Cerebral calcification from Fahr’s disease with co-existing haemochromatosis

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An elderly man with a history of hereditary haemochromatosis, Parkinsonism and a pituitary macroadenoma presented with limb weakness and slurred speech. He underwent computer tomography of his head, which showed extensive basal ganglia, and periventricular and cerebellar calcification consistent with Fahr’s syndrome. The degree of the calcification and lack of precipitating factors led to a likely diagnosis of Fahr’s disease.

Figure 1. CT head scan showing cerebral calcification

Figure 2. CT head showing cerebellar calcification

Figure 3. CT head showing basal ganglia calcification

Figure 4. MRI brain showing abnormally high intensity signals due to calcification
This man was living with his wife and received help from carers with activities of daily living. Prior to this presentation, his mobility on foot was limited to short distances with the aid of a walking frame.

He had seven brothers, the eldest of which had died. Five of these siblings had haemochromatosis. The older brother was also diagnosed with a brain tumour, which was the cause of his death; it is unknown whether he also suffered with haemochromatosis.

Physical examination was largely unremarkable apart from hypomimia, a resting tremor in the upper limbs, bradykinesia, reduced power in both arms 4/5, and reduced power in the lower limbs 3/5 bilaterally (MRC scale).

**Investigations**

He previously had multiple MRI scans of his brain for follow up of his macroadenoma but no CT scans prior to this admission. CT head showed extensive calcification around the lateral ventricles, basal ganglia and cerebellum (Figures 1–4).

His standard blood tests were within normal values apart from a slightly elevated parathyroid hormone level of 13.4pmol/L (normal range 1.2–5.8pmol/L) and an elevated urea and creatinine in keeping with stage 4 chronic renal failure.

Also of note, his corrected serum calcium was 2.24mmol/L (normal range 2.12–2.57mmol/L) and with a serum phosphate of 1.31mmol/L (normal range 0.8–1.45mmol/L).

Overall imaging findings were thought to be consistent with Fahr’s disease. However, without genetic testing for a mutation of the SLC20A2 or PDGFRB genes this could not be confirmed.

**Discussion**

Fahr’s disease was first described by the German neurologist Karl Theodor Fahr in 1930.1 It is a rare, inherited neurodegenerative disease characterised by extensive basal ganglia calcification.2

The inheritance pattern of Fahr’s disease can be either autosomal recessive or dominant. The first chromosomal locus for Fahr’s disease was described on chromosome 14q;3 a second locus has been identified on chromosome 8 (SLC20A2 gene),4 a third on chromosome 2 in location 2q37,5 and a fourth on chromosome 5 of the PDGFRB gene.6 There are also cases where there appears to be no previous family history of the disease.7,8

**Pathological characteristics**

The pathophysiology of this disease is thought to be caused by defective phosphate transport.9 This results in calcium and other minerals being deposited within the capillaries and within the perivascular spaces. The exact pathological process is not fully understood; however, it is thought to be a slowly progressing metabolic or inflammatory process within the brain.

Histological examination shows concentric calcium deposits, which can also be found in the small and medium sized arteries. These mineral deposits appear as amorphous or crystalline materials that surround the basement membrane. However, the picture is indistinguishable from that of hypoparathyroidism.

**Affected brain regions**

The most common regions affected are the lenticular nucleus and the globus pallidus.10 Other areas of the brain affected include the caudate, dentate nuclei, putamen and thalami, cerebellar gyri, brain stem and also the centrum semiovale.

**Symptoms of disease onset**

The onset of the disease is insidious. It tends to affect patients in the third to fifth decade of life.11 Most commonly it presents with a variety of neurological and psychiatric symptoms. These can include general symptoms of Parkinsonism; there may be difficulty with walking, dysarthria and dysphagia. A patient may demonstrate involuntary movements, muscle cramps or could present with any form of seizure. The disease can also present with neuropsychiatric problems including psychosis, personality changes and dementia.12

**Diagnostic markers**

Diagnosis is made by excluding other causes of basal ganglia calcification such as infective causes, or hypoparathyroidism,10,12 pseudohypoparathyroidism,11,15,14 lupus, mitochondrial disorders14 and Down’s syndrome.10

Genetic tests can also be performed looking for mutations, the most common of which is the mutation of the gene SLC20A2, which is located on chromosome 8.8,15 It is suggested that a CT head that is normal at the age of 55 can exclude the diagnosis of Fahr’s disease.16,17

Unfortunately, there is no cure for Fahr’s disease. Management lies with symptomatic treatment: levodopa for Parkinsonian features, and haloperidol and lithium can be used for the management of psychotic symptoms.18 There has been one case report of functional improvement with the use of bisphosphonates.19

In patients where a positive family history cannot be documented the following five features should be met in diagnosis of Fahr’s disease:7,20–22
Fahr’s disease

Case notes

• Neuroimaging showing bilateral calcification of the basal ganglia or other brain regions.
• Neuropsychiatric manifestations and/or progressive neurological dysfunction.
• Although it can also present earlier in life, onset of symptoms occurs typically in the fourth or fifth decade of age.
• Absence of other causes for intracranial calcification such as biochemical abnormalities and somatic features suggestive of a mitochondrial or metabolic disease or other systemic disorder.
• Absence of an infectious, toxic or traumatic cause.

Types of haemochromatosis

With regard to haemochromatosis, there are four types, with types 1–3 being inherited in an autosomal recessive pattern, and type 4 in an autosomal dominant inheritance. Type 1, the most common type, is caused by a defect in the \( HFE \) gene on chromosome 6, type 2 (juvenile haemochromatosis) is caused by a defect in the \( HFE2 \) gene (type 2A) on chromosome 1 or the \( HAMP \) gene (type 2B) on chromosome 19, and type 3 is due to a mutation of the \( TFR2 \) gene on chromosome 7. Type 4 is related to a mutation in the \( SLC40A1 \) gene located on chromosome 2 (2q32.2) which encodes for the transmembrane protein, ferroportin.23–27

It is possible that this man had type 4 haemochromatosis, given the strong prevalence in his family. As this is caused by a defect in chromosome 2 in the region of 2q32.2, it is theoretically possible that he also had a related defect in chromosome 2 in the 2q37 region leading to Fahr’s disease.

Conclusion

Fahr’s disease is an extremely rare disease, which commonly runs in families. Haemochromatosis is usually inherited in an autosomal recessive pattern; in this family it is likely that the inheritance is autosomal dominant.

This man has intracerebral and intracerebellar calcification, without an obvious secondary cause. This raises the likelihood that he has Fahr’s disease. Whether this is related to his haemochromatosis is uncertain; there have been no previous associations documented in the literature.

Informed consent

Received

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Declaration of interests

There are no conflicts of interest declared.

References