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Relationship Between Iron Status and Chronic Akathisia in an In-patient Population with Chronic Schizophrenia

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Iron status and akathisia were assessed in 105 long-stay in-patients who fulfilled DSM-III-R criteria for schizophrenia, all but three of whom were receiving antipsychotic medication. Chronic akathisia was diagnosed in 23% and pseudoakathisia in 20%. No significant correlation was found between serum iron concentration and the severity of akathisia. There was no significant difference in serum iron concentration between patients with chronic akathisia and those without. However, serum iron and percentage saturation were significantly raised in patients with pseudoakathisia compared with patients with chronic akathisia, and tended to be higher than in patients with akathisia. These findings do not support an association between low serum iron and chronic akathisia.

Akathisia is a common and often distressing syndrome of motor restlessness that occurs as an adverse effect of both acute (Braude *et al*, 1983; Van Putten & Marder, 1987; Adler *et al*, 1989) and chronic treatment (Barnes & Braude, 1985) with antipsychotic medication. Acutely, the development of akathisia tends to be associated with higher doses of antipsychotic drugs and a rapid increase in dose (Ayd, 1961; Braude *et al*, 1983; Sachdev & Loneragan, 1991), although some patients can exhibit the condition soon after starting low doses of antipsychotic medication (Freedman & De Jong, 1961; Van Putten *et al*, 1984; Stein & Pohlman, 1987).

The only other predisposing factor suggested has been iron deficiency. Brown *et al* (1987) noted the association between iron deficiency and the 'restless legs syndrome' (Gibb & Lees, 1986), a condition that shows some similarity to akathisia (Blom & Ekbom, 1961), and speculated that there might be a similar association with akathisia. In their study of long-stay psychiatric in-patients, Brown *et al* (1987) found that both serum iron concentration and percentage saturation were significantly decreased in 13 cases of chronic akathisia compared with the same number of non-akathisic controls, while total iron-binding capacity (TIBC) was correspondingly increased. They also found a negative correlation ($r = -0.42$, $P < 0.1$) between the akathisia rating and serum iron, suggesting a relationship between iron deficiency and the severity of chronic akathisia.

In a replication study, Barton *et al* (1990) compared 15 patients with akathisia with pair-matched patients without. The values for plasma iron, transferrin, and percentage saturation of transferrin were low, but within the normal range. However, ferritin levels in the akathisic group were below the normal range, and significantly decreased compared with the non-akathisic group. In addition, a significant inverse correlation was found between plasma iron levels and akathisia rating. The investigators took these findings as broad support for the notion that akathisia in patients receiving chronic treatment with antipsychotic drugs may be related to a depletion of iron stores. However, in a further replication study, Nemes *et al* (1991) compared serum iron and haematological profile in 25 chronic psychiatric patients with chronic akathisia, 25 matched patients without the condition, and 22 normal control subjects. These investigators failed to find lower serum iron or ferritin levels in those patients with akathisia, and there was no correlation between serum iron levels and akathisia ratings.

Studies of iron status in acute akathisia have also yielded somewhat contradictory data. Sachdev & Loneragan (1991) reported that 15 (30%) out of 50 patients with acute psychotic illness developed akathisia within two weeks of starting antipsychotic drugs. There were no differences between the akathisic patients and the 35 patients who did not develop the condition in terms of serum iron and transferrin levels or haemoglobin values. Similarly, in a study of 30 acutely psychotic patients, O'Loughlin *et al* (1991) found that the six patients developing acute akathisia were not characterised by low levels of iron or transferrin. However, a follow-up assessment at two to three weeks revealed that akathisia scores were highly correlated with serum transferrin levels, and that iron and transferrin levels had decreased significantly only in those patients with akathisia.

The findings referring to acute akathisia cannot be confidently generalised to chronic akathisia, and vice versa, as the two conditions may be pathophysiologically distinct (Barnes, 1990). The purpose of the present study was to examine further the

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possible relationship between iron status and chronic akathisia by surveying a population of long-stay schizophrenic in-patients receiving antipsychotic medication.

Method

The study population comprised all 137 patients between the ages of 18 and 65 years of age who had been resident on the wards of a psychiatric hospital for more than one year and who fulfilled DSM-III-R criteria for schizophrenia (American Psychiatric Association, 1987).

Basic demographic information was collected for all patients, as well as details of current medication. For each patient, the antipsychotic drug dose was converted to chlorpromazine equivalents in mg a day (Rey *et al*, 1989).

Akathisia was assessed using the Barnes Akathisia Rating Scale (BARS; Barnes, 1989). The first 42 cases were assessed by two raters (SMH, TREB) to establish adequate inter-rater reliability (Barnes & Halstead, 1988). All the subsequent ratings were carried out by SMH. Akathisia was diagnosed if the score on the global item of the BARS was 2 or more. This item rates the severity of akathisia on a six-point scale (0–5), ranging from no to severe akathisia.

'Pseudoakathisia' refers to the exhibition of the characteristic movements of akathisia in the absence of the typical subjective report of restlessness (Munetz & Cornes, 1982; Barnes & Braude, 1985). This diagnosis was made if a patient scored 1 or more on the objective item of the scale, rating akathisic movements, but scored 0 on the subjective item, which rates awareness of restlessness.

A blood sample was taken from each patient between 7.00 and 8.30 a.m. for determination of serum iron, full blood count, and TIBC. In each case, the percentage saturation was calculated by dividing the serum iron by the TIBC.

Data analysis

Data were analysed using the SPSSX package. The relationships between variables and their distribution in the sample were examined using Pearson correlation coefficients, and Mann-Whitney (two-tailed) and Kolmogorov-Smirnov goodness of fit tests, as appropriate. The haematological variables in the sample subgroups were compared using analysis of variance and the *t*-test (two-tailed).

Results

One hundred and twenty patients consented to the study and were assessed using the BARS. Blood samples were obtained in 106 cases, but one patient (patient 9, Table 2) was excluded because of a pathologically high level of serum iron (48 μmol/l). There were no significant differences in age, sex or dosage of antipsychotic medication between the 105 patients for whom haematological data were available and those for whom they were not. Four samples were insufficient for the determination of TIBC, but these were included for the other analyses.

All akathisia identified in this population was diagnosed as chronic in that the onset of symptoms had not occurred as a recent response to starting antipsychotic medication or receiving an increase in dose (Barnes & Braude, 1985). No further classification of chronic akathisia (i.e. acute, persistent, or tardive) was attempted (Fahn, 1983; Barnes & Braude, 1985). Chronic akathisia was present in 24 (23%) of the 105 patients. The severity was rated as mild in 13, moderate in 8, marked in 2, and severe in only 1 case. Pseudoakathisia was diagnosed in 21 (20%) patients, all but one of whom was male.

The age distribution in the sample was not normally distributed (Kolmogorov-Smirnov goodness of fit test, $P=0.01$), but skewed towards the older age range (Table 1). Subjects with chronic akathisia were significantly younger than those without akathisia (Mann-Whitney *U*-test, $P=0.007$); the age of patients with pseudoakathisia did not differ significantly from that of the other groups.

The daily dosage of antipsychotic medication, expressed as mg equivalents of chlorpromazine, was also not normally distributed (Kolmogorov-Smirnov goodness-of-fit test, $P<0.001$). Patients with chronic akathisia were receiving higher doses of antipsychotic medication than those without akathisia (Mann-Whitney *U*-test, $P=0.015$). The subgroup of patients with pseudoakathisia was also receiving higher doses of antipsychotic drugs than the non-akathisia group, although this difference did not reach statistical significance. There were no significant differences between the akathisia subgroups in the proportion receiving anticholinergic agents.

Table 1
Demographic and medication details of the total sample and akathisia subgroups

	Total sample ($n=105$)	Chronic akathisia ($n=24$)	Pseudoakathisia ($n=21$)	No akathisia ($n=60$)
No. of women/men	26/79	8/16	1/20	17/43
Median (range) age: years	55 (31-65)	48 (31-62)	55 (35-65)	56 (32-65)
Antipsychotic medication median (range) dose: chlorpromazine equivalents, mg/day	896 (0-7800)	1254 (149-3429)	1193 (119-7800)	714 (0-3886)
No. (%) receiving depot but no oral medication	26 (25)	7 (29)	6 (29)	13 (22)
No. (%) not receiving antipsychotic drugs	3 (3)	0 (0)	0 (0)	3 (5)

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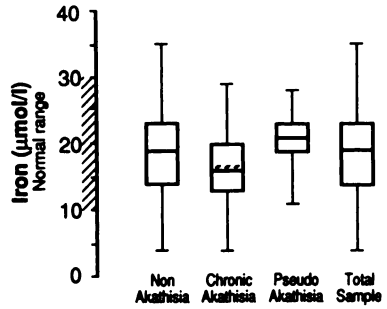


Fig. 1 Plot of serum iron by akathisia subtype. Bars show upper and lower values in each group; boxes show upper and lower quartiles and median values (---mean).

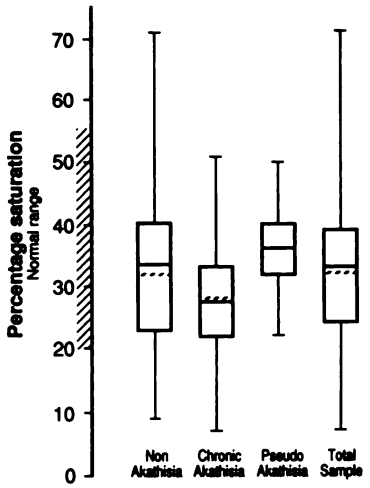


Fig. 2 Plot of percentage saturation by akathisia subtype. Bars show upper and lower values in each group; boxes show upper and lower quartiles and median values (----mean).

There was a significant negative correlation between the daily dose of antipsychotic drug and increasing age ($r = -0.37$, $P = 0.001$). There was no significant correlation between serum iron level and either age ($r = -0.15$) or daily dose of antipsychotic drug ($r = 0.03$). Further, there were no significant differences in either age or chlorpromazine equivalents between men and women.

The 105 patients in the sample were divided into those receiving and those not receiving oral antipsychotic medication, irrespective of whether they were receiving an intramuscular depot preparation. There was no significant difference between the mean serum iron concentrations in the two groups ($t = 1.33$, $P = 0.188$).

Akathisia and iron physiology

No strong, consistent relationship emerged between serum iron concentration and the severity of akathisia ($r = 0.16$, $P = 0.45$). Analysis of variance of serum iron, TIBC, and percentage saturation by sample subgroups (non-akathisia, chronic akathisia, and pseudoakathisia groups) revealed no interactions significant at the $P < 0.01$ level. However, the significance of the interaction was at a trend level for serum iron level ($F = 2.77$, $P = 0.07$) and percentage saturation ($F = 2.65$, $P = 0.08$). Serum iron levels and TIBC were normally distributed, so t-tests were used for further analysis. The mean serum iron concentration was lower in patients with chronic akathisia than in patients without akathisia, but this difference was not statistically significant ($t = 1.23$, $P = 0.224$). The mean serum iron concentration tended to be higher in the pseudoakathisia group than in the non-akathisia group ($t = -1.99$, $P = 0.051$) and was significantly higher than in the chronic akathisia group ($t = 3.05$, $P = 0.004$). These data are presented in Fig. 1.

The mean serum iron concentration was slightly higher in the 79 men (19.3 μmol/l, s.d. 6.5) than in the 26 women (16.8 μmol/l, s.d. 5.1), but not significantly so, and this

Table 2
Patients with abnormal haemoglobin or serum iron levels[1]

Patient	Sex	Age: years	Iron: μmol/l (10-30)	TIBC: μmol/l (40-70)	Percentage saturation (20-50)	Haemoglobin: g/dl (13-18 M, 11.5-16.5 F)	Mean corpuscular volume:fl (77-93)	Haematocrit (0.4-0.54 M, 0.37-0.47 F)	Mean corpuscular haemoglobin concentration: g/dh (31-35)	Akathisia subtype	Severity score
1	M	33	4	57	7	12.1	79.0	0.39	31.0	Chronic	2
2	M	59	4	48	8	14.2	87.8	0.42	33.8	Nil	-
3	M	51	5	54	9	15.5	93.0	0.47	33.0	Nil	-
4	M	65	6	57	11	11.7	79.0	0.36	32.0	Nil	-
5	M	51	8	54	15	13.6	84.0	0.41	33.0	Nil	-
6	M	49	9	78	12	13.9	74.0	0.42	33.0	Nil	-
7	F	56	12	74	16	11.4	81.0	0.35	33.0	Nil	-
8	M	55	13	45	29	12.2	85.8	0.36	33.5	Chronic	3
9	M	62	48	80	60	17.2	87.9	0.51	33.8	Chronic	2

1. Normal ranges are given in parentheses.
Patient 1 had a peptic ulcer and was on iron supplements.
Patient 6 had indices of iron deficiency, but normal haemoglobin.
Patient 9 was excluded from analysis because of high serum iron level.

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difference did not explain the higher serum levels in the patients with pseudoakathisia. Mean TIBC figures were almost identical across the groups, so the analysis of percentage saturation by the above categories added nothing to the analysis by iron alone (Fig. 2). The mean TIBC values for the men (59.3 μmol/l, s.d. 9.8) and women (60.9 μmol/l, s.d. 9.4) were not significantly different.

Table 2 provides information on the six patients in the sample who had serum iron levels below the lower limit of normal (patients 1 to 6), only one of whom (patient 1) had akathisia. Table 2 also gives details of four patients (patients 1, 4, 7 and 8) whose haemoglobin levels were below normal. However, no patient showed all of the three key features of iron deficiency, that is, low haemoglobin, low serum iron, and raised TIBC.

Discussion

This study confirms that chronic akathisia is relatively common in chronic schizophrenia, being diagnosed in virtually a quarter of a population of long-stay schizophrenic in-patients. However, the results do not support the postulated association between chronic akathisia and decreased serum iron concentration (Brown *et al*, 1987), in that the patients with chronic akathisia did not show significantly lower serum iron concentrations compared with the patients without akathisia, and there was no significant inverse relationship between serum iron level and severity of akathisia in the sample. Only one of the patients with chronic akathisia was found to have a serum iron value below the normal range, and his aberrant result may be explained by a history of peptic ulcer.

The subgroup of patients with akathisia were younger and receiving higher doses of antipsychotic drugs than those without the condition, although the relevance of this to the serum iron data is difficult to interpret. Neither daily antipsychotic dose nor age, at least in the age range of the patients in the sample, are known to have a strong, consistent influence on serum iron. In the sample, there was no significant correlation between serum iron and either of these two variables.

The mean serum iron level in the subgroup of patients with pseudoakathisia was significantly higher than that found in the chronic akathisia group, although all the levels in the pseudoakathisia group were within the normal range. The explanation for this finding remains obscure.

Several neuropharmacological explanations for the association between akathisia and iron status originally reported by Brown *et al* (1987) have been propounded. For example, it has been suggested that the D_2 dopamine receptor is an iron-containing protein (Ben-Schachar *et al*, 1985) and that low serum iron causes a hypofunction of D_2 receptors that renders patients on antipsychotic drugs vulnerable to akathisia. Similarly, it has been suggested that the capacity of antipsychotic drugs to ligate with iron is related to their ability to induce akathisia (Blake *et al*, 1986; Pall *et al*, 1986). There is also evidence that antipsychotic medication may lead to an accumulation of iron in certain brain structures (Hunter *et al*, 1968; Campbell *et al*, 1985), although this may be compatible with, and even the result of, functional depletion of iron due to ligation and the subsequent deposition of iron complexes in the central nervous system.

The significant decrease in plasma ferritin in the selected group of patients with akathisia studied by Barton *et al* (1990) suggests some depletion of iron stores in patients with chronic akathisia who are receiving antipsychotic medication. Such a finding would be compatible with the notion that either coexisting but unrelated iron deficiency aggravates drug-induced akathisia or that antipsychotic drugs can have a long-term effect on iron homeostasis in some patients that increases their liability to develop akathisia. One possible mechanism for the latter hypothesis would be that oral antipsychotic drugs cause chelation of dietary iron. If this were the explanation, patients receiving oral antipsychotic drugs would be expected to have lower serum iron levels than those who were not. However, this was not the case in our study.

These neuropharmacological hypotheses are intriguing, and further exploration may help to improve our understanding of the pathophysiology of akathisia and the pharmacology of antipsychotic drugs. However, they are partly based on the premise that an association exists between low serum levels of iron and akathisia. The finding of an association does not necessarily imply a causal relationship, and Tench & Soni (1993) suggested that the low serum iron values found by Brown *et al* (1987) could be related to the relatively poor nutritional state of some long-term psychiatric in-patients.

Thus far, this association between low serum levels of iron and akathisia has only been reported in one study, and not confirmed in recent studies of chronic akathisia (Barton *et al*, 1990; Nemes *et al*, 1991) or acute akathisia (Sachdev & Loneragan, 1991; O'Loughlin *et al*, 1991), nor in the present investigation. An issue for discussion is whether differences in method could account for the inconsistency of these findings. Differences in laboratory techniques are unlikely to be relevant. Strict quality-control procedures operate for all the assays, and results are comparable. However, the present study differs from that of Brown *et al* (1987) in being a

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population survey rather than a case-control study of patients selected on the basis of a diagnosis of akathisia in the absence of other movement disorders. Only 9 of the 120 patients studied here would have satisfied such a criterion. Furthermore, this population covered a smaller age range, and all had the same psychiatric diagnosis. Whether such considerations could explain the disparity of the findings between the two studies is unclear.

The measurement of serum iron bound to transferrin is more a reflection of iron in transit than a reliable indicator of functionally important iron levels within tissues. Diurnal variation in serum iron concentration may be as much as 40% (Wiltink *et al*, 1973), with the lowest values found during sleep and the highest values a few hours after waking. The TIBC does not show a similar variation. In order to control for the diurnal variation, ideally multiple samples should be obtained at the same time on different days and compared with a reference range obtained in the same way. This was not feasible in the present study, but all blood samples for the estimation of serum iron were taken between 7.00 and 8.30 a.m. in order to eliminate this source of error as far as possible.

Further studies might consider examining the significance of iron concentration in the cerebrospinal fluid (CSF). The iron concentration of CSF might be expected to be a better reflection of iron homeostasis within the central nervous system. Iron levels in the CSF are much lower than those in serum, being less than 0.4 μmol/l, and changes in CSF iron values do not appear to reflect fluctuation in serum iron (Kjellin, 1966).

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