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ORIGINAL ARTICLE

Characterization of 3-hydroxyisobutyryl-CoA hydrolase deficiency in Bahrain: a retrospective cohort study

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ABSTRACT

Background: 3-hydroxyisobutyryl-CoA hydrolase (HIBCH) deficiency is a rare inborn error of valine catabolism associated with progressive neurological impairment. This retrospective cohort study aimed to characterize the clinical, biochemical, genetic, and respiratory chain (RC) profiles of HIBCH deficiency patients in Bahrain.

Methods: Eight HIBCH deficiency patients were evaluated from a larger cohort of 90 individuals assessed for Leigh-like syndrome at the metabolic clinic of Salmaniya Medical Complex, Bahrain, between 2000 and 2020. Clinical features, neuroimaging findings, biochemical profiles, genetic analyses, and RC activities were systematically examined.

Results: Developmental delay and acute encephalopathy were the main presenting symptoms. Neuroimaging demonstrated heterogeneous, often progressive basal ganglia and white matter changes. Biochemical profiling revealed elevated C4-OH acylcarnitine, with variable abnormalities in blood lactate, amino acids, and RC complexes. Genetic analysis identified a novel homozygous HIBCH variant (c.860A>G, p.Asp287Gly) in all patients. Despite clinical interventions, five of eight patients exhibited severe, persistent developmental delay, and three patients succumbed to sepsis.

Conclusion: This study provides a comprehensive characterization of the clinical, biochemical, and genetic changes in HIBCH deficiency patients in Bahrain, including the identification of a novel genetic variant. The progressive, debilitating nature of this disorder underscores the critical importance of early diagnosis and tailored management strategies for this rare metabolic condition.

Keywords: HIBCH deficiency, Leigh/Leigh-like syndrome, C4-OH, valine metabolism, children.

Introduction

3-hydroxyisobutyryl-CoA hydrolase (HIBCH) deficiency (OMIM# 250620) (1) is an autosomal recessive inborn error of valine metabolism (2) resembling Leigh syndrome caused by homozygous or compound heterozygous mutation of *HIBCH* (610690) gene maps to chromosome 2q32.2 (1-3). The estimated incidence of HIBCH deficiency in the general population varies between 1 in 127,939 in East Asians and 1 in 551,545 in Europeans, according to the OMIM database (4). Whole exome sequencing helped in describing more cases of this deficiency from around the world with an estimated incidence of approximately 1:551,545 in Europe and 1: 127,939 in South Asian individuals (2). Five of them were from Arab regions (one Egyptian, one Tunisia, two Lebanese, and one Saudi Arabia) (3,5-7). The presentation and findings of this disease overlap with other mitochondrial disorders especially Leigh syndrome, making it a challenge to be diagnosed (8,9). It includes mild dysmorphic facial features, hypotonia, seizures, and episodes of encephalopathy with or without ketoacidosis, and in some patient's optic

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atrophy, nystagmus and strabismus were reported (10). In addition, movement disorders dominated by progressive ataxia and dystonia have been described (7,11). Brain MRI abnormalities were consistent with Leigh-like basal ganglia changes with bilateral symmetric lesions (12). The disease is caused by the deficiency of a nuclear mitochondrial enzyme that involves the conversion of 3-hydroxyisobutyryl-CoA to 3-hydroxyisobutyrate in valine metabolism (13). As such, the deficiency leads to the accumulation of methacrylyl CoA and acryloyl-Co A. These are free radicals that conjugate with sulfhydryl moieties disrupting intramitochondrial enzymes including pyruvate dehydrogenase and respiratory chain (RC) enzymes (10). As a result, patients have clinical features similar to Leigh's disease and other mitochondrial disorders. From a biochemical perspective, serum lactate is inconsistently elevated (13). Also, elevated levels of serum hydroxyl-C4 carnitine were noticed in most patients which is proposed to be helpful for screening this disease in plasma or dried blood spots (DBS) (14). The enzyme also acts on 3-hydroxypropionyl CoA in the secondary pathway of propionate metabolism (Figure 1) but does not appear to be clinically correlated (1). Currently, there is no definitive treatment for HIBCH deficiency. Management is largely supportive; some patients may benefit from a low-valine diet with carnitine and N-acetylcysteine (12,15,16).

This retrospective cohort study aimed to characterize the clinical, biochemical, and genetic features of eight patients diagnosed with HIBCH deficiency at a metabolic clinic in Salmaniya Medical Complex, which is the only center for inborn errors of metabolism services in the Kingdom of Bahrain.

Subjects and Methods

A retrospective cohort study was conducted at the metabolic clinic of Salmaniya Medical Complex in Bahrain, which included eight patients diagnosed with HIBCH deficiency (genetic testing performed) as part of a larger cohort of 90 individuals evaluated for Leigh-like syndrome between November 2000 and December 2020. The diagnosis of Leigh-like syndrome was based on previously published clinical and radiological criteria of the disease (17). For the eight HIBCH deficiency patients, the researchers collected and analyzed data on patient demographics, clinical features, biochemical findings (including amino acids, acylcarnitines, and urine metabolites), brain imaging results, and molecular genetic analysis (with four out of eight patients undergoing either whole exome sequencing or targeted mutation analysis). Additionally, RC complex activities were assessed via muscle biopsy in five of the eight HIBCH deficiency patients. This study was approved by the institutional review board at Salmaniya Medical Complex, and written informed consent was obtained from all participating legal guardians.

Results

This retrospective cohort study evaluated eight patients (six male, two female) from three consanguineous Bahraini families with confirmed HIBCH deficiency. The affected individuals were distributed across three families - family A comprised three siblings, family B also had three affected siblings, while family C included one proband and their one affected cousin, as summarized in Table 1. All patients were born via uncomplicated vaginal delivery, except for one individual delivered by cesarean section due to failure to progress; birth weights

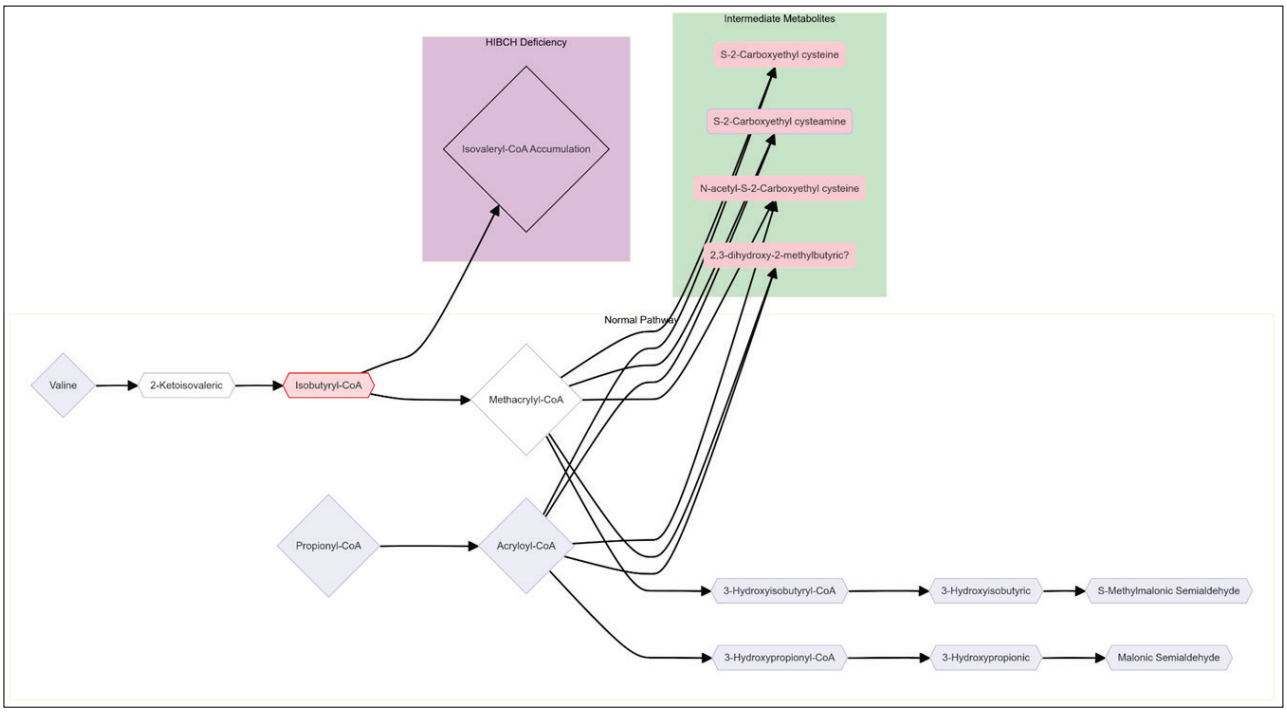

Figure 1. *Valine and propionyl-CoA catabolism in HIBCH deficiency.*

Table 1. *Clinical, biochemical, and outcome characteristics of eight patients with HIBCH.*

	Family A				Family B		Family C	
Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Gender	**Male**	**Male**	**Male**	**Male**	**Female**	**Male**	**Male**	**Female**
Age at presentation (month)	6	3	3	2	1	2	4	6
Initial presentation	Acute encephalopathy	Development delay	Seizure	Acute encephalopathy	Seizure	Developmental delay	Developmental delay	Developmental delay
Dysmorphism	Yes	No	Yes	Yes	No	No	No	No
Strabismus	Yes	No	Yes	No	Yes	No	No	No
Nystagmus	No	No	Yes	No	Yes	Yes	No	No
Hypotonia	No	No	No	Yes	Yes	Yes	No	No
Dystonia	Yes	Yes	Yes	No	No	No	Yes	Yes
Seizure	No	No	No	Yes	No	No	No	No
Episodes of acute encephalopathy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Feeding problem	Yes	Yes	Yes	No	No	No	No	No
Hepatomegaly	Yes	Yes	Yes	No	No	No	No	No
Diet therapy	No	No	Yes	No	No	Yes	Yes	No
Age at deasth (years)	8	Alive (12)	Alive (8)	12	Alive (10)	Alive (1.5)	Alive (12)	7
Lactate (normal 0.5-2.2 mmol/l)	2.2	1.7	6.8	4.5	3.4	4.5	1.8	No record
OH-C4 acylcarnitine levels (normal <1 µM)	2.9	2.9	2.9	1	2.2	1.45	2.3	2.2

ranged from 3 to 4 kg. The diagnosis was established by molecular genetic testing in at least one affected member from each family and presumptively extended to other symptomatic relatives based on concordant clinical features and biochemical abnormalities.

The mean age at symptom onset was (3.35) months. Initial clinical presentations included developmental delay (4/8 patients), myoclonic seizures (1/8), and acute encephalopathy (2/8). Common follow-up findings were strabismus (3/8), feeding difficulties (3/8), nystagmus (3/8), hypotonia (3/8), and dystonia (5/8) as summarized in Table 1. Dysmorphic features were noted in three patients - two siblings in family A had a long face, thin lips, large ears, and periorbital fullness (Figure 2), while one patient from family B was born with a scalp defect and microcephaly. All patients experienced recurrent episodes of encephalopathy provoked by intercurrent illness but did not develop chronic epilepsy. Hepatomegaly was noted in 3/8 individuals during decompensation, exclusively within one family.

Neuroimaging findings were heterogeneous but often featured basal ganglia and white matter changes. Brain MRI and MRS were performed on all patients, with findings summarized in Table 2. It is important to note that the radiological features described reflect the latest brain MRI (Table 2), as all patients underwent serial imaging approximately every 2-3 years. Over time, the changes were progressive in terms of both the site and intensity of involvement. No specific radiological pattern was identified, though basal ganglia and white matter changes were the predominant findings. Hyperintensity in the cerebellum was observed in two out of eight patients from family A during follow-up imaging. Increased lactate peak on MRS was detected in only one

Figure 2. *Dysmorphic features in a patient with HIBCH deficiency. The patient exhibited athin lips, large ears, and periorbital fullness.*

patient from family B, which did not correlate with their serum lactate levels.

Comprehensive biochemical profiling of the eight patients revealed several key abnormalities. Elevated C4-OH acylcarnitine levels on DBS testing were observed in seven out of eight patients, with levels ranging from 1.45 to 2.9 μM (normal <1 μM). Notably, one patient (patient 3 from family A) had a normal initial C4-OH level that subsequently increased to 2.9 μM on a repeat sample at 1 year of age. Amino acid analysis on the newborn screening DBS showed slightly low methionine (5.5 μM, normal 6-63 μM) in 1 out of 8 patients. Urine organic acids analysis revealed elevated 3-hydroxyisovaleric acid (27.2 mmol/mol creatinine, normal 5.1-10.7) in 1 out of 8 patients, though comprehensive urine cysteamine testing could not be performed on all individuals. Blood lactate was elevated in 5 out of 7 patients during acute illness, with levels ranging from 3.4 to 6.8 mmol/l (normal 0.5-2.2 mmol/l). Finally, muscle biopsy and RC complex analysis, conducted in five out of eight patients, demonstrated variable abnormalities.

Detailed genetic analysis of the patients' samples revealed a significant finding in the *HIBCH* gene. DNA sequencing identified a homozygous single nucleotide substitution, specifically an A to G change at position 860 of the *HIBCH* coding sequence (NM_014362.3:c.860A>G). This nucleotide alteration results in an amino acid substitution, where the reference aspartic acid (D) residue at position 287 is replaced by a glycine (G) residue (p.Asp287Gly). While its pathogenic significance has not been extensively characterized, the consistent presence of this variant in multiple individuals with the condition provides stronger evidence for its role in the molecular basis of the disorder. The identification of this *HIBCH* gene variant, and its segregation pattern in the affected families, offers valuable insights that may inform the patient's diagnosis, prognosis, and potential therapeutic interventions targeting this key metabolic enzyme. A trial of dietary valine restriction was attempted in three patients, with initial symptomatic benefit observed in two cases, although long-term improvements were not sustained. Despite the intervention, six out of eight patients remain alive but severely developmentally delayed and bedridden, while 3 individuals tragically passed away due to sepsis at ages 12, 8, and 7 years.

Discussion

The study investigated eight patients from three consanguineous Bahraini families diagnosed with HIBCH deficiency (18), a rare autosomal recessive disorder characterized by progressive neurodegeneration (18). The study identified a novel homozygous mutation (c.860A>G, p.Asp287Gly) in the *HIBCH* gene, expanding the genetic landscape of this disorder and highlighting the importance of comprehensive genetic testing in patients with suspected HIBCH deficiency or Leigh-like syndrome.

The study clarified the heterogeneous clinical presentation of HIBCH deficiency, with variable clinical manifestations, neuroimaging findings, and biochemical profiles even among siblings within the same family. While the initial presentation often involves motor delay or encephalopathy, the clinical course can vary significantly. The age of symptom onset in these patients ranged from as early as 6 weeks to 6 months; furthermore, the average age of death was at 10 years of age. The study's findings align with previous case reports on HIBCH deficiency, where most reported

Table 2. *Neuroimaging abnormalities in HIBCH patients.*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
T2W hyperintense signal								
Globus pallidus	-	+	-	+	+	+	-	+
Putamina	++	-	-	+	+	-	-	++
Caudate heads	++	-	-	+	+	-	-	++
Thalami	+	+	-	-	-	-	-	-
Cerebral crura	-	+	-	-		-	++	+
Periaqueductal gray matter	-	-	-	++	-	-	-	-
Pons	-	+	-	-	-	-	-	-
Cerebellum	+	+	-	-	-	-	-	-
Restricted diffusion	-	-	-	-	-	+	-	-
Brain volume loss								
Supratentorial	+	+	+	++	-	-	++	+
Infratentorial	-	+	-	++	-	-	+	-
MRS (lactate peak):	-	-	-	-	-	+	-	-

+, positive; ++, markedly positive; -, negative, MRS, magnetic resonance spectrometry.

cases had initial symptoms within 2 years of age, usually exacerbated by infection, and earlier onset was associated with poor prognosis (3,16,19). For instance, Karimzadeh et al. (20) identified a novel heterozygous variant in the *HIBCH* gene (c.641C>T; p.Thr214Ile and c.913A>G; p.Thr305Ala) in a 15-month-old male who presented with recurrent episodes of weakness, nystagmus, and myoclonus following febrile illness. This patient subsequently developed developmental delay, inability to walk, and speech impairment, emphasizing the significant clinical burden associated with HIBCH deficiency.

The study patients' main clinical manifestations included developmental delay/regression, hypotonia, encephalopathy, and feeding difficulties as summarized in Table 1. As the patients aged, hypertonia and dystonia also manifested, which are characteristic of Leigh syndrome. Three main distinguished types of clinical presentation have been described in the literature: neonatal type - syndromic progressive neurodegenerative disease (17), with or without intractable seizures (15,19); Leigh-like syndrome - progressive or acute/subacute onset in the first 2 years of life, with neurological decompensation during infectious or cellular stress; and isolated paroxysmal dyskinesia - recurrent episodes of weakness, nystagmus, and myoclonus (17).

Liver involvement was a rare manifestation of HIBCH deficiency, only one case had reported liver dysfunction, while three out of eight patients in this study had hepatomegaly during disease acute exacerbation with normal liver function (8,9). Seizure disorders were noticed in two of the patients but did not seem related to phenotypic severity.

The neuroimaging of the cohort showed symmetrical lesions in the basal ganglia, with or without brain stem involvement. Two patients also had cerebellum involvement on follow-up MRI. This was distinct from the generalized signal abnormalities typically seen in Leigh syndrome, where the globus pallidum involvement may have indicated valine disturbance including HIBCH deficiency (21). A lactate peak on MRS was observed in one patient but was not correlated to serum lactate or disease severity. Lactate peak and corpus callosum abnormalities were uncommon but may have been associated with a more severe phenotype.

The HIBCH deficiency led to 3-hydroxy-isobutyryl-CoA accumulation, and the C4-OH metabolite panel was used for diagnosis, though not completely specific. Seven out of eight patients in this cohort had elevated C-OH levels, with one patient showing elevation only on subsequent follow-up. Higher C-OH levels had been associated with poor prognosis, but this was not observed in this patient group. More specific testing for S-(2-caboxypropyl) cysteamine in urine was unfortunately not available at the study center. The observed heterogeneity in clinical presentation and biochemical profiles, even among siblings, suggests that factors beyond the identified genetic variant may influence disease severity and progression. The high prevalence of consanguinity in the Bahraini population (7%) (19) likely contributes to the observed clustering of cases within families, but further research is needed to explore the potential role of environmental factors, genetic modifiers, and epigenetic mechanisms in shaping the phenotypic variability of HIBCH deficiency.

These findings align with previous case reports on HIBCH deficiency (3,8,20), which also demonstrate a wide range

of clinical presentations and variable outcomes. However, the novel mutation identified in our study distinguishes it from previously reported cases, highlighting the need for continued research to understand the full spectrum of genetic variations associated with this disorder.

To date, no confirmed founder mutation of the *HIBCH* gene has been reported, but it was mentioned that p.His343Asp may be a hot spot mutation in Chinese individuals (8,16). We speculate that the mutation detected in our cohort could be a founder mutation for the Bahraini population. To date, there is no treatment approach for HIBCH deficiency. In addition, the literature has mentioned that patients with truncating mutations tend to have more severe symptoms (22). Treatment with a restricted valine diet with a high-carbohydrate intake may show some benefit, with or without supplementation of thiamine. This approach aims to avoid ATP production from valine metabolism. Additionally, it has been noted that a ketogenic diet may worsen the patient's condition (15,23). Furthermore, treatment with antioxidants and vitamin cofactors has shown some effect in a few case reports (15).

It is crucial to differentiate HIBCH deficiency from other neuro-metabolic syndromes that present with similar manifestations, particularly Leigh syndrome, a rare genetic neurometabolic disorder (23). While both conditions can present with bilateral basal ganglia lesions and other neurological abnormalities, HIBCH deficiency is specifically associated with valine metabolism, whereas Leigh syndrome is a genetically heterogeneous disorder with a broader range of metabolic defects (8,16,24). D'Gama et al. (3) emphasize the importance of early whole genome sequencing in suspected metabolic disorders. They present a case where a newborn with feeding difficulties and nystagmus was initially discharged due to normal metabolic studies but later died from HIBCH deficiency after showing worsening MRI findings. This case, along with patient 4 in the current study, demonstrates the value of early genetic testing in identifying HIBCH deficiency and potentially improving outcomes. Varying mutations in the *HIBCH* gene across studies can be attributed to genetic diversity, differences in testing methodologies, and phenotypic variability. Distinct population backgrounds and methods like whole exome sequencing can yield different findings. Additionally, clinical presentations may vary, with some mutations showing incomplete penetrance, leading to underreporting. Environmental factors can also influence mutation expression, contributing to discrepancies in reported mutations.

The study, while limited by its retrospective nature and small sample size, provides valuable insights into the clinical, metabolic, genetic, radiological, and clinical outcomes of HIBCH deficiency in a specific population. Future research on HIBCH deficiency should focus on 3 key areas: understanding the newly identified genetic variant, exploring the role of environmental and genetic factors in disease variability, and developing novel therapies.

Conclusion

This study identified a heterogeneous biochemical and neuroimaging phenotype associated with HIBCH deficiency, and characteristic basal ganglia and white matter changes on brain MRI. The long-term clinical outcomes were poor even with supportive care; most patients remained seriously delayed in their development, and several unfortunately died from problems in their early childhood. To understand the underlying pathophysiology and create efficient treatments for this fatal inherited metabolic defect, more research is required.

List of Abbreviations

DBS	dried blood spot
HIBCH	3-hydroxyisobutyryl-CoA hydrolase
RC	respiratory chain

Conflicts of interests

The authors declare that they have no conflict of interest regarding the publication of this article.

Funding

None.

Consent to participate

Informed consent was obtained from the parents of the patients.

Ethics approval

This study was approved by the Institutional Review Board at Salmaniya Medical Complex, Manama, Bahrain. Ethical approval was granted on 01/08/2021 (Approval No. 128011121)

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