

Serum iron levels in schizophrenic patients with or without akathisia

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Abstract

The pathophysiology of akathisia still remains controversial. Iron deficiency was proposed to be an important factor in the development of akathisia. In the present study, it was aimed to compare levels of serum iron and linked variables in chronic akathisic ($n=30$), and non-akathisic patients ($n=30$) with schizophrenia and healthy controls ($n=30$) because of the controversy in the association of iron and akathisia. The Barnes Akathisia Scale for akathisia and Simpson–Angus Rating Scale for extrapyramidal side effects were used. Serum iron and linked variables and hematological profile of the patients and control subjects were determined. Serum iron levels were significantly lower both in akathisic and non-akathisic groups compared to the control group ($P<0.001$). Moreover, akathisic patients had significantly lower iron levels than non-akathisic patients ($P<0.05$). Total iron binding capacity was significantly higher in patients with akathisia compared to the control group ($P<0.01$). Although non-akathisic patients had a mild increase in total iron binding capacity, it was not statistically significant compared to the control group ($P>0.05$). Ferritin levels were determined to be significantly lower in both groups compared to the control group ($P<0.01$). In addition, there was a significant difference in ferritin levels between the patients with and without akathisia ($P<0.05$). In conclusion, our results support the hypothesis that an association between akathisia and iron metabolism exists.

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1. Introduction

Akathisia is a common side effect of neuroleptic medication, which is seen frequently. It is characterized by an abnormal state of subjective and objective motor restlessness.

In a study on the epidemiology of chronic akathisia related to antipsychotic use, Sachdev (1995) suggested that the prevalence of akathisia in the patients chronically treated with neuroleptics might be closer to 30%. Not only neuroleptics but also other drugs such as selective serotonin reuptake inhibitors (SSRI), heterocyclic antide-

pressants, carbamazepine, calcium channel blockers and lithium can cause akathisia. However, conditions like head injuries, Parkinson's disease, encephalitis lethargica and basal ganglion abscesses are also among the causes of akathisia (Stein and Pohlman, 1987; Marder and Van Putten, 1995; Yuksel, 1996). The characteristic of intolerable restlessness of akathisia causes therapeutic non-compliance (Van Putten, 1975). Violent behaviour (Schulte, 1985) and even impulsive suicide attempts are also encountered (Shaw et al., 1986).

Under normal conditions, iron is present in high concentrations in the basal ganglia and may form an integral part of the dopamine (D_2) receptor (Ben-Schachar et al., 1985). Controversial results in regard to serum iron and linked variables were reported in patients who experience acute or chronic akathisia. In addition, iron deficiency resulting in motor restlessness in rats (Weinberg et al.,

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1980) suggests that the role(s) of iron deficiency in akathisia needs to be further investigated.

Since the association of iron and akathisia is rather controversial, in the present study, we aimed to compare the levels of serum iron and linked variables, such as total iron binding capacity, ferritin and transferrin percentage saturation, and hematological profile in chronic akathistic patients, non-akathistic patients and healthy controls.

2. Experimental procedures

2.1. Patients

Thirty patients with drug-induced chronic akathisia, with emergence or exacerbation in patients on long-term admission, and 30 non-akathistic patients who had volunteered to take part in to the study and met the admission criteria were recruited to the Mental Health Hospital, in Elazig, and Department of Psychiatry, Fýrat University Medical Center, in Elazig. They were pair-matched with regard to age, sex, duration of illness, duration of treatment and equivalent chlorpromazine dose. All patients were diagnosed with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders-IV.

Barnes Akathisia Rating Scale (BARS) (Barnes, 1989) was used for the evaluation of akathisia. Patients having a global score over 2 were accepted as akathistic according to BARS. Extrapyramidal side-effects were rated by the scale described by Simpson and Angus (1970).

The patients admitted into the study were required to meet inclusion criteria; informed consent from the patients and/or first-degree relatives, normal physical and neurological examination, no use of iron therapy, nonsteroidal anti-inflammatory agents and antiacids and no history of alcohol dependence and/or drug abuse. In the differential diagnosis, agitation, psychotic excitation and restless legs syndrome were taken into consideration (Brown et al., 1987; O'Loughlin et al., 1991; Soni et al., 1993; Hoffman et al., 2000).

All patients were maintained on fixed doses of neuroleptic

medication for 4 weeks prior to collection of blood samples.

2.2. Control subjects

The control group was composed of healthy subjects ($n=30$) who applied to the Department of Psychiatry, College of Medicine at Fýrat University, for driving license examination and were evaluated to be normal. In addition, controls did not have a history of major mood disorder, dementia, mental retardation and psychosis in their first-degree relatives.

2.3. Determination of serum iron and related biochemical parameters

Serum iron, total iron binding capacity, ferritin, transferrin percentage saturation, hematological profile of the patients and control subjects were determined by using Olympus AU600 autoanalyzer (Olympus, Japan) and Advia 120 (Bayer Diagnostics, Germany).

2.4. Statistical analysis

Statistical analysis was performed with the statistical package for social sciences (SPSS/PC 9.05 version, 1998) using Student's *t*-test. $P<0.05$ was considered as statistically significant.

3. Results

Both akathistic and non-akathistic patient groups comprised 16 males (53.3%) and 14 females (46.7%), whereas the control group was composed of 15 males and (50.0%) 15 females (50.0%). The mean age was 34.8 ± 9.5 years in the patient group and 35.1 ± 9.2 years in the control group ($P>0.05$). The sociodemographic characteristics, neuroleptic dose, duration of illness, duration of treatment and scale scores are presented in Table 1.

There were no statistically significant differences between hematological parameters among the groups.

Table 1
Characteristics of patients and controls

	Control	With akathisia	Without akathisia	<i>P</i>
Sex (F:M)	15:15	14:16	14:16	NS
Age (years)	38.1 ± 5.21	41.98 ± 4.15	39.78 ± 3.97	NS
Duration of illness (years)	–	17.4 ± 2.78	17.6 ± 5.1	NS
Duration of treatments (years)	–	14.2 ± 1.91	13.8 ± 2.21	NS
Dose of medication in chlorpromazine units per day	–	1013 ± 241	987 ± 278	NS
BARS scores	–	$2.71\pm 0.27^*$	0.35 ± 0.08	$*P<0.001$
EPS scores	–	$4.27\pm 0.48^*$	1.19 ± 0.39	$*P<0.001$

NS, significant.

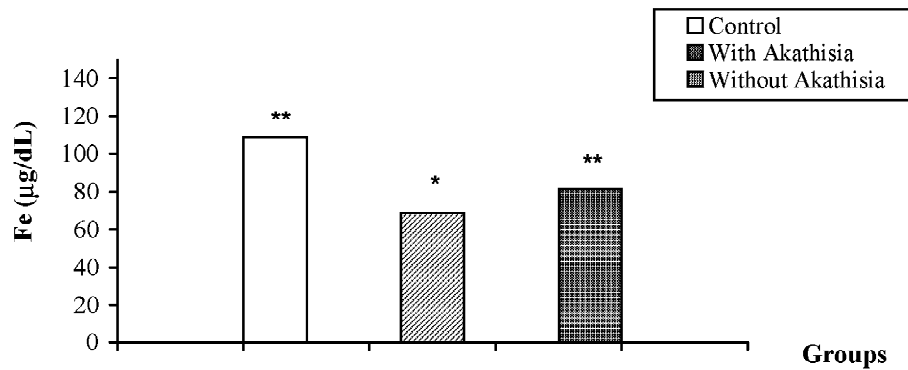


Fig. 1. Serum iron levels in patients with schizophrenia with or without akathisia and controls. * $P < 0.05$ (with akathisia versus without akathisia), ** $P < 0.001$ (control versus with akathisia, control versus without akathisia).

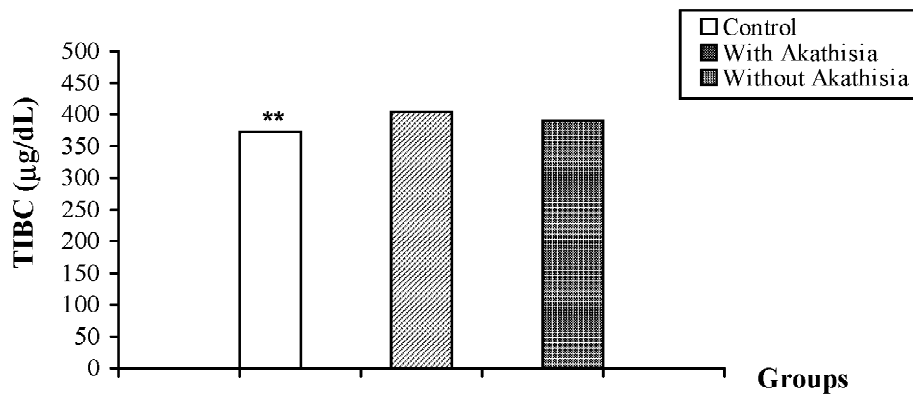


Fig. 2. Total iron binding capacity (TIBC) in patients with schizophrenia with or without akathisia and controls. ** $P < 0.01$ (control versus patients with akathisia).

The serum iron levels were significantly lower in the akathic ($68.87 \pm 9.2 \mu\text{g/dl}$) and non-akathic groups ($81.30 \pm 10.57 \mu\text{g/dl}$) compared to the control group ($108.84 \pm 16.56 \mu\text{g/dl}$) ($P < 0.001$, $P < 0.001$). There was a statistically significant difference between the patients with and without akathisia ($P < 0.05$) (Fig. 1).

Total iron binding capacity was significantly higher in patients with akathisia ($404.30 \pm 20.91 \mu\text{g/dl}$) compared to the control group ($371.30 \pm 32.56 \mu\text{g/dl}$) ($P < 0.01$). Al-

though the non-akathic patients had a mild increase on the total iron binding capacity ($390.15 \pm 15.16 \mu\text{g/dl}$), it was not statistically significant (Fig. 2).

The ferritin levels significantly decreased in both groups compared to the control group ($121.16 \pm 15.97 \text{ ng/ml}$) ($P < 0.01$). There was a significant difference in the ferritin levels between the patients with ($53.37 \pm 7.92 \text{ ng/ml}$) and without akathisia ($65.94 \pm 11.08 \text{ ng/ml}$) ($P < 0.05$) (Fig. 3).

The transferrin levels were $225.13 \pm 13.34 \text{ mg/dl}$ in the

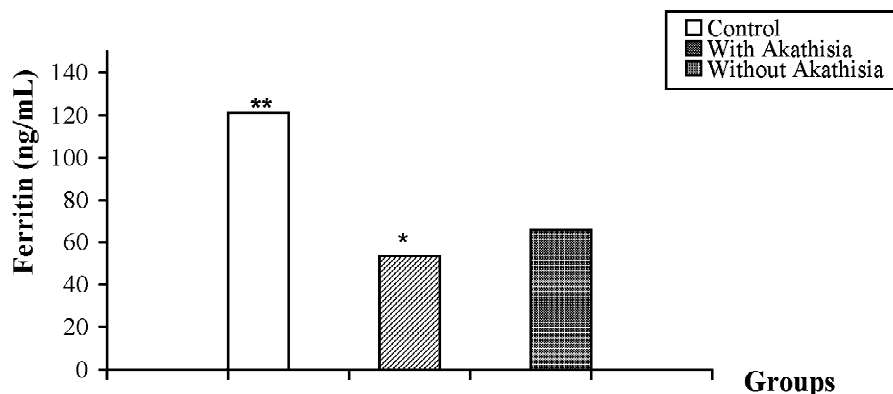


Fig. 3. Ferritin levels in patients with schizophrenia with or without akathisia and controls. * $P < 0.05$ (with akathisia versus without akathisia), ** $P < 0.01$ (control versus with akathisia, control versus without akathisia).

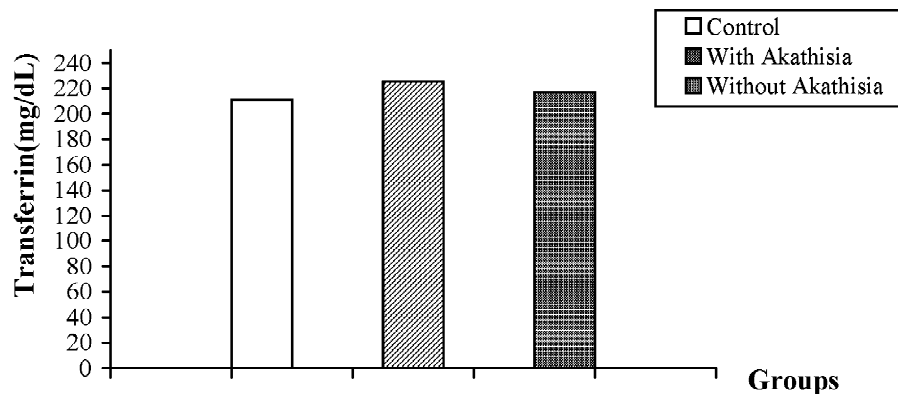


Fig. 4. Transferrin levels in patients with schizophrenia with or without akathisia and controls. $P > 0.05$ No significance was determined among the groups.

patients with akathisia, 217.28 ± 16.36 mg/dl in the patients without akathisia and 211.42 ± 12.26 mg/dl. Although there are slight differences among the groups, they were statistically insignificant (Fig. 4).

4. Discussion

The pathophysiology of akathisia still remains controversial and related neuroanatomic associations have not been established yet. The iron deficiency was proposed to be an important contributing factor in the development of akathisia (Barnes et al., 1992). It was proposed that antipsychotics led to akathisia by effecting the serum iron and linked variables (transferrin, percentage saturation, ferritin, total iron binding capacity) or that low levels of these could initially lead to development of akathisia (O'Loughlin et al., 1991).

In previous studies which evaluated the serum iron and linked parameters in akathic and non-akathic patients, controversial results were reported. Some of them noted that there were lower serum iron and related parameters in akathic patients (Brown et al., 1987; Barton et al., 1990), whereas others did not support such a relation (Nemes et al., 1991; Sachdev and Loneragan, 1991; Barnes et al., 1992; Soni et al., 1993). On the other hand, O'Loughlin et al. (1991) pointed out that akathic patients had significantly lower serum iron and transferrin levels than those without akathisia within 2 or 3 weeks but not at baseline. In a study carried out by Hoffman et al. (2000), an insignificant difference was determined though some reduction in the serum ferritin was found in patients with akathisia compared to patients without akathisia. Therefore, they suggested that iron deficiency had a minor role in the acute akathisia.

In the present study, we determined that both the akathic and non-akathic patients had lower serum iron levels compared to the control group. Additionally, there was a significant difference in serum iron levels between the patients with and without akathisia. Total iron binding

capacity was statistically significantly higher in the patients with akathisia compared to the control group. On the other hand, the patients without akathisia had mildly, but statistically insignificant increase in total iron binding capacity compared to the control group. Ferritin levels were decreased in both patient groups compared to the control group and, additionally, there was a significant difference between the patients with or without akathisia. The finding of low serum iron levels in patients with or without akathisia compared to the control group may be attributed to the following reasons. In general the patients had long-term admission, including long-stay ward admission. For example, one of the patients was in the Mental Health Hospital for over 35 years. Therefore, whether these patients had received sufficient nutritional support was unconfirmed, so this condition could have affected serum iron and linked variables. It was well established that antipsychotic binding capacity with iron might cause akathisia (Pall et al., 1986; Blake et al., 1986). In addition, it has been suggested that D_2 dopamine receptor is an iron-containing protein and low serum iron level results in hypofunction of D_2 receptors, which predisposes patients on antipsychotic medication vulnerable to akathisia (Ben-Schachar et al., 1985; Ben-Schachar et al., 1987; Ben-Schachar and Youdim, 1987). In addition, iron depletion has been demonstrated to lead to a reversible reduction of B_{max} for [3H]spiperone binding in the caudate nucleus (Yehuda and Youdim, 1988).

The finding of differences in the serum iron and linked variable levels may be explained as follows: this difference may be first attributed to the lack of sufficient nutritional support. However, all patients (akathic or non-akathic) received standard hospital diet. Therefore, we cannot only attribute the condition to nutritional insufficiency. With respect to the difference between the patient groups, it can be speculated that the patients with akathisia may be too restless to eat, and need greater food intake because of such constant exercise. However, it seems difficult to objectively determine this situation.

In summary, our results support the hypothesis that there

is an association between akathisia and iron metabolism. However, further studies with much larger samples are needed to clarify whether serum iron and linked variables can be used as an indicator of management of akathisia.

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