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## Case Report

# MRI of 3-hydroxyisobutyryl-CoA hydrolase (HIBCH) deficiency ☆,☆☆

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## ABSTRACT

3-Hydroxyisobutyryl-CoA hydrolase (HIBCH) deficiency is a rare mitochondrial disorder of valine metabolism which may present with motor delay, hypotonia, ataxia, dystonia, seizures poor feeding, and organic aciduria. Neuroimaging findings include signal abnormalities of the deep gray matter, particularly the globus pallidi, and cerebral peduncles. We report a 15-month-old male patient with HIBCH deficiency who presented with paroxysmal tonic upgaze of infancy, motor delay, and hypotonia. MRI revealed characteristic bilateral, symmetric signal abnormalities in the basal ganglia and a mutation in HIBCH was confirmed with whole exome sequencing. HIBCH should be a consideration in patients with Leigh-like features, especially if neuroimaging changes primarily affect the globus pallidi. Recognition of this pattern may help guide targeted testing and expedite the diagnosis and treatment of this rare disease.

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## Introduction

3-Hydroxyisobutyryl-CoA hydrolase (HIBCH) deficiency is a rare mitochondrial disorder caused by mutation of the HIBCH gene. This mutation leads to defective valine catabolism

and buildup of toxic metabolites, which inhibit normal mitochondrial function [4,5]. HIBCH deficiency is inherited in an autosomal recessive fashion with a predicted incidence of 1 in 127,939 among East Asians and 1 in 551,545 in Europeans [3]. Only 21 cases of this disorder are reported in the literature to date [1-3,6-16]. Patients generally present

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during the first year of life with delayed motor development or secondary regression following an infection or other illness [2,3,7,8,10,12,13,15,16]. Symptoms include motor delay, hypotonia, ataxia, dystonia, seizures, poor feeding, failure to thrive, infantile spasms, organic aciduria, and elevated hydroxy-C4-carnitine [1,2,3,12-16]. Brain MRI often shows symmetric signal abnormalities of the globus pallidi and cerebral peduncles and may demonstrate white matter atrophy [1,2]. HIBCH deficiency is ultimately confirmed through genetic testing, but neuroimaging can provide critical diagnostic information [1].

The clinical presentation of HIBCH deficiency overlaps with that of other Leigh-like syndromes and mitochondrial diseases, resulting in diagnostic challenges and misdiagnosed patients [1,10]. Here we report a male patient who presented in infancy with several mild, nonspecific symptoms that evolved over time. He was ultimately found to have bi-allelic variants in the *HIBCH* gene. The case illustrates specific neuroimaging findings that may aid in the diagnosis of HIBCH deficiency. More broadly, this case demonstrates how neuroradiologic data can help clinicians optimize diagnostic testing for rare disorders.

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## Case report

A Latino male patient presented at 2 months of age, following an uncomplicated, full-term pregnancy to healthy, nonconsanguineous parents. At first presentation, the patient had a reported brief, resolved, unexplained event at an outside hospital with cyanosis and a short period of unresponsiveness. Electroencephalogram (EEG) and MRI were normal, and the patient was discharged. At 10 months of age, the patient presented to the emergency room with 2 weeks of intermittent upward eye deviation, which was concerning for seizure activity. Repeat MRI and video EEG were normal, and the patient was presumptively diagnosed with tonic upgaze of childhood.

At 15 months of age, the patient presented to the emergency department again with dehydration, poor feeding, lethargy, abnormal movements, moderate respiratory distress, and severe acidosis. Labs were positive for low bicarbonate, elevated ammonia, elevated urine ketones, and he was found to have respiratory syncytial virus. He was treated for respiratory failure secondary to respiratory syncytial virus bronchiolitis in the Pediatric intensive care unit (PICU). On physical exam, he again demonstrated tonic upward gaze which, according to the mother, had recently worsened. Additionally, despite diffuse hypotonia, he had occasional episodes of arm and leg stiffening as well as periods of unresponsiveness, which seemed to accompany the abnormal eye movements. The mother reported that these episodes occurred regularly at baseline. Developmentally, the patient had significant gross motor delay. He had not started crawling or walking, but was able to sit unassisted, speak 2-3 word sentences, and gesture appropriately to his parents. Repeat MRI demonstrated bilateral, symmetric signal abnormalities in the cerebral peduncles and bilateral globus pallidi with sparing of other structures of the basal ganglia (Fig. 1). The imaging studies did not lead to a specific diagnosis at

that time; however, the pattern of diffusion restriction was consistent with an active neurometabolic disease.

This patient's acute decompensation and metabolic acidosis following a viral illness, along with highly elevated urine ketones, raised suspicion for a disorder of ketone metabolism. However, targeted testing for disorders of ketone metabolism proved unremarkable. Out of concern for the patient's developmental delay, a chromosomal microarray was ordered, but was also normal. Ultimately, whole exome sequencing revealed a homozygous c.365A>G mutation in *HIBCH*, with each parent confirmed as a heterozygous carrier of the pathogenic allele.

After the diagnosis, the patient was followed by Genetics and Neurology for 3 years and did not require additional hospitalization during this time. The patient demonstrated no further acute episodes, but remained developmentally delayed with significant hypotonia and an inability to walk independently.

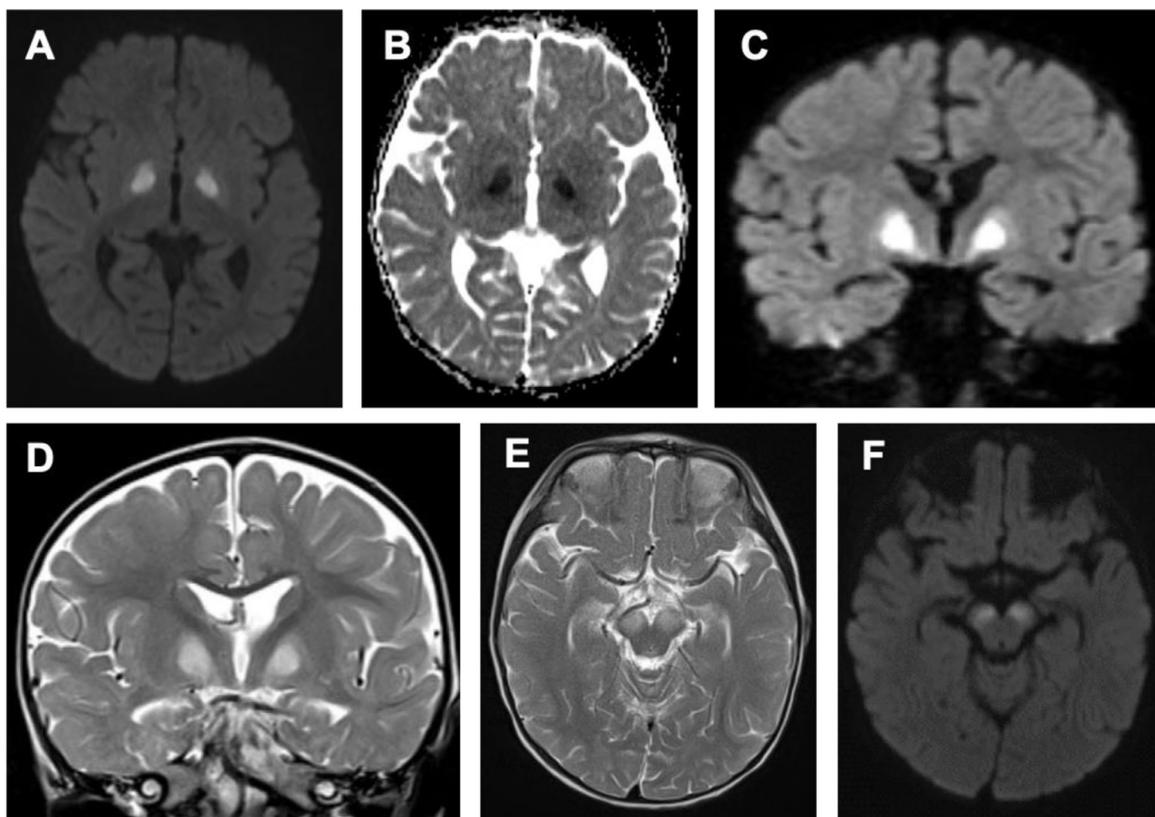
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## Discussion

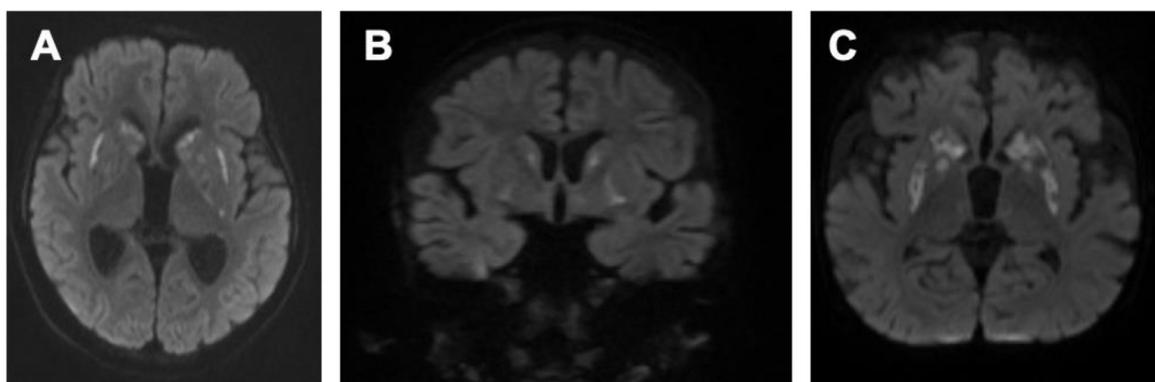
The patient's clinical and imaging findings align with the phenotype of HIBCH deficiency. Similar to previously reported cases, our patient presented with delayed motor development and further regression following a viral infection [2,3,7,8,10,12,13,15,16]. Additionally, his symptoms of motor delay and hypotonia are common features of this disease [1-3,12-16]. His clinical course was milder than that of many reported patients, though his developmental impairments persisted. These clinical findings, however, are nonspecific and can be seen with Leigh syndrome or other mitochondrial diseases.

Although HIBCH deficiency has few reported cases in the literature, it is important to learn the clinical and imaging manifestations to help expedite diagnosis. Treatment of this disease differs from other mitochondrial disorders, and patients generally benefit from a high carbohydrate, low protein diet with carnitine, valine, vitamin C, and vitamin E supplementation [1,17]. Despite medical management, disease progression is difficult to predict. Some reports suggest that HIBCH patients have a milder course than other Leigh-like syndromes, although patients generally continue to have neurodevelopmental difficulties [19]. Furthermore, the natural history of this disorder may change with earlier diagnosis and early introduction of supportive care and nutritional therapies.

In the present case, MRI signal abnormalities affected the globus pallidi and cerebral peduncles, with notable sparing of other parts of the basal ganglia and brain. Although not specific, this particular affinity for the globus pallidi is seen in cases of HIBCH deficiency, but is an uncommon pattern in other Leigh-like syndromes [1,2,18, 19]. In a study by Valanne et al, 8/8 patients with Leigh syndrome had an MRI showing moderate to severe changes in the putamen, 5/8 showed moderate to severe changes in the caudate, and only 3/8 patients showed mild to moderate changes in the globus pallidi [18]. None of these patients showed disease isolated to the pallidum [18]. Other lesions were noted in



**Fig. 1** – MRI of a 15-month-old boy with HIBCH. Axial DWI (A), ADC (B), and coronal DWI (C) imaging demonstrate bilateral, symmetric diffusion restriction in the globus pallidi suggesting active metabolic disease. Notably, the caudate and putamen are spared. Coronal-T2-weighted image (D) shows corresponding T2 hyperintensity in the globus pallidi. Axial T2 (E) and DWI (F) images more inferiorly demonstrate similar symmetric signal changes in the cerebral peduncles.



**Fig. 2** – MRI of Leigh syndrome. DWI imaging in 3 patients with Leigh syndrome: a 3-year-old male (A); a 19-month-old female (B); and an 8-month-old male (C). Each image demonstrates the typically symmetric, more diffuse involvement of the basal ganglia with abnormalities in the putamina and caudate heads.

the thalamus, substantia nigra, red nucleus, medulla, and white matter of several patients [18]. MRI findings in Leigh syndrome classically include signal abnormalities of the basal ganglia including the putamina, but typically are generalized, affecting multiple structures (Fig. 2) [1,2,18]. This case, together with other reports in the literature, indicates

that signal abnormalities isolated to the globus pallidi and cerebral peduncles suggest HIBCH deficiency.

We suggest that neuroimaging studies can facilitate the diagnosis of HIBCH deficiency. This patient's neuroimaging studies were abnormal by 15 months of age and revealed a pattern highly suggestive of neurometabolic disease. These neu-

roimaging findings can help guide diagnostic testing, which may expedite the diagnosis of HIBCH deficiency and other rare metabolic disorders. Additionally, this case highlights that HIBCH deficiency should be considered in patients with Leigh-like clinical features, especially if neuroimaging shows signal abnormalities that primarily affect the globus pallidi and cerebral peduncles. Given the rapid advances in genetic testing and potential for dietary management of metabolic disorders, neuroradiologists' assessment of these rare imaging findings is critical in facilitating optimal patient management.

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