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Serum iron and ferritin in acute neuroleptic akathisia

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Abstract

Acute akathisia is a common and disturbing side effect of classic antipsychotic medication. Some evidence suggests a role for iron deficiency in chronic and tardive akathisia. In acute akathisia, however, the data are contradictory. Serum iron and ferritin levels of 33 inpatients with acute akathisia during classic neuroleptic medication were compared with those of 23 patients on classic neuroleptics without this side effect. Akathisia was rated by means of the Hillside Akathisia Scale. The groups were balanced for age (mean 38.5 ± 14.5), medication (butyrophenone- and phenothiazine-derived neuroleptics) and diagnosis (schizophrenia, schizoaffective disorder, psychotic affective disorder). Patients with acute akathisia had significantly lower serum ferritin levels than the patients in the control group. However, the ferritin (56.94 ± 39.54 ng/ml) and iron (88.52 ± 40.0 mg/dl) levels in these patients were within the normal range (ferritin 30–300 ng/dl, iron 80–180 mg/dl). No correlations between serum iron or ferritin and akathisia ratings could be found. Although some reduction in serum ferritin was found in patients with acute akathisia compared to patients without akathisia, the difference was small and the ferritin levels were within the range of the normal population. These findings suggest a minor role for iron deficiency in acute akathisia.

Keywords: Extrapyramidal side effects; Antipsychotics; Neuroleptics; Schizophrenia

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1. Introduction

Akathisia is considered one of the most troubling side effects of neuroleptics and is a predominant reason for non-compliance (Van Putten, 1974; Schmidt et al., 1984). Clinical subtypes include acute, withdrawal (Barclay and Lang, 1992), tardive and chronic akathisia (Sachdev and Lonergan, 1991b; Sachdev, 1994). The onset of acute akathisia is within hours or days (Sachdev, 1995a) of drug initiation or dose increase (Braude et al., 1983; Miller et al., 1997). In approximately 80%, acute akathisia develops within 2 weeks (Miller et al., 1997). Akathisia that develops after 3 months or more is termed tardive akathisia (Sachdev, 1995b).

The pathogenesis of akathisia has been poorly understood. In recent years the role of iron metabolism as a possible pathophysiological factor in the development of akathisia has received increasing attention. Clinical studies on the relationship between iron metabolism and akathisia

Table 1
Sample characteristics (mean ± S.D.)

	Akathisic ($n = 33$)	Non-akathisic ($n = 23$)	$P^{a,b}$
Age	38.5 ± 14.5	34.0 ± 9.6	0.33[a]
Male/female	12/21	13/10	0.22[b]
Number of hospitalisations	4.4 ± 4.3	4.2 ± 4.0	0.67[a]
Duration of the disease (years)	8.5 ± 8.2	7.9 ± 6.5	0.96[a]
Latency until onset of akathisia (weeks)[c]	1.5 ± 1.1		
Diagnoses (DSM-III-R)			
Schizophrenia:			
Paranoid, episodic	13	8	
Disorganised, catatonic	5	5	
Schizoaffective disorder:	10	9	
Affective disorder:			
Psychotic mania	1	1	
Psychotic depression	3		
Other:			
Drug-induced psychosis	1		
Neuroleptic medication			
High-potency butyrophenone: (haloperidol, benperidol, bromperidol)	21	10	
Phenothiazine derivates: (perazine, flupenthixol, trifuoperazine)	7	12	
Others: (pimozide, chlopenthixol dec.)	4	1	
CPZ/week[d]	6199 ± 4400	5583 ± 3750	0.93[a]
CPZ/day[e]	1031 ± 651	818 ± 517	0.38[a]

[a] Student's *t*-test.
[b] χ^2-test.
[c] Latency until akathisia developed after onset of neuroleptic treatment.
[d] Cumulative neuroleptic dosage given during the week preceding the onset of akathisia calculated into chlorpromazine equivalents (CPZ) according to Gelenberg (1983).
[e] Chlorpromazine equivalents on the day of iron status analysis (chlorpromazine equivalents in the week before and on the day of the examination for control subjects, respectively).

have yielded contradictory results (for review, see Gold and Lenox, 1995). Of nine studies, five found iron deficiency associated with akathisia (Brown et al., 1987; Barton et al., 1990; Fornazzari et al., 1991; Horiguchi, 1991; Valles et al., 1992). In contrast, however, another study yielded inconclusive results (O'Loughlin et al., 1991) and three studies yielded negative results in terms of such an association (Sachdev and Lonergan, 1991a; Barnes et al., 1992; Nemes et al., 1992). Of the six studies that investigated chronic and tardive akathisia, four reported a correlation with iron deficiency (Brown et al., 1987; Barton et al., 1990; Horiguchi, 1991; Valles et al., 1992). Of the two studies on acute akathisia, one prospective study did not find an association (Sachdev and Lonergan, 1991a) and another study yielded ambiguous results (O'Loughlin et al., 1991).

Given the inconsistent data in case of acute akathisia, the aim of the present study was to examine serum iron and serum ferritin levels in patients with acute akathisia. In contrast to existing studies on acute akathisia (O'Loughlin et al., 1991; Sachdev and Lonergan, 1991a), we measured serum ferritin, in addition to serum iron, as it represents a more sensitive peripheral marker of the body's iron stores.

2. Methods

2.1. Subjects

The subjects were 56 inpatients with acute psychotic disorders who received antipsychotic medication. Thirty-three patients (21 women, 12 men) who developed mild to severe akathisia under classical neuroleptics were compared with 23 (10 women, 13 men) neuroleptic-treated patients who did not develop this side effect. Nine of 21 women in the akathisic group and four of 10 subjects in the control group were pre-menopausal. The diagnoses were established by psychiatrists independent of this study according to DSM-III-R criteria (Table 1). Diagnoses in the akathisic group included acute exacerbations of schizophrenia and schizoaffective disorders, and affective disturbances with psychotic features. One patient suffered from an amphetamine-induced psychosis. In the control group, 22 patients were diagnosed as having either schizophrenia or schizoaffective disorder, and one patient suffered from mania with psychotic features.

There were no significant differences between the two groups regarding age, duration of disease, number of hospitalisations and neuroleptic medication.

2.2. Medication

Medications are listed in Table 1. None of the patients received an atypical antipsychotic. The cumulative neuroleptic dosage given during the week preceding the onset of akathisia and on the day of the iron/ferritin analysis was recorded. No group difference existed regarding neuroleptic medication expressed in chlorpromazine equivalents calculated according to Gelenberg (1983).

2.3. Exclusion criteria

Exclusion criteria included iron replacement therapy, significant blood loss (trauma, surgery) during the preceding 3 months, organic brain disease, alcohol abuse, diabetes mellitus, tumors, inflammatory processes, pregnancy, and suicidality. Furthermore, patients receiving amitriptyline, propranolol or benzodiazepines were excluded. Biperiden co-medication (2–4 mg/day) was allowed since its therapeutic influence on acute akathisia is small and probably has to be attributed to the amelioration of coexisting Parkinsonian side effects.

2.4. Blood sampling

All venous blood samples were taken between 07.00 and 08.00 h and were analysed for serum iron, serum ferritin, sodium, potassium, chloride, calcium, white and red blood counts, haemoglobin, haematocrit, and mean corpuscular haemoglobin concentration. Serum iron reflects only an unrepresentative part of the body's iron levels and changes markedly throughout the day and menstruation cycle. Inferences about iron status are only possible if plasma iron is determined in

combination with ferritin which best reflects the body's iron stores (Wick et al., 1991).

2.5. Akathisia rating

Akathisia was rated with the Hillside Akathisia Scale (HAS, Fleischhacker et al., 1989). The HAS has two subjective (sense of inner restlessness, urge to move; 0 = absent, 1 = questionable, 2 = present and easily controlled, 3 = present and barely controlled, 4 = present and not controlled) and three objective items (akathisia of head and trunk, akathisia of hands and arms, akathisia of feet and legs) for which anchored rating points are provided (0 = no akathisia, 1 = questionable, 2 = small amplitude movements part of the time, 3 = small amplitude movements all of the time, large amplitude movements part of the time, 4 = large amplitude movements all the time). Akathisia is rated in a sitting, standing and recumbent position under three different conditions: at rest, during mental activation (serial subtraction 100 − 7 − 7...) and during motor activation (finger-tapping of the dominant hand). Akathisia is thus rated in three body parts in three body positions at rest and under two provocation tasks. The scores of the subjective/objective items are summed to form a 'subjective'/'objective score'. The subjective and objective scores are combined in the 'total akathisia score'. For the German version used in this study, a reliability of 0.89 for the total akathisia score (reliability for the subjective score, 0.92; reliability for the objective score, 0.84) was reported (Fleischhacker et al., 1991). The correlation between the HAS and a global assessment of akathisia (modified Clinical Global Impression, CGI) was 0.87, which indicates sufficient validity (Fleischhacker et al., 1991).

2.6. Statistics

The Mann–Whitney's *U*-test was used to analyze group differences. The relationship between serum iron, serum ferritin and akathisia rating was calculated with Spearman rank correlation (Spearman-ρ corrected for ties).

3. Results

3.1. Subtype of akathisia

Among the akathisic patients, akathisia started 1.5 ± 1.1 weeks (range 1 day–4 weeks) after initiation, change, or increase of neuroleptic medication. All patients met one of the main criteria for the 'acute' type of neuroleptic-induced akathisia as described by Sachdev and Lonergan (1991a) and Sachdev (1995b). Neither the patients nor the control subjects showed pathological haematological results.

3.2. Serum ferritin

The akathisic group revealed a mean serum ferritin level of 56.94 ± 39.54 ng/ml (range 3–159) within the normal range of 30–300 ng/ml. Male patients had somewhat lower ferritin values (mean 77.55 ± 47.48 ng/ml, range 10–159) compared to female patients (mean 45.60 ± 30.01 ng/ml, range 3–108). This difference was, however, not significant. Pre-menopausal women showed slightly lower serum ferritin levels but did not differ significantly from the post-menopausal group ($P = 0.43$).

Comparison with the control group revealed a significant ($P = 0.036$) difference in serum ferritin. The patients of the control group had a significantly higher mean level of 102.13 ± 87.73 ng/ml (range 7–362). The mean serum ferritin level of the female (75.80 ± 67.66 ng/ml, range 25–256) and male control subjects (122.4 ± 98.3, range 7–362) were within the normal range (Fig. 1).

3.3. Serum iron

The akathisic group revealed a mean serum iron level of 88.52 ± 40.00 mg/dl (range 19–185 mg/dl) which was within the normal range of 80–180 mg/dl. Male patients had somewhat higher serum iron levels (mean 102.92 ± 45.64 mg/dl, range 35–185 mg/dl) than women (mean 80.29 ± 34.91 mg/dl, range 19–135 mg/dl), and pre-menopausal women higher (n.s.) levels (mean 87.67 ± 32.96 mg/dl, range 19–135 mg/dl) than

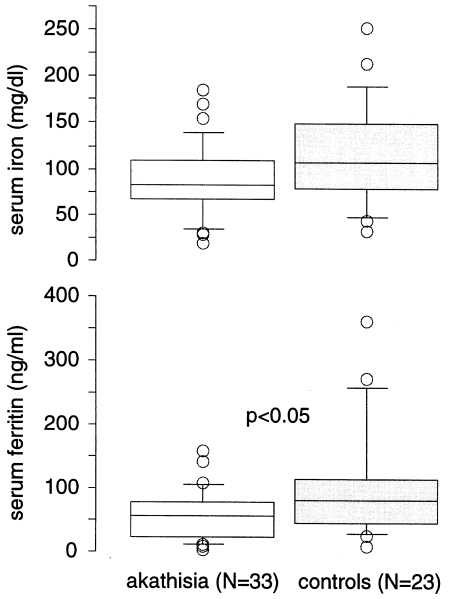

Fig. 1. Serum ferritin and serum iron levels in patients with akathisia and without. The five horizontal lines of the box plots represent the 10th, 25th, 50th, 75th and 90th percentiles of the variables. Values above the 90th percentile and below the 10th percentile are plotted separately ($P < 0.05$, Mann–Whitney *U*-test).

post-menopausal women (mean 74.75 ± 36 mg/dl, range 28–133 mg/dl). The differences between these groups, however, were not significant.

No significant differences in serum iron were found between the akathisic and non-akathisic patients. In the control group the mean serum iron level was 114.74 ± 55.10 mg/dl (range 32–252 mg/dl). Similarly to the akathisic group, the mean levels of the male patients (126.77 ± 61.11 mg/dl, range 43–252 mg/dl) were higher (n.s.) than those of the female patients (99.10 ± 44.29 mg/dl, range 32–183 mg/dl) and were within the normal range in all subjects (Fig. 1).

Since females had somewhat lower iron and ferritin levels (n.s.) compared to males, a two-way ANOVA with factor 'gender' and factor 'akathisia' was calculated, but no significant confounding effect was found. Ferritin: gender: $F_{1,50} = 4.93$, $P < 0.05$; akathisia: $F_{1,50} = 4.50$, $P < 0.05$; gender × akathisia: $F_{1,50} = 0.17$, $P = 0.68$ (n.s). Iron: gender: $F_{1,52} = 3.89$; $P < 0.1$; akathisia: $F_{1,52} = 2.80$, $P = 0.1$; iron × akathisia: $F_{1,52} = 0.39$, $P = 0.84$ (n.s.).

Spearman's ρ did not reveal a correlation between serum iron and serum ferritin values ($\rho = 0.037$).

3.4. Akathisia ratings

The 33 akathisia patients had a mean score on the HAS of 61.9 ± 31.14 (range 17–159). This wide range indicates the broad variety of the cases included. The male patients had significantly higher total akathisia ratings than the female patients. This was related to significantly higher objective scores, whereas subjective scores did not differ significantly (Table 2).

Spearman's ρ between the total akathisia rating vs. serum iron ($\rho = -0.072$) and vs. serum ferritin ($\rho = 0.16$) did not reveal any significant correla-

Table 2
Akathisia scores as measured by the Hillside Akathisia Scale (HAS, Fleischhacker et al., 1989)

	Akathisic patients mean ± S.D. (range)	Males mean ± S.D. (range)	Females mean ± S.D. (range)	Spearman's ρ
Total HAS score	62 ± 31 (17–159)	78 ± 40 (17–159)	53 ± 21 (24–113)	0.03
Objective symptoms score	23 ± 24 (0–108)	36 ± 31 (0–108)	15 ± 14 (0–55)	0.04
Subjective symptoms score	39 ± 13 (10–72)	42 ± 14 (17–72)	37 ± 12 (10–58)	0.39

tion. Neither the objective item score (iron: $\rho = -0.12$; ferritin: $\rho = 0.19$) nor the subjective item score (iron: $\rho = 0.038$; ferritin: $\rho = -0.056$) showed a correlation with serum iron or serum ferritin status.

4. Discussion

We found significantly lower serum ferritin levels in acutely akathisic compared to non-akathisic patients. However, no difference was found for serum iron. Iron and ferritin levels were within the 95% confidence interval of the normal population. There was no correlation between iron status and the degree of akathisia as rated by means of the Hillside Akathisia Scale.

Regarding ferritin, our data are in line with two studies on chronic akathisia: Barton et al. (1990) found a significant reduction of ferritin in 15 patients with chronic or tardive akathisia compared to pair-matched control subjects (and an inverse correlation between serum iron and akathisia ratings); and Fornazzari et al. (1991) described a low ferritin and a low iron level in a case report. Two studies in chronic akathisia did not find any reduction of ferritin (Nemes et al., 1992; Wirshing et al., 1998).

Since we investigated acute akathisia, our results have to be compared with two prospective studies on acute akathisia. Neither of them revealed a correlation between serum iron and acute akathisia. Sachdev and Lonergan (1991b) found no correlation between iron, transferrin and acute akathisia at all. O'Loughlin's study of 30 cases with acute akathisia produced ambiguous results including normal iron levels but a significantly reduced transferrin (O'Loughlin et al., 1991). Because there were no studies, to our knowledge, that measured serum ferritin in acute akathisia, a direct comparison with our data is, however, not possible. We focused on serum ferritin as a marker since it reflects the body's iron stores most accurately and is the most sensitive indicator of iron deficiency (Wick et al., 1991). Furthermore, nutritional factors, which might play a role in psychotic patients, are less likely to influence ferritin levels.

Our data have to be interpreted with caution because of the limited number of patients and methodological confounding factors: We conducted a retrospective study in a naturalistic setting. Control subjects were also selected retrospectively to match the clinical and demographic parameters of the akathisic group. Due to acute and severe psychotic exacerbations, a considerable percentage of the subjects received relatively large doses of neuroleptics, which might mask the effect of other predisposing factors.

Because of the correlational nature of our study, no pathophysiolgical inferences can be drawn. It has been proposed that postsynaptic dopamine D2 receptor blockade in mesocortical dopaminergic pathways is among the most likely factors that may underlie akathisia (Marsden and Jenner, 1980). Because iron is part of the D2 receptor (Youdim et al., 1982), it has been hypothesized that iron deficiency may alter D2 receptor function such that the propensity to develop hyperkinetic states like acute akathisia increases (Youdim et al., 1982; Youdim, 1985). Although interesting from a theoretical point of view, there is a lack of data about the correlation of peripheral iron status markers and iron concentrations in relevant central structures like the basal ganglia in humans. Nevertheless, our results may help to critically evaluate the role of iron metabolism in akathisia. The normal iron levels and the lack of correlation between iron status and akathisia ratings suggest that the overall contribution of iron deficiency in the development of acute akathisia, if any, is minor.

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