Iron status, movement disorders, and acute phase response in elderly psychiatric patients

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Abstract

The previously reported relation between iron deficiency and movement disorders was studied in a population with a high prevalence of both problems. There was no evidence of a direct statistical relation between iron deficiency and movement disorders. Significant associations were, however, found between movement disorders and features of the acute phase response to physiological stress. Indices of iron status are known to be affected by the acute phase response and it is suggested that the previously reported abnormalities in iron status may be secondary to this.

(*J Neurol Neurosurg Psychiatry* 1994;57:208-210)

Several studies have suggested that there is an association between serum iron status and neuroleptic-induced akathisia.¹⁻³ Brown *et al*¹ found decreased serum iron and saturation in long stay patients with established akathisia, although serum ferritin was slightly increased. Barton *et al*² found that serum ferritin was decreased whereas iron and iron saturation were not significantly reduced in patients with akathisia recruited from acute and long stay wards. In a subsequent prospective study O'Loughlin *et al*³ found no evidence of low serum iron or transferrin at admission, but that this developed after the onset of akathisia with low iron and transferrin being found on follow up at 17 days. More recently Barnes *et al* found no relation between chronic akathisia and low serum iron in adult schizophrenic patients.⁴ It has also been suggested that tardive dyskinesia may be related to abnormal iron status.⁵ Serum iron falls during episodes of the neuroleptic malignant syndrome despite being normal before and after.⁶ In the same study it was noted that during the neuroleptic malignant syndrome total iron binding capacity was at the lower end of the normal range and ferritin was marginally increased. It was suggested that these changes were the result of the acute phase response. This is the response of the body to physiological stress and consists of a rise in erythrocyte sedimentation rate, C-reactive protein and other acute phase proteins such as α -1-antichymotrypsin and α -1-acid-glycoprotein, along with increased protein turnover leading to raised urea and associated with increased globulins and reduced albumin.⁷ In chronic inflammation the erythrocyte sedimentation

rate and other indices of ill health such as urea, weight, and haemoglobin are better guides to the acute phase response than acute phase proteins, which show a response within hours initially,⁷ but this may tail off reflecting down regulation.⁸ The acute phase response is probably initiated through interleukins 1 and 6 and prostaglandin E₂.⁹ Iron metabolism is significantly affected by the acute phase response with serum iron, total iron binding capacity, and saturation being reduced and ferritin generally increased. With the proviso that a serum ferritin concentration below 15 μ g/l and a low saturation with a raised total iron binding capacity remain suggestive of iron deficiency, changes due to the acute phase response can be sufficiently pronounced for it to be difficult to interpret abnormalities of either ferritin or iron saturation alone as indicative of iron deficiency.¹⁰

We investigated iron status and movement disorders along with the acute phase response in a population that we expected to have a high prevalence of both akathisia and iron deficiency.

Methods

All patients in three long stay psychogeriatric wards for a single District Health Authority in a large mental hospital were included in the study. Patients were weighed, physically examined, and venous blood samples were taken. Movement disorders were assessed with the abnormal involuntary movement scale (AIMS)¹¹ and the akathisia scale.¹ A score for tardive dyskinesia was generated from the AIMS according to the method of Davis *et al*.¹² Current medication was recorded and neuroleptic medication was converted into an equivalent dose of chlorpromazine.¹³ Full blood count, biochemical profile, serum iron, total iron binding capacity (Roche MA-KIT10 UIBC and Roche MA-KIT30 iron ferrozine methods), serum ferritin (Roche sandwich immunoassay ferritin kit), erythrocyte sedimentation rate (Westergren method), C-reactive protein, α -1-antichymotrypsin, and α -1-acid-glycoprotein (binding site immunoassay kits) concentrations were measured. Iron deficient patients were identified by two clinical chemists from the criteria of Shek *et al*¹⁴ which uses serum ferritin of less than 15 μ g/l or low iron saturation and high total iron binding capacity, along with examination of haematological data. Scores of movement disorders in iron deficient and non-iron deficient

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Received 20 July 1992
and in revised form
14 April 1993.
Accepted 15 June 1993

Table 1 Median values (ranges) of movement disorder scores for iron deficient and non-iron deficient patients

Movement disorders	Iron deficient	Non-iron deficient	p Value
n	16	39	
Akathisia	2 (0–19)	0 (0–30)	0.45
AIMS	12 (0–29)	6 (0–40)	0.94
Tardive dyskinesia	3 (0–13)	4 (0–16)	0.76

Table 2 Spearman's rank correlation coefficients between scores of movement disorders score and indices of iron status, acute phase proteins, other biochemical and haematological indices, body weight, and dose equivalent of neuroleptic medication expressed in mg of chlorpromazine¹³

	Akathisia	AIMS	Tardive dyskinesia
Urea	0.30*	0.30*	0.24*
ESR	0.15	0.25*	0.25*
Body weight	-0.23*	-0.26*	-0.18
Haemoglobin	-0.21	-0.23*	-0.19
AGP	0.15	0.08	0.15
Iron saturation	-0.19	-0.19	-0.12
Ferritin	-0.19	-0.19	-0.18
Iron	-0.13	-0.12	-0.08
TIBC	0.15	0.12	0.05
Dose equivalent	0.13	0.15	-0.17

*p < 0.05; **p < 0.01. ESR = Erythrocyte sedimentation rate; AGP = α -1-acid-glycoprotein; TIBC = total iron binding capacity.

patients were compared by Mann-Whitney U tests. Associations between erythrocyte sedimentation rate, haemoglobin, urea, weight, and α -1-acid-glycoprotein were tested with Spearman's rank correlation coefficient. Because C-reactive protein and α -1-antichymotrypsin operate on an interleukin and complement triggered cascade system with the result that concentrations of C-reactive protein and α -1-antichymotrypsin within normal ranges are not thought to be indicative of subclinical triggering of the acute phase response,⁷ Mann-Whitney U tests were used to differentiate between groups with raised and normal concentrations at laboratory cut off points of 8 mg/l and 1 mg/l respectively. All statistical tests were computed with the Statistical Package for Social Sciences (SPSS) for Windows version 5.0 (SPSS Inc, USA). Non-parametric tests were used throughout in view of the pronounced skew of movement disorder scores towards zero. The study was approved by the Bexley Hospital ethics of research committee.

Results

Fifty-seven patients were eligible for inclusion in the study. Two patients refused examination leaving 37 women (mean age 80 (SD 8) years) and 18 men (mean age 79 (SD 7) years). The mean duration of stay in hospital

was 16 (SD 20, range 0.4–67) years. No patient had a history of development of any movement disorder within the past six months. There were no significant differences for movement disorder ratings between men and women. Sixteen (29%) patients were judged to be iron deficient by the clinical chemists. Table 1 shows the medians and ranges of ratings of movement disorders compared between iron deficient and non-iron deficient patients. There were no significant differences between akathisia, AIMS, or tardive dyskinesia scores. Table 2 shows correlations between movement disorders and indices of iron status, body weight, α -acid-glycoprotein, biochemical and haematological indices, and dose equivalent of neuroleptic medication. Significant correlations were found between movement disorders and erythrocyte sedimentation rate, urea, body weight, and haemoglobin but there were no significant associations with indices of iron metabolism. Table 3 gives comparisons of movement disorders between patients with normal and raised C-reactive protein and α -1-antichymotrypsin. Median scores of movement disorders were higher for all three forms of movement disorder for both C-reactive protein and α -1-antichymotrypsin. Three of the differences reached statistical significance.

Discussion

The hypothesis that iron deficiency is associated with movement disorders in long stay patients was not supported by this study. The correlations between akathisia and iron status and akathisia and serum ferritin, were weak and although in the same direction as in the work of those who found iron status to be associated with akathisia,^{1–3} seem more consistent with the work of Barnes *et al.*⁴ Also, there were no differences between the ratings of movement disorders between iron deficient and non-iron deficient patients. There was no significant relation between movement disorders and the amount of neuroleptic medication that patients were receiving and we believe that this reflects the long standing nature of movement disorders in our patients as well as confirming previous studies of this issue.¹⁵

Interestingly, the acute phase response as judged by erythrocyte sedimentation rate, urea, body weight, and haemoglobin was significantly associated with increased scores of movement disorders. Whereas all the correlation coefficients were small, we believe that this is not unexpected in view of the absence of exclusion criteria for our sample and the high incidence of physical disorder in psychogeriatric populations. All median movement disorder scores were higher among those patients with raised C-reactive protein and α -1-antichymotrypsin and three of these differences were significant. We believe that these data are compatible with the hypothesis that movement disorders are associated with the acute phase response and that this may explain some of the findings in previous

Table 3 Median values (ranges) of scores of movement disorders for patients with and without raised C-reactive protein and α -1-antichymotrypsin scores

	C-Reactive protein			α -1-Antichymotrypsin		
	Raised	Normal	p Value	Raised	Normal	p Value
n	12	43		5	50	
Akathisia	5 (0–30)	0 (0–26)	0.04	13 (0–30)	0 (0–26)	0.07
AIMS	19 (0–40)	7 (0–26)	0.11	20 (0–40)	7 (0–29)	0.06
Tardive dyskinesia	11 (0–16)	4 (0–13)	0.03	16 (0–16)	4 (0–13)	0.03

studies¹⁻³; in particular the study of O'Loughlin³ in which abnormal iron metabolism developed only after the onset of akathisia.

Our study can be criticised for the use of three separate scales of movement disorders with differing but overlapping components. The scales were used because they have been widely used in the assessment of tardive dyskinesia and akathisia. Whereas these two movement disorders do seem different, it may be that any clear distinction between them is difficult. Indeed one scale of tardive dyskinesia incorporates akathisia as one of its components.¹⁶

Given that indices of iron status are known to be highly susceptible to the acute phase response, the abnormal iron status in previous studies¹⁻³ may have been due to the acute phase response rather than to iron deficiency itself. This would not necessarily imply that the acute phase response causes movement disorders; it may be associated with a further independent factor that also predisposes to movement disorders. What is clear, however, is that iron deficiency does not seem to be associated with movement disorders and that treatment of such disorders with iron is inappropriate.

We are grateful to the nurses and consultants of Bexley Hospital and to Professor Swaminathan for their cooperation with this study.

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