Serum Iron, Total Iron Binding Capacity and Ferritin in Early Huntington Disease Patients

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Summary

Serum iron, total iron binding capacity and ferritin was estimated in 42 patients with early Huntington disease (HD) and in 148 matched controls. Ferritin levels were significantly low in affected male subjects as compared to controls. Iron levels and total iron binding capacity were normal in HD patients. The importance of this finding, that occurs early in the pathogenesis of HD, is unknown.

Introduction

Iron has a central role in erythropoiesis, and is also associated with catecholamine metabolism, DNA synthesis and collagen formation. Excess iron stimulates ferritin synthesis, forming a small intracellular store[1]. Ferritin is a soluble protein consisting of two sub-units H and L. The expressed gene for the H sub-unit is located on chromosome 11 and that for the L sub-unit on chromosome 19. Recently, a second Ferritin H locus has been assigned to chromosome 11[2]. Haemosiderin, an amorphous insoluble storage compound is probably formed by partial digestion of ferritin protein shells with a consequent condensation of these molecules[1] resulting in a higher iron content than of the original ferritin. There have been several reports of excess iron, either as iron pigment or haemosiderin deposits in the brain of HD patients[3,4]. Goldberg et al.[5] found that iron concentrations are highest in the substantia nigra, globus pallidus, caudate nucleus and the putamen. Iron is stored in the nervous system as ferritin. Only one report[6] has examined ferritin levels in HD patients, and found a significant decrease in ferritin for both sexes, compared to controls. However there was only a small number of patients and no account was taken of the stage of the disease. Serum iron or ferritin has not been studied in patients with early stage HD. We have investigated an HD population[7]. Serum ferritin levels from all early onset HD patients were examined thus avoiding the variables likely to induce low values, such as poor nutrition due to social circumstances or inability to eat a good diet due to moderate or severe choreic movements.

Methods

Forty-two patients with HD (21 males, 21 females) with ages ranging from three to 61 years, were studied. All affected patients had a positive family history of HD. None of the subjects were receiving medication. 148 age matched controls were selected from relatives including spouses who were living under the same social situation as the affected members. The purpose of the study was explained to the patients and controls, and informed verbal consent was obtained. Blood samples were collected in a glass container without anticoagulant between 8:00 am and 11:00 am. Samples were allowed to stand at room temperature and then centrifuged to separate serum. Total serum iron content (Fe), total iron binding capacity (TIBC) and ferritin (F), was measured in the serum, using standardised laboratory assays (Department of Clinical Chemistry, Belfast City Hospital). The mean value was determined for male and female patients in each group. The results were analysed using the analysis of variance test, the student T test for comparisons between the means and the standard error. P values of less than 0.05 were considered significant.

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Results

The serum levels of iron, TIBC and ferritin in both HD patients and controls are shown in Table I. There was a decrease in the serum ferritin level in HD patients. The difference between affected and control males was significant ($p < 0.001$). The difference between the affected and control females showed a value of less than 60% of that of normal controls, but this was not statistically significant. No significant difference was found between serum iron and TIBC levels.

Discussion

A decrease in the serum ferritin level in HD patients was more marked in male patients. The reason for this remains unclear. Ferritin itself may protect the brain from the

TABLE I
Serum concentration of Iron, TIBC and Ferritin in HD patients.

Groups	n	Sex	Iron (umol/L)	TIBC (umol/L)	Ferritin (ug/L)
CONTROLS	87	F	19.57 ±1.80	64.57 ±5.23	71.24 ±16.51
	61	M	18.57 ±2.00	68.24 ±1.65	94.76 ±6.71
AFFECTED	21	F	16.52 ±3.06	67.05 ±2.71	42.57 ±8.05
	21	M	17.19 ±1.44	63.62 ±2.50	39.81 ±7.30

Values represent means ± standard error of the mean
* Significantly different from control values of the same sex ($p<0.001$).

fluctuations in serum iron concentration and resultant variations in iron brain storage. No significant correlation was detected between ferritin levels and those of iron or TIBC, and it may be that selective neuronal changes in HD patients induce neurotransmitter changes in the brain. As non heme iron is a cofactor of several enzymes involved in catecholamine regulation[8], changes in ferritin levels may be an end result of this process, as even though the precise interactions are not well delineated, there appears to be a relative excess of dopamine in the brain[9]. The caudate and putamen also shrink markedly in affected HD patients[10], and their unknown role in iron and ferritin biochemistry may be disordered.

Patients in this study had early HD (Shoulson & Fahn Stage I) with mild chorea, and were free from medication. It is unlikely that significant differences in nutritional status exist between early affected HD patients and the control subjects. Differences would be expected in patients in the late stages of the disease when swallowing and choking limit patients' diets and excessive hyperkinetic activity renders the patient malnourished[11]. The HD gene IT15, is a trinucleotide repeat[12], and produces a protein called 'Huntingtin'[13]. This protein may be altered in HD patients but its role, if any, in causing abnormal ferritin levels is unknown. Decreased ferritin levels have been reported in the brain of Parkinson Disease patients[14], and there may be a common mechanism for this, perhaps mediated by dopamine. Characterisation of the 'Huntingtin' gene product, and further iron turnover studies, may provide an answer to the variation of ferritin levels in HD patients, and will allow simplification of the complex neurochemistry of HD.

Acknowledgements

PJM is supported by a Royal College of Physicians of Ireland Glaxo Fellowship in Molecular Biology. We thank the Department of Clinical Chemistry, Belfast City Hospital Trust, for the biochemical analyses.

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