

SHORT REPORT

Serum iron and transferrin in acute neuroleptic induced akathisia

V O'Loughlin, A C Dickie, K P Ebmeier

Abstract

Thirty acute psychiatric patients were examined prospectively at the beginning of neuroleptic treatment for acute psychotic symptoms and on average 16 days later. Two alternative hypotheses were examined: 1) neuroleptic treatment affects the levels of serum iron and transferrin; 2) acute akathisia developing during the initial few weeks of treatment is associated with low levels of serum iron and transferrin, either initially or at follow up or both. Serum iron levels did not change on repeat measurement, while there was a small, but significant decrease of serum transferrin. There was a significantly greater decrease in iron and transferrin levels in patients with akathisia on follow up compared with non-akathisics. In addition, akathisia ratings were highly correlated with serum transferrin levels on follow up.

Two independent studies^{1,2} have reported an inverse correlation between tardive akathisia and plasma or serum iron levels in chronic psychiatric patients stabilised on neuroleptic drugs. The authors argued that akathisia might therefore be related to D2-receptor hypofunction due to a relative deficit of serum and consequently brain iron. Both studies were cross-sectional and included only patients whose medication had not changed for at least one month. In addition, we examined a rather selected sample of chronic psychiatric inpatients, and felt that a prospective study should be carried out on acutely admitted patients who were either just starting to take neuroleptic treatment or whose medication was being substantially increased on admission. It was predicted that about 20% would develop symptoms and signs of akathisia.³

Patients and methods

Thirty acute psychotic patients were recruited from subsequent admissions to two acute admission wards of the Royal Cornhill Hospital, Aberdeen. They were assessed as soon as possible after admission and followed up for two to three weeks after the initial examination. The assessment procedure has recently

been described in detail.² Akathisia was defined as a score of ≥ 10 on the akathisia scale used in the two previous studies.^{1,2}

Venous blood samples, for the estimation of serum iron and transferrin were taken following a standardised procedure. Serum iron estimation was carried out using a ferrozine colorimetric method on a Technicon RA-1000 analyser (Technicon Instrument Corp, Tarrytown, New York).⁴ The reference range in our own laboratory is 11–30 $\mu\text{mol/l}$. Transferrin estimation was carried out using the same instrument, with an immunoturbidimetric method and a Technicon material as calibrator.⁵

Ethical approval was given by the Joint Ethical Committee of the Grampian Health Board and the University of Aberdeen. Informed consent was obtained from all subjects.

Results

Patients were examined on average (SD) 22.9 (13.6) hours after admission. The follow up examination took part on average 16 (4.8) days after the first. Patients' mean (SD) age was 32.9 (12.1). There were 16 men and 14 women, 17 of the patients were diagnosed as bipolar disorder, manic, 13 as schizophrenia or schizophreniform disorder (DSM III-R).⁶ Clinical and laboratory data at both examinations are presented in the table. Six patients (20%) qualified for a diagnosis of akathisia at follow up.

In these six patients serum iron levels were 25.8 $\mu\text{mol/l}$ on admission and 20.2 $\mu\text{mol/l}$ at follow up (paired *t* test: ns). To detect a decrease of serum iron levels by 5.6 $\mu\text{mol/l}$ ($= 25.8 - 20.2$) with a power of 0.8 and *p*-value of 0.05, given the observed standard deviations and assuming an incidence of akathisia of 20%, about 50 patients would be needed. The comparative values were 21.4 and 23.1 $\mu\text{mol/l}$ for non-akathisics (ns). Serum transferrin levels were 2.8 g/l on admission and 2.0 g/l at follow up in akathisics (*p* = 0.006) and 2.7 and 2.6 g/l for non-akathisics (ns). While there were no group differences for iron and transferrin levels on admission, akathisic patients had significantly lower transferrin levels at follow up (*t* test: *p* = 0.016). There was a significant difference between groups for mean changes over time of iron levels (*p* = 0.0028) and transferrin levels

University of
Aberdeen,
Foresterhill, Aberdeen
Department of Mental
Health
V O'Loughlin
K P Ebmeier

Department of
Clinical Biochemistry
A C Dickie

Correspondence to:
Dr Ebmeier, MRC Brain
Metabolism Unit, Royal
Edinburgh Hospital,
Morningside Park,
Edinburgh EH10 5HF, UK

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Table 1 Clinical and laboratory data for 30 patients (SD) at original examination and at follow up

	Time 1	Time 2	p*
Chlorpromazine units	70.8 (82.0)	540 (234.7)	0.0001
BPRS	31.6 (10.9)	23.8 (12.6)	0.0001
HAS	9.1 (6.2)	6.9 (6.5)	0.035
Simpson and Angus scale	2.9 (4.7)	7.0 (5.6)	0.0003
AIMS	1.7 (4.2)	2.1 (4.1)	0.4283
Akathisia scale	2.6 (1.8)	5.3 (4.1)	0.0002
Serum iron ($\mu\text{mol/l}$)	22.3 (7.1)	22.5 (6.0)	0.8497
Serum transferrin (g/l)	2.7 (0.6)	2.5 (0.6)	0.0333

*paired *t* test.

($p = 0.0105$). There were no group differences for changes over time in medication, measures of neuroleptic induced movement disorders, apart from akathisia and clinical improvement.

Of the correlations between akathisia scores and iron and transferrin levels at both examinations, only the correlation of transferrin at follow up with akathisia scores at follow up was significant ($r = 0.61$, $df = 28$, $p = 0.0004$). Transferrin and iron levels were significantly correlated with each other at the time of first examination ($r = 0.44$, $p = 0.0146$) and at follow up ($r = 0.66$, $p = 0.0001$). There was no correlation between Simpson and Angus scores for neuroleptic induced Parkinson's syndrome⁷ and akathisia scores ($r = 0.06$). Using a cut-off score of 3/4 on the Simpson and Angus scale, no differences between Parkinsonian and non-Parkinsonian patients were found for mean changes of iron (*t* test: $p = 0.1827$) and transferrin levels ($p = 0.7503$).

Discussion

As the table shows, we were successful in recruiting an acutely treated group of psychotic patients whose neuroleptic medication increased between examinations, together with Parkinsonian side effects and akathisia scores, whereas psychiatric symptom scores decreased. Across all patients there was a small but significant decrease of transferrin levels, whereas iron levels stayed the same. This overall effect hides, however, a significant difference between groups, in that both iron and, to a larger extent, transferrin levels decreased significantly only in the akathistic patients. It appears, moreover, that patients developing akathisia during the first two weeks of admission are not characterised by initially low iron or transferrin levels. This finding is supported by the inverse correlation between akathisia scores and transferrin levels at follow up (figure), but not on admission.

Although this study is correlational and cannot lead to conclusions about causal relationships, it is tempting to explore possible mechanisms which would explain our findings. Serum transferrin concentrations are regulated in vitro in chorioid plexus epithelial

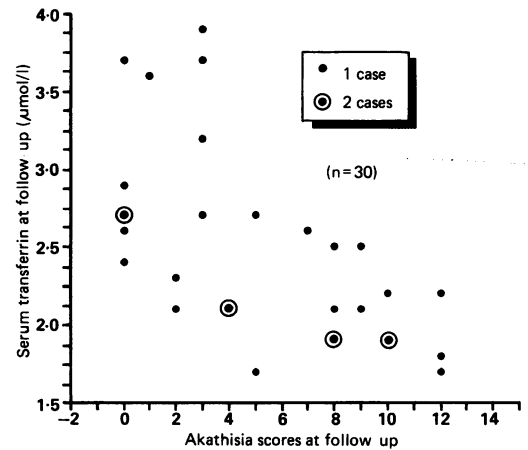


Figure Transferrin levels plotted against akathisia scores at follow up ($n = 30$).

cells by serotonin in that both transferrin and transferrin mRNA concentrations increase in response to it.⁸ This could provide a rationale for an effect of neuroleptics, many of which are 5HT-2 receptor blockers. A differential effect on transferrin levels of patients who do and those who do not develop akathisia would require a difference in this regulation mechanisms between subjects. Transferrin is the main transporter protein for iron in the human body and is involved in the regulation of iron metabolism in the human brain,⁹ so that a reduction of transferrin levels might lead to a relative reduction of the availability of iron to a number of brain regions. As discussed in detail in a previous paper,² iron depletion has been found to mimic D-2 receptor blockade in a variety of animal models and leads to a reversible reduction of B_{max} for ³H-Spiperone binding in the caudate nucleus. A relative lack of iron due to decreased transporter protein in combination with the acute receptor blockade by neuroleptics might therefore combine to produce akathisia in some patients.

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