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A Case of Fahr's Disease with Epilepsy as the First Symptom in Infancy

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Abstract

Background: Fahr's disease, also recognized as Idiopathic Basal Ganglia Calcification (IBGC) or Primary Familial Brain Calcification (PFBC), was first identified by the German neurologist Karl Theodor Fahr in 1930. This rare condition, which involves the calcification of the basal ganglia and presents significant treatment challenges, is most commonly diagnosed in middle-aged adults and is notably uncommon in children. Purpose: We report a case of a younger patient and review this disease as an aid to early detection and diagnosis of the disease. Case Introduction: In this report, we present a unique case of Fahr's disease in a child, where epilepsy manifested as the initial symptom during infancy. In this report, we present a case of Fahr's disease in a child who presented with epilepsy as the first symptom in infancy. The child had no imaging abnormalities at the onset of the seizure, and subsequent antiepileptic drugs were reduced and discontinued, and when the seizure recurred 3 years later, a perfect cranial CT revealed symmetrical calcifications in the brain, which gradually worsened, and subsequently the child was unable to take care of himself and had regression of his psychomotor development, and the family requested discharge from the hospital, and then the child died during the follow-up visit. Conclusion: The disease is currently associated with a number of disorders for which there is no specific treatment, and half of all patients currently have a well-defined gene, emphasizing more importantly the importance of genetic counseling for parents known to be at risk prior to conception.

Keywords

Fahr, Primary Familial Brain Calcification, Epilepsy

1. Clinical Data

A 7-year-old boy, born on May 8, 2016, was hospitalized for "fever and seizures."

He was diagnosed with epilepsy one month after birth and received treatment with "levetiracetam and phenobarbital." By the age of one, he could walk, but later regressed and could no longer walk independently. He was then diagnosed with psychomotor retardation and Fahr disease. In June 2018, "phenobarbital" was completely discontinued without any further seizures or discomfort reported. However, in December 2019, he had one episode of seizures along with fever. Treatment with "phenobarbital" once again successfully controlled the seizures. On February 18, 2019, "levetiracetam" was discontinued, with no seizures or other issues reported. In December 2019, he experienced another seizure during a fever, characterized by staring eyes, clenched teeth, blueness around the mouth, and limb stiffness lasting more than a minute. In June 2020, he had one seizure during a cold, similar to previous episodes, with the left side being particularly affected. He had another seizure on June 28, 2022.

His personal and family history showed no abnormalities. He was the first child born through normal delivery at 36 + 1 weeks, with no other anomalies reported. Developmentally, he was able to raise his head at 3 or 4 months, but currently struggles to sit alone. During the physical examination, the cardiopulmonary assessment showed no clear abnormalities. However, there were significant signs of psycho-linguistic-motor regression, as the patient was unable to sit alone and had difficulty crawling. His head was tilted to the left, and there were corns present. He displayed irritability and vocalized yelling, experienced decreased sleep, and had involuntary movements. The muscle strength in both lower limbs was unstable, with the left hand showing a preference for grasping large objects. There was flexion of the wrist joints, dorsal extension of the feet, inward turning of the feet, particularly noticeable on the left side. Supportive standing was challenging, and his toes touched the ground instead of being properly raised. He also had difficulty chewing, excessive salivation, and evident wasting. Tests for Brinell's sign, Bartholomew's sign, and Kirschner's sign were negative. There was slightly low muscle tone in all four limbs, uncooperative muscle strength, warm limb ends, and a capillary refill time (CRT) of 2 seconds.

In terms of the electroencephalography (EEG) results:

In June 2016, the video EEG showed a normal pattern at 4 - 5 Hz.

In June 2017, the video EEG was roughly normal, with a frequency of 5.5 - 7.0 Hz.

In January 2018, the video EEG showed a roughly normal pattern at 6 - 7 Hz.

In July 2018, the video EEG displayed a normal pattern at 6 - 7 Hz.

In February 2019, the video EEG showed a discharge in the right middle temporal region.

In July 2020, the video EEG revealed a discharge in the right middle temporal region.

In July 2022, the ambulatory EEG showed abnormal epileptiform discharges over a 24-hour period.

2. Discussion

Fahr's disease is clinically uncommon and its pathogenesis remains unclear. Calcification is not limited to the basal ganglia but also occurs in several other sites, such as the thalamus, hippocampus, dentate nucleus, cerebral cortex, and subcortical white matter of the cerebellum [1]. Abnormal calcium deposits are metastatic deposits due to abnormal brain calcium metabolism or localized alterations of the blood-brain barrier [2]. Calcium deposits begin in the vessel wall and perivascular space and slowly extend to involve entire neurons [3]. Progressive calcification compresses nearby blood vessels and reduces blood flow, thus continuing the vicious cycle of reduced blood flow, tissue damage, and mineral deposition and can vary in clinical features depending on the site of the victorious anatomy or the level of calcification, and can have a persistent worsening course [2].

Four genes are currently recognized as the molecular basis of Fahr's disease [4], namely, a loss-of-function mutation in SLC20A2, a gene encoding type 3 sodium-dependent phosphor transporter protein 2 (PiT2) on chromosome 8p (40%), a mutation in the XPR1 gene that encodes a retroviral receptor with phosphate export function on chromosome 1q (2%), a mutation in the gene encoding the platelet-derived growth factor Mutations in family member receptors-gene PDGFRB on chromosome 5q (2%) and gene PDGFB on chromosome 22q (11%). 46% of cases have some unknown mutation. Other loci associated with Fahr disease include the IBGC1 locus on chromosome 14q, a locus on chromosome 2q, and another locus on chromosome 8 [5].

XPR1 (1q25.3) encodes a retroviral receptor with a phosphate export function involved in phosphate homeostasis. PDGFRB (5q32) and PDGFB (22q13.1) play a role in pericyte recruitment, blood-brain barrier regulation and angiogenesis. MYORG gene has been identified as a new genetic cause of autosomal recessive PFBC .MYORG gene encodes a glycosyl hydrolase involved in myogenesis and is widely expressed in brain, especially cerebellum, but its role in pathogenesis of PFBC is not clear [6].

Grangeon [6] *et al.* studied the clinical and radiological characteristics of 16 MYORG patients from 11 families and compared them with 102 patients who carried mutations in four other PFBC genes. The study found that patients with MYORG showed a higher rate of clinical presentation, the main symptom was dyskinesia, in which dysarthria was the first sign. Compared to patients with autosomal dominant PFBC, 80% of symptomatic MYORG patients ended up with at least four of the symptoms such as disarticulation, cerebellar syndrome, gait disorder of any origin, dyskinesia-hypertonic syndrome, and pyramidal signs. In addition, the pattern of calcification was more severe in patients with MYORG, with brainstem calcification and pontine calcification more prominent in these patients than in patients with autosomal dominant PFBC. In addition, all patients showed varying degrees of cerebellar atrophy. In three families, fathers showed small pale-toothed calcifications while carrying the mutation in a heterozygous state, suggesting that a putative phenotypic expression may be

present in some heterozygous carriers. In summary, MYORG is a new major PFBC pathogenic gene, and phenotypes associated with mutations in this gene can be identified based on lineage, clinical, and radiological characteristics.

Patients with Fahr's disease often present with extrapyramidal symptoms, including dystonia, dyskinesia, and tardive dyskinesia, or neuropsychiatric manifestations such as memory loss, personality changes, delusions, hallucinations, and depression. Movement disorders, especially parkinsonism, ataxia, and cognitive impairment are the most common presentations. Seizures are rare and a few patients may not show any neurological, cognitive, or psychiatric symptoms [7].

In this case, at the beginning of the disease, the seizures of the child were characterized by unresponsive to crying, staring eyes, lockjaw, slightly blue around the mouth, foaming at the mouth, and stiffness of the limbs. The serum levels of calcium, phosphorus, and parathyroid hormone were not abnormal, there was no history of fever infection, poisoning, or special metabolic diseases (**Table 1**), and there was no special family history, which was consistent with the characteristics of Fahr syndrome and was idiopathic calcification. After that, he developed mental language and motor regression, could not sit alone, had difficulty crawling, difficulty chewing, head tilt to the left, drooling, poor diet, obvious weight loss, opisthotonos, accompanied by irritability and Shouting, and decreased sleep. The seizures of the child were manageable at the beginning, and then the medication was gradually withdrawn, but the seizures recurred again after fever, and the imaging showed the impression ological characteristics of Fahr disease, with abnormal signal shadows in the brain. In this case, there was no indication of brain calcification on the initial imaging, and after the subsequent occurrence of brain calcification, the disease showed progressive deterioration. Due to the lack of special treatment for this disease at present, the child became unable to take care of himself in his subsequent life, so his family members requested to be discharged from the hospital independently and treated with levetiracetam orally at home, but the progression of the disease could not be controlled. During follow-up, the patient died in March 2023. The follow-up during the disease and this case report have obtained the verbal consent of the child's parents.

Table 1. Laboratory tests.

Laboratory tests		
plasma ammonia	29.0 umol/L	18 - 72 umol/L
blood calcium	2.05 mmol/L	2.2 to 2.7 mmol/L
blood phosphorus	1.13 mmol	0.65 to 1.05 mmol/L
free triiodothyronine	7.09 pmol/L	3.5 to 7.7 pmol/L
free thyroxine	9.27 pmol/L	12 to 22 pmol /L
thyrotropin	5.07 mU/L	0.27 to 4.20 mU/L
Parathyroid hormone measurement	41.090 ng/ml	15 to 65 μg/L

Nicholas *et al.* [8] developed a rating scale in which calcifications in many parts of the brain (lens, caudate, thalamic nuclei, subcortical white matter, cortex, cerebellar hemispheres, earthworms, pons, and medulla) were scored from 0 (no calcification) to 5 (severe and confluent), with a maximum total calcification score of 80. Calcifications appear as areas of hyperdensity on CT scans, and maybe in the early stages with conventional MRI sequences, they are more difficult to detect, although dedicated sequences are increasingly capable of detecting intracranial calcifications. The severity of CT calcifications correlates with advancing age, with more calcifications in symptomatic patients compared with asymptomatic patients. Whereas CT is still the preferred choice for diagnostic imaging, roughly 20% of asymptomatic patients are detected incidentally on scans from imaging [9]. At the beginning of the disease, the child did not show brain calcification on imaging (**Figure 1**). 3 years after the diagnosis of epilepsy, it was found that the child appeared symmetrical calcification shadow during the re-examination of brain CT when the seizure occurred again, and the calcification gradually increased uncontrollably in the subsequent treatment (**Figure 2**).

A potential treatment for patients with Fahr's disease is bisphosphonate therapy; newer nitrogen-containing bisphosphonates, such as alendronate, primarily inhibit osteoclasts; although used in the treatment of osteoporosis, older, non-nitrogen-containing bisphosphonates initially proved to prevent ectopic calcification, and the bisphosphonate etidronate, a molecular homolog of the circulating calcification inhibitor inorganic pyrophosphate, is a molecular homolog of inorganic pyrophosphates, and based on the etidronate's treatment of vascular calcification status, the application is still more convincing in patients with calcification disorders [10].

D. Keasey *et al.* [11] human suggested that the gene SLC20A2 is regulated by vitamin D, which reduces calcification in the brain, and they found that patients with Fahr's disease are deficient in vitamin D. Vitamin D can bind to the promoter

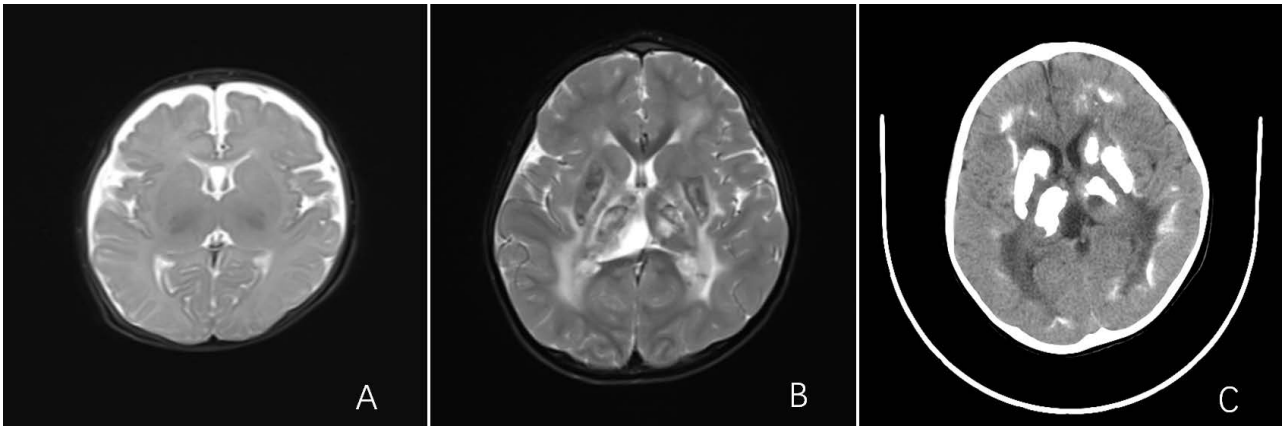

Figure 1. A: 2016 cranial MR sweep and diffusion-weighted imaging: widening of the extracerebral space in the bilateral frontal hazel region; B: 2019 cranial MRI sweep and diffusion-weighted imaging: multiple widespread abnormal signals in the medulla of the bilateral cerebral hemispheres, the thalamic region of the bilateral basal ganglia, the brainstem, and the bilateral cerebellar hemispheres suggestive of calcification; C: 2019 cranial CT sweep: 1. Multiple symmetrical calcified intracranial shadows. Patchy slightly hyperdense shadows in the brainstem.

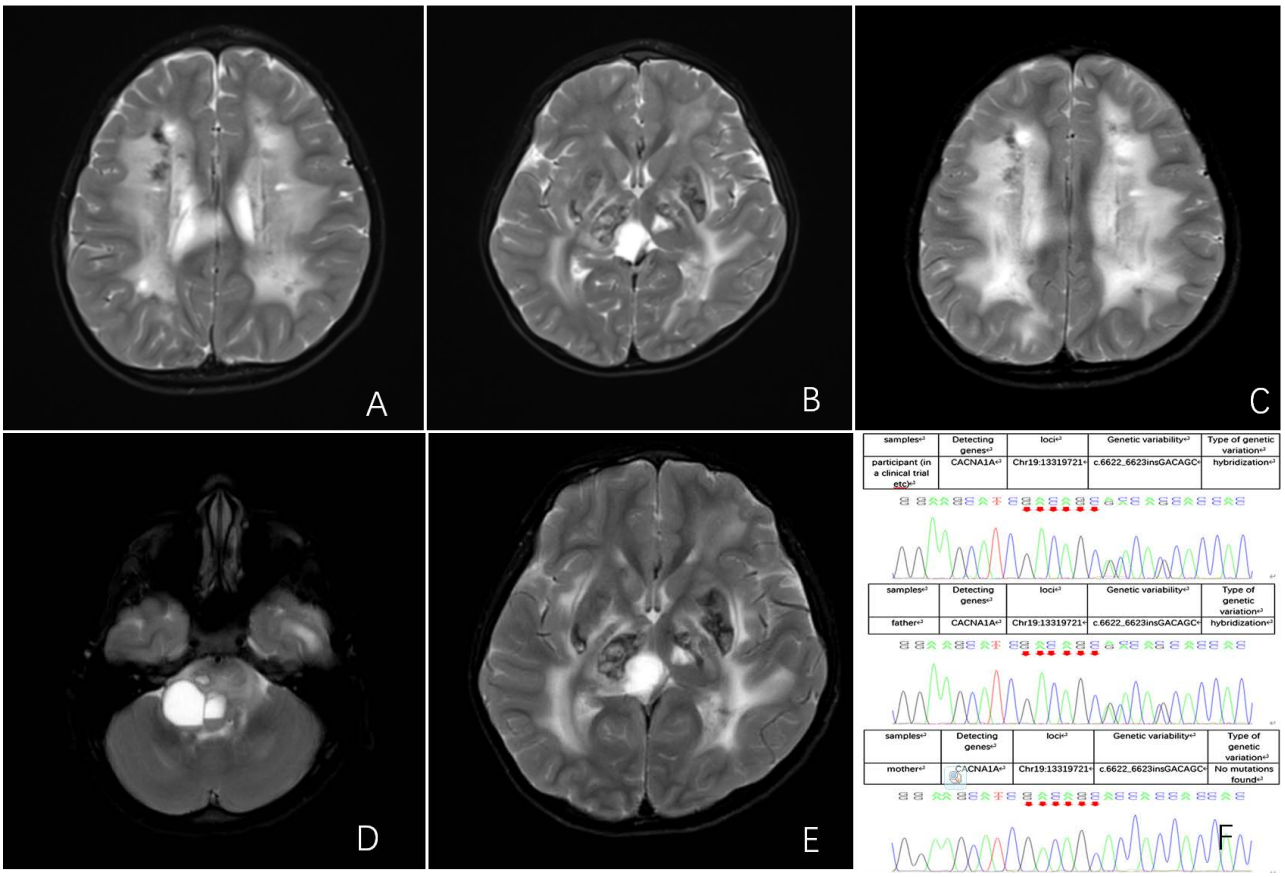

Figure 2. A and B: for 2020 cranial MRI scanning and diffusion-weighted imaging: 1. Diffuse abnormal signals in the medulla of bilateral cerebral hemispheres, bilateral basal ganglia thalamus region, brainstem, bilateral cerebellar hemispheres: metabolic disease possible, internal combination of calcification; 2. Cystic enlargement of the right ventricle, with insignificant changes above cysts to be discharged compared to the previous slice. C, D and E: for 2022 cranial MRI: Diffuse abnormal signals in the medulla of bilateral cerebral hemispheres, bilateral basal ganglia thalamic region, brainstem, and bilateral cerebellar hemispheres, with obvious progression of the brainstem lesion: metabolic disease is possible, with internal consolidation of calcification, cystic enlargement of the right ventricle, and cysts to be discharged; F: for the genetic test: heterozygous for the gene CACNA1A, de novo mutation, but the evidence of causation of this child's genetic test is insufficient, and the genetically-induced seizures are not considered.

region of the SLC20A2 gene and up-regulate the SLC20A2 mRNA, so this mechanism may be a possibility for the treatment of patients with Fahr's disease; first of all, the possibility of treating patients with Fahr's disease should be consider whether patients with Fahr disease often have vitamin D deficiency and the SLC20A2 mutation, and if the mutation is not in the vitamin D binding site, vitamin D therapy could be considered. Considering that vitamin D can cross the limited blood-brain barrier and that high levels of vitamin D may be harmful, further research is certainly needed.

3. Conclusion

At present, there are few clinical case reports and related studies on Fahr. There is no cure for this disease, only symptomatic treatment, and potential treatments still need to be researched and used in actual clinics, such as persistent status ep-

ilepticus in this case, and adherence to antiepileptic medication; although the child in this case adhered to antiepileptic medication, the progressive exacerbation of the disease could not be slowed down. Therefore, some patients with symptoms of extrapyramidal system, seizures, and limb tremor can detect the disease in time by typical imaging evidence of characteristic calcification on cranial MRI and CT. The treatment of the disease, however, requires future exploration of the etiologic and pathophysiologic mechanisms of the disease at the molecular level to develop more effective treatments as a means of improving the quality of life of patients with Fahr's disease.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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