Iron Overload Among a Psychiatric Outpatient Population

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Background: Iron overload has been suggested to be an unrecognized cause of psychiatric morbidity. This study sought to estimate the prevalence of iron overload in a large outpatient psychiatric clinic.

Method: A retrospective review of screening blood chemistries was conducted on 661 active outpatients at a large, university outpatient psychiatric clinic to identify elevated iron status results (plasma iron, percentage of iron saturation) suggestive of iron overload. Patients with positive profiles were asked to undergo a subsequent blood chemistry to confirm positive results (plasma iron, percentage of iron saturation, plus plasma ferritin). Patients with positive repeated iron chemistry results were considered likely candidates for iron overload.

Results: Twenty-one patients (3.2%) were identified as meeting one of the criteria suggestive of iron overload on initial screening reports. Thirty-one percent of those who underwent subsequent, confirmatory testing (5/16) continued to meet one of the criteria. On the basis of these results, we estimated a 1% (3.2×0.31) prevalence rate of likely candidates for iron overload. A review of these patients' charts indicated that they carried an unexpectedly high rate of bipolar affective disorder (80%) as a diagnosis and were, without exception, atypical in that they were resistant to conventional psychiatric treatment and lacked a family history for this disorder. The prevalence of positive iron overload profiles on a routine blood chemistry was similar to the prevalence of positive thyroid abnormalities based on TSH results in this population.

Conclusion: Blood chemistry profiles suggestive of iron overload may be associated with a small portion of treatment-resistant psychiatric patients. Routine screening for iron abnormalities, especially in treatment-resistant patients, should be considered. Further studies are required to determine the causal association, if any, between iron excess and primary psychiatric illnesses.

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Iron plays an important role in the regulation of enzymes involved in neurotransmitter function such as tyrosine hydroxylase,[1] the regulation of postsynaptic dopamine receptors,[2,3] and the permeability of the blood-brain barrier.[3] It is also believed to play an important role in the production of free radicals, which have been implicated as possible contributors to many disorders of the brain.[4] Iron overload syndromes can result from a hereditary abnormality in iron absorption (primary hemachromatosis) or secondary to various other medical causes such as alcoholic cirrhosis.[5] The brain has a greater tendency to retain iron than do peripheral organs.[3] Excess iron can form insoluble deposits in the brain[6] and may initiate a state of relative oxidative stress.[7] Iron excess has been implicated in the pathogenesis of several neuropsychiatric illnesses and syndromes such as Parkinson's disease, Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, and tardive dyskinesia.[4,8,9] Little, however, is known about the association of iron overload and primary psychiatric illnesses. Depressed mood, lethargy, dementia, and disorientation are some manifestations found in patients with hereditary hemachromatosis.[10] Cutler[11,12] has suggested that iron overload is a significant, unrecognized contributor to psychiatric morbidity, particularly in patients with chronic symptoms that are unresponsive to conventional treatment. He reported a case series of seven patients with various psychiatric presentations of a chronic, refractory nature who were discovered to have iron overload and responded to iron chelation treatment with deferoxamine.[12]

The importance of a putative contributor to the expression and/or course of any illness depends on two factors: the strength of its causal association with the illness and its prevalence among those with the illness. Indirect evidence is accumulating regarding the causal association of iron excess and diseases of the brain. Nothing is known, however, of the prevalence of iron overload syndromes among populations suffering from such diseases. This study attempted to estimate the prevalence of excess iron abnormalities in a large community psychiatric outpatient clinic by conducting a retrospective chart review and follow-up of laboratory blood analyses. A secondary goal was to assess the usefulness of routine blood chemistry tests as screens for iron excess syndromes in such a population.

Table 1. Iron Overload Candidates at Initial Blood Analysis*

Psychiatric Diagnosis (DSM-III-R)	N	%
Bipolar affective disorder	7	33
Polysubstance abuse	6	29
Major depressive disorder, recurrent	4	19
Psychosis NOS	3	14
Seizure disorder	3	14
Narcissistic personality disorder	2	9
Panic disorder	1	5
Borderline personality disorder	1	5

*Total N = 21; 57% were men, 43% were women; mean age = 37.4 y, range = 22–56.

METHOD

The clinical charts of 661 active patients at the University of California, San Diego, Outpatient Psychiatric Services who received routine blood chemistry screening were reviewed to identify those patients whose results suggested iron overload. Any patient with one or more of the following abnormalities was considered a candidate for iron overload: elevated plasma iron (> 170 mg/dL) or elevated (> 50%) transferrin saturation index (calculated as plasma iron/total iron binding capacity) or ferritin (> 450 ng/mL). These values are based on the normal reference range the laboratory used for these blood tests as well as the criteria utilized by Cutler[12] and recommended by others.[6] Those patients with one or more elevated values on these tests were contacted and asked to undergo another blood analysis, including complete blood count and a chemistry panel (plasma iron, transferrin saturation, plus serum ferritin), to provide more current iron evaluation.

Patients who continued to exhibit one or more of the abnormal iron status results described above were considered strong candidates for primary or secondary iron overload. Prevalence rates of iron overload were calculated. As a control comparison, abnormalities in thyroid-stimulating hormone (TSH), a common screen of thyroid function, were also recorded. The charts of those patients who met one or more of the criteria were systematically reviewed for clinical information including diagnosis, treatment, and response and items endorsed on a medical symptom checklist completed at registration. Candidates with a high potential for iron overload were contacted and informed that they might have an iron overload symptom, and further medical evaluation was recommended (assistance with referrals was offered when requested).

RESULTS

Of the 661 charts reviewed, 21 subjects (3.2%) were identified as potential iron overload candidates based on one or more of the above criteria noted on initial blood chemistry screening reports. Table 1 describes the characteristics and prevalence of specific diagnoses among this group of patients according to DSM-III-R criteria.

Table 2. Iron Overload Candidates at Repeated Blood Analysis*

Psychiatric Diagnosis	N	%
Bipolar affective disorder	4	80
Polysubstance abuse	3	60
Major depressive disorder, recurrent	1	20
Narcissistic personality disorder	1	20

*Total N = 5; 60% were men, 40% were women; mean age = 39.4 y, range = 29–48.

Of these 21 patients, all but 5 (N = 16) were successfully contacted by us and consented to a subsequent blood test (including analysis of ferritin). In 5 of those 16 patients, blood chemistry results continued to suggest iron overload on the basis of the same criteria. These patients were considered strong candidates for iron overload. Tables 2 and 3 describe the clinical characteristics of this group of patients. The following are clinical synopses of these 5 patients.

Case Reports

Case 1. Mr. A is a 41-year-old homosexual man who tested positive for human immunodeficiency virus (HIV) 4 years prior to admission to the outpatient clinic in 1993 for depression and suicidal ideation. He had a several-year history (preceding his acquisition of HIV) of mood swings that included distinct periods of depressed mood and hopelessness. On other occasions, he experienced episodes of mood elevation, hypersexuality, decreased need for sleep, impulsivity, and spending sprees. He began to abuse alcohol as mood swings worsened, but had been sober for 3 months prior to admission into the outpatient service. This patient was diagnosed with bipolar affective disorder and alcohol abuse in partial remission. His mood has resisted stabilization despite multiple drug regimens including lithium, carbamazepine, and valproate. Medical complaints included only intermittent night sweats. Iron status test results showed elevated plasma iron (211 μg/dL) and iron saturation (96%) on initial screening reports and elevated ferritin (457 ng/dL) at subsequent analysis 4 months later. Other abnormal laboratory blood results were mildly elevated blood glucose and low hemoglobin.

Case 2. Ms. B is a 40-year-old divorced woman admitted to the outpatient clinic in 1992 with complaints of a several-year history of mood swings. She experienced many episodes of depressed mood and decreased energy alternating with other episodes of excessive well-being, increased energy, and decreased sleep. She was diagnosed as bipolar affective disorder NOS. She failed lithium monotherapy, as well as lithium plus several antidepressants, and continues to have significant symptomatology on treatment with lithium plus carbamazepine. Medical complaints include persistent fatigue and joint pain. Iron status test results showed elevated plasma iron (177 μg/dL)

Table 3. Individual Patients With Laboratory Results Suggestive of Iron Overload

Patient	Sex	Age (y)	Diagnosis	Iron (μg/dL)	Saturation (%)	Ferritin (ng/dL)	Other Abnormalities
1	Male	41	Bipolar affective disorder, polysubstance abuse	211[a] 96	96[a] 45	… 457[a]	Glucose = 131 mg/dL, hemoglobin = 13.5 g/dL, GGT = 59 mU/mL
2	Female	40	Bipolar affective disorder	177[a] 135	63[a] 56[a]	… 80	
3	Female	31	Bipolar affective disorder	232[a] 166	58[a] 52[a]	… 84	
4	Male	39	Bipolar affective disorder, polysubstance abuse	188[a] 261[a]	57[a] 76[a]	… 276	Elevated liver enzymes
5	Male	49	Major depressive disorder, polysubstance abuse, narcissistic personality disorder	215[a] 134	62[a] 36	… 1133[a]	

[a]Elevated.

and iron saturation (63%) on initial screening reports and elevated saturation (56%) at subsequent analysis 12 months later. No other abnormal blood analysis results were noted.

Case 3. Ms. C is a 31-year-old woman who presented to the clinic in 1994 with depressed mood, fatigue, and anhedonia. She reported a 7- to 10-year history of general "moodiness" characterized by episodes of extreme irritability and depressed mood with poor sleep and periods of increased and decreased energy. This patient reported episodes of drinking alcohol to counter her moods, interspersed with periods of sobriety. Initially, she was diagnosed with major depression. She became demonstrably manic during antidepressant treatment and exhibited mixed features of dysphoria and suicidal ideation, plus excessive energy and decreased need for sleep. Her diagnosis was subsequently changed to bipolar affective disorder, mixed type. Her condition improved slightly on lithium monotherapy, but she continued to experience breakthrough episodes of depression and mixed mania. Addition of valproate and an antidepressant brought only modest relief. Medical complaints include chronic headaches and fatigue. Iron status test results revealed elevated plasma iron (232 μg/dL) on initial screening reports and elevated iron saturation (58%) at subsequent analysis 4 months later; this elevated iron saturation persisted.

Case 4. Mr. D is a 39-year-old divorced man with a history of unstable moods for several years and a 20+-year history of intermittent alcohol and drug use. He was admitted to the clinic in 1994, reporting periods of distinct depression plus suicidality sometimes associated with increased energy, excessive and unrealistic goal-directed activity, insomnia, and distractibility. He was diagnosed with bipolar affective disorder and polysubstance abuse. During a 1-year period of abstinence since admission, this patient continued to experience mood instability despite lithium, valproate, carbamazepine, and verapamil use in monotherapeutic and combined regimens. Medical complaints include persistent fatigue and weakness. Iron status test results showed elevated plasma iron (188 μg/dL) and iron saturation (57%) on initial screening reports and also at subsequent analysis 5 months later (261 μg/dL and 76%, respectively). Other abnormal laboratory blood values were mildly increased liver enzymes (ALT, AST, GGT).

Case 5. Mr. E is a 49-year-old man admitted in 1993 for recent recurrence of decreased energy, low mood, poor sleep, poor concentration, and anhedonia. This patient experienced two previous similar episodes in the past 6 years, both of which remitted spontaneously. He had a long history of intermittent drug and alcohol abuse but had been abstinent for over 1 year at admission. He was given a diagnosis of recurrent major depression, polysubstance abuse in remission, and narcissistic personality disorder. Since admission, this patient has continued to have significant depression despite six different trials of antidepressant medication in various pharmacologic classes as well as a trial of lithium augmentation. Medical complaints are significant only for intermittent night sweats. Iron indices showed elevated plasma iron (215 μg/dL) and iron saturation (62%) on initial screening reports and elevated ferritin (1133 ng/dL) at follow-up 8 months later. No other abnormal blood analysis results were noted.

DISCUSSION

The estimated prevalence of a single elevated result for each of the three iron status tests used is approximately 2.5% in the normal population.[13–15] Thus the prevalence of elevated results on at least one of these tests during a single screening in the studied population is not significantly higher than what would be expected in a normal population. Alone, this suggests that there may not exist, among outpatient psychiatric patients, a substantially higher rate of iron overload than that found in the population at large.

This study employed a repeated blood chemistry to reduce the rate of false positive iron overload profiles obtained with a single screening, which reduced the number

of candidates for iron overload by two thirds. The specificity of elevated iron chemistry values (primary or secondary hemachromatosis) on two separate blood chemistries at least 4 months apart is unknown, and confirmation of iron overload in these patients would require tissue examination such as a liver biopsy. However, the 1% prevalence of a persistent blood chemistry profile suggestive of iron overload in this studied population is substantially higher than the 0.25% rate of iron overload reported in the general population.[16]

Of interest, one third of the patients identified as iron overload candidates after their initial blood chemistry analysis carried a primary psychiatric diagnosis of bipolar affective disorder. The rate of bipolar affective disorder among those patients identified as strong candidates for iron overload, based on positive findings of a second blood analysis, increased to 80% (N = 4/5). This rate of bipolar affective disorder diagnosis is substantially higher than the overall rate of this diagnosis among the clinic population as a whole, where it is slightly less than 13%. The chance of obtaining this result by chance, given the diagnostic distribution in this clinic, is less than 1 in 700 ($0.13^4 \times 5$).

The strong association of iron excess with bipolar affective disorder seen in this study has not been reported in other studies and stands in distinction to Cutler's report[12] of a wide range of psychiatric presentations associated with iron excess. Arguably, more than any other diagnosis, bipolar affective disorder is consistent with a wide range of symptomatology (including depressive neurovegetative, psychotic, and irritable) and a highly variable expression over time. An alternate explanation for the high prevalence of bipolar affective disorder diagnosis in this cohort, therefore, is that bipolar affective disorder is a diagnosis of "best fit" for patients with excessive iron who present with a wide range of symptoms that display instability over time and that do not fit into any classical diagnostic pattern. Supporting the notion that these patients differ in some essential manner from those with primary (versus secondary) psychiatric illnesses is the high resistance to standard treatment seen in this cohort and the absence of family history of bipolar affective disorder reported by patients diagnosed with this disorder. All of the candidates who had excessive blood levels of iron continued to express significant ongoing symptomatology at the time of the chart review despite a mean of six medication trials per patient. This supports Cutler's findings[12] and suggestion that iron excess may be associated with treatment-refractory psychiatric illness.

This study also suggests that using plasma iron in conjunction with transferrin iron-binding capacity (from which percentage saturation is calculated), both common and inexpensive elements of a routine blood chemistry, as a screen for iron overload will result in an approximately 3% positive rate in a psychiatric outpatient population. Up to as many as two thirds of these will show no psychiatric stability over time as assessed by a repeated blood chemistry, based on these results. Thus, on the basis of these results, we estimate that 1% ($3.2\% \times 0.31$) of psychiatric outpatients meet laboratory criteria for iron overload based on consecutive blood analysis.

The rate of positive results for thyroid abnormalities confirmed by laboratory screening in this study population was 2.6%. This is similar to the positive screening rate found by Fava et al.[17] in a recent survey of 200 psychiatric outpatients tested for thyroid abnormalities using TSH as an index. It suggests that the outpatient sample in this study is fairly representative of other psychiatric outpatient populations. In the study by Fava et al., only one in five of those with elevated TSH (0.5% of the sample) were found to have a corroborating abnormality in another thyroid function index such as triiodothyronine resin uptake (T_3RU) or free thyroxine (FT_4). Screening for thyroid abnormalities by using TSH is a widely accepted practice within the psychiatric field. Our results suggest that prevalence of abnormal iron status results suggestive of iron overload is at least as great as that for abnormalities found on routine screens of thyroid function among a psychiatric outpatient population. This is not surprising, given that hemachromatosis is the most common genetic disorder and that liver disease due to alcohol or substance abuse, a prevalent condition among psychiatric patients, is a strong potential contributor to iron overload. Unlike the established causal association between abnormal thyroid function and psychiatric presentations, however, the link between iron overload and psychiatric presentations has not yet been firmly demonstrated.

Limitations to this study are many. The most obvious limitation is its retrospective, chart-review design. In addition, only strong candidates for iron overload could be identified. Definitive evidence of iron overload requires further diagnostic studies such as a liver biopsy. Nevertheless, this study presents the first estimate of iron overload prevalence in a large outpatient psychiatric population. More study of the potential role of iron excess in psychiatric morbidity is needed. At present, however, a conservative conclusion seems to be that there exists some theoretical and some clinical evidence to suggest iron overload may be a contributor to psychiatric illness. In patients with psychiatric symptoms resistant to conventional treatment, medical syndromes including iron overload should be considered and screened for. In addition, based on these findings, patients who have modestly elevated iron status results on a single blood chemistry screening in the absence of clear clinical signs of iron overload should have a repeated chemistry performed before progressing to more invasive diagnostic steps, since many of these modest abnormalities will not persist. Patients who are candidates for iron overload based on consistently elevated iron status results from multiple screening should

be referred for liver biopsy to confirm the diagnosis. Treatment options for iron overload include phlebotomy and chelation therapy with deferoxamine.[18] Problems with phlebotomy include induction or exacerbation of anemia, cardiac symptoms, and objections on religious grounds. Deferoxamine chelation is relatively nontoxic; however, long-term administration of this agent by intravenous infusion or subcutaneous or intramuscular injection is required since it is not orally active.[18]

Drug names: carbamazepine (Tegretol and others), deferoxamine (Desferal), verapamil (Calan and others).

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