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Movement disorders in valine métabolism diseases caused by *HIBCH* and *ECHS1* deficiencies

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Abstract

Background and purpose: *HIBCH* and *ECHS1* genes encode two enzymes implicated in the critical steps of valine catabolism, 3-hydroxyisobutyryl-coenzyme A (CoA) hydrolase (*HIBCH*) and short-chainenoyl-CoA hydratase (*ECHS1*), respectively. *HIBCH* deficiency (*HIBCHD*) and *ECHS1* deficiency (*ECHS1D*) generate rare metabolic dysfunctions, often revealed by neurological symptoms. The aim of this study was to describe movement disorders spectrum in patients with pathogenic variants in *ECHS1* and *HIBC*.

Methods: We reviewed a series of 18 patients (*HIBCHD*: 5; *ECHS1D*: 13) as well as 105 patients from the literature. We analysed the detailed phenotype of *HIBCHD* (38 patients) and *ECHS1D* (85 patients), focusing on MDs.

Results: The two diseases have a very similar neurological phenotype, with an early onset before 10years of age for three clinical presentations: neonatal onset, Leigh-like

syndrome (progressive onset or acute neurological decompensation), and isolated paroxysmal dyskinesia. Permanent or paroxysmal MDs were recorded in 61% of HIBCHD patients and 72% of ECHS1D patients. Patients had a variable combination of either isolated or combined MD, and dystonia was the main MD. These continuous MDs included dystonia, chorea, parkinsonism, athetosis, myoclonus, tremors, and abnormal eye movements. Patients with paroxysmal dyskinesia (HIBCHD: 4; ECHS1D: 9) usually had pure paroxysmal dystonia with normal clinical examination and no major impairment in psychomotor development. No correlation could be identified between clinical pattern (especially MD) and genetic pathogenic variants.

Conclusions: Movement disorders, including abnormal ocular movements, are a hallmark of HIBCHD and ECHS1D. MDs are not uniform; dystonia is the most frequent, and various types of MD are combined in single patient.

KEYWORDS

dystonia, inherited metabolic disease, ECHS1, HIBCH

INTRODUCTION

3-hydroxyisobutyryl-CoA hydrolase (*HIBCH*, 2q32.2) and short-chain enoyl-CoA hydratase (*ECHS1*, 10q26) are two genes that encode enzymes involved in valine catabolism and, to a lesser degree, in the catabolism of additional branched amino acids and mitochondrial functions such as fatty acid oxidation. HIBCH deficiency (HIBCHD) and ECHS1 deficiency (ECHS1D) are two rare autosomal recessive inborn metabolic diseases. An increase in plasma C4-carnitine and urinary excretion of 2-methyl-2,3-dihydroxybutyric acid has been reported in some patients [1-18]. Approximately one-third of inborn metabolic diseases cause movement disorders (MDs) that are difficult to treat and generate disability [19]. Increased severity of MD correlates with a decrease in quality of life [20]. Studies focusing on MDs in patients with HIBCHD or ECHS1D are scarce. Description of MDs in both conditions could contribute to improving diagnosis by considering metabolic screening in the diagnostic evaluation of patients with MD of unclear aetiology. The aim of this study was to characterize MDs in patients with pathogenic variants of *ECHS1* and *HIBCH*, and to determine whether there is a correlation between genotype and MD occurrence.

METHODS

Patients and ethics

Eighteen patients, born after 1994, harbouring pathogenic variants of the *HIBCH* and *ECHS1* genes were included in this multicentric, observational and retrospective study. Genetic analyses were performed using whole-exome sequencing or next-generation sequencing. For ECHS1D, an enzymatic assay of crotonase [6] was performed in fibroblasts of patients when available, to confirm the pathogenicity of the identified novel variants.

The study was approved by the Institutional Ethics Committee of the *Institut de Recherche en Biothérapies de Montpellier* according to the guidelines issued by our institutions for clinical studies which are in accordance with the Helsinki Declaration (MR004: 2019_IRB-MTP_11-23). Parents or legal guardians provided informed consent for genetic analysis in accordance with appropriate French legislation. Video authorization was obtained for disclosure (consent to disclose). Anonymized data will be shared by the corresponding author on request from a qualified investigator.

Cases of pathogenic variants of *HIBCH* or *ECHS1* previously published in the international literature were also analysed. The combination of our series with patients from the literature is referred to hereafter as the 'total series'.

Clinical and paraclinical assessment

Data concerning medical history and clinical and biological examinations were collected from medical files. Special attention was paid to the information on MDs, which were classified according to the established nosology (Fahn et al., 2011 [21]). Analysis of the MD videos was performed by two clinicians (M.-C.F.-H. and A.R.), one of whom is an expert in MDs (A.R.).

Brain magnetic resonance imaging (MRI) scans (T2, fluid-attenuated inversion recovery [FLAIR], T1, T2, diffusion and spectroscopy) were reviewed by a paediatric neuroradiologist (N.L.) and paediatric neurologist (M.-C.F.-H.).

Leigh-like syndrome diagnosis was established according to previously published clinicoradiological definition (subacute necrotizing encephalopathy with progressive neurological impairment and involvement of basal ganglia and/or brainstem. Neuroimaging criteria are bilateral symmetrical hypodensities on CT or bilateral symmetrical T2-weighted MRI hypersignal involving the brainstem and/or basal ganglia) [20].

Data on patients in previously published studies were extracted from the literature.

Statistical analysis

Patient characteristics are presented as mean (avg), median, standard deviation (σ), and maximum and minimum extreme values in the form $\text{avg} \pm \sigma$, median (min; max) for continuous variables and frequencies and proportions (%) for categorical variables. Groups (defined by HIBCHD or ECHS1D) were compared using the Wilcoxon Mann-Whitney test for continuous variables and the χ^2 or Fisher's test for categorical variables. The statistical bilateral significance threshold was set at 5%.

RESULTS

Population: general characteristics

The distribution of patients is shown in [Figure 1](#). Eighteen patients (five with HIBCHD and 13 with ECHS1D) from 10 centres were enrolled in our series ([Appendix S1](#)). Data on a total of 105 patients (33 with HIBCHD and 72 with ECHS1D) [4-47] were collected from the literature. The clinical and paraclinical characteristics of the patients are summarized in [Table 1](#). There were few clinical differences between our series (OS) and the total series (TS), but male sex, developmental regression, febrile neurological decompensation, hypotonia and spasticity (pyramidal hypertonia)/limbs hypertonia (non-pyramidal: extrapyramidal or indetermined) were more frequent in our series. Age of onset was approximately

14 ± 12 months, median 11 months (0day; 3years) in OS, and 13 ± 17 months, median 7 months (0day; 8years) in TS. The clinical presentation at onset depended on the age at disease onset and psychomotor development. We distinguished three main types of clinical presentation: neonatal (hypotonia, feeding difficulties); Leigh-like syndrome (progressive or acute/subacute onset with neurological decompensation during infectious or cellular stress); and isolated paroxysmal dyskinesia. Neonatal presentation tended to be more common in ECHS1D than in HIBCHD ($p = 0.10$). Approximately 55%–60% of patients presented with Leigh-like syndrome, with an acute/subacute onset in approximately one-third of patients. More than 80% of patients with neonatal onset or Leigh-like syndrome had psychomotor delay. Approximately 10% of the patients exhibited isolated paroxysmal dyskinesia with normal neurodevelopment and a few systemic symptoms. With the exception of patients with isolated paroxysmal dyskinesia, additional neurological symptoms and systemic symptoms were found in all patients in our series (HIBCHD: $n = 3$; ECHS1D: $n = 12$). When information was available, neurological symptoms were present in all patients (HIBCHD: $n = 31$; ECHS1D: $n = 71$) and systemic symptoms in two-thirds (HIBCHD: $n = 22$; ECHS1D: $n = 60$). Consanguinity, psychomotor delay, irritability, and cognitive impairment were more frequent in those with HIBCHD, whereas hearing loss and respiratory disorders were more frequent in ECHS1D. Laboratory biomarkers are non-specific and inconsistent in the literature, and disturbed acylcarnitine profiles with an increase in C4-carnitine have been reported occasionally. Energy metabolism dysfunction was indicated by hyperlactataemia, hyperlactatorachia, hyperalani-naemia or decreased pyruvate dehydrogenase complex (PDHc) and mitochondrial respiratory chain complex activities in half of the analysed patients ([Table 1](#); OS and TS).

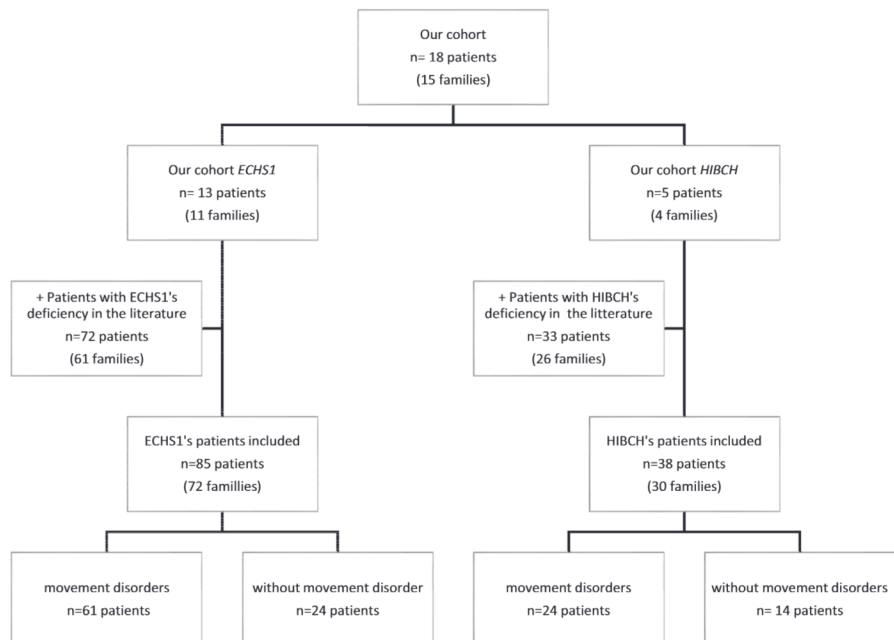


FIGURE 1 Flow chart

Movement disorders

Movement disorders were more prevalent in our series than in the literature (L) for the two pathologies (HIBCHD: OS = 100%, L = 58%, $p = 0.18$; ECHS1D: OS = 92%, L = 68%, $p = 0.15$), especially regarding chorea, athetosis, tremor and parkinsonism, but their distributions were similar (Table 2). MD was permanent in 72 patients with neonatal presentation or Leigh-like syndrome (HIBCHD: OS = 3/5 patients, TS = 20/38; ECHS1D: OS = 11/13, TS = 52/85) and paroxysmal in 13 patients with an isolated paroxysmal dyskinesia phenotype (HIBCHD: OS = 2/5 patients, TS = 4/38; ECHS1D: OS = 1/13, TS = 9/85). Dystonia was recorded in 80% of the patients with permanent MD, whereas chorea, athetosis, myoclonus, parkinsonism and tremors were less frequent. Choreic and athetoid movements were more frequently seen in the ECHS1D group ($p > 0.17$). Tics or stereotypies were not reported. MD could be isolated (HIBCHD: OS = 3/5, TS = 19/38; ECHS1D: OS = 5/13, TS = 43/85) or mixed, such as choreodystonia, choreoathetosis, dystonia-athetosis or myoclonic dystonia (HIBCHD: OS = 2/5, TS = 5/38; ECHS1D: OS = 7/13, TS = 18/85). Some MDs were complex and accompanied by neurological or systemic manifestations, such as dystonic spastic hemiparesis or dystono-ataxia (HIBCHD: OS = 5/5, TS = 22/38; ECHS1D: OS = 13/13, TS = 57/85). All continuous MDs, including isolated and combined MDs, were complex (Table 2).

Paroxysmal dyskinesia was also common in both groups: 15% in HIBCHD ($n = 4$ [43,48]; Patients 1 and 3) and 17% in ECHS1D ($n = 9$ [24,25,38,39]; Patient 13). Isolated paroxysmal dystonia started at the age of 38.2 ± 26.4 months (median 32.5 months [17 months; 8 years]) in the ECHS1D group and at 29 ± 11.5 months (median 36 months [16 months; 3 years]) in the HIBCHD group. Eight patients presented with exercise-induced dystonia (three with HIBCHD and five with ECHS1D). All patients with isolated paroxysmal dystonia had normal psychomotor development, except for two patients with ECHS1D (one with stroke-like episodes and one with isolated speech disorder). The ECHS1D patient with neonatal dyskinesia presented a different phenotype, with severe developmental delay (no head control at 1 year).

Approximately 40% of patients with HIBCHD and ECHS1D presented abnormal ocular movements, mainly nystagmus. These occurred without MD in six patients with ECHS1D (including one from our series) and seven patients with HIBCHD. Nystagmus can be rotational, horizontal, vertical, pendular and uni- or bilateral with neurological or ophthalmological origin. Strabismus was mainly convergent but could also be divergent. Other abnormal ocular movements, such as opsoclonus, eye wandering, erratic eye movements, and eye flutter were reported.

Video analysis

We analysed videos of three patients with HIBCHD (Patients 1, 2 and 3) and five patients with ECHS1D (Patients 7, 8, 12, 13 and 15; see Video S1, Appendix S1). Patients 1, 3 and 13 presented

with exercise-induced dystonia at 3 years, 16 months and 3 years, respectively. Patients 1 and 3 were recently reported [49]. Patient 13 presented with daily paroxysmal movements of the lower limbs (left > right) at the age of 3 years, at the end of the day, triggered by effort and aggravated by fatigue and no rest, without involvement of the upper limbs and with no pain, lasting from 2 min to 1 h. For other patients (Patients 2, 7, 8, 12 and 15) continuous MD was combined with dystonia, parkinsonism choreoathetosis, dystonia-athetosis, choreodystonia, and/or myoclonus (see Videos S1–S4, Appendix S1). Patients 1 and 2 were siblings with different phenotypes and severities. While Patient 1 presented with exercise-induced dystonia with almost normal psychomotor development (language disorder), Patient 2 was more severely affected by psychomotor delay and permanent MD (Video S1). Patients 7 and 8 displayed a similar Leigh-like syndrome, onset with abnormal ocular movements (divergent strabismus, horizontal nystagmus, unilateral amblyopia, opsoclonus, ocular bobbing, astigmatism and/or myopia), and combined MD (dystonia, choreodystonia, choreoathetosis and/or myoclonus). In Patients 2, 7 and 8, MD progressed from hyperkinetic syndrome at disease onset to hypokinetic syndrome after some years (Videos S1 and S2).

Brain MRI scans

Brain MRI was available for 114 patients (HIBCHD: OS = 5 patients, TS = 35; ECHS1D: OS = 13, TS = 79), and all of these patients had brain MRI abnormalities (Table 3, Figures 2 and 3). One patient had a normal brain MRI at the onset of the disease but presented with basal ganglia abnormalities at the follow-up conducted 3 months later [34]. Radiological evolution of the lesions sometimes occurred without clinical decompensation.

In HIBCHD and ECHS1D, lesions were more often bilateral with T2 hypersignal and T1 hypo/iso-signal and sometimes with diffusion restriction (hyperB1000, hypo-apparent diffusion coefficient). There was no difference in imaging patterns between patients with and without MD. Involvement of the basal ganglia was very common in both groups, affecting approximately 80%–90% of all patients. The globus pallidus was most frequently affected in the HIBCHD group, whereas involvement of the striatum was more frequent in the ECHS1D group. Indeed, among patients with MD or abnormal ocular movements, basal ganglia lesions were often restricted to the globus pallidus (HIBCHD: OS = 80% [four patients], TS = 74% [23 patients]; ECHS1D: OS = 8% [one patient], TS = 18% [12 patients]), while isolated involvement of the striatum (caudate nucleus and/or putamen) only (HIBCHD: OS = 0%, TS = 3% [one patient]; ECHS1D: OS = 0%, TS = 15% [10 patients]), or combined lesions of the globus pallidus and striatum (HIBCHD: OS = 20% [one patient], TS = 16% [five patients]; ECHS1D: OS = 69% [nine patients], TS = 53% [35 patients]) were also observed. Four patients presented with aspecific involvement of the basal ganglia (HIBCHD: $n = 2$; ECHS1D: $n = 2$), and seven patients with ECHS1D, including three from our series, had no lesions in the basal ganglia.

TABLE 1 Clinical and paraclinical characteristics in HIBCH and ECHS1 deficiencies

	Our series HIBCH (OS, n = 5)	Total series HIBCH (TS, n = 38)	Our series ECHS1 (OS, n = 13)	Total series ECHS1 (TS, n = 85)	p value (comparison within our series)	p value (comparison within total series)
Sex, % (n/N)						
Male	80 (4/5)	68 (25/37)	77 (10/13)	56 (47/84)	1	0.230
Female	20 (1/5)	32 (12/37)	23 (3/13)	44 (37/84)	1	0.230
Consanguinity, % (n/N)	40 (2/5)	50 (15/30)	8 (1/12)	17 (11/64)	0.19	0.0009
Neonatal disorders, % (n/N)	20 (1/5)	29 (11/38)	31 (4/13)	31 (26/85)	1	0.85
Feeding difficulties, % (n/N)	0 (0/5)	16 (6/38)	15 (2/13)	9 (8/85)	1	0.30
IUGR, % (n/N)	20 (1/5)	8 (3/38)	0 (0/13)	11 (9/85)	0.28	0.64
Prematurity, % (n/N)	20 (1/5)	15 (3/20)	0 (0/11)	13 (6/47)	0.31	0.8
Age of onset, avg ± σ, median (min, max)	20 ± 12 months, 16 months (1 year, 3 years)	16 ± 20 months, 7 months (0 days, 7 years)	12 ± 12 months, 12 months (0 days, 3 years)	11.7 ± 16.2 months, 6.5 months (0 days, 8 years)	0.20	2.39
Presentation at onset, % (n/N)						
Neonatal	0 (0/5)	14 (5/37)	38 (5/13)	27 (23/85)	0.24	0.10
Leigh-like syndrome	60 (3/5)	76 (28/37)	54 (7/13)	56 (48/85)	1	0.64
Acute or subacute	40 (2/5)	41 (15/37)	46 (6/13)	27 (23/85)	0.54	0.0029
Chronic	20 (1/5)	35 (13/37)	8 (1/13)	29 (25/85)	0.54	0.0029
Paroxysmal dyskinesia	20 (1/5)	11 (4/37)	8 (1/13)	8 (7/85)	0.49	0.175750
Other	0 (0/5)	0 (0/37)	0 (0/13)	8 (7/85)		
Primary psychomotor retardation (except neonatal onset)	50 (2/4)	53 (10/19)	8 (1/13)	17 (6/35)	0.02	0.007
Psychomotor retardation	80 (4/5)	91 (32/35)	92 (12/13)	93 (79/85)	0.49	0.77
Regression	60 (3/5)	45 (17/38)	69 (9/13)	40 (34/85)	1	0.62
Neurological decompensation in an infectious context	75 (3/4)	50 (19/38)	54 (7/13)	20 (17/85)	0.60	0.0007
Death, % (n/N)	20 (1/5)	22 (8/37)	54 (7/13)	39 (33/85)	0.31	0.064
Death, avg ± σ, median (min, max)	14 months	34.5 ± 30, 8 months (27 days, 8 years)	63.0 ± 65.7 months, 60.8 months (3 months, 15 years)	35.8 ± 50.7 months, 13 months (0 days, 32 years)		
Alive, % (n/N)	80 (4/5)	78 (29/37)	46 (6/13)	61 (52/85)	Global: 0.89	Global: 0.14
GMFCS score, % (n/N)						
I	50 (2/4)	10 (3/29)	17 (1/6)	10 (5/52)	0.5	1
II	0 (0/4)	3 (1/29)	17 (1/6)	2 (1/52)	1	1
III	25 (1/4)	14 (4/29)	17 (1/6)	13 (7/52)	1	1
IV	25 (1/4)	24 (7/29)	17 (1/6)	4 (2/52)	1	0.009

(Continues)

TABLE 1 (Continued)

	Our series HIBCH (OS, n = 5)	Total series HIBCH (TS, n = 38)	Our series ECHS1 (OS, n = 13)	Total series ECHS1 (OS, n = 85)	p value (comparison within our series)	p value (comparison within total series)
V	0 (0/4)	28 (8/29)	33 (2/6)	38 (20/52)	0.47	0.46
Other neurological symptoms, % (n/N)						
Microcephaly	20 (1/5)	26 (10/38)	62 (8/13)	29 (25/85)	0.29	0.72
Hypotonia	80 (4/5)	68 (26/38)	85 (11/13)	51 (43/85)	1	0.66
Spasticity/limbs hypertonia	80 (4/5)	47 (18/38)	77 (10/13)	36 (31/85)	1	0.25
Ataxia/cerebellar syndrome	20 (1/5)	26 (10/38)	38 (5/13)	19 (16/85)	0.61	0.35
Dysarthria	20 (1/5)	13 (5/38)	23 (3/13)	15 (13/85)	1	0.76
Irritability	40 (2/5)	29 (11/38)	15 (2/13)	12 (10/85)	0.53	0.019
Cognition disorders (language or interactions disorders)	80 (4/5)	75 (24/32)	69 (9/13)	53 (45/85)	1	0.031
Seizure	20 (1/5)	24 (9/38)	54 (7/13)	33 (28/85)	0.31	0.30
Others clinical symptoms						
Feeding difficulties	40 (2/5)	39 (15/38)	69 (9/13)	51 (43/85)	0.33	0.25
Failure to thrive	40 (2/5)	37 (14/38)	62 (8/13)	26 (22/85)	0.61	0.22
Visual dysfunction	40 (2/5)	24 (9/38)	38 (5/13)	31 (26/85)	1	0.43
Hearing loss	0 (0/5)	8 (3/38)	23 (3/13)	34 (29/85)	0.52	0.0022 (Fisher: 0.0017)
Cardiopathy	20 (1/5)	13 (5/38)	23 (3/13)	19 (16/85)	1	0.44 (Fisher: 0.60)
Respiratory disorders	0 (0/5)	13 (5/38)	38 (5/13)	29 (25/85)	0.25	0.052 Fisher: 0.069
Dysmorphia	0 (0/5)	13 (5/38)	15 (2/13)	7 (6/85)	1	0.27
Blood and urine abnormalities, % (n/N)						
Acylcarnitine profile	25 (1/4)	55 (16/29)	0 (0/7)	27 (13/48)	0.36	0.0137
Urine organic acids	50 (2/4)	61 (11/18)	64 (7/11)	66 (49/74)	1	0.68
Urine 23DH2MB	0	44 (4/9)	18 (2/11)	43 (32/74)		0.94
Hyperlanaemia	40 (2/5)	26 (6/23)	46 (6/13)	40 (20/50)	1	0.25
Hyperlactaemia	60 (3/5)	42 (14/33)	77 (10/13)	78 (62/80)	0.58	0.0003
Hyperlactorachia	60 (3/5)	35 (6/17)	38% (5/13)	47 (15/32)	0.61	0.43
↓Respiratory chain complex activity	0 (0/2)	47 (7/15)	75 (6/8)	59 (17/29)	0.13	0.45
↓PDHc activity	100 (2/2)	50 (5/10)	60 (6/10)	50 (18/36)	0.51	1
↓Enzymatic activity (HIBCH/ECHS1)	100 (1/1)	100 (15/15)	100 (9/9)	100 (39/39)		

Abbreviations: ECHS1, short-chain enoyl-CoA hydratase; ECHS1D, short-chain enoyl-CoA hydratase deficiency; GMFCS, Gross Motor Function Classification System; HIBCH, 3-hydroxyisobutyryl-Coa hydrolase; HIBCHD, 3-hydroxyisobutyryl-Coa hydrolase deficiency; IUGR, intrauterine growth retardation; OS, our series; PDHc, pyruvate dehydrogenase; PDHc, pyruvate dehydrogenase complex; TS, total series.

Abnormalities in the basal ganglia could change over time, with an initially significant T2 hypersignal in the globus pallidus that decreased over time, while T2 hypersignal in the striatum appeared and intensified (Patient 15 with ECHS1D) [18]. In three patients with ECHS1D with dystonia, athetosis and myoclonus, there was a heterogeneous, cloudy T2 hypersignal in the basal ganglia (Patients 7, 11 and 15; Figure 3.2 and 3.6). Worsening lesions progressing to atrophy, necrosis with cystic evolution of the basal ganglia, and secondary cerebral atrophy were observed (Patients 2, 7, 8, 11 and 12). Basal ganglia lesions could also regress, with transient diffusion restriction of the globus pallidus and striatum over 1 month (Patient 6), or remain stable (Patients 1, 3 and 13).

T2 hypersignals in the white matter were more frequent in the ECHS1D group. They were localized in the posterior periventricular white matter, but in neonatal presentations, they could be more diffuse, resembling the pattern observed following anoxic-ischaemic injury (Patient 6).

All patients with paroxysmal dystonia presented only T2 hypersignal in the globus pallidus that remained stable over time (HIBCHD: $n = 3$ [43], Patients 1 and 3; ECHS1D: $n = 5$ [24,25,38,39], Patient 13). Information was not available for one patient with involvement limited to the basal ganglia [48]. One patient presented with cerebellar atrophy (Patient 1).

Treatment

Levodopa and dichloroacetate were ineffective in the HIBCHD group. Carbamazepine (Patient 1) [43], trihexyphenidyl (Patient 2), clonazepam and baclofen (Patient 2) [14,16,43] showed variable effects. Gabapentin could be effective for paroxysmal dyskinesia at a dose of 10–20 mg/kg/day [43]. In the ECHS1D group, trihexyphenidyl, baclofen and levodopa were ineffective. Tetrabenazine could show partial or total effectiveness (Patients 8, 12, 13 and 17) against dysarthria and MD. An intrathecal baclofen pump was implanted in one patient [31] with no information regarding its effectiveness. A low protein and valine-restricted diet ± acetylcysteine supplementation may show some benefit [18,33,36,38,44,45,46,51] (Patients 8 and 15). A ketogenic diet worsened the patients' condition, as we observed in four patients in our series (Patients 4, 6, 7 and 14) and as reported in the literature [1,6,26,29]. Thiamine supplementation was effective in Patients 6 and 15 [24,50]. Exercise-induced dyskinesias improved or disappeared with carbamazepine or tetrabenazine treatment despite unrestricted physical activity. Patient 11 underwent deep brain stimulation (DBS). After febrile neurological decompensation at 22 months featuring developmental regression and necrosis of the basal ganglia, MD appeared and progressed to drug-resistant asymmetric dystonic tetraparesis, requiring DBS at 9 years. The patient improved transiently with respect to oromandibular and hemicorporeal dystonia, pain and dysphagia, but anarthria remained unchanged. Following infections with explantation and reimplantation of electrodes, DBS became inefficient, with an

increase in diffuse hypertonia and dystonia at 13 years of age, and the patient died at 15 years of age.

Genotype–phenotype correlation

Correlation between phenotype and genotype was performed in 84 patients with ECHS1D (missing genetic information in one patient) and 38 patients with HIBCHD. A total of 96 pathogenic variants were found (*HIBCH*: OS = 5 variants, TS = 32; *ECHS1*: OS = 18, TS = 62), of which six new pathogenic variants were described in *ECHS1* and three in *HIBCH* (Appendix S1). All variants were either homozygous or compound heterozygous. Allelic segregation by parental study confirmed autosomal recessive inheritance in most of the patients. Two ECHS1D variants were probably acquired de novo one parent carried a normal variant, and one parent was not tested (Patient 15, Carlston et al. [30]). The most common variant, c.476A>G p.(Gln159Arg), was identified in 16 patients (six homozygous and 10 compound heterozygous). Another common variant, c.913A>G p.(Thr305Ala), was present in 11 patients in a homozygous or compound heterozygous state associated with another variant. In one HIBCHD family, two affected children and their affected father were homozygous carriers of a variant, and the mother was heterozygous.

No correlation could be identified between pathogenic variants and phenotypic profiles, including the clinical presentation of onset, type of MD, or brain imaging abnormalities. Patients with the same pathogenic variant may have a very different MD phenotype (for example, c.913A>G in the *HIBCH* gene or c.518C>T in the *ECHS1* gene), ranging from isolated paroxysmal dyskinesia to permanent dystonia with severe psychomotor delay. The homozygous pathogenic variant c.913A>G in the *HIBCH* gene could be associated either with isolated paroxysmal dyskinesia (Patients 1 and 3) or with a severe clinical pattern with permanent dystonia, choreoathetosis, and motor regression without complete recovery (no walking and impaired communication; Patient 2), myoclonus [44], or absence of MD [16]. Brain MRI showed stable T2 hypersignal in the globus pallidus (Patient 1) or evolution with necrosis and cysts in the globus pallidus (Patient 2). In patients with HIBCHD, we noted that c.913A>G was more frequently associated with mild phenotypes, such as paroxysmal dyskinesias with a Gross Motor Function Classification System Expanded and Revised (GMFCS E&R) score of I. Indeed, the four patients with paroxysmal dyskinesias were carriers of the c.383T>A/c.1027C>G variants [43] and the c.913A>G variant in the homozygous state (Patients 1 and 3) [48]. Conversely, pathogenic variants such as c.173A>G [41], c.196C>T [14], c.287C>A [34], c.353T>C [18], c.536G>A (Patient 5), c.777T>A [18], c.808A>G [41], 950A>G [2], and c.1033G>A [4] were associated with severe phenotypes resulting in death or GMFCS E&R score V. In ECHS1D, two heterozygous variants tended to be more often associated with paroxysmal dyskinesias and a better prognosis: c.817A>G [18,25] and c.518C>T [18,25,26] (Patient 13). The c.518C>T variant was mostly reported

TABLE 2 Movement disorders and abnormal ocular movements in ECHS1 and HIBCH deficiencies

	Our series HIBCH (OS, n = 5)	Total series HIBCH (TS, n = 38)	Our series ECHS1 (OS, n = 13)	Total series ECHS1 (TS, n = 85)	p value (comparison within our series)	p value (comparison within total series)
Movement disorders, % (n/N)	100 (5/5)	63 (24/38)	92 (12/13)	72 (61/85)	1	0.22
Dystonia	60 (3/5)	71 (17/24)	75 (9/12)	87 (52/61)	1	1
Chorea	20 (1/5)	4 (1/24)	33 (4/12)	16 (10/61)	1	0.27
Athetosis	20 (1/5)	4 (1/24)	33 (4/12)	18 (11/61)	1	0.17
Myoclonus	0 (0/5)	13 (3/24)	33 (4/12)	11 (7/61)	0.26	1
Tremors	20 (1/5)	9 (2/24)	17 (2/12)	3 (2/61)	1	0.30
Tics	0 (0/5)	0 (0/24)	0 (0/12)	0 (0/61)		
Stereotypies	0 (0/5)	0 (0/24)	0 (0/12)	0 (0/61)		
Parkinsonism	20 (1/5)	9 (2/24)	33 (4/12)	20 (12/61)	1	0.27
Paroxysmal dyskinesia	40 (2/5)	17% (4/24)	8% (1/12)	15% (9/61)	0.19	1
Of which exercise-induced dyskinesia	40 (2/5)	13% (3/24)	8% (1/12)	8% (5/61)	0.19	0.39
Abnormal ocular movements, % (n/N)	40 (2/5)	37 (14/38)	62 (8/13)	41 (35/85)	0.61	0.65
Nystagmus	100 (2/2)	93 (13/14)	75 (6/8)	69 (24/35)	1	0.14
Strabismus	100 (2/2)	50 (7/14)	38 (3/8)	14 (5/35)	0.44	0.023
Movement disorders + abnormal ocular movements, % (n/N)	40 (2/5)	21 (8/38)	54 (7/13)	34 (29/85)	1	0.14

Abbreviations: ECHS1, Short chain enoyl CoA hydratase; ECHS1D, short-chain enoyl-CoA hydratase deficiency; HIBCH, 3-hydroxyisobutyryl-Coa hydrolase; HIBCHD, 3-hydroxyisobutyryl-Coa hydrolase deficiency; OS, our series; TS, total series.

TABLE 3 Magnetic resonance imaging characteristics in HIBCH and ECHS1 deficiencies

	Our series HIBCH (OS, n = 5)	Total series HIBCH (TS, n = 38)	Our series ECHS1 (TS, n = 13)	Total series ECHS1 (OS, n = 85)	p value (comparison within our series)	p value (comparison within total series)
Hypersignal T2 of basal ganglia, % (n/N)	100 (5/5)	94 (33/35)	77 (10/13)	87 (69/79)	0.52	0.27
Globus pallidus	100 (5/5)	88% (29/33)	77% (10/13)	56 (44/79)	0.52	0.0011
Striatum	0 (0/5)	15 (5/33)	69 (9/13)	56 (44/79)	0.029	0.00008
Hypersignal T2 of thalamus, % (n/N)	0 (0/5)	9 (3/35)	15 (2/13)	11 (9/79)	1	0.75
Hypersignal T2 of white matter, % (n/N)	20 (1/5)	26 (9/35)	69 (9/13)	47 (37/79)	0.12	0.034
Cerebellar atrophy, % (n/N)	40 (2/5)	17 (6/35)	38 (5/13)	22 (17/79)	1	0.8
Cerebellar signal abnormalities, % (n/N)	0 (0/5)	3 (1/35)	8 (1/13)	1 (1/79)	1	0.5
Hypersignal T2 of dentate nucleus, % (n/N)	0 (0/5)	14 (5/35)	8 (1/13)	4 (3/79)	1	0.057
Cerebral atrophy, % (n/N)	20 (1/5)	40 (14/35)	46 (6/13)	39 (31/79)	0.60	0.94
Thinning of corpus callosum, % (n/N)	0 (0/5)	9 (3/35)	31 (4/13)	18 (14/79)	0.11	0.54
Hypersignal T2 of corpus callosum, % (n/N)	20 (1/5)	14 (5/35)	46 (6/13)	19 (15/79)	0.6	0.6
Mesencephalon, % (n/N)	20 (1/5)	26 (9/35)	23 (3/13)	18 (14/79)	1	0.33
Metencephalon, % (n/N)	0 (0/5)	0 (0/35)	8 (1/13)	3 (2/79)	1	1
Hypersignal T2 of substantia nigra, % (n/N)	0 (0/5)	0 (0/35)	0 (0/13)	8 (6/79)	1	0.17
Lactate peak, % (n/N)	66 (2/3)	78 (7/9)	75 (6/8)	67 (22/33)	1	0.52
Decrease in N-acetylaspartate, % (n/N)	33 (1/3)	33 (3/9)	25 (2/8)	21 (7/33)	1	1
Leigh syndrome, % (n/N)	60 (3/5)	89 (31/35)	85 (11/13)	84 (66/79)	0.53	0.58

Abbreviations: ECHS1, Short chain enoyl CoA hydratase; ECHS1D, short-chain enoyl-CoA hydratase deficiency; HIBCH, 3-hydroxyisobutyryl-CoA hydrolase; HIBCHD, 3-hydroxyisobutyryl-Coa hydrolase deficiency; MRI, magnetic resonance imaging; MRS, magnetic resonance spectrometry.

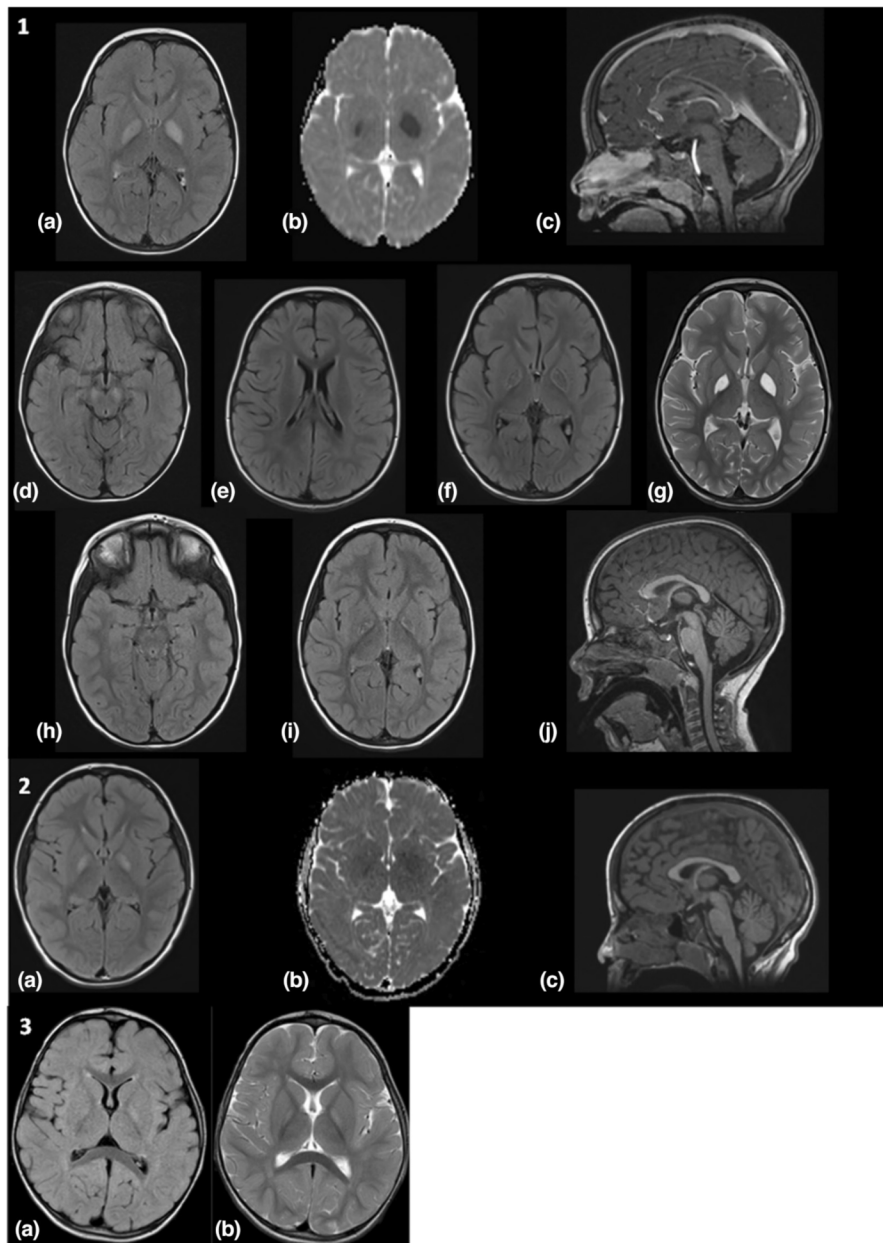
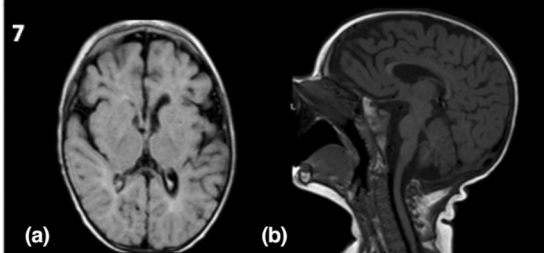
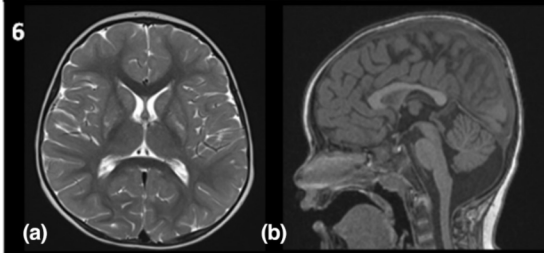
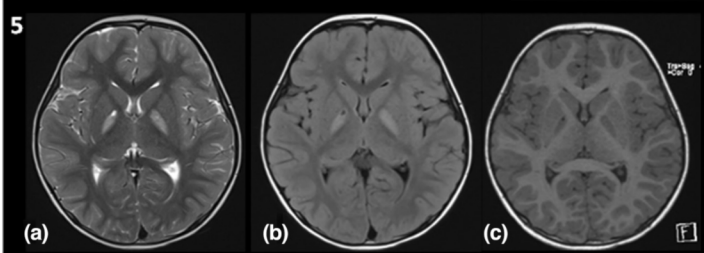
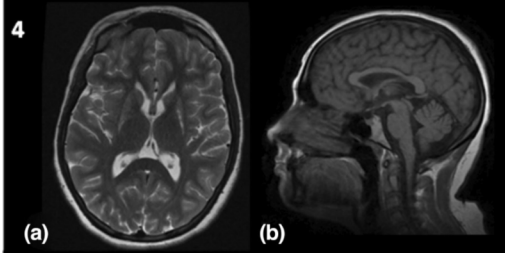
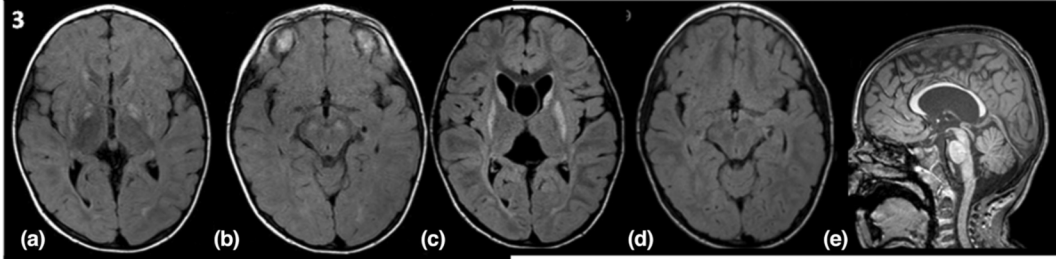
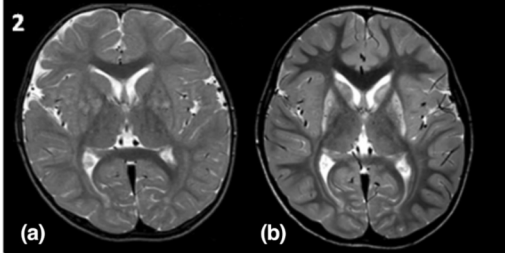
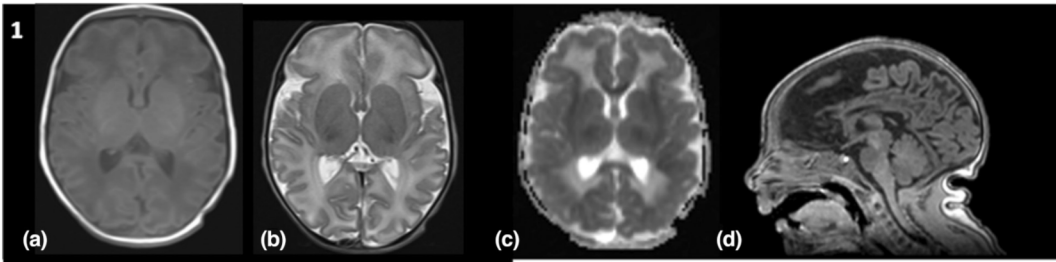


FIGURE 2 Magnetic resonance imaging (MRI) scan of patients with 3-hydroxyisobutyryl-Coa hydrolase deficiency (HIBCHD). 1/MRI scan of Patient 2 at 2 years old, 6 days after onset of disease (A–D), 1 month after (E–H) and 6 months after (I–K). After 6 days: bilateral hypersignal T2 fluid-attenuated inversion recovery (FLAIR) images of globus pallidus (axial T2 FLAIR, A) with restriction of diffusion (axial apparent diffusion coefficient [ADC], B) and respect for the striatum and cerebellum (sagittal T1, C). After 1 month: appearance of a transient FLAIR hypersignal of posterior corticospinal tracts in brain peduncles (axial FLAIR, D). Necrosis and cavitation of globus pallidus in FLAIR sequences (axial FLAIR, E and F) and T2 sequence (axial, G). After 6 months: disappearance of FLAIR hypersignal of brain peduncles (axial FLAIR, H). Persistence of globus pallidus hypersignal FLAIR (axial FLAIR, I). Atrophy of the cerebellum (sagittal T1, J). 2/MRI Scan of Patient 1 at 6 years old: hypersignal FLAIR of globus pallidus (axial FLAIR, A) with restriction of diffusion (axial ADC, B) and cerebellum vermis hypotrophy (sagittal T1, C). 3/MRI brain of Patient 3 at 1 year: bilateral hypersignal FLAIR of globus pallidus (axial FLAIR, A) and T2 (axial T2, B). MRI of patients 2, 1 and 3 showed a Leigh-like pattern.

with the mild phenotype, suggesting a genotype–phenotype correlation (possibly related to reduced impact on protein function) but it was also identified in one patient with a severe phenotype

[51], suggesting the involvement of other genetic or environmental factors. Regarding severity, two other variants tended to be associated with a better prognosis regarding learning to walk,

FIGURE 3 Magnetic resonance imaging (MRI) scan of patients with short-chain enoyl-CoA hydratase deficiency (ECHS1D). 1/MRI scan of Patient 6: at 7 days: hyposignal T1 (A) and hypersignal T2 (B) of deep and peripheral bihemispheric white matter. Restriction of diffusion of basal ganglia (striatum and globus pallidus) and thalami (axial apparent diffusion coefficient [ADC], C). At 1 month: diffuse cerebral atrophy and atrophy of the corpus callosum (sagittal T1, D). 2/MRI scan of Patient 7: at 12 months: heterogenous hypersignal T2 of striatum and globus pallidus; hypersignal T2 of white matter (axial T2, A). At 6 years: atrophy of putamen and globus pallidus; persistence of hyposignal T2 of white matter (axial T2, B). 3/MRI scan of Patient 8: at 15 months: heterogenous hypersignal T2 of striatum and globus pallidus (axial fluid-attenuated inversion recovery [FLAIR], A). Hypersignal FLAIR of cerebral peduncles (Axial FLAIR, B) At 6 years: attenuation of the FLAIR hypersignal of globus pallidus with accentuation of the signal in the striatum (axial FLAIR, C). Disappearance of cerebral peduncles hypersignal FLAIR (axial FLAIR, D). Vermal hypotrophy at the 3rd percentile (sagittal T1, E). 4/MRI scan of Patient 12 at 15 years: hypersignal T2 (axial T2, A) of striatum with atrophy of caudate nucleus. Vermal hypotrophy (sagittal T1, B). 5/MRI scan of Patient 13 at 3 years: hypersignal T2 (axial T2, A), hypersignal FLAIR (axial FLAIR, B) and hyposignal T1 (axial T1, C) of globus pallidus. 6/MRI scan of Patient 15: bilateral heterogenous hypersignal T2 of globus pallidus (axial T2, A). Vermal hypotrophy (sagittal T1, B). 7/MRI scan of Patient 16: cerebral atrophy, pontocerebellar hypoplasia (axial FLAIR, A and sagittal T1, B). MRI of patients 7, 8, 12, 13 and 15 showed a Leigh-like pattern.



as observed in the three patients carrying the c.830C>T variant (Patients 15 and 17) [18] and two-thirds of the patients carrying the c.244G>A variant (Patient 10) [36].

DISCUSSION

HIBCH deficiency and ECHS1D are two autosomal recessive diseases with common pathogenesis mechanisms and shared characteristics, including clinical and paraclinical patterns, mode of onset, and management. The mode of onset can be categorized into three patterns: neonatal onset, Leigh-like syndrome, or paroxysmal dyskinesias. MDs are very frequent symptoms occurring in 60% to 70% of patients; abnormal ocular movements occur in 40% of patients. MDs vary widely, being permanent or paroxysmal. They are typically characterized as mixed MD (dystonia, chorea, tremor, myoclonus, parkinsonism and athetosis), with dystonia as a major feature. MDs tended to be more frequently reported and more diverse in our series; chorea, athetosis and parkinsonism were more prevalent in our group of patients than in the literature (OS = 28% vs. L = 13%–16%). Thus, the frequency and diversity of MDs were probably underestimated in the total series. The course of MD in patients with HIBCHD and ECHS1D has been rarely described in the literature. In our series, MD follow-up assessment using sequential video recordings of three patients revealed MD progression from hyperkinetic to hypomobile choreodystonia over 3–4 years (Patients 2, 7 and 8). This time-dependent motor pattern could reflect an interaction between neurodevelopment and disease-related static lesions of the motor circuits [52]. In keeping with this hypothesis, a very similar age-dependent course has been reported in other neurometabolic disorders involving striatopallidal dysfunction, such as GM1 gangliosidosis [53] and Lesch-Nyhan disease [54]. Alternatively, change from a hyperkinetic to a hypokinetic phenotype might reflect an ongoing progressive neurodegenerative process, as reported in other hereditary neurodegenerative disorders [55].

The MD spectrum related to HIBCHD and ECHS1D is similar to that of other inherited metabolic diseases, especially organic acidurias, mitochondriopathies and PDHc deficiency. Paroxysmal dyskinesias occur in mitochondrial diseases, PDHc deficiency, and *GLUT1* deficiency [20]. Similarly to our patients, patients with PDHc deficiency may exhibit exercise-induced dyskinesia. While a ketogenic diet is the 'gold standard' management for these patients, it can be very deleterious for patients with HIBCHD and ECHS1D, as reported in four patients in our series (Patients 4, 6, 7 and 14), although secondary enzymatic PDHc deficiency was demonstrated in the cells of Patients 4 and 6 (Appendix S1). Thus, we suggest that secondary PDHc deficiency be ruled out before attempting a ketogenic diet, when the patient's clinical status allows delay, using biomarkers that may be suggestive but are not constant (increased C-4 carnitine on acyl carnitine profile, or increased urinary excretion of 2-methyl-2,3-dihydroxybutyric acid) or using molecular analysis (gene panels or next-generation sequencing). Moreover, we propose that a poorly tolerated ketogenic diet in patients with Leigh-like syndrome or suspected PDHc deficiency strongly suggests a diagnosis

of HIBCHD or ECHS1D. Low-protein and valine-restricted diet with or without acetylcysteine supplementation could then be tested [56].

Despite the rarity of these pathologies, we were able to enroll 18 patients and included 123 patients from the literature. Establishing correlations remained difficult because of the lack of statistical power. We found no specific correlation between MD and MRI brain scan lesions; however, given the lack of consistent biomarkers, MRI may assist in the differential diagnosis of MD. MRI scans showed basal ganglia T2 hypersignal preferentially in the globus pallidus of patients with HIBCHD and involved the globus pallidus and putamen in patients with ECHS1D, with a heterogeneous pattern [57]. MRI of patients with paroxysmal dyskinesias was characterized by isolated T2 hypersignal of the globus pallidus; therefore, we propose that, in a patient with MD, T2 hypersignal of the pallidum may suggest a diagnosis of valine metabolism disturbances. In general, we found no correlation between the pathogenic variants and clinical phenotypes. Indeed, in contrast to Marti-Sanchez et al. [18], we could not establish a correlation between the location of the abnormality on the protein and the severity of the phenotype.

Data concerning MDs in our series were collected retrospectively from medical files, which clearly represents a limitation of our study. We were unable to focus on speech disturbance (especially orofacial dystonia, hyperkinetic dysarthria, and speech ataxia) because of the lack of clinical data in the medical files, as previously performed for a group of patients with type 1 glutaric aciduria [52]. Moreover, patients in previously published studies were not specifically assessed by physicians skilled in MD, and details concerning MD were sometimes poorly reported or missing. This may explain some of the discrepancies between our series and the literature.

A limited number of videos were available for expert analysis; video analysis by experts allowed the identification of parkinsonism in three videos, which had not been described in the patients' medical file. Patient video recording, according to a specific protocol of MD, would allow reliable proofreading by expert centres, and thereby help standardize and refine the characterization of MD.

In conclusion, deficiencies in HIBCH and ECHS1 are involved in valine catabolism and various mitochondrial functions. MDs, including abnormal ocular movements, are a hallmark of these diseases. MDs are not uniform; dystonia is the most frequent, and MDs are mainly combined. Our retrospective study highlights the difficulties in MD assessment in daily practice; follow-up of the patients will help clarify the long-term course of MD in this group of patients.

AUTHOR CONTRIBUTIONS

Marie-Céline François-Heude: Data curation (equal); formal analysis (lead); writing – original draft (lead). **Elise Lebigot:** Data curation (equal); formal analysis (equal); writing – original draft (equal); writing – review and editing (equal). **Emmanuel Roze:** Data curation (equal); writing – review and editing (equal). **Marie-Therese ABIWARDE:** Data curation (supporting). **Claude Cancès:** Data curation (equal). **Lena Damaj:** Data curation (equal). **Caroline Espil-Taris:** Data curation (equal). **Joel Fluss:** Data curation (equal). **Pascale Delonlay:** Data curation (equal); writing – review and editing (equal). **Ilse Kern:** Data curation (equal). **guy lenaers:** Data curation (equal). **Arnold Munnich:**

Data curation (equal). **P Meyer**: Data curation (equal); writing – review and editing (equal). **Marie-Aude Spitz**: Data curation (equal). **Stephanie Torre**: Data curation (equal). **Diane Doummar**: Data curation (equal). **Guy Touati**: Data curation (equal); writing – review and editing (equal). **Nicolas Leboucq**: Data curation (equal); investigation (equal); validation (equal). **Agathe Roubertie**: Conceptualization (lead); data curation (lead); methodology (lead); supervision (lead); validation (lead); writing – review and editing (equal).

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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