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(CASE REPORT)

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Case report: Intracranial calcifications in an 11-year-old girl: diagnostic approach

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Abstract

In childhood neurological pathology, the frequency of intracranial calcifications varies according to etiology. In fact, intracranial calcifications can be a worldwide finding in some diseases, in others it is a habitual occurrence, and in some it is only an occasional finding. The discovery of cerebral calcifications in children is a challenge for the pediatric neurologist, raising a number of questions and prompting a search for an underlying cause. Calcifications of the basal ganglia represent a distinct radiological entity. When described comprehensively and contextualized within the clinical framework, these calcifications permit the identification of etiologies that range from genetic origins to secondary causes.

The aim of this article is to emphasize the importance of a well-established reasoning process that takes into account the age of calcification discovery, the clinical context, the physical examination, and the scannographic characteristics of the calcifications in developing a diagnosis. Here we describe a case of basal ganglia calcifications in a 11-year-old girl, in order to suggest a diagnostic approach to this type of calcification in children.

Keywords: Intracranial calcifications; Basal ganglia; Phosphocalcic balance; Fahr's disease; Case report

1. Introduction

Intracranial calcifications are a common finding in children and raise questions about their origin. It is important to be able to recognize their radiological characteristics (nature and location, white matter anomaly associated), and their age of onset in order to identify the cause. The origin of these calcifications varies from physiological anatomy to congenital, endocrine, vascular, infectious, genetic and neoplastic pathology. A rigorous etiological investigation, incorporating both clinical history and imaging data, helps guide the diagnostic. Early recognition and intervention are key to improving outcomes for children with intracranial calcifications and their associated conditions.

2. Case presentation

An 11-year-6-month-old girl presented to the consultation department with headaches. She has no significant neonatal history and normal psychomotor development. She was admitted to the hospital at the age of 3 months for investigation of an afebrile seizure. The seizure, lasting five minutes, involved generalized clonic movements, eye rolling, and loss of consciousness, without any postictal deficit. Her clinical examination, including neurological, was normal. An EEG showed no epileptic abnormalities, and a CT scan revealed no neurological or vascular malformations. The patient was treated with an antiepileptic: Valproic Acid, discontinued after two years.

No history of chemotherapy or radiotherapy noted. No family history of neurologic nor psychiatric conditions was reported.

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One year prior to her current consultation, she developed moderate headaches, not associated with fever, vomiting, or insomnia, and relieved by analgesics. They can occur at any time of day, worsened by physical exertion. A CT scan performed due to these chronic headaches revealed multiple bilateral, symmetrical, hyperdense calcifications in the striatum, lenticular nuclei, and dentate nuclei. Additional linear and round calcifications were noted in the bilateral frontoparietal and right occipital subcortical white matter. (Fig.1, A)

We were therefore faced with cerebral calcifications revealed by chronic headaches. No neurological or extra-neurological abnormalities were found on the physical examination.

These calcifications had the following characteristics:

- Location: Basal ganglia and white matter
- Distribution: bilateral
- Isolated: No brain malformations associated

As always, radiological data must be interpreted in the context of the clinical history, particularly the age of presentation, and the exam findings.

It is important to emphasize that basal ganglia calcification is infrequent in the pediatric population. Therefore, in pediatric neurology practice, the presence of basal ganglia is regarded suspicious and should prompt a comprehensive evaluation.

Our attitude in searching for an etiology was as follows:

The first step was to eliminate a phosphocalcic disorders such as hypoparathyroidism, hyperparathyroidism and pseudohyperparathyroidism. A level within the normal range for calcium, phosphorus, and parathyroid hormone has allowed for the exclusion of Fahr's syndrome.

Infections responsible for cerebral calcifications are seen in newborns and infants (TORCH syndrome), but HIV can be responsible for clinical manifestations revealing themselves at an older age. It was therefore essential to rule out HIV infection. Indeed, HIV viral serologies were negative.

The patient's female sex and age should suggest systemic lupus erythematosus, but the absence of clinical signs in favor of this diagnosis and the negative autoantibody and Cerebrospinal fluid analysis ruled it out.

The absence of intoxication exposure allowed for the immediate exclusion of a toxic etiology.

A large number of hereditary diseases can be responsible for bilateral calcifications of the basal ganglia such as: MELAS (mitochondrial encephalopathy), Kearns-Sayre, Cockayne syndromes, Aicardi Goutières, Coat’s disease. Normal psychomotor development and the absence of neurological and extra-neurological signs meant that these diagnoses, which are rare in pediatrics and often manifest at a younger age, could not be evoked.

A complementary MRI scan shows:

Basal ganglia signal abnormalities in the head of the left caudate nucleus, bi-pallidal, posterior arm of the left internal capsule, hypointense on T2 and FLAIR sequences.

At the supratentorial area : at the level of the left caudate nucleus, bi-pallidal, posterior arm of the left internal capsule, and at the right capsulothalamic level, there is an asignal on the SWI sequence, and an hypersignal in T2 and FLAIR. (Fig.1, B)

The diagnosis of Primary Familial Brain Calcification (PFBC) was established following the exclusion of alternative etiologies for bilateral basal ganglia calcifications.

A genetic study to support this diagnosis is currently underway.

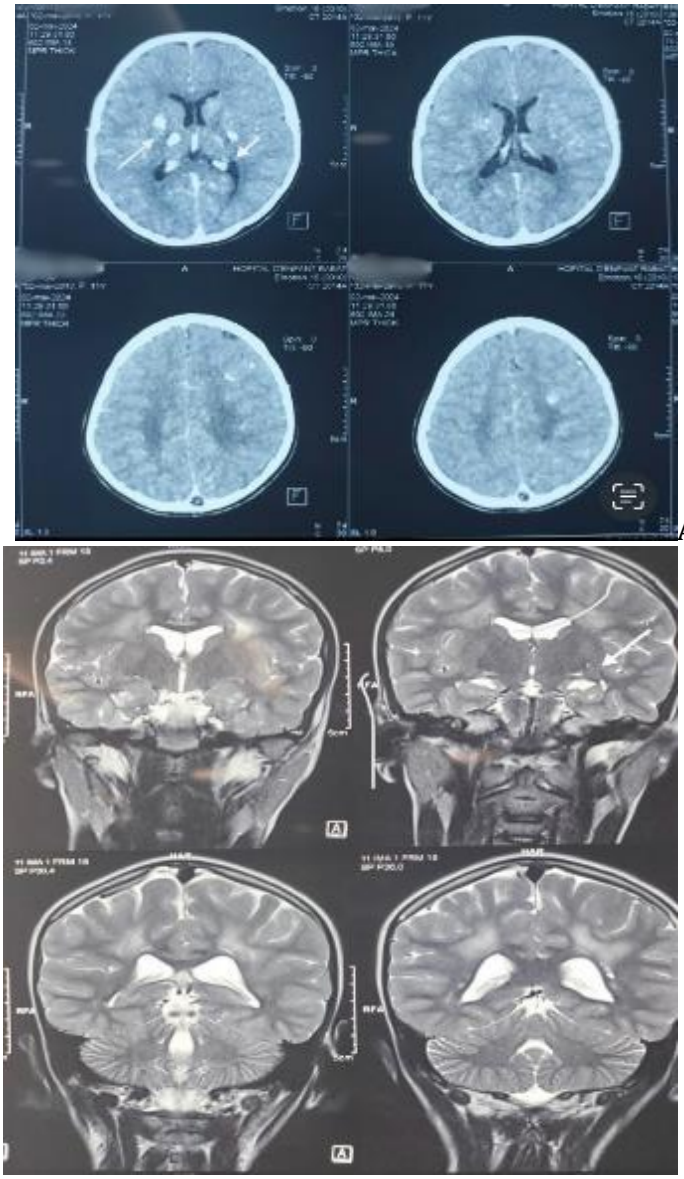

Figure 1 A Injection-free CT scan showing bilateral asymmetric calcifications of the basal ganglia.

B Frontal images on MRI: Signal abnormalities in the basal ganglia and dental nuclei, hypersignal in T2 sequence.

3. Review of literature and discussion

Intracranial calcifications (ICC) as the name suggests, are defined by calcium deposits in the cranial cavity, and is usually taken to mean calcification within the parenchyma of the brain or its vasculature. Easier access to brain imaging in recent years, and wider indications for brain CT in children have made the visualization of brain calcifications more frequent than ever before. Their prevalence ranges from 1% in young individuals to up to 20% in elderly.[1]

They can have either physiological or pathological origin. Physiological calcifications, also known as age-related calcifications, are typically seen in adults. In childhood, they can happen as children grow older. In fact, calcifications in the brain are not expected in neonatal and infantile stages especially before the age of 5 years old. In a study of 500 patients in their first decade, Whitehead et al discovered that 40% had physiologic calcifications, with 97% being older than 5 years of age. Calcifications were found to be more common in the choroid plexus followed by the habenula and pineal gland. [2]

The pathological causes of intracranial calcifications can be subdivided into 5 main groups: infectious, congenital, metabolic, neoplastic and vascular. The various etiologies of intracranial calcification in pediatrics are recapitulated in Table 1.

The discovery of intracranial calcifications on brain imaging, whether incidental or secondary to neurological symptoms, should lead to a thorough etiological investigation in children. The location and characterization of intracranial calcifications (IC), the age of onset, and associated neuroimaging features are the three key elements on which the diagnostic assessment is based.

The case we have reported concerns a particular type of intracranial calcification: calcifications of the basal ganglia. We will therefore focus on this type of calcification in the following discussion to analyze the reported case.

The term "calcifications of the basal ganglia" refers to the calcification of structures including the caudate and the lentiform nuclei, the latter is composed of the putamen and globus pallidus. This term also includes calcifications in the thalamus, substantia nigra, and subthalamic nuclei, which are integral components of the extrapyramidal system within the deep gray matter. [3]

Basal ganglia calcifications are frequently visible on neuroimaging particularly in the Globus Pallidus, and could be an accidental finding in 5,5 % to 20% of asymptomatic individuals over 50 years old undergoing computed tomography scan.[4] This type of calcification is considered physiological and increases with age, according to Yamada M et al.[5] However, Such calcifications should not be present in children under 13–15 years of age. [6] Consequently, the existence of basal ganglia calcification, in pediatric neurology practice is considered suspect and prompts the search of a potential underlying neurological pathology. The lesions may be unilateral or more commonly bilateral.

The first recorded description in the literature is by Delacour in 1850. He reported the presence of vascular calcifications in the basal ganglia in a 56-year-old man who had tremor and lower extremity stiffness. [7] Five years later, Bamberger described the histopathological entity of calcifications in the thinner cerebral vessels in a woman who had mental retardation and seizures. [8] It wasn't until 1930 that the German pathologist Theodore Fahr identified this disease in a 81-year-old man with dementia symptoms and in which calcifications were found in the cerebral blood vessels during autopsy.

Bilateral calcifications of basal ganglia are reported under various terminologies in the literature, often wrongly referred to as Fahr type calcifications. From 1939 to 1997, thirty-five names were reported in the literature, making the classification and understanding of this pathology misleading. Indeed, the nosological classification of this specific radiological entity remains poorly defined. In 2005, Manyam suggested a classification based on the anatomical sites of calcification, distinguishing three types of calcification: bilateral striopallidodentate calcinosis, striopallido ("basal ganglia") calcinosis, and dentate (cerebellar) calcinosis and their respective etiologies. [9] In 2019, Donzuso and al proposed another interesting classification that classify primary, secondary and genetically determined forms. [4]

Primary forms refer to Primary familial basal ganglia calcification (PFBC) (previously known as idiopathic basal ganglia calcification or Fahr disease), characterized by symmetrical bilateral striopallidodentate calcinosis. They can be subdivided into three forms: 1. Autosomal dominant; 2. Familial; 3. Sporadic. The autosomal dominant form involves different people in the same parental line, and seems associated mainly to chromosome locus 14q48 mutation (IBCG1). Other genes have been incriminated IBCG2, SLC20A2, PDGFRB, PDGFB, XPR1. A familial form is identified when multiple members of the same family are affected. And it is considered sporadic when it affects only one individual within a family. [10,11]

Secondary forms, grouped by some authors under the name of Fahr syndrome, are predominantly related to phosphocalcic endocrine disorders, with additional etiologies including infectious agents (HIV, CMV, toxoplasmosis, tuberculoma), autoimmune conditions (systemic lupus erythematosus), hypoxic-ischemic brain injury and toxic exposures (carbon monoxide, lead, methotrexate). However, some authors consider that Fahr's syndrome includes Fahr's disease as well as secondary causes of striopallidodentate calcinosis.[12]

Lastly, other conditions are related to genetic determinants, and occur mainly with systematic signs or symptoms. We cite pseudohypoparathyroidism, Aicardi-Goutières syndrome, Cockayne syndromes (CS type I and type II), Krabbe disease, mitochondrial diseases, Canavan disease, neurodegenerative conditions (NBIA, PKAN). [13]

CT scanning is the most common method to detect calcifications in the basal ganglia. It is also superior to MRI for detecting calcification according to the American College of radiology appropriateness criteria. [14]

Calcifications in the basal ganglia are therefore easily detected by brain scans. However, the etiologies are diverse. Identifying this anomaly should start a diagnostic workup based on key points. Considering that idiopathic or secondary hypoparathyroidism is prevalent and easily recognized, phosphocalcic disorders should be excluded. When the clinical context is suggestive: presence of developmental and growth retardation, particular facial features, neurosensory impairment such as in Cockayne syndrome, cerebral calcifications are not the revealing feature of the disease and the diagnosis is often already made. The history and the specific blood tests are essential to exclude drug-induced or poisoning-related brain calcifications, and may also help exclude central nervous system (CNS) infection, radiation exposure, or a metabolic cause. [15] When the secondary causes are excluded, molecular genetic testing should be considered in view of Fahr disease. When the family history is suggestive, we think of an autosomal dominant or familial form. If not a sporadic form is the most likely diagnosis.

We propose a diagnostic approach for basal ganglia calcifications in children. (Fig.2).

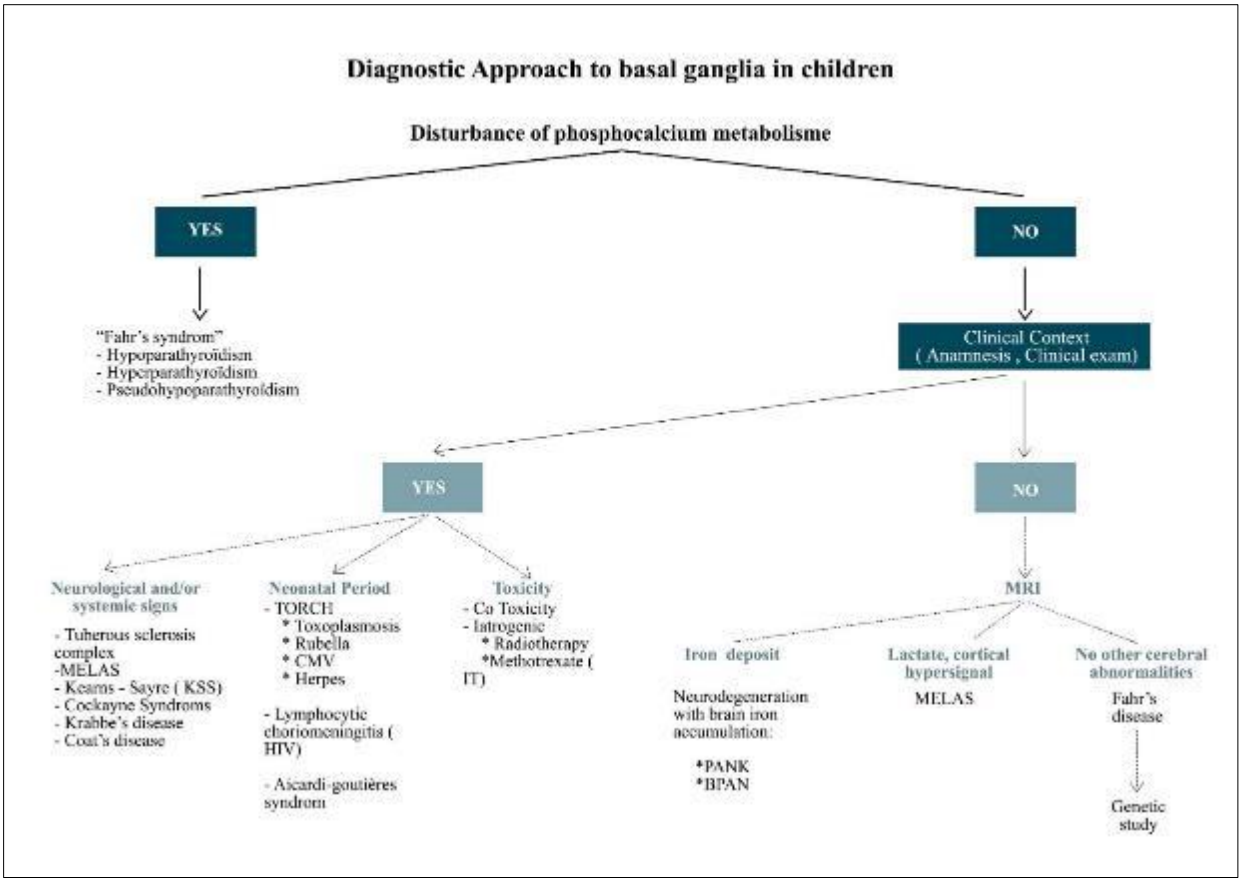

Figure 2 Diagnostic approach to basal ganglia in children.

Table 1 Table summing up etiologies of intracranial calcifications in children (non-exhaustive list).

Types of calcifications	Diagnosis	Location (L), and neuroimaging description (D)	Age	Symptoms / Clinical context
Physiological		L: Habenula, Pineal gland, Choroïd plexus, Dura mater (exclusively in the tentorium and falx cerebri), Bilateral basal ganglia D: Typically small and curvilinear, punctiform	Absent in younger than 3 y.o Increases with age	Incidental finding
Pathological	CMV		0-3 months	

Neonatal infection		L: Basal ganglia, Periventricular, Brain parenchyma D: Thick, chunky, fine or punctuate		Microcephaly, low birthweight Chorioretinitis, hepatosplenomegaly
	Toxoplasmosis	L: No ventricular predilection , diffuse D: Large, subtle, coarse and chunky	0-3 months	Hydrocephalus, hepatosplenomegaly Seizures chorioretinitis
	Rubella	L: Periventricular, Basal ganglia, Thalamus	0-3 months	Developmental delay, Congenital heart disease, Cataracts, Microphthalmia,
	Herpes	L : Basal ganglia, Periventricular white matter, Thalamus, D: progressive and diffuse	0-3 months	Microcephaly, chorioretinitis, skin lesions, myocarditis, hepatosplenomegaly
	HIV	Symmetrical in the basal ganglia and subcortical matter	3 months and 10 years	Neurodevelopmental disability, seizures, hydrops, microcepaly
Disorders with metastatic calcification	Parathyroid disorders : Hyper, hypo and Pseudohypoparathy-roïdism	L: Symmetrical basal ganglia and thalamic calcification D: Deep gyral	All ages	Short stature dysmorphic features
	Carbonic anhydrase type 2 deficiency (renal tubular acidosis)	D: Similar to hypoparathyroïdism	Adolescence	Developmental delays, seizures Glaucoma Osteopetrosis
Congenital syndromic causes	Tuberous sclerosis complex	Found in 88 to 93 of subependymal nodules	Congenital (Neonatal)	Typical skin lesions Seizures Hamartomas heart, lungs, brain
	Sturge Weber Syndrome	Tram track calcifications typically appearing as gyriform calcification	First decade	Angiomas face Glaucoma Seizures
	Aicardi-Goutières Syndrome (Pseudo TORCH)	Spot like calcification: in the basal ganglia and deep white matter	4 months to 2 years old (Infants or Neonatal)	Encephalopathy with mental abnormalities, seizures, progressive microcephaly
	Cockayne Syndrome	Bilateral rock or spot calcifications at the level of the basal ganglia with or without gyral calcifications	Early childhood 3 to 8 years old	Increased spasticity, ataxia, tremor, hearing and visual loss

	Krabbe disease	Internal capsule and corona radiate	4 months to 2 years old	Irritability, feeding difficulty, Flaccidity and bulbar palsy
	MELAS	Bilateral calcification of basal ganglia	Middle childhood 9 to 11 years old	Epilepsy strock like Psychiatric disorders or learning disabilities
	Down syndrome	Typically in the basal ganglia and particularly in the globus pallidus	Early childhood	Facial dysmorphia, intellectual delay, heart disease
	Fahr's Disease	symmetrical, involving the caudate, putamen, globus pallidus, thalamus, deep cortex and dentate.	Middle childhood and adolescence	Progressive neurologic dysfunction, which generally includes a movement disorder and/or neuropsychiatric manifestations
Neoplastic	Craniopharyngioma	Thin and circumferential or chunky.	Early childhood 3 to 8 years	Intracranial hypertension syndrome Weight loss Neurological symptoms
	Medduloblastoma	Tiny scattered dots or clumped	Early childhood 3 to 8 years	
	Glioma	Mural calcified nodule	Middle childhood 9 to 11 years	
	Germ cell tumors	Heterogenous	Adolescence	
Inflammatory	Systemic lupus erythematosus	Diffuse calcification over Basal Ganglia, centrum, semiovale and cerebellum mainly	Adolescence	Diverse clinical features

4. Conclusion

Calcifications of the basal ganglia are frequently detected on brain scans. In children, they are often abnormal and require an etiological assessment, even in the absence of symptoms. A disturbance in phosphocalcic metabolism will be investigated in the presence of bilateral involvement. If this assessment is normal, in addition to the clinical examination and the study of the medical history, the analysis of the topography of the calcifications and the MRI sequences will provide diagnostic guidance. Fahr's disease is a diagnosis of elimination that must be confirmed by a genetic study.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no competing interest.

Funding Declaration

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Statement of informed consent

A written informed consent was obtained from the patient's parents.

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