Brief Report

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Syndromic progressive neurodegenerative disease of infancy caused by novel variants in HIBCH: Report of two cases in Colombia

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Summary **3-Hydroxyisobutyryl-coenzyme A (CoA) hydrolase deficiency (HIBCHD; MIM: #250620) is a rare autosomal recessive inborn error of metabolism caused by a defect in the HIBCH enzyme, resulting in a deficiency of the conversion of 3-hydroxy-isobutyryl-CoA to 3-hydroxy-isobutyric acid, a critical step in valine catabolism. This neurodegenerative disease of infancy is associated with hypotonia, developmental delay, cerebral atrophy and lesions in the basal ganglia on magnetic resonance imaging (MRI). In this study, we describe two unrelated patients with infantile-onset progressive neurodegenerative disease and mutations in HIBCH identified using whole exome sequencing (WES). In Case 1, WES revealed a novel homozygous variant in the *HIBCH* gene: c.808A>G (p.Ser270Gly). In Case 2, a novel compound heterozygous mutation in the *HIBCH* gene is described: c.808A>G (p.Ser270Gly) and c.173A>G (p. Asn58Ser). Parent analysis revealed that c.808A>G (p.Ser270Gly) was inherited from the father and c.173A>G (p. Asn58Ser) from the mother. These novel mutations were predicted as a disease-causing mutation. Plasma acylcarnitine analysis was normal in both patients. Physical examination showed similar features, such as axial hypotonia and spastic hypertonia in the legs. The first patient presented with difficult-to-treat seizures, while the second patient has not yet experienced documented seizures. In conclusion, our findings would widen the mutation spectrum of HIBCH deficiency and the phenotypic spectrum of the disease. The potential genotype–phenotype correlation would be profitable for the correct diagnosis, treatment and integral management of patients with HIBCH deficiency.**

Keywords: 3-hydroxyisobutyryl-CoA hydrolase deficiency, amino acid metabolism, inborn errors, inborn errors of metabolisms, seizures, hereditary neurodegenerative diseases

1. Introduction

In humans, essential amino acids, such as leucine, isoleucine and valine, contribute to energy production through catabolism (*1*). When parts of this catabolism are interrupted, heterogeneous groups of diseases are generated, normally called inborn errors of metabolism. The term usually refers to primary disorders affecting the metabolism of amino acids, organic acids, lipids and complex carbohydrates that interfere with healthy brain development leading to developmental delay or intellectual disability (*2*).

3-Hydroxyisobutyryl-coenzyme A (CoA) hydrolase

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deficiency (HIBCHD; OMIM #250620) is a rare inborn error of metabolism caused by a defect in the HIBCH enzyme, resulting in deficiency in conversion of 3-hydroxy-isobutyryl-CoA to 3-hydroxy-isobutyric acid, a critical step in valine catabolism (*3*). This deficiency presumably leads to accumulation of toxic metabolites in mitochondria (*3*). Only 16 patients from 10 unrelated families, 6 of which are consanguineous, have been reported in the worldwide literature (Supplementary Table S1, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=44*). This autosomal recessive condition is characterised by the developmental delay of motor milestones in early infancy, which is associated with episodes of ketoacidosis and high concentrations of pyruvate and lactate in the cerebrospinal fluid (*4*) and neurologic regression within the first year of life. Magnetic resonance imaging (MRI) abnormalities are striking for bilateral involvement of the basal ganglia with varying degrees of white matter atrophy (*2*).

We report on two unrelated Colombian patients with neurologic disease. Whole exome sequencing (WES) was performed in both cases and two novel mutations in the *HIBCH* gene were identified. Patients presented with remarkable psychomotor developmental delay and in one case infantile neurodegenerative disease. The suspicion of an inborn error of metabolism existed in both cases, but difficulty in diagnosis was due to heterogeneity of the clinical presentation.

2. Patients and Methods

Clinical and family history and diagnostic findings were obtained in a clinical setting. The following clinical variables were obtained for each proband: evidence of consanguinity, abnormal perinatal period, anthropometric variables, age of diagnoses, developmental milestones, symptoms and signs, dysmorphic facial features, brain image abnormalities, blood and biochemical analysis, muscle skeletal biopsy results, status of variant inheritance and survival rate. Written informed consent to participate in the study and to publish clinical information and photographs was obtained from the parents. A local ethics committee of the Faculty of Health Sciences of the Universidad Icesi approved the study.

2.1. *Case 1*

A 1-year-old Colombian girl, born to consanguineous parents, was the product of a first pregnancy that ended *via* caesarean section at 39 weeks due to a prolonged delivery stage. She weighted 2,725g (between 9th and 25th percentile), seize 50cm (9th and 2nd percentile) and head circumference 35.5cm (91st and 75th percentile) according to world health organization growth chart. There was no family history of any heritable

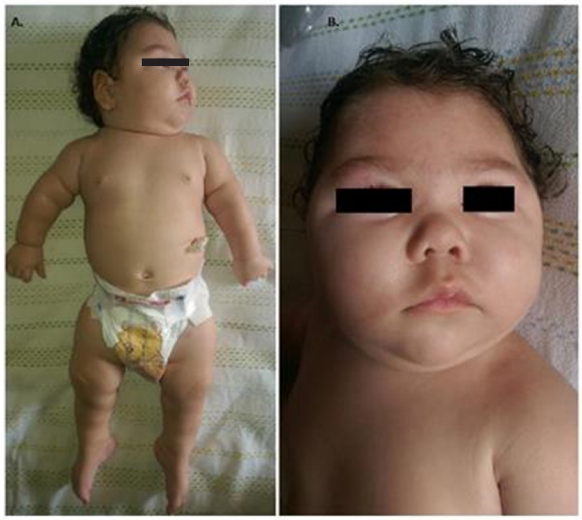

Figure 1. Case 1 phenotype. (A), Front profile at age 1 year shows short forehead, wide palpebral fissures, epicanthus fold, synophrys, nasal bone hypoplasia, low nasal bridge, bulbous nose, prominent philtrum groove, small mouth with cupid's bow, and microcephaly; **(B)**, Spastic legs show generalised hypotonia. Permission was obtained from the patient's parents for presentation.

progressive neurodegenerative disease. The patient was frequently hospitalised for persistent vomiting, anorexia, irritability, swallowing difficulties, poor feeding, psychomotor developmental delay, no language skills and developmental regression since she was 2 months old. For that reason, a gastrostomy tube was placed and Nyssen fundoplication was performed to treat gastroesophageal reflux disease (GERD) at 3 months old. At 9 months old, multiple episodes of seizures and myoclonus developed. Physical examination showed a short forehead, wide palpebral fissures, epicanthal fold, synophrys, nasal bone hypoplasia, low nasal bridge, prominent philtrum groove, small mouth with cupid's bow, microcephaly, punctate anterior fontanelle, axial hypotonia, decreased tendon reflex, spastic legs (Figure 1 A and 1B) and hepatomegaly, with severe milestones growth development delay. She has never achieved cephalic support, ability to sit, ability to walk or ability to speak. Multiple tests revealed an elevated pyruvate/lactate ratio and lactate in the blood and cerebrospinal fluid. Brain MRI showed bilateral hyperintensity in the basal ganglia in DWI sequences (Figure 2A) and hypodensity in ADC sequences (Figure 2C) due to restriction. A metabolic abnormality was suspected due to a vast number of differential diagnoses. Magnetic spectroscopy revealed elevations in lactate (Figure 2C and 2D), which were more pronounced in regions where abnormalities were seen (Figure 2A, 2B and 2F). T1 sequences (Figure 1E and 1F) showed hypointensity on basal ganglia, which enhance with contrast. Axial potency in T2, showed bilateral damage of the basal ganglia and general cerebral volume loss in white and grey matter, with a significant increase in the number of gyri and sulci (Figure 2G) and deeply generalized

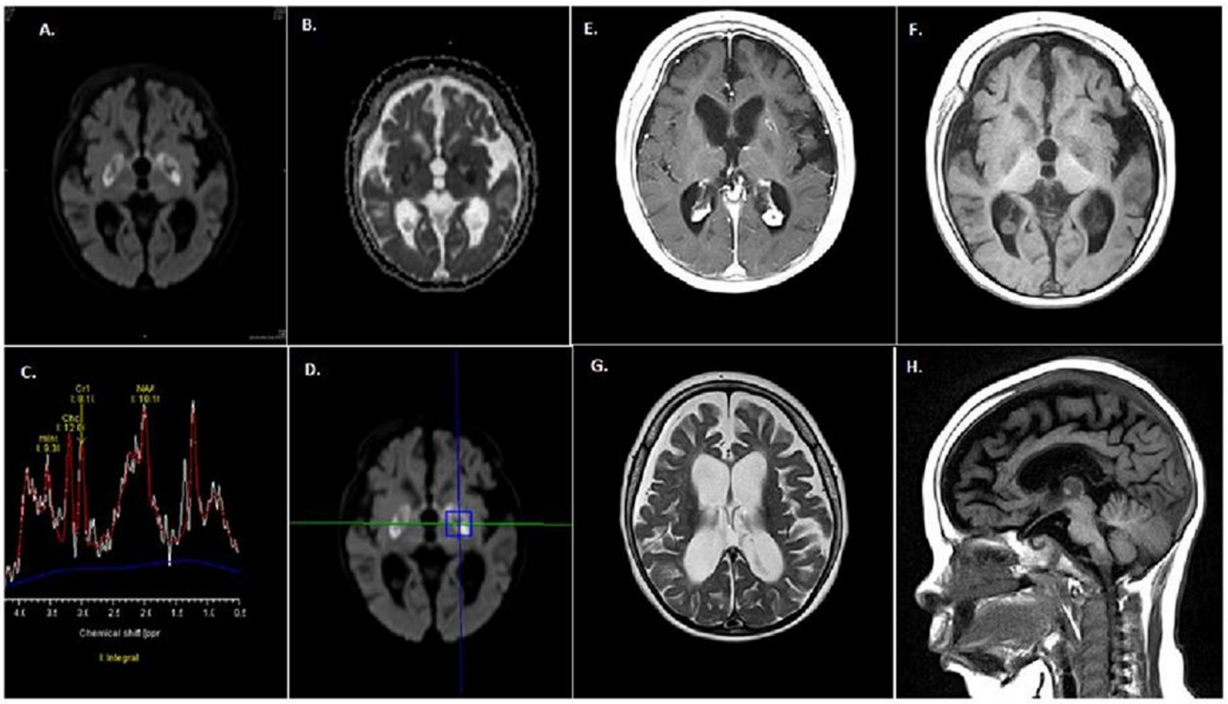

Figure 2. Case one MRI Images. (A), Axial section diffusion-weighted imaging (DWI) shows hyperintensity in the basal ganglia; **(B)**, Axial section shows apparent diffusion coefficient (ADC) basal ganglia restriction; **(C,D)**, Spectral curve with echo time (TE) of 30 mseg localises in the left globus pallidus; , where lactate and lipids peak with high concentration of myo-inositol are observed; **(E)**, Axial T1 Gadolinium (Gad), shows enhancement the basal ganglia **(F)**, Axial T1 image shows hypointensity in the basal ganglia; **(G)**, Axial T2, decline in brain volume. Gyrus, sulcus, subarachnoid space and ventricular system were prominent; (H), Sagital T1, section shows severe slimming of the corpus callosum and brain stem.

reductions in brain volume with predominance in grey and white matter, basal ganglia and pedunculus cerebri (Figure 2E). There was strong progression of cerebral atrophy compared to the other MRI scan and thickening of the corpus callosum and cerebral volume loss mainly in the supratentorial area (Figure 2H). Cardiac ultrasonography showed septal ventricular hypertrabeculation.

Her latest evaluation by the genetic consultant showed that the patient was still unable to walk, sit or communicate and a gastrostomy tube was kept due to increasing feeding difficulties. She received motor therapy and achieved mild cephalic support in prone position and slight gain of movement. Currently, she is receiving total enteral valine-free amino acid feeding, which allows changes in her behaviour including; less irritable but it does not contribute to control of seizure episodes and global development delay. Enzymes and the pyruvate dehydrogenase (PDHc) complex levels were not determined.

2.2. *Case 2*

A 4-year-old male from the southwest region of Colombia was the product of a 29-year-old mother and 43-year-old father (nonconsanguineous parents). The pregnancy was uncomplicated, and ultrasonography and prenatal care were normal. Vaginal delivery at week 36 of gestation was without complications. Birth weight was not documented and the cephalic perimeter at birth was 36 cm (54th centile). Apgar scores were 9 and 10 at 1 and 5 minutes, respectively. No phenotypic abnormalities or dysmorphism features were noticed at birth. Family history was positive for epilepsy in two cousins, and his mother had two previous miscarriages.

Generalised muscular hypotonia and poor weight increase were noticed 3 months after birth. Additionally, psychomotor development was significantly delayed. Neuropediatric follow-up at 6 months, due to previous clinical signs and symptoms, and brain MRI at 10 months revealed bilateral symmetrical hyperintense lesions in the basal ganglia on DWI sequences with hypointensity for restriction in the basal ganglia (Figure 3A and 3B) and fluid-attenuated inversion recovery (FLAIR) images globus pallidus (Figure 3D and 3E) associated with enlarged ventricles, suggestive of cerebral atrophy (Figure 3G and 3H). There were no structural brain anomalies, myelination defects or heterotopia. At 15 months of life, brain MRI spectroscopy demonstrated normal N-acetylaspartate, choline, creatinine and lactate peaks in the basal ganglia (Figure 3C and D), but imaging showed a compromise of the basal ganglia and posterior periventricular white matter (peritrigonal) without ischemia or active demyelination (Figure 3E and 3F). Axial potency T2, showed volume loss and hyperintensity on the basal

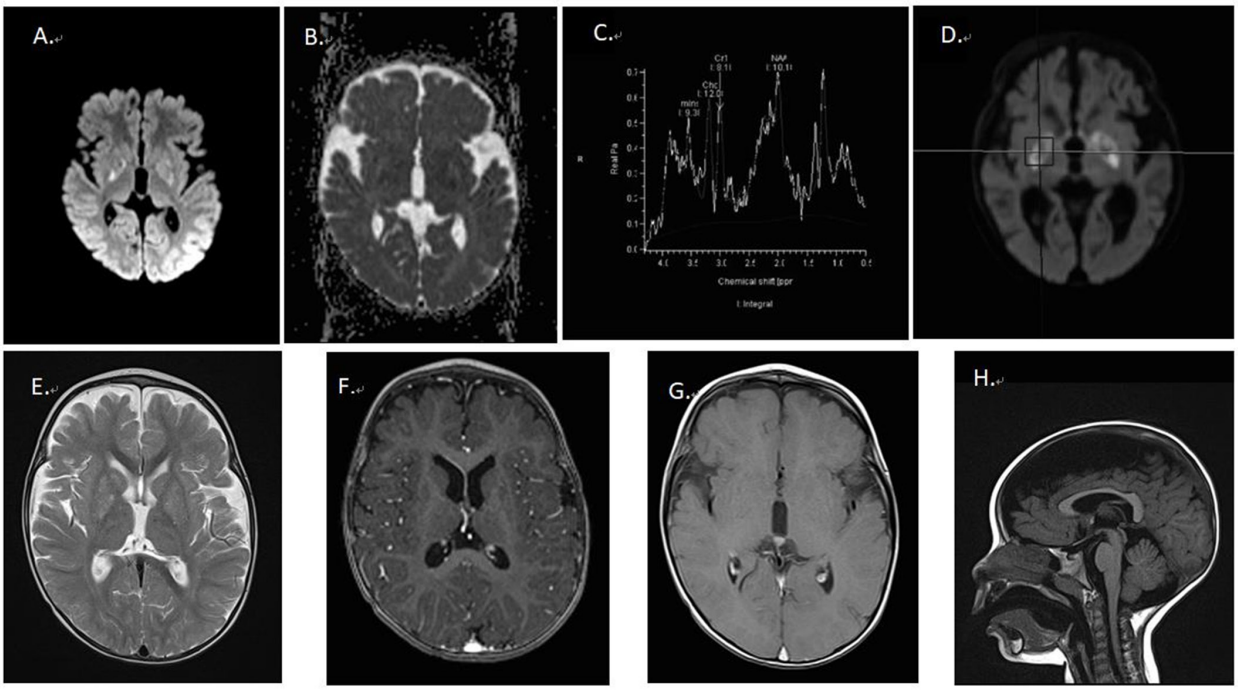

Figure 3. Case two MRI Images. (A), DWI-weighted imaging shows hyperintensity in the right basal ganglia; **(B)**, Axial section shows apparent diffusion coefficient (ADC) basal ganglia restriction; **(C,D)** Spectral curve with echo time (TE) of 30 mseg localises in the left globus pallidus; , where lactate and lipids peak with high concentration of myo-inositol are observed **(E)**, Axial T2 image, shows hyperintensity in the basal ganglia and decline in brain volume; **(F,G)**, Axial T1-weighted with and without contracts image shows hypointensity in the basal ganglia without enhanment ; **(H)**, Sagittal section shows slimming of the corpus callosum and brain stem.

ganglia (Figure 3G). Electroencephalogram (EEG) at 18 months showed background slowing activity and immature rhythms not expected at that age, and visual evoked potentials showed bilateral optic disorders with a right predominance. For that reason, Ophthalmology considered strabismus and torsional (rotary) nystagmus that required surgical correction. Auditory evoked potentials were normal.

Biochemical test results at 2 years of age were normal, including lactate, ammonium and liver function tests. Routine metabolic screening for aminoacidopathies and organic acidurias were normal. Plasma acylcarnitine analyses revealed no abnormalities. However, this screening did not routinely include hydroxy-C4-carnitine. At 3 years of age, he presented with an episode of gastrointestinal disturbance and fever that rapidly progressed to lethargy and worsened hypotonia. Similar clinical manifestations were present at 4 years of age, when he was hospitalised for upper respiratory symptoms with a fever that progressed to encephalopathy.

At age 4 years, he was medically assessed by Genetics. Physical examination revealed weight 15 kg (fourth centile), height 100 cm (first centile) and head circumference 51 cm (35th centile). A broad forehead, rotary nystagmus, convergent strabismus, facial symmetry with hypotonia, protruding tongue, ogival palate, axial hypotonia, spastic hypertonia predominantly in the lower limbs, hyperreflexia in the upper and lower limbs with bilateral extensor plantar reflex and hamstring contractures and immature clamp also were noted. The patient had insufficient trunk stability and was not able to sit or stand independently, or had he acquired any language. Repeat plasma acylcarnitine analysis was normal. The patient received an oral diet without difficulties and video fluoroscopic swallowing exam did not show any evidence of bronchoaspiration. At the moment he is taking multiple developmental therapies without any significant improvements.

Due to a large number of differential diagnoses, a blood sample for the patient and parents was collected, as well as medical records including clinical findings and the most relevant family history and WES was performed by using a trio approach with massive sequencing platform with Ion ProtonTM technology. The library preparation was designed with Ion AmpliSeq Exome technology (Life Technologies, Carlsbad, CA, USA) which captures > 97% of consensus coding sequences (CCDS; > 19,000 genes and > 198,000 exons) and flanking intronic regions (± 20 base pairs [bp]). Only variants in the coding and flanking intronic regions with a minor allele frequency (MAF) < 1.5% were evaluated. MAFs were based on the following databases: 1000 Genomes, dbSNP, Exome Variant Server (ESVor In-house), and Exome Aggregation Consortium (ExAc). In this study, we identified two novel mutations in a compound heterozygous state in

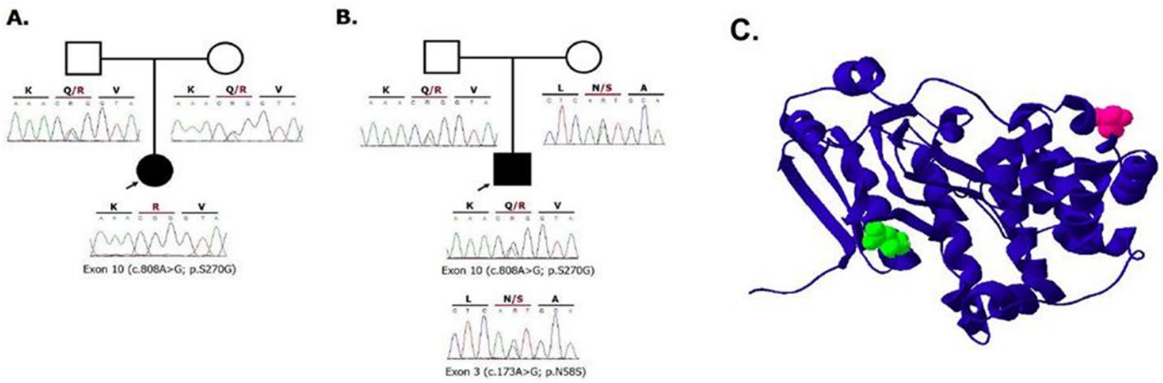

Figure 4. Pedigree information of patients and Sanger sequencing electropherogram of patients and parents. (A), Homozygous missense mutation (c.808A>G, p.Ser270Gly), both parents are carriers of the same mutation; **(B)**, Heterozygous compound mutation (c.808A>G, NM_014362.3) and (c.173A>G, p.Asn58Ser) at the cytoband 2q32.2 identified in patient. The first c.808A>G (p.Ser270Gly) was of paternal origin and c.173A>G (p.Asn58Ser) was of maternal origin. Variants were confirmed using Sanger sequencing. Both mutations are reported for the first time in this study to our knowledge; **(C)**, Visualisation of HIBCH *via* Swiss-PDB Viewer (v4.1.0) software. The locations of the mutations in the protein are shown. The amino acid marked *pink* corresponds to mutation c.173A>G, (p.Asn58Ser) and *green* to mutation c.808A>G (p.Ser270Gly) described in this report. Both are located in principal chain (aminoacids 33 to 386).

the *HIBCH* gene, the first c.808A>G (p.Ser270Gly) of paternal origin and c.173A>G (p.Asn58Ser) of maternal origin (Figure 4B and 4C).

To our knowledge, both variants have not been reported previously in the literature and the finding was confirmed using Sanger sequencing (Figure 4B) and was compatible with the diagnosis of 3-hydroxybutyryl-CoA hydrolase deficiency. Variant, functional prediction software tools SIFT and FATHMM classified the first variant (paternal origin) as Tolerated, while Mutation taster classified it as Disease-causing and Polyphen as possibly damaging (Score 0.613); the second variant (maternal origin) was predicted by SIFT, FATHMM, Mutation taster and Polyphen as Damaging (Disease-causing). No additional variants were identified.

3. Results and Discussion

HIBCHD is a rare inborn metabolism syndrome; in many cases, it can generate a secondary mitochondrial disorder caused by homozygous or compound heterozygous mutation in the HIBCH gene on chromosome 2q32 (*5*). The estimated incidence of HIBCH deficiency in the general population ranges from 1 in 127,939 in East Asians to 1 in 551,545 in Europeans (*6*), while there is no data as yet for the incidence in South America.

The prevalence of this disease is underestimated due to the nonspecific clinical presentation and its similarities with Leigh syndrome, which is a common neurometabolic disorder associated with different genes (*6*).

We reported two novel mutations in the *HIBCH* gene. The first, c.808A>G (p.Ser270Gly), was found in a homozygous state Case 1 by WES. To our knowledge, this mutation has not been previously reported as disease causing for *HIBCH* deficiency. Moreover, a phenotype correlation was found between the patient and the described phenotype by others in the medical literature (*1,7*), including cardiac defects (*7*). Additionally, parents carrying the same mutation and consanguinity provided evidence of autosomal recessive inheritance, previously described by others (*8*). Several *in silico* tools predict this mutation as damaging, based on the conservation of the position through the species. The second mutation, c.173A>G (p.Asn58Ser), was found to be of maternal origin in Case 2. Due to its location in the gene (Figure 4C), it was predicted by *in silico* tools as Disease-causing and called attention to the presence of the same mutation in two unrelated patients in our country.

HIBCH is a biallelic enzyme and its perturbation produces variable biochemical deficits in skeletal muscle, and a variable accumulation of toxic valine metabolites, the majority being methacrylyl-CoA (*9*). The high levels of this metabolite in multiple tissues cause multiple characteristics of this disease. Indeed, it is hypothesised that intramitochondrial methacrylyl-CoA reacts with thiol groups (cysteine and cysteamine conjugates) that are known to accumulate in multiple tissues particularly, liver, kidney and brain (*7*). Therefore, early and consequent dietary restriction might help to prevent neurodegeneration in HIBCHD (*9*).

We reported hepatomegaly and extensive brain damage in our patients and this metabolite produces glutathione and pools of cysteine depletion, a deficiency that could lead to oxidative damage (*3*). Furthermore, Methacrylyl-CoA could react with multiple essential residues containing cysteine, including pyruvate dehydrogenase complex (PDHc) and respiratory chain enzymes and reduce their activity (*10*), producing irreversible binding cofactors, such as CoA and lipoid

acid (*11*). A lack of CoA would be expected to inhibit the Krebs cycle and to decrease adenosine triphosphate (ATP) production. These effects are likely to vary according to the levels of oxidative stress. As a result, cell damage will be generated and abnormal MRI findings in the basal ganglia may be produced (Figure 2).

These findings can be illustrated in our patient by the high levels of multiple biochemical products measured in blood and urine, such as repeatedly elevated blood lactate levels, and a high ratio of lactate/pyruvate in the blood and in the cerebral fluid. On MRI, basal ganglia necrosis generated hyperintense lesions in the globus pallidus, cerebral atrophy, corpus callosum thinning and the steady decline of brain volume with slimming of the brain stem and pedunculus cerebri and high signal abnormality in these areas, without alteration of myelination. Similar findings have been detected on MRI in Leigh syndrome (*12,13*) as described previously (*8,14*) representing metabolic damage to the metabolites of valine catabolism accumulation.

4. Conclusion

We present a summary of the sociodemographic, clinical presentation, brain imaging abnormalities and mutations present in our cases and in patients previously described in the literature (Supplementary Table S1, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=44*) to delineate the clinical spectrum of HIBCHD. Recognised signs include seizures, developmental delay, motor disorders, absence of milestones growth achievements and multiple brain abnormalities. Recognizable symptoms and signs will help clinicians to diagnose low prevalence inborn errors of metabolisms, such as HIBCH deficiency. Additionally, a novel mutation was identified in two unrelated cases in a different inheritance status. In the first case as homozygous status and in the second case as heterozygous status is added to the literature by the first cases published in south-America and Colombia with different clinical findings and variable phenotype expression.

To successfully evaluate a patient with delayed development, hypotonia, early feeding problems and deterioration of neurologic function, an inborn error of metabolism must be suspected, and MRI must be performed. As seen in our HIBCHD patients, suggestive lesions detected on MRI are generalised lack of white matter, global atrophy or hyperintense basal ganglia.

Different treatment options have been suggested for patients with HIBCH deficiency based on the physiopathology of the disease. Replacement of the primary energy source in patients to carbohydrates (*8*) and a low-valine diet with carnitine supplementation could reduce the production of methacrylyl-CoA in neuronal cells (*15*). Recently, antioxidants have been described as additional treatment. However, although they were effective in reversing basal ganglia abnormalities, they cannot prevent progression of the disease (*4*).

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Ethics

Written informed consent was obtained from the patient's parents for the publication of the case details and accompanying images. Data was collected following the Declaration of Helsinki Good Clinical Guidelines. This study was approved by the Ethics Committee of Fundación Valle del Lili.

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