes [11] or whole blood samples [12]. Patients included in this study were those with enzyme activity close to zero, i.e. hemizygous men and women in the homozygous range. Patients who attended the department between 1993 and 1999 were also genotyped for the G6PD-Mediterranean (G6PD-Med) mutation, which is responsible for the majority of severe enzyme deficiency in Sardinia [13].

### Results

Demographic and clinical data regarding the 29 subjects included in this study are shown in Table 1. Some characteristics of index episodes abstracted from available hospital charts are shown in Table 2. Hospital diagnoses varied greatly and reflected criteria used in Italy over the last three decades. However, all patients shared RDC manic schizoaffective diagnosis on reevaluation, based, besides on the common cluster of mania (i.e. elevated or expansive mood, decreased need for sleep, hyperactivity, and inflated self-esteem), on the presence of mood-incongruent delusions (N = 18) (persecutory delusion or delusion of being influenced or of thought broadcasting) and/or loosening of associations (N = 12). Grandiose delusions were reported in 11 cases. Religious, philosophical, scientific, or magical themes were manifested by 12 patients. Hallucinations were reported in 10 cases, but were not a prominent characteristic. Involuntary hospitalization was often required, mainly due to negativism, mutism or stupor (N = 11), or psychomotor agitation (N = 9). Several patients (N = 7) manifested transient confusion.

The onset of episodes was invariably acute, ranging from a few days to a few weeks. A substantial proportion of patients showed abnormalities in routine laboratory tests performed on admission to the hospital. A common pattern (80% of cases) was characterized by mild hyperbilirubinemia (1–2.5 mg/dl) and/or urobilinogenuria (1–3 Ehrlich Units %), which returned to normal ranges when checked a few days later. An additional frequent finding (80% of cases) was a transitory low serum cholesterol concentration (lower than 160 mg/dl). Ketonuria and proteinuria were evidenced in three cases characterized by catatonic features. Psychotic and manic symptoms subsided in the majority of patients within a few weeks after treatment with neuroleptics. Where necessary, a combination with benzodiazepines and/or lithium was administered. In six cases, a few days of ECT achieved a successful outcome. The course of illness was recurrent. The majority of patients (90%) had been hospitalized at least once. Depressive episodes, if any, were generally rarer or milder than manic ones. Median duration of follow-up after onset was 13 years. The long-term prophylactic effectiveness of lithium treatment was rarely complete, often

**Table 2: Characteristics of index episodes requiring hospitalization in 21 patients with available records**

Age/Gender	Hospital diagnosis	Delusions	Hallucinations	Loosening of Associations	Additional Symptoms
66/F	Manic-depressive illness	Unspecified		+	Mutism, Confusion
23/F	Mixed psychosis	Persecutory	+		Agitation, Confusion
17/F	Dissociative syndrome	Thought broadcasting		+	Agitation, Posturing, Rigidity
29/F	Brief reactive psychosis	Thought broadcasting, Guilt			
27/M	Dissociative syndrome	Grandiose, Scientific		+	Agitation
29/M	Dissociated mania	Religious, Magic		+	Agitation
32/M	Psychomotor agitation	Grandiose, Persecutory, Religious	+	+	Agitation
35/M	Manic-depressive psychosis	Persecutory, Grandiose, Religious	+		
22/M	Schizoid disorder	Grandiose, Persecutory			Stupor, Negativism, Confusion
34/M	Confusional episode	Being influenced, Grandiose	+		Confusion
20/M	Acute delusional psychosis	Grandiose, Persecutory		+	Agitation, Confusion
27/M	Dissociative syndrome	Religious, Grandiose	+	+	Agitation
48/M	Confusional episode	Being influenced		+	Mutism, Confusion
40/M	Manic-depressive psychosis	Being influenced			Blocking of speech
22/M	Paranoid syndrome	Grandiose, Scientific			Confusion, Posturing
44/M	Dissociative syndrome	Grandiose, Persecutory		+	Stupor, Negativism
27/M	Borderline syndrome	Religious, Scientific	+	+	Agitation
37/M	Manic bipolar disorder	Religious, Grandiose, Persecutory			Mutism
39/M	Manic bipolar disorder	Grandiose, Persecutory	+		Agitation, Mutism, Posturing
47/M	Mixed psychosis	Persecutory, Jealousy	+		Stereotypies, Posturing, Negativism
21/M	Psychotic mania	Religious, Persecutory	+	+	

Note: Hospital diagnoses were based on various criteria used in Italy over the last three decades. In particular, the term dissociative syndrome refers to loosening of association, and is not related to DSM-IV dissociative disorders.

requiring combined treatment with antipsychotics or other mood-stabilizers. However, recurrences during lithium were milder than previous episodes and new hospitalizations were generally required only in patients who were not compliant or had abandoned lithium treatment. A substantial proportion of men also abused alcohol.

Many patients had a history of favism-related hemoglobinuric jaundice during childhood. The majority of patients (64%) had a first-degree relative suffering from psychiatric illness.

## Discussion

This description of psychotic mania in a substantial proportion of G6PD-deficient subjects attending our department is to be discussed in the context of existing literature. The role of G6PD deficiency in psychiatric disorders has not been definitely established, studies varying from reports of acute psychotic cases [6,7] to surveys of enzyme activity in hospitalized populations [8–10,14]. G6PD deficiency was also used as a traditional X-chromosome marker in linkage studies [4,15–17]. The first study dates back to 1962, when Dern et al [6] reported a not-otherwise-described temporary psychosis during primaquine

administration in two G6PD-deficient subjects several weeks after the subsidence of acute hemolytic anemia.

In 1976, Nasr reported two consecutive acute psychotic episodes in a young Afro-American woman [7]. An abstract of the description of the latter case is worthy of mention: "She was in good mental health until one week prior to admission, when she started to become irritable and insomniac and heard voices telling her that people were going to kill her. On mental status examination, she was staring at the wall. Her mood was depressed and her affect inappropriate. She admitted to auditory hallucinations and ideas of reference and persecution. She was alternately oriented and disoriented to place, person, and time. It was assumed that she was suffering from an acute paranoid psychosis. The routine laboratory work revealed a hemoglobin level of 11.1 g/dl; a hematocrit reading of 34.6%, and a total bilirubin value of 1.7 mg/dl. These findings suggested a hemolytic process. On her second admission, she was found to be confused, agitated, and disoriented; had auditory and visual hallucinations; and manifested more bizarre behavior, like barking and pacing the hall nude with a lampshade on her head. She had a G6PD level in the homozygote-deficient range. She

admitted to having eaten "funny Italian beans" two days before the onset of her first illness." The author commented: "the excellent recovery of this patient, the absence of any family history of mental illness, the absence of clear stressful life events leading to her psychosis, and the presence of G6PD deficiency with suggestive evidence of hemolysis led to the possibility of an organic delirium as opposed to an acute paranoid schizophrenia".

Despite a different diagnosis and lack of clear manic symptoms, there are striking similarities between the latter case and the majority of cases described here. Conceivably, hospital diagnoses (Table 2) have varied according to the prominence of different "atypical" symptoms during the index episode (e.g. persecutory delusion, loosening of associations, or confusion) as well as to the prior course of illness (first episode as opposed to recurrence). The ascertainment of patients from lithium clinics might have led to a selection of patients with manic features, recurrent episodes, or a bipolar course. However, the excessive rate of RDC schizoaffective diagnoses among G6PD deficient patients is consistent with the hypothesis that this enzyme deficiency could confer greater severity to manic episodes. In this series of patients, the most peculiar picture resembles second and third stages of mania according to Carlson and Goodwin [18]. The presence of catatonic features and/or confusion also recalls delirious mania as described in the past by Bell [19] and more recently by Bond [20] and Fink [21]. Bond treated his patients with haloperidol and lithium [20], while Fink [21] opted for ECT especially when an underlying systemic illness was suspected. Similar treatments were used in patients from this series.

With regard to laboratory findings, data from available hospital charts are suggestive of a transient metabolic disorder on admission. An association of excitement, delusional thoughts, restlessness and confusion is known to occur in medical conditions including toxic and metabolic disorders. The most peculiar findings in a substantial proportion of our G6PD-deficient subjects suffering from acute psychotic mania were transitory hyperbilirubinemia and/or hyperurobilinogenuria, the causes of which are difficult to identify retrospectively. We have already described elsewhere two men from this sample whose psychotic episodes were possibly associated with hemolysis after ingestion of fava beans [22]. In an additional patient, onset of illness was associated with three consecutive hospitalizations in the following order: favism-related hemolysis, appendectomy, and psychosis. In the remaining cases, hyperbilirubinemia was generally mild and no overt signs of hemolysis, such as jaundice or icteric sclerae, were reported. It is known that hyperbilirubinemia can have serious CNS consequences. One of the latter is kernicterus in newborns, that has also been

reported in association with G6PD deficiency [2]. In this case, however, the cause of jaundice is not entirely clear, since hemolysis does not seem to have a major role. One possibility is that the enzyme deficiency in the liver is sufficiently severe to impair the catabolism of bilirubin. Another example of potentially relevant non-erythrocyte enzyme deficiency is found in hepatitis. In fact, alarming hyperbilirubinemia may be found in the presence of G6PD deficiency, even in adults [2]. The relevance of bilirubin in these cases of psychotic mania cannot be established, but it may be of interest to mention that bilirubin has been suggested to play a role in hepatic encephalopathy presenting as delirium and mania [23]. Moreover, an excess of idiopathic hyperbilirubinemia has recently been reported in patients hospitalized for schizophrenic psychosis [24,25], as the possible consequence of increased vulnerability of red cell membranes and/or the common polymorphism of the glucuronyl transferase gene (Gilbert's syndrome).

Hypocholesterolemia, which was often observed in patients from this study, might be merely related to neglect of nutritional needs during restless psychotic mania, even though lowering of cholesterol levels has also been reported after primaquine-induced hemolysis [26].

Whatever the role of hyperbilirubinemia and low cholesterol concentrations, another potential mechanism in G6PD-related psychoses may be an enzyme deficiency in the CNS. There are no data concerning the CNS expression of G6PD mutations, but it is known that the brain is one of the organs with the highest activity of G6PD in normal humans [27]. Interestingly, the activity of the hexose monophosphate shunt, whose first step is catalyzed by G6PD, can be stimulated in the brain by monoamine transmitters, perhaps in relation with the detoxication of monoamine-oxidase-dependent metabolites [28,29]. With regard to catatonic features, Dern et al [8] had already raised the hypothesis of a potential role of G6PD deficiency, even though the context was that of schizophrenia subtypes. Their hypothesis was based on results from a survey of 351 Afro-American patients hospitalized for schizophrenia for longer than 8 months in Illinois. G6PD deficiency was significantly in excess in the subgroups of both sexes classified as catatonic in comparison to paranoid, especially in early onset cases. A replication study of 562 men and 235 women hospitalized in New York State could not confirm or deny previous findings [9]. G6PD-deficiency rates were in excess in catatonic compared with paranoid subtypes in males from four hospitals, but the results were in the opposite direction at the fifth hospital. A nonsignificant excess in the catatonic subtype was also reported in females when the lowest 10% enzyme activity was analyzed. In a third study, no catatonic/paranoid differences were found in 783 Afro-Amer-

ican men hospitalized for schizophrenia in Alabama [10]. In view of such inconsistent results, the hypothesis of a role of G6PD deficiency in catatonic schizophrenia was abandoned. It was concluded that the discrepancies were probably due to unreliability of subcategories of schizophrenia as well as to the choice of samples of chronic patients as opposed to the acute hemolysis-related psychosis that had prompted the initial survey [6,8]. However, assuming that positive data were real despite difficulties in replication, one might speculate as to potential relationships between catatonic schizophrenia as diagnosed in the 1960s and psychotic mania with catatonic features of our present-day patients. In fact, it is known that catatonia was classified only as a subtype of schizophrenia until DSM-III, and only recently has it been recognized as a frequent manifestation of affective disorder.

Whatever the relevance of catatonic features, over the last two decades the interest in potential behavioral effects of G6PD deficiency has been addressed to bipolar disorders. In 1982, Nasr et al [14] reported a trend for increased proportions of enzyme deficiency in bipolar patients from a population of 104 psychiatric patients hospitalized in Illinois. Similarly, as mentioned above, our survey of 662 Sardinian outpatients revealed excessive rates of G6PD deficiency in bipolar compared to nonbipolar patients [5]. The three-fold variation was consistent with the hypothesis of G6PD deficiency as a susceptibility factor to mania/hypomania in geographical areas with high incidence. Our hypothesis was discussed in view of historical pedigrees in the genetics of bipolar disorder, which used G6PD deficiency as a marker in studies supporting the once popular X-linkage hypothesis. We commented that association with the marker itself rather than linkage with a close gene might have played a role, since 12 out of 12 bipolar members in those pedigrees were G6PD deficient [15–17].

The degree of contribution of cases with psychotic mania to those pedigrees is not known, as clinical details were not provided. Description of peculiar features, such as psychotic symptoms or concurrence of medical conditions, is currently being encouraged in psychiatric genetic studies, and might provide useful clues [30,31]. We have already reported that RDC manic schizoaffective disorder clusters in families of our patients, and suggested G6PD deficiency as one potential susceptibility factor [32]. In published pedigrees with G6PD deficiency [15–17], since the presence of psychotic features was not specified, the only inferable clinical peculiarity was the tendency towards a less severe phenotype (i.e. unipolar depression) in heterozygotes compared to hemizygotes or homozygotes, which is consistent with an X-linked condition.

In attempts at confirming the hypothesis of X-linked transmission of affective disorder in pedigrees segregating for G6PD deficiency, we have studied parents of 274 bipolar probands, including 99 with a RDC diagnosis of manic schizoaffective disorder [33]. The results were as expected, because a significant excess of affective disorders in mothers of hemizygotes for the G6PD-Mediterranean mutation was found. The explanation may be that of a susceptibility gene in linkage disequilibrium with the G6PD gene on the Xq28 chromosome or of a direct role of G6PD deficiency itself.

## Conclusions

Based on previous reports of acute psychosis [6,7], surveys of enzyme activity in psychiatric samples [5,14], genetic linkage/association studies [4,15–17,33], and on the series of cases described here, a relationship between psychiatric disorder and G6PD deficiency should be searched in the bipolar spectrum, particularly among patients with a history of acute episodes with psychotic and/or catatonic symptoms or with transient confusion.

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