Haemochromatosis and dementia: cause or contributor?

Bheemraya Hanmanthraya MRCPsych, Andrew Byrne MRCPsych, MMedSc

Haematological conditions, including haemochromatosis, have been reported as predictors of cognitive decline in their own right. Here, the authors describe a case of accelerated cognitive decline in a patient newly diagnosed with Alzheimer’s dementia and the possible effect of haemochromatosis on the patient’s dementia progression.

Haemochromatosis is a complex genetic disease where there is primary iron overload. Hereditary haemochromatosis is common, particularly in people of northern European extraction, and has an autosomal recessive mode of inheritance. Prevalence is estimated at 1 in 200 to 1 in 400. Early diagnosis of individuals at risk of the development of haemochromatosis is important, because survival and morbidity are improved. The clinical manifestations are the result of the specific pattern of organs affected, and most often seen are weakness and weight loss, arthralgia, abdominal pain, skin pigmentation, hepatomegaly, hepatic cirrhosis, diabetes mellitus, arthropyathy, cardiac manifestations and hypogonadism. The most common laboratory abnormalities are raised percentage saturation of transferrin and serum ferritin concentration, increased amounts of stainable iron in hepatocytes and an increased hepatic iron concentration.

Haemochromatosis rarely presents with CNS manifestations. However, there have been several cases reported in recent literature. One such case report discussed cognitive decline in association with haemochromatosis. Further case reports described patients developing dementia associated with haemochromatosis. Two cases have been described where there has been a presentation of dementia and ataxia. In both cases the patients died within two years of the onset of neurological symptoms.

In this case, we describe a female patient in her 70s with a history of haemochromatosis who was diagnosed with dementia and who presented with a very rapid decline in her cognitive functioning.

Case presentation

A lady in her early 70s who lived at home with her husband presented with a one-year history of rapid, non-fluctuating, moderate cognitive impairment. At initial assessment her Addenbrooke’s Cognitive Examination-Revised (ACE-R) score was 50 out of 100 with a Mini-Mental State Examination (MMSE) score of 15 out of 30.

She had been diagnosed with hereditary haemochromatosis ten years prior and received regular venesection. She had developed liver cirrhosis two years following her diagnosis of haemochromatosis. She was closely monitored by her haematologist and her haemochromatosis was well controlled. At the time of our initial assessment, ferritin was normal at 38ug/L. Haemoglobin was within normal range, haematocrit was low at 0.334L/L and mean corpuscular haemoglobin was high at 32.3pg. Gamma glutamyl transferase was raised at 101U/L and all other liver function tests were normal. Erythrocyte sedimentation rate and C-reactive protein were normal. There had been no episodes of delirium or hepatic encephalopathy. Several years prior to the onset of cognitive impairment, she developed hypothyroidism, which was satisfactorily treated. There was no history of alcohol-related problems. Of note, she had no family history of cognitive impairment, dementia or other significant relevant medical condition.

It was apparent that neurological signs and symptoms were evident early in the course of her cognitive decline. She initially displayed more significant receptive and expressive dysphasia than would be expected at her stage of dementia. She had additional symptoms of visuo-spatial disorientation. At times, she presented with motor disturbances leading to gait ataxia and repeated falls. She had episodes of urinary incontinence several times per week. Significant behavioural and psychological symptoms developed, including irritability and hostility directed at her husband and bouts of agitation. She also presented with infrequent auditory hallucinations associated with distress but no visual hallucinations. There were no parkinsonian symptoms. In
terms of functioning, she was initially able to attend to some basic personal activities of daily living with supervision and help. Socially, she had excellent support from her husband and children.

Given her unresponsiveness to behavioural and psychological management of her distressing behavioural and psychological symptoms, risperidone 0.5mg at night was required in the first two weeks of initial assessment. This resulted in a significant improvement in her behavioural and psychological symptoms. She was closely monitored for any adverse effects of risperidone treatment, of which there were none. Risperidone treatment was subsequently discontinued.

During her assessment, dementia screening investigations, including relevant blood tests (apart from the above mentioned blood tests) were within normal limits. Her CT head scan showed both atrophic and periventricular ischaemic changes. Further neuroradiological investigations (eg MRI, DaTSCAN) were considered not feasible due to her mental state. Lewy body dementia was clinically excluded. She was diagnosed with probable Alzheimer’s dementia (AD) and commenced on donepezil treatment, which was titrated up to 10mg daily and was well tolerated.

It was very evident that the patient began to quickly decline, with a marked deterioration in cognitive skills and daily functioning over the following six months. At eight months her MMSE score was 8 out of 30. She continued to receive venesection treatment for her haemochromatosis. However, she further declined rapidly without additional medical comorbidities and soon required 24-hour elderly and mentally ill nursing care after one year from initial presentation.

Discussion
There is a need to explore in more detail the effect of iron deposition and disorders such as hereditary haemochromatosis causing increased cerebral iron in conditions such as AD. This is especially important, as hereditary haemochromatosis is relatively common. Clinical cases such as the one described above prompt the question of how significant iron deposition is in the progression of common conditions such as AD. In the case described, there was an unusually rapid clinical deterioration with significant neurological symptoms evident. The overall presentation and progression was not entirely typical of AD. So, how important clinically is abnormal iron deposition in this presentation and progression?

Though iron deposition has been observed in the brain with normal ageing, increased iron has also been shown in many chronic neurological disorders including AD, Parkinson’s disease (PD), and multiple sclerosis. It has also been postulated that hemochromatosis gene mutations may be risk factors for, or modulators of AD. Although iron deposition has been observed in the brain, the link between haemochromatosis and AD is still not entirely typical of AD. So, how important clinically is abnormal iron deposition in this presentation and progression?

Though iron deposition has been observed in the brain with normal ageing, increased iron has also been shown in many chronic neurological disorders including AD, Parkinson’s disease (PD), and multiple sclerosis. It has also been postulated that hemochromatosis gene mutations may be risk factors for, or modulators of AD. In fact, animal models, pathological studies, and MRI imaging studies have linked iron to AD. Increased iron deposition has been observed, especially in the hippocampus, in some cases of AD.

Interesting case reports have described a combination of cognitive and neurological symptoms where haemochromatosis has been present. In one such case report, two patients were described with haemochromatosis and a syndrome of ataxia, rigidity, myoclonic jerks, and dementia. Other associated symptoms due to haemochromatosis may include, for example, diminished libido, decreased hearing, peripheral neuropathy, and large joint disease.

However, the link between brain iron deposition and pathology underlying diseases of the brain is poorly understood. One study in particular emphasised the link between brain iron dysregulation and the development of white matter lesions, which may cause impairment in cognitive functioning. Iron deposition is being examined further as a contributory factor in the pathogenesis of AD. It has been seen that the iron content in the brain tends to increase with age, in particular at the sites of the typical lesions of AD and PD. One hypothesis put forward to explain the link between haemochromatosis and AD and PD suggests that changes in the genes regulating iron metabolism act together with acquired endogenous and environmental (toxins) factors in the aetiopathogenesis of sporadic cases of AD and PD.

Studies have examined the mechanism by which excessive iron may cause cognitive decline. These in vitro studies have demonstrated that excessive iron can lead to free radical production, which can promote neurotoxicity. In fact, animal models, pathological studies, and MRI imaging studies have linked iron to AD. Increased iron deposition has been found, especially in the hippocampus, in some cases of AD. Post-mortem studies have indicated that the brain stores more iron as it ages and imaging studies by Bartzokis and others have shown increased levels of iron in the hippocampus and basal ganglia of patients with AD, PD and Huntington’s disease. The very rapid cognitive decline in our case could be linked with iron deposition. Similarly, the atypical and prominent neurological signs could be explained by increased basal ganglia iron deposits.

We sought to consider whether haemochromatosis accelerated the pre-existing cognitive decline in this case as well as considering haemochromatosis as a stand-alone cause for dementia. Other
Haemochromatosis and dementia

Case notes

Progress in Neurology and Psychiatry
May/June 2015

Haemochromatosis and dementia

Case reports have shown that people presenting with cognitive decline who are later diagnosed and treated for haemachromatosis subsequently improve in their cognitive functioning. This suggests that haemochromatosis itself may cause cognitive decline. We postulate that in our described case, haemochromatosis may have accelerated the patient’s cognitive decline.

It is clear that when haemochromatosis co-exists with cognitive decline, haemochromatosis should be closely monitored and adequately treated to minimise the extent and rapidity of the cognitive decline. In addition, there is a need for increased awareness of the potential link between haemochromatosis and cognitive impairment, particularly in primary care but also in secondary care. As symptoms of haemochromatosis can be reversed by phlebotomy, appropriate laboratory studies should be considered where haemochromatosis is suspected in any patient with unexplained cognitive impairment, encephalopathy, and/or gait ataxia. Reflecting on this case, the authors suggest that haemochromatosis should be considered as part of the differential diagnosis or as a possible contributor where prominent neurological symptoms accompany rapid, atypical and unexplained cognitive deterioration as part of a dementia syndrome.

The case report highlights the need for further studies exploring the effect of haemochromatosis on cognitive decline in dementia.

Declaration of interests

No conflicts of interest were declared.

Dr Han Manhoveya is an ST5 in Old Age Psychiatry at Bensham Hospital, Gateshead and Dr Byrne is a Consultant Old Age Psychiatrist at St George’s Park, Morpeth

References