Journal of Alzheimer's Disease 20 (2010) 617–623
DOI 10.3233/JAD-2010-1402
IOS Press

A Cross-Sectional Community Study of Serum Iron Measures and Cognitive Status in Older Adults

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Handling Associate Editor: Craig S. Atwood

Accepted 18 January 2010

Abstract. The relationship of iron status with cognition and dementia risk in older people is contentious. We have examined the longitudinal relationship between serum ferritin and cognition in 800 community-dwelling Australians 60 years or older. Iron studies (serum iron, transferrin saturation, serum ferritin) were performed in 1994/5 and 2003/4 and clinical and cognitive assessments were conducted in 2003/4 for 800 participants of the Busselton Health Study. All participants completed the Cambridge Cognitive test (CAMCOG). Those with CAMCOG scores < 84 underwent expert clinical review for cognitive disorders, including the Clinical Dementia Rating scale. Mean serum iron (18.3 μmol/l) and transferrin saturation (28.5%) in 2003/4 did not differ significantly from 1994/5 whereas mean serum ferritin decreased from 162 μg/l in 1994/5 to 123 μg/l in 2003/4, possibly reflecting aging or dietary changes. No relationships were observed between serum iron or transferrin saturation and presence or absence of dementia ($p > 0.05$). In participants without dementia ($n = 749$), neither serum ferritin in 1994/5 or 2003/4 nor change in serum ferritin between these times was related to total CAMCOG or executive function scores, with or without adjustment for gender, age, National Adult reading test, or stroke history (all $p > 0.05$). No relationships were observed between ferritin and cognition for participants with possible or probable dementia ($n = 51$). All participants identified as HFE C282Y homozygous or with serum ferritin $>$ 1,000 ng/ml had normal CAMCOG scores. We conclude abnormal body iron stores (low or high) are unlikely to have clinically significant effects on cognition or dementia risk in community-dwelling older people.

Keywords: Alzheimer's disease, cognition, dementia, ferritin, iron

INTRODUCTION

Iron is the most abundant trace metal in the brain, where it has many important functions, however, too much iron can be neurotoxic [1,2]. There has been considerable speculation that both iron deficiency and excess affect cognitive or motor performance and contribute to neurodegenerative disease, leading to proposals that chelation or other approaches may be of therapeutic relevance in this context [3–6]. This is supported by a limited amount of intriguing, but largely circumstantial, evidence derived from animal models and small patient groups [1,7–10].

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ISSN 1387-2877/10/$27.50

Abnormalities in serum ferritin or other measures of systemic or brain iron status have been observed in small clinical studies of a range of brain diseases including Alzheimer's disease [7–9]. Ferritin and other proteins important in iron metabolism are implicated in neurodegeneration with brain iron accumulation [11], which encompasses a group of rare disorders including pantothenate kinase associated neurodegeneration, previously Hallevorden-Spatz syndrome [12], neuroferritinopathy [13,14], and aceruloplasminemia [5].

Iron deficiency is associated with cognitive impairment in children [15–17], however, it is unclear whether the mature brain is also vulnerable to perturbations in systemic iron or whether there is enhanced vulnerability in older adults already at risk of cognitive impairment. Poorer cognition was associated with lower serum ferritin levels in 35 elderly patients [18] and with either low or high plasma iron in 1,451 community dwelling elderly people [19], but plasma iron is often not a reliable estimate of body iron stores and in general little is known about the long-term relationships between iron status and cognition. In this study, we have investigated the relationship of global cognition and executive function with iron measures at the time of cognitive survey or a decade earlier in a community-based survey of 800 older Australians.

MATERIALS AND METHODS

Surveys of all adults in the town of Busselton, Western Australia, were conducted every three years from 1966 to 1981. A follow-up survey of people from the 1966–81 surveys was conducted in 1994/5 [20,21]. A second follow-up survey of a random subset of 1994/5 survey participants, of age 60 years or more on December 31, 2003, was conducted in 2003/4. In total, 1,883 were suitable for inclusion. Of these, 114 were deceased, 567 could not be found or contacted, and 230 declined participation leaving 972 participants (80% of those alive and able to be contacted).

Genotyping for the hemochromatosis HFE C282Y mutation was performed as previously described [20]. The Cambridge Cognitive Test (CAMCOG) and the cognitive testing component of the revised Cambridge Examination for Mental Disorders of the Elderly (CAMDEX-R) [22,23] were used to assess global cognition. CAMCOG also includes questions on executive function independent of the global score. In total, 800 participants underwent CAMCOG and National Adult Reading Testing (NART, a measure of pre-morbid IQ) at 2003/4 survey and also had serum iron, transferrin saturation (TRS) and serum ferritin (Ft) measured in both the 2003/4 and 1994/5 surveys. Using a cut-off of CAMCOG $\leqslant$ 83, selected to maximize sensitivity [23], 87 participants were invited for clinical assessment conducted by physicians with expertise in diagnosing cognitive disorders. The clinical interviews included a suitable informant where possible and the Clinical Dementia Rating (CDR) scale was used to classify subjects with dementia and possible/questionable dementia (CDR = 0.5) [24]. Participants were classified as having no dementia ($n = 749$) if their CAMCOG score was above 83 or if judged to be cognitively normal at clinical interview (CDR = 0). The diagnosis of dementia was based on DSM IV criteria.

Serum ferritin and other iron measures were assayed in morning blood samples from fasting subjects. Serum iron and ferritin can both show diurnal variation but this does not occur consistently [25] and in general serum ferritin is usually considered a more accurate gauge of body iron stores than serum iron [26,27]. The normal ranges for serum ferritin were 20–200 μg/l in women and 30–300 μg/l in men. Serum ferritin levels were stratified as low (women $<$ 20 and men $<$ 30 μg/l), normal-low (women 20–110 and men 30–165 μg/l), normal-high (women 111–200 and men 166–300 μg/l), and high (women $>$ 200 and men $>$ 300 μg/l). The ferritin variables from the two survey times 1994/5 and 2003/4 are referred to as Ft (T_1) and Ft (T_2). Average ferritin levels declined between 1994/5 and 2003/4, therefore, the change between the two times ΔFt = Ft (T_1) – Ft (T_2) is stratified into five groups of less than -50 μg/l, -50 to -20 μg/l, -20 to 20 μg/l, 20 to 50 μg/l, and more than 50 μg/l.

We examined Ft (T_1), Ft (T_2), and ΔFt in relation to total CAMCOG scores and CAMCOG executive function scores (ExecFn) in the study group both with and after excluding cognitively impaired participants. Both raw (unadjusted) and adjusted means for CAMCOG and ExecFn scores are provided in relation to ferritin level Ft (T_1) in 1994/5, ferritin level Ft (T_2) in 2003/4, and also in relation to the change in ferritin level ΔFt. The analysis of variance (ANOVA) and analysis of covariance (ANCOVA) F-test p-values are provided for means without adjustment or after adjustment for age, gender, NART score, and history of stroke (positive if the subject had a hospital admission with a diagnosis of stroke before the 2003/4 survey or reported a history of stroke at the 1994/5 survey). Selected post-hoc pairwise test p-values are also provided.

Table 1
Descriptive data for the full sample and by dementia group

Characteristic or measure	Total sample ($n = 800$)	Without dementia ($n = 749$)	Possible/probable dementia ($n = 51$)
Gender (male)	44%	43%	55%
Age (years)	72.4 ± 7.6	71.9 ± 7.3	80.1 ± 7.0
History of stroke	6%	6%	12%
NART score	18.1 ± 9.1	17.7 ± 9.0	22.9 ± 9.9
CAMCOG score	92.1 ± 9.3	93.6 ± 5.4	70.2 ± 20.5
ExecFn score	20.0 ± 4.4	20.5 ± 3.9	12.5 ± 5.4

Table 2
Iron measures for the full sample and by dementia group

Characteristic or measure		Total sample ($n = 800$)	Without dementia ($n = 749$)	Possible/probable dementia ($n = 51$)
TRS (T_1) (%)		28.5 ± 10.5	28.6 ± 10.6	27.9 ± 9.3
Iron (T_1) (μmol/l)		18.3 ± 5.3	18.3 ± 5.3	18.9 ± 5.2
Ft (T_1) (μg/l)		162 ± 227	163 ± 232	146 ± 120
Ft (T_1) groups	Low	5%	5%	6%
	Normal-low	50%	50%	51%
	Normal-high	29%	28%	31%
	High	16%	17%	12%
TRS (T_2) (%)		28.2 ± 9.9	28.2 ± 9.9	26.8 ± 9.8
Iron (T_2) (μmol/l)		18.3 ± 5.5	18.3 ± 5.5	17.9 ± 5.2
Ft (T_2) (μg/l)		123 ± 107	125 ± 109	104 ± 75
Ft (T_2) groups	Low	6%	6%	10%
	Normal-low	60%	60%	61%
	Normal-high	23%	23%	25%
	High	11%	11%	4%
Decline ΔFt = Ft (T_1) – Ft (T_2)		39 ± 203	39 ± 208	42 ± 108
Decline ΔFt group	< -50	12%	12%	6%
	-50 to -20	10%	9%	22%
	-20 to $+20$	28%	28%	27%
	$+20$ to $+50$	18%	19%	18%
	$> +50$	32%	32%	27%

Standard protocol approvals, registrations, and patient consents

The study was conducted in accordance with the revised Helsinki protocol and requirements of the appropriate internal review boards. The mortality and hospital morbidity linkage was approved by the Confidentiality of Health Information Committee of Western Australia and all protocols and analyses were approved by the Human Research Ethics Committees of the University of Western Australia and the University of Newcastle, Australia. Written, informed consent was obtained from all participants.

RESULTS

Tables 1 and 2 summarize the demographic characteristics, cognitive test scores, and iron measures for the total sample and for the subgroups according to dementia status. In comparison to the total sample and the group without dementia, the dementia group contained more men, was older, had a higher mean NART score, and contained more participants with a history of stroke (Table 1).

The groups with or without dementia did not differ significantly with regard to either serum iron or serum transferrin (Table 2). Subsequent analyses were therefore restricted to serum ferritin, which has been validated in an analysis of nine randomized controlled trials by the U.S. Centers for Disease Control and Prevention as an appropriate indicator of population responses to factors influencing iron status [26].

For the group without dementia, the mean ferritin level declined between 1994/5 to 2003/4 from 163 μg/l to 125 μg/l. The proportion of people in this group with low ferritin remained relatively stable at 5–6% over this period, however, the proportion with high ferritin was reduced from 17% ($n = 124$) to 11% ($n = 84$). The dementia group had lower mean ferritin levels at each time (146 μg/l in 1994/5; 104 μg/l in 2003/4), containing relatively more participants with low ferritin and

Table 3
Unadjusted (raw) and adjusted means for CAMCOG and ExecFn scores by ferritin level in 1994/5 and 2003/4 for the group without dementia

	Low	Normal-low	Normal-high	High	P-value
			Ft (T_1) level		
CAMCOG unadjusted	95.4	93.6	93.6	93.1	0.1849
CAMCOG adjusted	94.1	93.7	93.4	93.4	0.7065
			Ft (T_2) level		
CAMCOG unadjusted	94.8	93.5	93.3	93.9	0.3744
CAMCOG adjusted	93.8	93.7	92.9	94.1	0.1314
			Ft (T_1) level		
ExecFn unadjusted	22.3	20.5	20.4	20.3	0.0574
ExecFn adjusted	21.5	20.5	20.3	20.5	0.2533
			Ft (T_2) level		
ExecFn unadjusted	21.4	20.4	20.4	21.0	0.2144
ExecFn adjusted	20.9	20.5	20.2	21.0	0.2011

Table 4
Unadjusted (raw) and adjusted means for CAMCOG and ExecFn scores by change in ferritin level from 1994/5 to 2003/4 for the group without dementia

	Ferritin decline ΔFt (μg/l) = Ft (T_1) − Ft (T_2)					
	< -50	-50 to -20	-20 to $+20$	$+20$ to $+50$	$> +50$	P-value
CAMCOG unadjusted	94.3	93.8	93.4	93.3	93.6	0.6206
CAMCOG adjusted	94.2	94.0	93.1	93.5	93.7	0.2905
ExecFn unadjusted	21.5	20.3	20.5	20.5	20.3	0.1061
ExecFn adjusted	21.4	20.3	20.3	20.6	20.4	0.1014

fewer with high ferritin. However, these differences in mean ferritin levels between the two groups did not reach significance ($p = 0.0681$ for 2003/4 and $p = 0.3640$ for 1994/5).

The average ferritin decline of 39 μg/l from 1994/5 to 2003/4 in the group without dementia was associated with considerable individual variation (SD = 208 μg/l), with 28% having minimal change (-20 to $+20$ μg/l), 32% declining by more than 50 μg/l, and 12% increasing by more than 50 μg/l between the two surveys. The direction of change was not clearly related to baseline ferritin status. The 243 participants without dementia who had a ferritin decline of more than 50 μg/l were spread across the normal-low (19%), normal-high (44%) and high (37%) ferritin groups in 1994/5. The 92 participants without dementia who had a ferritin increase of more than 50 μg/l were spread across the low (11%), normal-low (58%), normal-high (22%), and high (9%) ferritin groups in 1994/5. The decline in ferritin level for the dementia group (42 μg/l) did not differ from the group without dementia ($p = 0.826$).

In the group without dementia, neither unadjusted nor adjusted overall test scores comparing global cognition or executive function were significantly different across the ferritin groups (Table 3). The relationships of the means for the CAMCOG and ExecFn scores to the changes in ferritin level between the two survey times for the group without dementia are shown in Table 4. The data were not consistent with increases in ferritin over time leading to impaired cognition and, overall, differences in ferritin level between 1994/5 and 2003/4 were not significantly correlated with either the CAMCOG or the ExecFn scores in 2003/4.

Damage to liver and other organs is rarely observed in people with ferritin levels below 1,000 μg/l [28,29]. No participants had ferritin levels above 1,000 μg/l in 2003/4 and only two, both men, in 1994/5 (1,476 and 5,233 μg/l). Both men had CAMCOG scores in 2003/4 that were within the normal range [22,23] and above the cut-off for clinical examination (87 and 97) and ExecFn scores (20 and 22) that were within one SD of the mean of the group without dementia.

Hemochromatosis in Caucasian populations is usually associated with homozygosity for the HFE C282Y gene mutation, affecting as many as 1 in 400 or more in Caucasian populations of Anglo-Celtic descent [30–32]. Individuals with HFE homozygosity have increased risk of developing iron overload and related disease manifestations [30–32] and might therefore have increased risk of cognitive impairment or dementia. Three participants were identified as being homozygous for the hemochromatosis HFE C282Y mutation, however, their iron measures were normal or only moderately elevated and all had CAMCOG scores in the normal range. They comprised a male age 64 years

with CAMCOG 93 and ferritins at T1 and T2 of 44 and 69 ng/ml respectively, a male age 67 years with CAMCOG 99 and ferritins at T1 and T2 of 647 and 103 ng/ml, respectively and a female age 78 yrs with CAMCOG 92 and ferritins of 870 and 304 at T1 and T2 respectively.

DISCUSSION

Abnormal serum ferritin, either at the time of cognitive testing or a decade earlier, was not associated with global cognitive performance, executive function, or dementia in this community study. The results are not consistent with the hypothesis that abnormal body iron status directly affects cognition in older people.

There was no evidence that high serum ferritin increased the risk of cognitive impairment or dementia in the sample, with the group with possible or probable dementia containing relatively few people with high ferritin at either time compared to the group without dementia. Liver fibrosis or cirrhosis and other tissue damage most commonly occurs with serum ferritin levels above 1000 μg/l [28,29], a level rarely seen in community cohorts, however, even the participants who had previously had levels above 1,000 μg/l were within normal ranges on cognitive testing.

Overall a reduction of around 25% was observed in the mean serum ferritin level of the cohort between 1994/5 and 2003/4, which may reflect age-related decline and changing dietary patterns such as reductions in red meat consumption or increased fruit consumption, both associated with lower ferritin levels [33]. This reduction, which primarily occurred in the subgroups with highest ferritin, did not affect cognition within the cohort. While this could not be assessed directly as baseline cognitive data were not available, there were no differences in cognitive performance between the groups with decreases in ferritin compared to the group with minimal change. In particular, the subset of people without dementia who underwent the greatest decline in serum ferritin from 1993/4 to 2003/4 did not perform better on tests of global cognition or executive function relative to the subsets showing minimal ferritin changes or those whose serum ferritin increased between the two surveys.

Since iron is present at particularly high concentrations in the basal ganglia and data from fMRI studies highlight the importance of the basal ganglia in executive function [34,35], we also examined the possibility that executive function might be particularly sensitive to iron abnormalities. In the early stages of frontotemporal lobar degeneration, executive function can be impaired without substantial memory changes [36] and executive function is also important in preserving instrumental activities of daily living in older people, a key factor in care requirements and progression to institutionalization [37,38]. However, we did not find any evidence for a clear relationship between serum ferritin and executive function. Sensitive tests might detect more subtle relationships but such effects may be less likely to be clinically relevant.

One explanation for the lack of any clear relationship between cognition and serum ferritin is that serum ferritin levels may not be a reliable gauge of brain iron. Serum ferritin levels do not always accurately reflect iron concentrations in systemic organs. For example, serum ferritin or transferrin saturation levels do not correlate well with hepatic iron content in most cases of hyperferritinemia [39]. In a study of older community-dwelling males (mean age 75.5 years), serum ferritin levels did not correlate with regional brain iron contents as gauged by magnetic resonance imaging proton transverse relaxation rate (R_2) [40]. Furthermore, in neuroferritinopathy, caused by mutations in ferritin light chain, abnormal iron deposition occurs in regions such as the basal ganglia despite low or normal serum ferritin [13,14,41] and neither venesection nor iron chelation is beneficial [41]. Even in people without severe neurogenetic disorders, abnormal iron levels localized to a particular brain region might affect specific functions without necessarily affecting the measures of global cognition or executive function used here.

The strengths of the present study include its large size relative to previous studies in this area, clinical examination of participants identified by epidemiological screening as having possible dementia and investigation of ferritin at two time-points a decade apart. Limitations include the lack of baseline cognitive data from 1994/5 and the low number of dementia cases precluding assessment of different dementia diagnoses or investigating correlations with dementia severity or progression rates. It remains possible that iron status influences cognition, functional performance, or dementia risk in a few individuals with chronic extremely low or high body iron levels or exacerbates neurodegeneration, severity or progression rate in people with pre-existing dementia or with particular types of dementia. Addressing these issues ideally requires large clinical groups with neuroimaging and preferably also postmortem data. However, in general, abnormal body iron stores (low or high) appear unlikely to have

clinically significant effects on cognition or dementia risk in community-dwelling older people. These findings should be taken into account in any consideration of whether to limit treatments for iron deficiency anemia or use venesection or chelation to protect against cognitive effects in older people [3–6].

ACKNOWLEDGMENTS

This work was supported by the National Health and Medical Research Council of Australia [grant number 254594 to E.M., J.O., D.B., M.K., A.J.]; the Health Promotion Foundation of Western Australia [MK]; and the Great Wines Estates of the Margaret River region, Western Australia [MK]. We thank Helen C. Bartholomew for contributing to this work (supervision of data entry and database management). We thank the Busselton Population Medical Research Foundation and the community of Busselton for their longstanding support and participation in the surveys. We also thank all those who helped organize or conduct the surveys.

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=298).

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