Case study

Familial idiopathic basal ganglia calcification (Fahr's syndrome): Initial clinical neuropsychiatric presentation without corresponding neurological deficit

Abstract

Familial idiopathic basal ganglia calcification (FIBGC) orFahr's syndrome is a rare disorder with various clinical presentations which can mimic - in particular - psychiatric illness. The following case is characterized by the typical basal ganglia calcifications and presentation of neuropsychiatric symptoms indicating the first clinical presentation in the absence of a neurological deficit. As previously reported, the extent of calcification did not predict neurological impairment, however, predicted severe psychosis.

Keywords: Basal ganglia, calcification, Familial idiopathic basal ganglia calcification (FIBGC), Fahr's syndrome, neurological deficits, psychosis,extra-pyramidal symptoms

Background

FIBGCor Fahr's disease or syndrome is a rare, neurological disorder characterized by abnormal calcified deposits in the basal ganglia and cerebral cortex, and typically affects individuals in the 3rd and 4th decades of their lives[1].

Etiologically, this syndrome has been most commonlyassociated with endocrine disorders, mitochondrial myopathies, dermatological abnormalities, and infectious diseases.The understanding of the molecular genetics of this disorder still remains limited.

Clinically, a range of symptoms including neurological symptoms such as extrapyramidal symptoms, parkinsonism, chorea, or tremors, to neuropsychiatric deficits of concentration andmemory have been described.

Case Report

Mr. A. is a 57-year-old male patient with pituitary germinoma, s/p resection and radiation therapy resulting in pituitary insufficiency requiring desmopressin substitution and no previous psychiatric history. The patient presented with a loss of consciousness and myoclonic seizures, followed by an altered mental state including hallucinations and delusions, as well as agitation and aggressive behavior. Police and ambulance had to be notified and the patient required sedation for the transfer to the emergency room.The initial presentation of symptoms occurred two months before, the family reported episodes of unresponsiveness, disorientation, inability to use the computer, and play video games.

In the emergency room, the patient continued to report hallucinations like grimacing faces, angels and the Holy Ghost, as well as delusions like his marriage was not going well, being wary his wife could be wearing a mask. Furthermore, he was disoriented, anxious and psychomotor retarded.

Initial laboratory findings revealed a discrete hyponatremia (125 mmol/l) from over-administration of desmopressin and a mildly increased creatinine kinase (320 U/l). The complete blood count and electrolytes were within normal limits, including calcium, phosphorus, and magnesium. Liver function tests including the alkaline phosphatase were normal. Endocrinologically, the parathormon level was within normal limits. The cerebral spinal fluid exam yielded no abnormalities.

A computed tomography scan of the brain revealed profound calcifications of the basal ganglia bilaterally (figure 1.). An MRI confirmed the post-ischemic changes in the right superior parietal lobes and obstruction of the right carotid artery and collateralization of the middle cerebral artery. An encephalographic study revealed discrete general changes and a mild focus in the right temporal lobe. Neurologically, a documented right amaurosis and

discrete post-ischemic hemiparesis of the left lower extremity were present, and no movement disorder discovered.

The patient was admitted for further management and work-up. The hyponatremia was corrected and over the following days and the neuropsychiatric symptoms remitted. The patient was able to return home and follow-up was arranged.

Molecular genetic testing was not deemed necessary, as no family history existed.

Review of the literature

The diagnostic criteria ofFIBGC or Fahr's syndrome include 1- bilateral calcification of the basal ganglia, 2- progressive neurologic dysfunction, 3- the absence of biochemical abnormalities, an infectious, traumatic or toxic cause, and 4- a significant family history[1].

The presentation of Fahr's syndrome varies and the diagnosis remains challenging. In adults,both loss of consciousness and seizures have been reported in patientswith hypothyroid hypocalcaemia[2].Tetany can occur, which is difficult to distinguish from occasional myoclonus caused by an epileptic disorder. Further neurologic manifestations include spasticity, gait disorder, speech impairment, dementia, parkinsonism, chorea, tremors, dystonia, myoclonus, and coma, paroxysmal choreoathetosis, even of the dystonic-choreoathetotictype, as well as papilledema due to intracranial hypertension, CSF-pleocytosis, [1].

The prevalence of the neurological symptomatology in Fahr's syndrome ranges fromone third to one half of patients [3,4]. Generally, the location and extent of lesions have an effect on the manifestation; in particular in patients with dementiaor patients with extrapyramidal symptoms, more extensive lesions causemore severe symptomatology[5].

On the genetic basis, FIBGC or Fahr's disease is most commonly transmitted as an autosomal dominant trait, however, also transmitted as an autosomal recessive trait, or occurs

sporadically. A locus at 14q (IBGC1) is commonly involved,a second locus on chromosome 8, and a third on chromosome 2. On the molecular level, on chromosome 8, a loss of function-mutation in the gene encoding type III sodium dependent phosphate transporter 2 (SLC20A2) has been thought to form the genetic basis for the pathophysiology of this disease. In instances, in which no identifiable mutation or deletion in SLC20A2 can be found, the platelet-derived growth factor receptor-subunit beta (PDGFRB) might be another sequence worthwhile evaluating [1]. In addition, in patients with mutations on the platelet-derived growth factor-subunit beta (PDGFB) gene, white matter lesions have been documented in various areas of the brain [6]. Another gene implicated in FIBGC, encodes the xenotropic and polytropic retrovirus receptor 1 (XPR1), a receptor with phosphate export function[7].

The neuropsychiatric symptoms range from mild cognitive impairmentto changes in personality and behavior, to dementia and psychosis[1]. In rare presentations, frontotemporal dementia, neurofibrillary tangles and calcification of the Fahr's type have been described, however, neither extra-pyramidal symptoms nor metabolic disorder occurred. In unusual presentations of pre-senile dementia,imaging revealed calcareous depositions of Fahr's type,as well as Alzheimer's as well as frontotemporal dementia were ruled out. In addition, severe compromised attention and memory were reported in a patient FIBGCand with intact basic and higher motor function. In all of these FIBGCpatients, neurological symptoms were not present[8].

Fahr’s syndrome may also present with frontal lobe symptomatology; initially, uncontrollable bursts of laughter and crying were noted and later dysarthria, as well as progressive changes in personality and behavior [9]. In another patient with disturbed selective attention and cognitive flexibility, verbal perseverations, and declarative memory deficits, a reduced glucose uptake in the Positon Emission Tomography (PET) scan was not only confined to the

putamen and globus pallidus, but extended to the bilateral temporal and parietal cortices, corresponding to the neuropsychological deficits observed. Functional imaging revealed that the changes preceded cerebral atrophy in Fahr's syndrome and reflected deficits in functional circuits involving the basal ganglia and the frontal, parietal and temporal lobes[10].

The current understanding indicates that the extent of calcification does not predict neurological impairment, however, predictsneuropsychiatric disorders.

Diagnostically, recommended imaging includes cranial CT or MRI and plain radiography of the skull. Further investigations of interest include blood and urine testing for hematologic and biochemical indices.

Calcification of the basal ganglia is an incidental finding in about 0.3%-1.5% of brain CT scans, especially in elderly individuals. Microscopic calcifications have been observed in the globuspallidus and dentate nucleus in up to 70% of autopsy series. However, calcifications confined to this area usually do not cause clinical symptomatology[1].

Endocrine disorders, in particular parathyroid disturbances such as hypo- and hyperparathyroidism have been most commonly associated with Fahr's syndrome and vitamin D, crucial for the calcium metabolism and its homeostasis, has significant implications[1].

To date, no curative approach exists for Fahr's syndrome;as a consequence, management strategies mainly focus on symptomatic relief and elimination of causative factors.Limited evidence suggests that early diagnosis and management can reverse the calcification process leading to complete recovery of mental functions.Various treatments have been administered to Fahr's patients in an attempt to achieve stabilization and remission. These approaches base on pathophysiological theories resulting in the proposal of small scale clinical experiences.

Conclusion

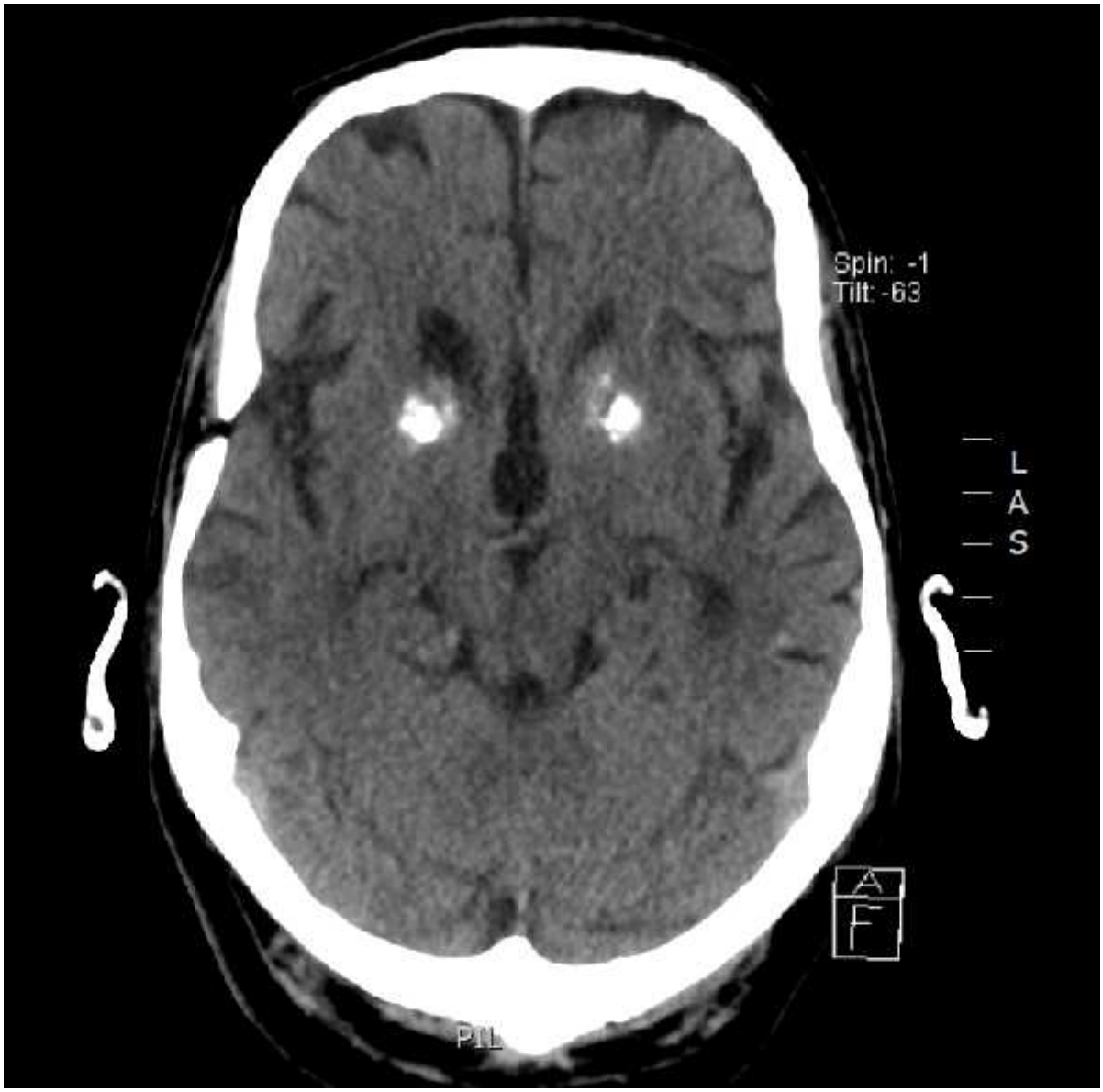
In summary, this case of FIBGC or Fahr's syndrome initially presenting with psychosis in the absence of neurological deficits, in particular movement disorder, and dementia, which, to date, has not yet been reported in the literature and adds to the evidence that the typical calcification predicts neuropsychiatric symptomatology in contrast to neurological deficits. Since other etiologies contributing to the presentation have been ruled out and the typical calcifications were present, this case illustrates the necessity for a heightened awareness of potential Fahr's syndrome and the obligatory requirement of cranial imaging in order to confirm the diagnosis.

Conflict of interest: None

Patient Consent

The patient consented to the publication of this case.

Figure 1. Cranial computed tomography. Profound calcifications of the basal ganglia bilaterally as typically seen in FIBGC or Fahr's syndrome.



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