

# Idiopathic Basal Ganglia Calcifications in a Patient with Pediatric Onset Multiple Sclerosis

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## Abstract

Idiopathic Basal ganglia calcification, also known as Fahr's Disease, has been associated with multiple etiologies. There have been case reports of basal ganglia calcifications in a number of patients with multiple sclerosis [MS]. Earlier hypothesis suggested the co-occurrence to be more than coincidental and might indicate an underlying overlapping pathophysiology of mitochondrial dysfunction. However further studies had failed to show higher prevalence of deep grey matter calcifications in MS individuals compared to healthy controls. Multiple sclerosis is known commonly to have a higher rate of co-existing autoimmune conditions (i.e., celiac disease, sarcoidosis, and type 1 diabetes etc.). In this case report we present an 11-years-old boy, known type 1 diabetes mellitus, who presented with a clinically isolated event in the form of cervical transverse myelitis. Neuroimaging fulfilled the McDonald criteria for dissemination in time and space, and he was diagnosed as clinically defined multiple sclerosis. Coincidentally his Brain CT showed symmetric globus pallidus calcification. The precedence of basal ganglia calcification brings into question the effects of early subliminal neuroinflammation on mitochondrial dysfunction and calcium deposition, and why it affects certain individuals. Previous studies had observed no correlation between multiple sclerosis and basal ganglia calcification when compared to the general population. The spectrum of mitochondrial dysfunction is known to be heterogenous, and may co-exist in Fahr's disease or in MS. Further longitudinal studies for this cohort may help identify if basal ganglia calcification may serve as an early prognostic marker for disease progression in the subsequent decades.

**Keywords:** Multiple Sclerosis, Fahr Disease, Intracranial Calcifications, Basal Ganglia, Neuroinflammation.

## Introduction

Pediatric Multiple Sclerosis (MS) represents 2.7 - 5% of MS patients, 1% of whom whose onset is before the age of 10 year (1). Although having an earlier onset of disease, their progression in motor disability is slower, reaching an EDSS of 4.0 in their 40s (2). In contrast, a third to half of children with multiple sclerosis will have cognitive impairment and psychiatric disturbances. MS is a multifactorial disease, with genetic, environmental, immune, and nutritional factors involved. T-cell and macrophage, and complement driven inflammatory process, along with humoral immune response involving oligoclonal bands, plasma cells, plasma blasts, and complement deposition (3). Other autoimmune conditions are known to exist as comorbidities in patients with MS such as type 1 diabetes, inflammatory bowel disease, etcetera (4-5).

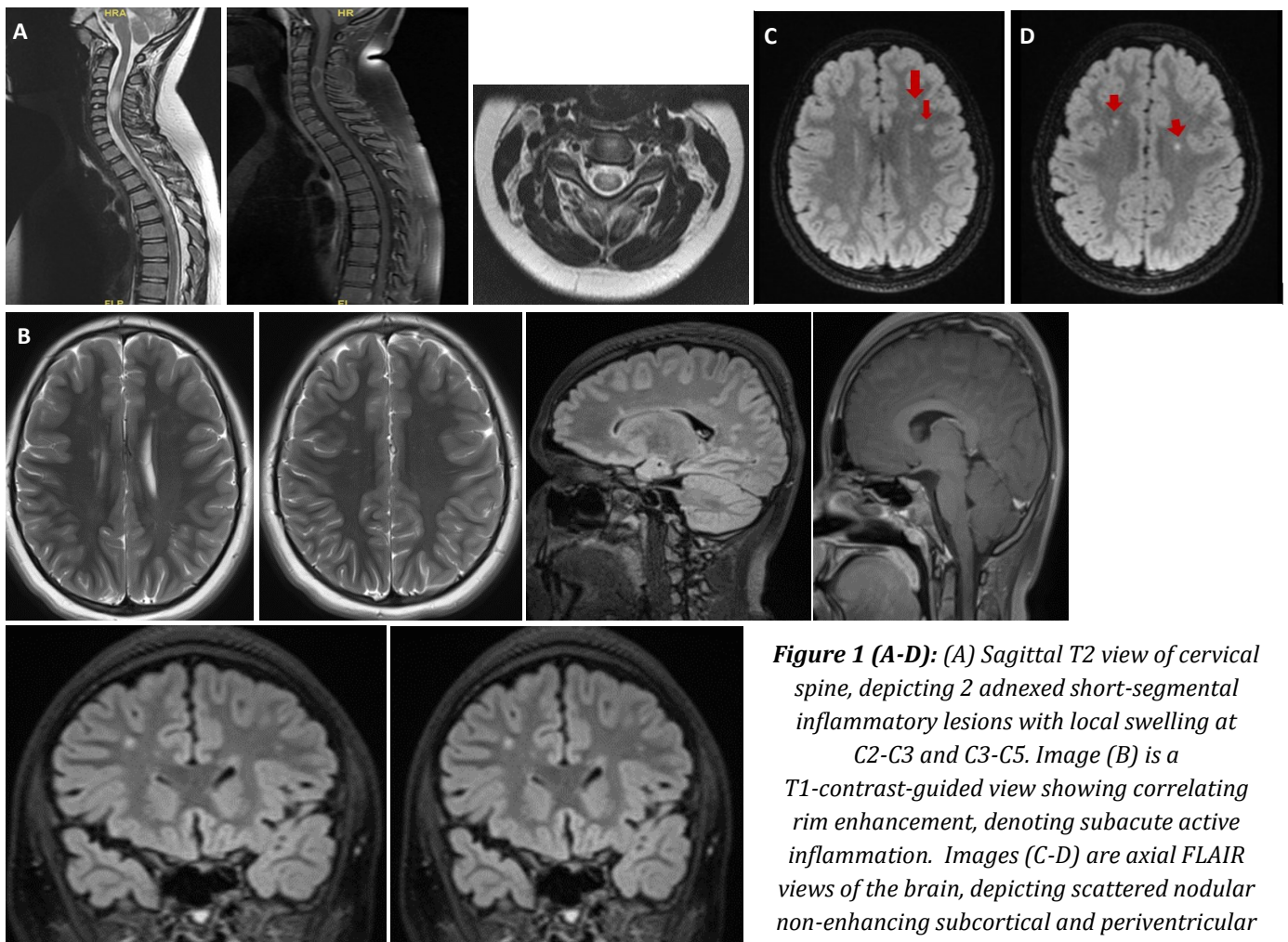
Idiopathic basal ganglia calcifications (IBGC), also known as Fahr's disease, is an uncommon disorder of sporadic or familial nature. It is characterized by symmetric basal ganglia calcifications that may involve centrum semiovale and thalami. They can be clinically silent or symptomatic. Its clinical features may include psychiatric disturbances, extrapyramidal movements disorders, intellectual disability, and seizures (6).

Previous case reports of the simultaneous occurrence of the two disorders have hinted at a shared underlying pathophysiology, namely that of mitochondrial dysfunction, noted prominently in the primary and secondary form progressive multiple sclerosis, denoting the neurodegenerative effects of chronic inflammation on mitochondrial functions, caused by glutamate excess, and raised reactive oxidative stress (ROS). Similar observations however were not appreciated in the relapsing forms of MS. This case report further explores the hypothesis that the co-existence of conditions with overlapping pathophysiology may precipitate basal ganglia abnormalities. Whether the finding bears any long-term implications on quality of life has yet to be determined.

**Case Presentation**

An 11-year-old, right-handed boy, with type 1 diabetes since early childhood, presented with subacute onset proximal weakness of extremities, impairing his ambulation. There were no associated sensory symptoms, and no sphincter dysfunction. There were no observed involuntary movements. Upper respiratory viral prodromal symptoms preceded the clinic event ten days earlier. His perinatal history was unremarkable. Family history was pertinent for maternal history of type 1 diabetes, and for multiple sclerosis in one maternal uncle. Neurologic assessment at presentation showed limited antigravity strength in both proximal arms and reduced anti-resistance power in both proximal lower extremities. Proprioception and vibration sense were impaired in both upper and lower extremities, Romberg’s sign was positive, with upgoing plantar responses (EDSS=2.5).

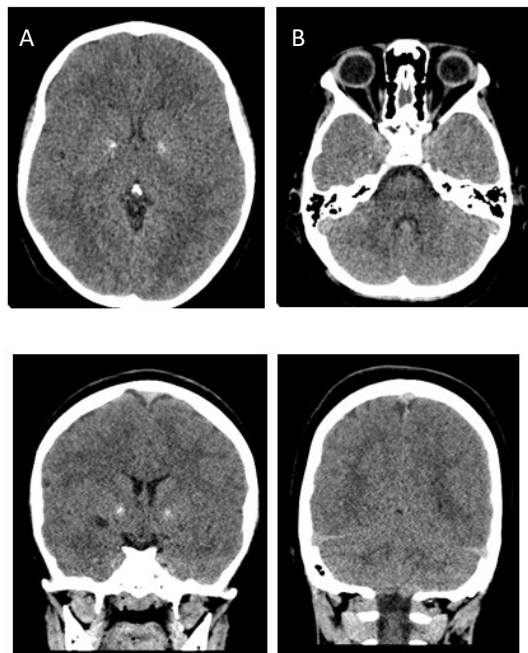
Brain and spine MRI revealed a prominent upper cervical short segmented inflammatory lesions with active enhancement and swelling at C2-C3 and C3-C-5 segments, with ring enhancement. Additional short segmented lesions were noted at lower thoracic and conus medullaris region. Brain MRI showed silent non-enhancing multiple T2 nodular demyelinating lesions, distributed in subcortical, periventricular regions (Figure1).



**Figure 1 (A-D):** (A) Sagittal T2 view of cervical spine, depicting 2 adnexed short-segmental inflammatory lesions with local swelling at C2-C3 and C3-C5. Image (B) is a T1-contrast-guided view showing correlating rim enhancement, denoting subacute active inflammation. Images (C-D) are axial FLAIR views of the brain, depicting scattered nodular non-enhancing subcortical and periventricular T2 hyperintensities (arrows).

T1 contrast view of active subcortical left medial temporal lesion enhancement. Perpendicular demyelination to lateral ventricular axis and callosal junctions, correlating mild t1 hypointensity on T1 views.

CT brain done initially in the emergency unit, had revealed a coincidental finding of symmetric punctate hyperdensities, consistent with calcifications in globus pallidi (Figure 2).



**Figure 2.** (A) Axial CT Brain: shows Bilateral globus pallidus calcifications. (B) shows normal dentate nuclei.

Autoimmune panel revealed positive CSF oligoclonal bands and positive serum transglutaminase antibody, and negative Myelin oligodendrocyte Glycoprotein (MOG) and Aquaporin-4 antibodies. Rheumatologic and Vasculitis panel returned with initial elevated ESR and CRP, elevated C4, normal C3, elevated antinuclear antibody (speckled 1:160), with negative Anti-DS-DNA titers, and negative ENA and ANCA profiles. C-reactive protein normalized on subsequent testing. Metabolic and endocrine tests, including parathyroid hormone, vitamin D and calcium levels were normal, except for hemoglobin A1C which was elevated (7.5%). The whole exome sequence for genetic factors yielded no pathogenic variants.

For his chief presentation, he received intravenous immunoglobulin (2 gm/Kg), and a 5-day course of Solumedrol pulse steroid therapy (30 milligram/kg/day), with subsequent oral steroid tapering course spanning 3 weeks. He had shown remarkable clinical response and returned to his baseline during follow-up during the subsequent 12 months from discharge (EDSS=0).

As he was meeting the McDonald Criteria (2017) for DIT and DIS, his diagnosis for multiple sclerosis was confirmed, and he started on an injectable disease modifying therapy [DMT], Interferon Beta-1-a (Avonex), administered 30mcg intramuscular weekly. Therapy was switched 24 months later to fingolimod due to clinical and neuroradiological evidence of relapse.

## Discussion

This patient, known for type 1 diabetes since early childhood, was otherwise asymptomatic, with normal development until the time of his first clinically isolated event (CIS). His CT findings of bilateral globus pallidus calcification was coincidental. He had no extrapyramidal signs, and no intellectual disability. IBGC is term used to label a heterogeneous group of disorders that characteristically present with symmetric basal ganglia calcifications, commonly in lentiform nuclei, thalami, subcortical white matter, internal capsules, and dentate nuclei. Although the underlying pathogenesis is not fully understood, it is believed to result from transportopathy in which defective iron transporters and subsequent free radicals production eventually lead to damaging sequelae with resultant calcifications that usually start intramurally within the blood vessels and extends into the neighboring perivascular spaces, followed subsequently by a vicious cycle of damage and calcifications. Other minerals transporters have also been reported to likely have a role in the pathophysiology of this syndrome (7-8). IBGC is not monogenic.

Multiple sclerosis has both an inflammatory and a neurodegenerative underlying pathophysiology. The former is associated with the inflammatory cellular and humoral responses, and involvement of chemokines, invoking in the process immune cell migration, and perivascular inflammation resulting in injury. Subsequent axonal and brain atrophy would result. Vascular endothelial dysfunction in the blood-brain barrier plays a pivotal role in the pathogenesis of MS, that may precipitate calcium deposition (9). Mitochondrial dysfunction may in turn result from inflammatory reactions. This can lead to disruption of calcium homeostasis, due to the high metabolic demand in basal ganglia. As basal ganglia have profuse mitochondrial volume, they are more liable to calcium deposition (10).

Diabetes mellitus may lead to basal ganglia disease (striatopathy), in both type 2 and type 1, being rare in the latter. In both cases, chronic hyperglycemia, and/or non-ketotic hyperosmolar hyperglycemia, may result in vascular and metabolic injury (11-12).

## Conclusion

In conclusion, the triple coexistence of IBGC, MS and type 1 diabetes, is quite rare, and in our opinion, has never before been presented in the literature. One case of MS and IBGC having been reported only once before in the pediatric population. The three conditions share in common the heterogeneity of underlying etiologies. Their underlying inflammatory, metabolic, abnormal mitochondrial/neurodegenerative pathophysiology leads to higher susceptibility for abnormal neuronal calcium metabolism in the sensitive pallidal regions. Further longitudinal studies for this group of patients are needed to observe for pertinent prognostic implications on quality of life during the subsequent decades.

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## Declaration of Conflict of Interest

The authors declare that there is no conflict of interest.

## Ethics Approval

Our institution does not require ethical approval for reporting individual cases.

## Informed Consent

Verbal informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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