Reminder of important clinical lesson

Ironing out the rough spots – cognitive impairment in haemochromatosis

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A man in his late 40s, referred by his general practitioner (GP) to a psychology-led pain management programme, made a subjective and spontaneous report of cognitive impairment. He further mentioned a ten year history of erectile dysfunction, joint pain, occasional nausea and excessive fatigue. He underwent cognitive assessment. Advised to return to his GP to seek further investigation, he was ultimately subsequently diagnosed with haemochromatosis and began radical therapeutic venesection. Repeat cognitive assessment, a year later and following stabilisation of the condition, found improvement on some cognitive measures. Subjective report was of vastly improved cognitive function.

BACKGROUND**Definition and prevalence**

Haemochromatosis can be described as the clinical condition of iron overload.¹ In 2000, The British Committee for Standards in Haematology published guidelines on the diagnosis of, and therapy for, genetic haemochromatosis² advising that genetic haemochromatosis ‘refers predominately to iron accumulations in the body due to the inheritance of mutations in the HFE gene on both copies of chromosome 6’ (pp.3). They noted, in addition, that other, rarer forms of inherited haemochromatosis exist which do not have a mutation in the HFE gene.

The condition typically affects individuals of North European or Celtic descent and has been described as the most common genetic disorder in Caucasian populations.³ Haemochromatosis sufferers are unable to metabolise excess iron. The consequent build-up can lead to widespread tissue damage, including cirrhosis of the liver, and other serious complications. Evidence suggests that early treatment, normally venesection, is successful in optimising chances of a normal life expectancy.^{4 5}

A retrospective study suggested that the likelihood of receiving a timely diagnosis of haemochromatosis has increased over time.⁶ Similarly, the incidence of diseases often associated with the condition (eg, diabetes mellitus) has decreased over time in a British sample. However, it is noted that a marked excess mortality from the disease persists by comparison to the general population.⁶

Cognitive impact of untreated haemochromatosis

There has been little investigation of the cognitive impact of haemochromatosis. Case reports have described patients with extrapyramidal or cognitive dysfunction,⁷ confusion and psychomotor retardation,⁸ fatigue and impaired short-term memory.⁹ A comparison of patients with haemochromatosis to those without the disease on the Mini Mental

State Examination over time (mean=3.2 years follow-up) found a link between bone lead levels and declining score over time in the haemochromatosis group.¹⁰ The assumed mechanism in this particular study is lead absorption.

Other groups have purported that cognitive dysfunction is secondary to hepatic failure¹¹ or indeed noted progressive cognitive impairment in haemochromatosis in cases where there appears to be no evidence of major symptomatic organ impairment.¹²

CASE PRESENTATION

A 48-year-old man was referred to the Lothian Chronic Pain Service by his general practitioner (GP) with chronic lumbar back pain. He reported a life-long history of such pain following a fall from a tree in childhood (with no loss of consciousness). On assessment however and adjunctively, he reported excess fatigue, more widespread joint pain, occasional nausea and long-standing erectile dysfunction. Some of these complaints had been investigated/treated in isolation. More specifically, and emerging during his initial attendance at a group based Pain Management Programme, the patient made initial reference to concerns regarding his ‘memory’. Confusion and examples further suggestive of cognitive difficulty were corroborated by his wife who attended for interview. A cognitive assessment was arranged and, meantime, in further consultation with his GP and ordered investigations, a diagnosis of haemochromatosis (C282Y homozygote) was made by genotyping and raised Ferritin level of 2300.

The patient stated that his memory had been poor for a number of years but had become progressively worse over the preceding year. He reported instances suggestive of decreased attention, problems with new learning, memory failure and confusion. Examples included becoming confused while following traffic signals, having to get up 4 h in advance of an appointment just half an hour’s drive away in order to ‘get my head round it’ organisationally, becoming confused by house numbers in the

street while hand-delivering Christmas cards, being confused by someone talking to him while he was trying to do something else and being unable to follow the plot of a book. There was no known family history of dementia although the patient reported that his father had been 'tired all the time' and died aged 55. The patient has no history of hypertension, cardiovascular or cerebrovascular disease, diabetes or hyperlipidaemia, renal failure (with ultrasound scan showing kidney of normal appearance) and nutritional deficiencies.

The patient had himself been a successful entrepreneur who grew, managed and then sold a number of pubs enabling him to 'retire' on the proceeds in his early 30s. He worked in a technical support centre as a 'hobby' but had given this up finding himself unable to keep up with assimilating the necessary emerging technical information. He had given up alcohol entirely at the time of presentation on account of associated nausea but he did report having drunk relatively heavily during his 20's and 30's when he was involved in pubs in the course of his work. His reports of cognitive impairment followed several years of abstinence from alcohol.

The patient's wife endorsed his reports noting, in addition, 'paranoia' and an ongoing complaint on the patient's part that she was trying to trick or catch him out and/or hide things from him. She reported that his memory was poor and that he failed to assimilate instructions, demonstrating an apparent 'knowing/doing' dissociation. For example, although the patient reportedly 'knew', and could report, that his sock drawer was the top one in the chest, he persisted, on a daily basis, in looking through all of the drawers in the chest 'searching' for his socks. The patient's wife stated that she had noticed that her husband's speech was 'deteriorating' in that he appeared to experience word finding difficulties and had a tendency to go 'blank' and lose his train of thought mid-sentence. She felt that his difficulties were getting progressively worse.

On assessment, the patient's speech was slightly pressured and there was indeed evidence of word finding difficulties and of failure to maintain focus in conversation.

INVESTIGATIONS

Neuropsychological investigation (cognitive assessment)

Current cognitive function and memory were assessed using standardised Wechsler Tests (Wechsler Abbreviated Scale of Intelligence),¹³ Wechsler Memory Scale (WMS-III).¹⁴

Higher level functions (attention, speed of processing, executive function) were screened using the Colour Trails Test,¹⁵ Digit-Symbol Coding from the Wechsler Adult Intelligence Scale, (WAIS-III)¹⁶ and the Controlled Oral Word Association Test (COWAT).¹⁷

Results

Performance was considered to be compromised by comparison to likely premorbid status as assessed on the basis of occupational achievement (the patient had failed to focus on a formal test of premorbid ability making results invalid).

- ▶ Current cognitive function (Full Scale IQ) fell at the very bottom of the average range.
- ▶ Visual memory (spontaneous recall) fell at the bottom of the low average range.
- ▶ Auditory (verbal) memory was in the average range.
- ▶ Working memory was in the average range.
- ▶ On a short measure of sustained attention, sequencing and hand-eye motor co-ordination, the patient performed in the high average range on Part I one of the task but fell off to 'average' performance on the cognitively more demanding second part of the task.
- ▶ Performance on a speed of processing task was at the bottom of the average range.
- ▶ Performance on the COWAT was poor. The patient produced unusual answers such as 'organic' and 'ubiquitous' under the 'words beginning with A' category suggesting confusion/poor self-monitoring.

TREATMENT

Medical Intervention

Following this initial cognitive assessment, the patient was diagnosed with haemochromatosis and began radical venesection treatment aimed at reducing toxic iron levels. Weekly venesection commenced until ferritin levels were

Table 1 Comparison of cognitive assessment results pre and postphlebotomy treatment expressed as index scores (100=Average, SD=15) or percentiles

	Prephlebotomy treatment	Postphlebotomy treatment
Full scale IQ (WASI)	91	97
Wechsler memory scale indices		
Auditory immediate	102	102
Visual immediate	81	97
Immediate memory	91	100
Auditory delayed	102	105
Visual delayed	100	109
General memory index	105	109
Working memory	99	102
Visual reproduction immediate	80	100
Visual reproduction delayed	90	95
Colour trails		
Part I	76th percentile	58th percentile
Part II	50th percentile	66th percentile
Speed of processing	90	95
Controlled Oral Word Association Test (COWAT)	<10th percentile	Between 50th and 60th percentile

WASI, Wechsler Abbreviated Scale of Intelligence.

maintained below 50 with regular testing of ferritin levels and repeat venesection conducted as required. He was also commenced on regular testosterone injections and reported welcome improvement in sexual function.

OUTCOME AND FOLLOW-UP

Re-assessment was undertaken some 14 months later (table 1). By this stage, the patient's ferritin level was being continually monitored, and at most recent testing, he reported that it had been slightly below normal limits (35). An appropriate ongoing maintenance programme was being determined. Triple phased CT scan of the liver showed no focal lesion and abdominal ultrasound scan showed normal appearance of the liver. Serum hyaluronic acid level test was normal at 9.97.

Subjectively, the patient reported that he had noticed marked cognitive improvement following his initial, intensive, phlebotomy treatment. He stated that he was 'thinking more clearly' and reported that he 'had not realised how bad I was. I was totally confused'. Anecdotally, he presented as more coherent, more focused and with increased perseverance and speed in completing tasks during assessment. He reported that he believed he had underperformed at the postphlebotomy assessment as he had experienced disturbed sleep on the night preceding the assessment.

DISCUSSION

The case highlights the importance of timely diagnosis in haemochromatosis. Symptoms of fatigue, erectile dysfunction, joint pain, occasional nausea and cognitive impairment together with a family history of fatigue and early death in first degree relative were reported in this instance for some time before relevant investigations were pursued and, importantly, coordinated.

Once a diagnosis of haemochromatosis had been made, straightforward and highly effective treatment, by way of radical therapeutic venesection, resulted in subjective report of vast improvement in relation both to cognitive function and levels of fatigue. Repeat cognitive assessment, a year later and following stabilisation of the condition, found modest objective improvement on some cognitive measures notably visual memory and verbal fluency.

Previous researchers have reported improvements in cognition following venesection treatment and suggest mechanisms including increased viscosity and reduced cerebral blood flow and/or liver dysfunction.⁸

This case tentatively suggests the possibility that at least some of the apparent objective cognitive 'deficits' observed in haemochromatosis are reversible. Certainly subjective report is of marked improvement in cognitive function – although the contribution of fatigue in and of itself should be considered here. These findings are contrary to reports of inevitable and progressive cognitive decline in patients with haemochromatosis and a posited link between haemochromatosis and genetic dementia¹² and highlight the need for timely diagnosis of the condition, given the possible impact on quality of life.

Weaknesses in the current study included a somewhat idiosyncratic case whom it was hard to definitively place in terms of likely premorbid ability (with little formal

education yet clear indication, both by report and occupational achievement, of high ability).

Learning points

- ▶ There are cognitive, as well as physical, markers of haemochromatosis.
- ▶ The cognitive difficulties reported in association with untreated haemochromatosis are personally troubling and have an impact on personal and family life.
- ▶ Cognitive difficulties are potentially reversible with appropriate management of the condition.
- ▶ A specialty-coordinated approach to the investigation and treatment of suspected haemochromatosis would be potentially cost effective and represent best practice from a patient perspective.
- ▶ Further research should explore the mechanism by which haemochromatosis can cause cognitive impairment.

Competing interests None.

Patient consent Obtained.

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