

# Fahr's disease with an initial presentation of crescendo TIA

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## SUMMARY

A 51-year-old man presented with vertigo, slurred speech and left facial droop. He had been previously diagnosed with transient ischaemic attack (TIA) and had a prior lacunar infarct. Imaging showed heavy symmetrical calcification in the globus pallidus, frontal white matter and cerebellar dentate nuclei/deep white matter. The imaging was pathognomonic for Fahr's disease and diagnosis was confirmed when other secondary causes of hypercalcemia were excluded. Fahr's disease is a rare, autosomal dominant, neurological condition characterised by primary brain calcification. Patients present with progressive neurological and psychiatric symptoms; commonly, Parkinsonian movement disorders, seizures, headaches, dysarthria, cognitive decline, psychosis and personality changes. There is an association with intracerebral ischaemic events. This case supports a growing body of anecdotal evidence of this association and is the first in which crescendo TIA may be the initial presentation of Fahr's disease. Referral for genetic counselling and symptomatic relief for neurological symptoms are the main management strategies.

## BACKGROUND

Fahr's disease, primary familial brain calcification, is an autosomal dominant neurological condition. It is caused by calcium deposition predominantly within the basal ganglia and dentate nuclei of the cerebellum with potential additional calcification of subcortical white matter in frontal or occipital lobes leading to characteristic CT imaging. It is typically diagnosed in middle age and can lead to various neurological presentations including movement disorders, progressive cognitive impairment and reduced mobility.<sup>1-5</sup>

This case was considered after typical CT imaging suggested the diagnosis following a presentation of possible acute stroke. After further investigation, there was an onward referral for specialist input, so early treatment initiatives and familial screening could be performed.

## CASE PRESENTATION

A 51-year-old man presented to transient ischaemic attack (TIA) clinic with recurrent episodes of vertigo, slurred speech and left facial droop that lasted between 5 and 15 min. These had increased in frequency and severity over the previous week, he reported three episodes on the day of presentation. There was no other medical history and reported no family history of stroke or hereditary conditions. Examination revealed no focal neurological deficit,

cranial nerve examination was normal, there was no facial droop, power was 5/5 bilaterally in upper and lower limbs, sensation was intact throughout, there was no dysarthria or dysphasia, coordination was normal, no past pointing and gait was normal with no ataxia. No formal cognitive assessment was performed; however, there was no clinical suspicion of cognitive impairment during history taking, examination and subsequent clinical interactions. His observations were unremarkable.

## INVESTIGATIONS

Blood samples taken on admission including screening for hypoparathyroidism, autoimmune and inflammatory conditions were unremarkable. ECG showed normal sinus rhythm and a carotid duplex scanning showed no significant stenosis of the internal carotid arteries. A CT of the brain demonstrated symmetrical heavy calcification of the dentate nuclei of the cerebellum, in the globus pallidus and frontal white matter (figure 1). Intracranial CT angiogram showed no significant stenosis of the intracranial vasculature (figure 2). For the patient's age, there was also a high degree of cerebral and to a greater extent cerebellar atrophy. A mature lacunar infarct was noted in the left frontal corona radiata (figure 1). An MRI of the brain did not show any evidence of an acute infarction.

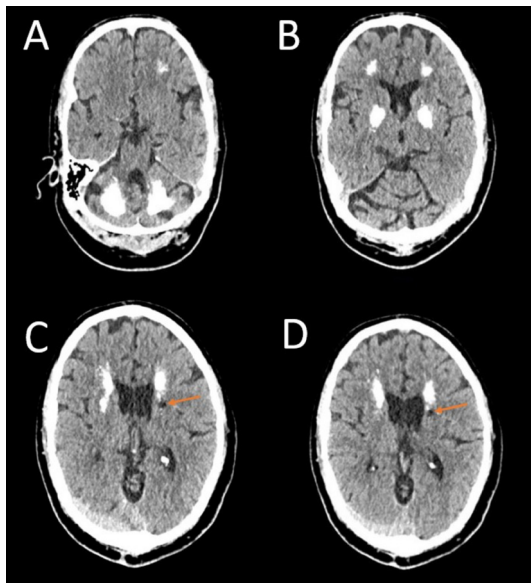
## DIFFERENTIAL DIAGNOSIS

The CT scan of the brain showed significant bilateral calcification which raised the strong suspicion of Fahr's disease. Although presentations can vary, literature studies suggest that more common symptoms include neuropsychiatric symptoms and cognitive disturbance rather than transient, focal neurological deficit. Crescendo TIA has been defined as recurrent TIA in which there is an increase in frequency, severity or duration of the events.<sup>6,7</sup> Based on the patient's progressively worse and increasing frequency of episodes of slurred speech, facial weakness and vertigo, and history of lacunar infarct, a clinical diagnosis of crescendo TIA was made. Focal atonic, or negative, seizures are a differential for TIA, they are usually associated with positive focal or general seizures.<sup>8</sup> Given the lack of seizure history and positive history of infarction, this seemed less likely. Investigations ruled out secondary causes of calcium metabolism and deposition, notably hypoparathyroidism, infection and autoimmune conditions which can cause basal ganglia calcification. Therefore, a diagnosis of Fahr's disease as opposed to Fahr's syndrome was also made.



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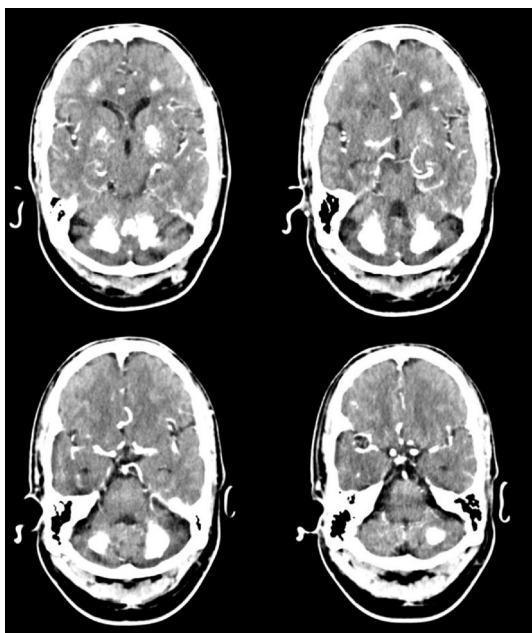
**Figure 1** Axial CT scan images of the brain showing calcification of the dentate nuclei and cerebellum (A), head of the caudate nuclei, the globus pallidii and frontal white matter (B) and of the subcortical white matter of the frontal lobe (C). Mature lacunar infarct is indicated with an arrow in (C) and (D).

## TREATMENT

The patient was referred to a genetic medicine clinic for Fahr's disease, and he did not require symptomatic treatment. Prior to TIA clinic review, he was treated with aspirin 300 mg daily which was then switched to aspirin 75 mg daily and clopidogrel 75 mg once a day for 21 days. He was also commenced on atorvastatin 80 mg once daily.

## OUTCOME AND FOLLOW-UP

At 6-week follow-up, the patient reported no recurrent symptoms.



**Figure 2** Axial intracranial CT angiogram images showing patency of the cranial arteries, no significant stenosis.

**Table 1** Diagnostic features of Fahr's disease versus Fahr's syndrome<sup>14</sup>

Consider Fahr's disease or Fahr's syndrome if	
▶ Basal ganglia movement disorder	▶ Cerebellar abnormalities
▶ Pyramidal signs	▶ Speech dysfunction
▶ Cognitive impairment	▶ Psychiatric presentations
▶ Gait disorder	▶ Sensory changes
Fahr's disease features	Fahr's syndrome features
▶ Age of onset 40–60 years	▶ Age of onset 30–40 years
▶ Evidence of bilateral symmetrical basal ganglia calcification	▶ Evidence of bilateral symmetrical basal ganglia calcification
▶ Presence of autosomal dominant or recessive trait	And
	▶ Hypoparathyroidism
	Or
	▶ Brucellosis infection, intrauterine or perinatal
	▶ Neuroferritinopathy
	▶ Polycystic lipomembranous osteodysplasia with sclerosing leucoencephalopathy
	▶ Cockayne syndrome
	▶ Aicardi-Goutieres syndrome
	▶ Tuberos sclerosis
	▶ Mitochondrial myopathy
	▶ Lipoid proteinosis
Management	
▶ Symptomatic therapy	▶ Treatment of underlying cause
▶ Genetic counselling	▶ Symptomatic therapy

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## DISCUSSION

Basal ganglia calcification was first described by German neurologist Karl Theodor Fahr in 1930.<sup>1</sup> It is rare with a prevalence of <1:1 000 000. Published cases of Fahr's disease report a heterogeneous range of presentations (table 1). The spectrum of clinical presentations are varied from dementia,<sup>9</sup> to dysarthria,<sup>5</sup> mania,<sup>10</sup> psychosis and choreoathetoid movement,<sup>11</sup> and, as in this case, ischaemic events.<sup>12 13</sup> These ranged in age from 21 to 71 years with a mean age of 40 years. More than half of patients (55%) are known to have movement disorders on first presentation and nearly 40% with psychiatric symptoms.<sup>3 6</sup>

Fahr's disease is a primary calcification of the brain and idiopathic as opposed to Fahr's syndrome which represents secondary calcification. Aetiologies of Fahr's syndrome include hypoparathyroidism, birth anoxia, toxoplasmosis and HIV.<sup>13</sup> Table 1 lists features which are diagnostic of Fahr's disease and Fahr's syndrome.<sup>14</sup>

In our patient, a diagnosis of crescendo TIA was made and causes were investigated. Emboli arising from the heart, carotid and vertebrobasilar arteries were excluded following investigation. As common causes of TIA were excluded out, it raised the possibility that there was a relation between Fahr's disease and the patient's presentation of TIA. It is well-recognised that there is a strong association between cardiac calcification and ischaemic heart disease. Although there is currently no published association between ischaemic cerebral events and Fahr's disease, there is an anecdotal evidence.<sup>4 13 15</sup> A suggested pathogenesis is that Fahr's disease is associated with increased calcium deposition in the small vessels.<sup>13 16 17</sup> The resulting reduction in arterial elasticity and vasomotor responsiveness causes cardiovascular disease, a known risk factor for stroke of cardioembolic origin.<sup>13</sup> Lacunar infarcts are known to be associated with intracranial small-vessel disease.<sup>18</sup> In our patient's case, a confirmed old lacunar infarct fits this pattern, supporting an anecdotal association between Fahr's disease and cerebral ischaemia. From

the literature and this case, there appears to be an association between Fahr's disease or syndrome and intracranial ischaemic events; however, this requires further investigation.

The patient did not describe any family history of Fahr's disease, this is atypical as inheritably dominant genes have been identified.<sup>12</sup> The following three genes are commonly reported to be associated with Fahr's disease: SLC20A2, XPR1 and PDGFRB. SLC20A2 and XPR1 code for the inorganic phosphate transporter PiT2, which is important in cellular calcium and phosphate homeostasis. SLC20A2 and XPR1 disruption cause deposition of calcium phosphate,<sup>19 20</sup> SLC20A2 is thought to be responsible for 40% of inherited cases.<sup>21</sup> PDGFRB is responsible for maintenance of the blood–brain barrier; a deterioration could lead to increased calcium deposition. Sporadic and autosomal recessive cases have also been reported.<sup>2 22</sup> Further suggested baseline testing not performed includes the Elisworth Howard test, cerebrospinal fluid evaluation, serum lactate acid at rest and after exercise, and assessment of natural killer cells.<sup>1</sup>

### Learning points

- ▶ In Fahr's disease, intracranial imaging shows a characteristic pattern of bilateral calcification of the basal ganglia.
- ▶ Differentiation between Fahr's disease, primary basal ganglia calcification and Fahr's syndrome, secondary basal ganglia calcification, is important as it guides management. Fahr's syndrome can be excluded by assessment and investigation for hypoparathyroidism, autoimmune and inflammatory conditions.
- ▶ If there is re-presentation with episodic symptoms in a patient with known Fahr's disease, then crescendo transient ischaemic attack (TIA) should be considered as differential.
- ▶ The underlying pathogenesis of TIA in Fahr's disease requires further investigation.

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### REFERENCES

- 1 Saleem S, Aslam HM, Anwar M, *et al.* Fahr's syndrome: literature review of current evidence. *Orphanet J Rare Dis* 2013;8:156.
- 2 Moskowitz MA, Winickoff RN, Heinz ER. Familial calcification of the basal ganglia: a metabolic and genetic study. *N Engl J Med* 1971;285:72–7.
- 3 König P. Psychopathological alterations in cases of symmetrical basal ganglia sclerosis. *Biol Psychiatry* 1989;25:459–68.
- 4 Bartecki BF, Kamiński J. [Transient focal ischemia in Fahr's disease]. *Neurol Neurochir Pol* 1979;13:443–7.
- 5 Asokan AG, D'souza S, Jeganathan J, *et al.* Fahr's Syndrome- an interesting case presentation. *J Clin Diagn Res* 2013;7:532–3.
- 6 crescendo TIA. TheFreeDictionary.com. Available: <https://medical-dictionary.thefreedictionary.com/crescendo+TIA> [Accessed 6 May 2021].
- 7 Wilson SE, Mayberg MR, Yatsu F, *et al.* Crescendo transient ischemic attacks: a surgical imperative. *Veterans Affairs Trialists. J Vasc Surg* 1993;17:249–55. discussion 255–256.
- 8 Kang M-J, Choi JY, An Y-S, *et al.* A patient with atonic seizures mimicking transient ischemic attacks. *Epilepsy Behav Case Rep* 2015;3:30–2.
- 9 Calabrò RS, Spadaro L, Marra A, *et al.* Fahr's Disease Presenting with Dementia at Onset: A Case Report and Literature Review. *Behav Neurol* 2014;2014:e750975.
- 10 Shoib S, Maqbool Dar M, Arif T, *et al.* Fahr's disease presenting as mania: a case report. *Iran J Psychiatry Behav Sci* 2012;6:102–4.
- 11 Alshomrani AT, Shuqdar RM. Drug induced movement disorder: case report and literature review. *J Taibah Univ Med Sci* 2010;5:120–6.
- 12 Samuels CR, Khanni JL, Barkley K, *et al.* Case report: an incidental finding of Fahr's disease in a patient with hypochondria. *Cureus* 2018;10:e3668.
- 13 Yang C-S, Lo C-P, Wu M-C. Ischemic stroke in a young patient with Fahr's disease: a case report. *BMC Neurol* 2016;16:33.
- 14 Perugula ML, Lippmann S. Fahr's disease or Fahr's syndrome? *Innov Clin Neurosci* 2016;13:45–6.
- 15 Asensio Moreno C, Arias Jiménez JL, Aramburu Bodas O. Accidente isquémico transitorio asociado a síndrome de calcinosis cerebral. *An Med Interna* 2008;25:33–5.
- 16 Duckett S, Galle P, Escourroule R, *et al.* Presence of zinc, aluminum, magnesium in striopallidodentate (SPD) calcifications (Fahr's disease): Electron probe study. *Acta Neuropathol* 1977;38:7–10.
- 17 Kobayashi S, Yamadori I, Miki H, *et al.* Idiopathic nonarteriosclerotic cerebral calcification (Fahr's disease): an electron microscopic study. *Acta Neuropathol* 1987;73:62–6.
- 18 Li Q, Yang Y, Reis C, *et al.* Cerebral small vessel disease. *Cell Transplant* 2018;27:1711–22.
- 19 Brighina L, Saracchi E, Ferri F, *et al.* Fahr's disease linked to a novel SLC20A2 gene mutation manifesting with dynamic aphasia. *Neurodegener Dis* 2014;14:133–8.
- 20 Erro R, Schneider SA. XPR1 Mutations: Another Cause of Primary Familial Brain Calcification. *Mov Disord Clin Pract* 2016;3:27–8.
- 21 de Oliveira DF, de Lemos RR, de Oliveira JRM. Mutations at the SLC20A2 gene and brain resilience in families with idiopathic basal ganglia calcification ("Fahr's disease"). *Front Hum Neurosci* 2013;7.
- 22 Foley J. Calcification of the corpus striatum and dentate nuclei occurring in a family. *J Neurol Neurosurg Psychiatry* 1951;14:253–61.

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