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ORIGINAL ARTICLE

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Brain MR patterns in inherited disorders of monoamine neurotransmitters: An analysis of 70 patients

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Abbreviations: AADCD, aromatic L-amino acid decarboxylase deficiency; ADC, apparent diffusion coefficient; adGTPCHD, autosomal dominant GTP-cyclohydrolase deficiency; arGTPCHD, autosomal recessive GTP-cyclohydrolase deficiency; BCR, bicaudate ratio; BH_2, 7,8-dihydrobiopterin; BH_4, tetrahydrobiopterin; CNS, central nervous system; CSF, cerebrospinal fluid; DHPRD, dihydropteridine reductase deficiency; DWI, diffusion-weighted imaging; iMND, inherited monoamine neurotransmitter disorder; iNTD, International Working Group on Neurotransmitter Related Disorders; MAOAD, monoamine oxidase A deficiency; MRI, magnetic resonance imaging; NOS, nitric oxide synthase; PRES, posterior reversible encephalopathy syndrome; PTPSD, 6-pyruvoyl-tetrahydropterin synthase deficiency; qBH_2, q-dihydrobiopterin; SRD, sepiapterin reductase deficiency; T1w, T1-weighted; T2w, T2-weighted; THD, tyrosine hydroxylase deficiency

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Abstract

Inherited monoamine neurotransmitter disorders (iMNDs) are rare disorders with clinical manifestations ranging from mild infantile hypotonia, movement disorders to early infantile severe encephalopathy. Neuroimaging has been reported as non-specific. We systematically analyzed brain MRIs in order to characterize and better understand neuroimaging changes and to re-evaluate the diagnostic role of brain MRI in iMNDs. 81 MRIs of 70 patients (0.1-52.9 years, 39 patients with tetrahydrobiopterin deficiencies, 31 with primary disorders of monoamine metabolism) were retrospectively analyzed and clinical records reviewed. 33/70 patients had MRI changes, most commonly atrophy (n = 24). Eight patients, six with dihydropteridine reductase deficiency (DHPR), had a common pattern of bilateral parieto-occipital and to a lesser extent frontal and/or cerebellar changes in arterial watershed zones. Two patients imaged after acute severe encephalopathy had signs of profound hypoxic-ischemic injury and a combination of deep gray matter and watershed injury (aromatic L-amino acid decarboxylase (AADCD), tyrosine hydroxylase deficiency (THD)). Four patients had myelination delay (AADCD; THD); two had changes characteristic of post-infantile onset neuronal disease (AADCD, monoamine oxidase A deficiency), and nine T2-hyperintensity of central tegmental tracts. iMNDs are associated with MRI patterns consistent with chronic effects of a neuronal disorder and signs of repetitive injury to cerebral and cerebellar watershed areas, in particular in DHPRD. These will be helpful in the (neuroradiological) differential diagnosis of children with unknown disorders and monitoring of iMNDs. We hypothesize that deficiency of catecholamines and/or tetrahydrobiopterin increase the incidence of and the CNS susceptibility to vascular dysfunction.

KEYWORDS

inherited neurotransmitter disorders, monoamines, MRI, tetrahydrobiopterin deficiency, watershed injury

1 | INTRODUCTION

Inherited monoamine neurotransmitter disorders (iMNDs) are rare disorders resulting from defects of biosynthesis, degradation, or transport of monoamine neurotransmitters, or of biosynthesis or recycling of tetrahydrobiopterin (BH_4), which is essential for their synthesis. This group of disorders include (a) disorders of BH_4 synthesis and recycling (autosomal recessive and autosomal dominant GTP-cyclohydrolase deficiency (arGTPCHD, adGTPCHD), 6-pyruvoyl-tetrahydropterin synthase deficiency (PTPSD), dihydropteridine reductase deficiency (DHPRD), sepiapterin reductase deficiency (SRD), pterin-4a-carbinolamine dehydratase deficiency), (b) primary disorders of monoamine neurotransmitter synthesis (aromatic L-amino acid decarboxylase deficiency (AADCD), tyrosine hydroxylase deficiency (THD)), (c) disorders of monoamine neurotransmitter catabolism (dopamine β-hydroxylase deficiency, monoamine oxidase A/B deficiency [MAOA/BD]), (d) disorders of monoamine neurotransmitter transport (dopamine transporter deficiency, vesicular monoamine transporter 2 deficiency), and (e) co-chaperone associated disorders (DNAJC12 deficiency). These deficiencies result in disruption of dopaminergic and/or serotoninergic neurotransmission mainly in the central nervous system.

Clinical manifestations range widely from mild infantile hypotonia, late-onset movement disorder to early infantile severe encephalopathy.[1] Thus, iMNDs can mimic many other more common neurological conditions such as neuromuscular disorders, cerebral palsy, or other genetic movement disorders and are very likely under-recognized.

Due to the manifold neurological signs and symptoms, recognizing suggestive motor signs such as dystonia, oculogyric crises and hypotonia is crucial and a high index of clinical suspicion of iMNDs is necessary. Diagnosis is based on the measurement of pterins in cerebrospinal fluid (CSF), urine and blood, measurement of monoamines and amino acids in CSF, and targeted molecular genetic investigations.[2,3] Since arGTPCHD, PTPSD, DHPRD and PCDD present with hyperphenylalaninemia,[4] early detection by newborn screening for phenylketonuria is possible.

To date, brain MRI is not part of the diagnostic investigations recommended in iMNDs,[5,6] since—in contrast to leukodystrophies where the pattern of brain structures involved has been shown to be highly specific and effective for differential diagnosis[7]—imaging findings so far reported in iMNDs are non-specific. These comprise predominantly normal findings as well as myelination delay, hypomyelination, white matter signal alterations, basal ganglia calcifications, and brain atrophy.[6,8-15] The majority of these findings, however, are based on case reports or questionnaires and no dedicated neuroradiological imaging analysis has been performed as yet.

SYNOPSIS

iMNDs are associated with MRI changes characteristic of chronic effects of a neuronal disorder and have a propensity to cause cerebral and cerebellar watershed injury, which is important for differential diagnosis and for monitoring.

In order to characterize brain imaging changes in iMNDs and re-evaluate the diagnostic role of brain MRI, we retrospectively and systematically analyzed 81 MRI scans of 70 patients enrolled in the international longitudinal patient registry of the International Working Group on Neurotransmitter Related Disorders (iNTD).[16]

2 | PATIENTS AND METHODS

Patients with genetically and/or biochemically proven iMNDs in the iNTD patient registry study (approved by the Institutional Ethics Committee of the University of Heidelberg, S-471/2014, subsequently by all contributing clinical partners and listed in the German Clinical Trials Register, https://www.drks.de, DRKS00007878, informed consent obtained from all patients or their legal guardians prior to being included in the study) who had undergone brain MRI as part of their clinical investigation, were retrospectively identified. Two of 72 patients were excluded from analysis due to imaging artifacts. For the resulting 70 patients the iNTD database was reviewed for disease type, clinical presentation, age at initial symptoms and at diagnosis.

All 81 MRI scans of the 70 patients (age at examination 0.1-52.9 years, mean 6.9 years, median 2.3 years, one follow-up MRI in five patients, two follow-up MRIs in three patients, follow-up interval 0.3-7.3 years) were systematically reviewed in consensus by two experienced pediatric neuroradiologists (IH, AM), blinded for the biochemical defect and clinical findings. T2-weighted (T2w) and T1-weighted (T1w) images were available for all patients and MRI scans, diffusion-weighted imaging (DWI) including apparent diffusion coefficient (ADC) for 47 patients (54 MRIs). MRI was assessed for myelination, for the presence and extent of signal changes of gray and white matter on T2w images, and for corresponding T1-signal changes. White matter signal changes in incompletely myelinated patients were assessed as not

consistent with delayed myelination if signal differed from that of unmyelinated white matter and/or later myelinating areas where normally myelinated. Diffusion was rated as restricted only in patients with corresponding low signal on ADC-maps. T2 gradient echo and susceptibility-weighted images, available for 24 patients (25 MRI scans) were checked for hypointensities due to calcifications and/or blood degradation products. Atrophy was evaluated visually as widened internal and/or outer CSF spaces and/or thin corpus callosum for age. In addition, the bicaudate ratio (BCR), a surrogate parameter of supratentorial brain atrophy and defined as the minimum intercaudate distance divided by the transverse width of the inner table of the skull at the same level, was determined and compared with controls using *z*-scores and age-adapted control values.[17]

3 | RESULTS

3.1 | Patients

Thirty-nine patients had BH_4 deficiencies (arGTPCHD (n = 2), adGTPCHD (n = 8), PTPSD (n = 13), DHPRD (n = 9) and SRD (n = 7)) and 31 patients had primary disorders of monoamine metabolism (AADCD (n = 12), THD (n = 16) and MAOAD (n = 3)).

In BH_4 deficiencies, onset of symptoms was predominantly during childhood in adGTPCHD and in early infancy in the others. Dystonia was the most common movement disorder and often the only symptom in adGTPCHD, whereas clinical manifestation in the other BH_4 deficiencies included hypotonia and developmental delay, in some with additional oculogyric crises. Epilepsy was very common in patients with DHPRD and PTPSD.

In AADCD onset of symptoms was in the neonatal period or early infancy. Patients presented with a complex clinical picture comprising hypotonia, seizures, developmental delay, as well as motor (dystonia, dyskinesia, oculogyric crises) and non-motor symptoms (sleep disorders and thermal dysregulation). The vast majority of patients with THD presented in early infancy with dystonia and hypotonia, accompanied by developmental delay. Sleep problems, epilepsy, and behavioral problems were the main symptoms of MAOA deficient patients. Two patients, one each with AADCD and THD, had acute, severe clinical deterioration in the setting of intercurrent infection necessitating intensive care.

Cardinal clinical manifestation is summarized in Table 1 and listed in more detail and per patient in Table S1.

TABLE 1 Summary of clinical findings for each disease

Disease		Age at initial symptoms (range, months)	Movement disorder	Epilepsy	Developmental delay	Hypotonia	Oculogyric crises	Autonomic symptoms (sleep and thermoregulation disorders)
Disorders of monoamine metabolism (n = 31)	AADCD (n = 12)	0-5	9/9	1/12	12/12	12/12	9/12	7/12
	THD (n = 16)	0-60	15/15	3/16	14/15	13/15	10/16	5/16
	MAOAD (n = 3)	1-24	0/3	2/3	3/3	1/3	0/3	3/3
BH_4 deficiencies (n = 39)	ArGTPCHD (n = 2)	1, 4	2/2	0/2	2/2	2/2	2/2	1/2
	AdGTPCHD (n = 8)	12-516	5/6	0/8	0/8	0/8	0/8	1/8
	PTPSD (n = 13)	0-192	6/12	3/12	7/11	7/13	4/13	2/13
	DHPRD (n = 9)	1-24	5/8	6/9	7/9	3/9	4/8	3/8
	SRD (n = 7)	2-6	4/6	0/7	5/6	2/7	5/7	3/7

Note: Number of total patients may vary between clinical findings for a disease depending on availability of data.

3.2 | Spectrum of MRI findings

Brain MRI changes were observed in 37 of 70 patients in at least one MRI, while 33 patients had normal imaging. Atrophy was the most common finding (n = 24) followed by signal alterations of supratentorial white matter with variable involvement of gray matter structures (n = 12), T2-hyperintensity of central tegmental tracts (n = 9), and myelination delay (n = 4).

Forty-four of 81 MRIs were acquired until diagnosis (age at MRI 4 months—15 years, mean 45 months, median 15 months; 0 months—12 years after onset of symptoms; n = 21 normal) and 37 after diagnosis (age at MRI 1 months—52 years, mean 126 months, median 72 months; 5 months - 37 years after onset of symptoms; n = 16 normal). MRI findings are summarized for the different disorders in Table 2 and tabulated per patient in Table S2.

3.3 | Myelination delay

Myelination was delayed by 2 to 3 months in four patients imaged between the age of 5 and 6 months (THD_03, THD_05, AADCD_02, AADCD_03). Follow-up MRIs available for THD_03 and THD_05 demonstrated progressing, though still delayed myelination at 10, 13, 15, and 22 months not related to treatment since these MRIs were acquired before diagnosis. In THD_03, T2-hyperintensity of parietal and subsequently frontal white matter became visible with progressing myelination (Figure S1). Myelination was complete in all patients imaged after the age of 2 years and a severe persisting deficit of myelin consistent with hypomyelination[7] was not observed in any patient.

3.4 | White and gray matter signal changes

White matter signal changes not consistent with delayed myelination and not confined to central tegmental tracts were present in 12 patients imaged between 8 months and 25 years (DHPRD (n = 6), AADCD (n = 2), MAOAD (n = 2), THD (n = 2)) and were accompanied by gray matter changes in six patients.

Eight patients had a common pattern consisting of bilateral changes of parieto-occipital and to a lesser extent of frontal white and/or cortical gray matter with variable additional involvement of cerebellar cortex (DHPRD (n = 6), MAOAD (n = 1), THD (n = 1); age at MRI 15 months—15 years, MRI before diagnosis (n = 3), MRI 2.5-12 years after diagnosis (n = 5)). The extent of changes ranged from patchy and small circumscribed changes, in one patient confined to parietal white matter, to larger, wedge-like changes in cerebrum and cerebellum (Figures S1 and S2). The cerebral cortex was affected in three patients, involving parieto-occipital cortex in all, frontal cortex in two, and the cerebellar cortex was affected in two patients. Distribution of lesions was consistent with injury in cerebral and cerebellar watershed zones.[18] In the three patients with DWI, restricted diffusion of some but not all cortico-subcortical lesions was consistent with repetitive ischemia (DHPRD_05, DHPRD_06, DHPRD_07; Figure 1C, Figure S2A,B). Intracranial time-of-flight MR angiography, obtained in DHPRD_06, was normal, and acute clinical deterioration was not reported for any of these eight patients.

Two patients (AADCD_04, MAOAD_03; Figure 2) imaged 8 month and nearly 5 years after diagnosis had mild T2-hyperintensity of supratentorial white matter, decreased contrast at the cortical-white matter interface, and mildly thinned cortex. This is a characteristic though nonspecific imaging pattern seen in neuronal disorders of post-infantile onset.[19,20] In patient AADCD_04 this pattern was preceded by circumscribed T2-hyperintensity of the optic radiation in the initial MRI at 8 months.

Two patients were imaged after acute encephalopathic episodes triggered by intercurrent infection: Patient AADCD_06 with a classic severe neurologic phenotype, diagnosed at 18 months, was hospitalized at the age of 9 months following an upper respiratory tract infection, which required intubation, mechanical ventilation, and prolonged intensive care. Subsequent MRI demonstrated changes consistent with profound hypoxic-ischemic injury comprising restricted diffusion of supratentorial white matter, T1-hyperintense cortical laminar necrosis, deep gray matter injury to thalami, basal ganglia, and dentate nuclei, and cerebellar watershed injury (Figure 3A,B). In patient THD_10 with developmental delay, epilepsy, dystonia, thermal dysregulation, sleep problems, and diagnosis at 29 months of age, a first MRI at 17 months demonstrated only mild cerebral atrophy. At 25 months loss of consciousness and arterial hypotension following a fever episode necessitated cardiopulmonary resuscitation. MRI revealed new cerebral and cerebellar watershed injury and involvement of dentate nuclei and basal ganglia. Diffusion was neither restricted nor facilitated consistent with pseudonormalization (Figure 3C,D).

T2-hyperintensity of central tegmental tracts was present in 9 patients. It was an isolated finding in six patients (arGTPCHD (n = 2), PTPSD (n = 2), AADCD (n = 1), DHPRD (n = 1)), follow-up MRIs demonstrating its transient character in PTPSD_03. It was combined with a thin corpus callosum in DHPRD_03, and with

TABLE 2 Summary of MRI findings for each disease

Diagnosis		n	Normal*	Myelination delay	Supratentorial white matter		Cortical gray matter		Deep gray matter		Pattern			Centr. tegm. tract	Atrophy	Other
					Total	Localization	Total	Localization	Total	Localization	Watershed	Neuronal	Other			
Disorders of monoamine metabolism (n = 31)	AADCD	12	6	2	2	Diffuse	1	Supratentorial (diffuse) and cerebell.	1	bgl., thalamus, dentate		1	1 diffuse posthypoxic injury	1	3	1 no bright posterior pituitary
	THD	16	7	2**	2**	par. and frontal (1), diffuse (1)	1	cerebellar	1	bgl., dentate	1		1 watershed and diffuse and deep gray matter	1	9	1 IHI
	MAOAD	3	0	0	2	par.occ. (1), diffuse (1)	1	par.occ., frontal, cerebellar	1	bgl.	1	1		0	3	1 IHI, small pituitary, no bright spot
BH_4 deficiencies (n = 39)	AdGTPCHD	8	6	0	0		0		0					0	0	1 IHI, 1 arachnoid cyst
	ArGTPCHD	2	0	0	0		0		0					2	0	
	PTPSD	13	7	0	0		0		0					2	4	1 IHI
	DHPRD	9	1	0	6	par.occ. (6), frontal (2)	2	par.occ. (2), cerebellar (1)	2	subst. nigra	6			3	4	2 IHI
	SRD	7	7	0	0		0		0					0	1	
	Sum	70	36	4	12		5		5		8	2	2	9	24	

*Normal in patents with follow-up(s) only if all MRIs were normal.

**THD_03 with myelination delay and subsequent white matter changes included in both columns. bgl., basal ganglia; IHI, incomplete hippocampal inversion; par.occ., parieto-occipital.

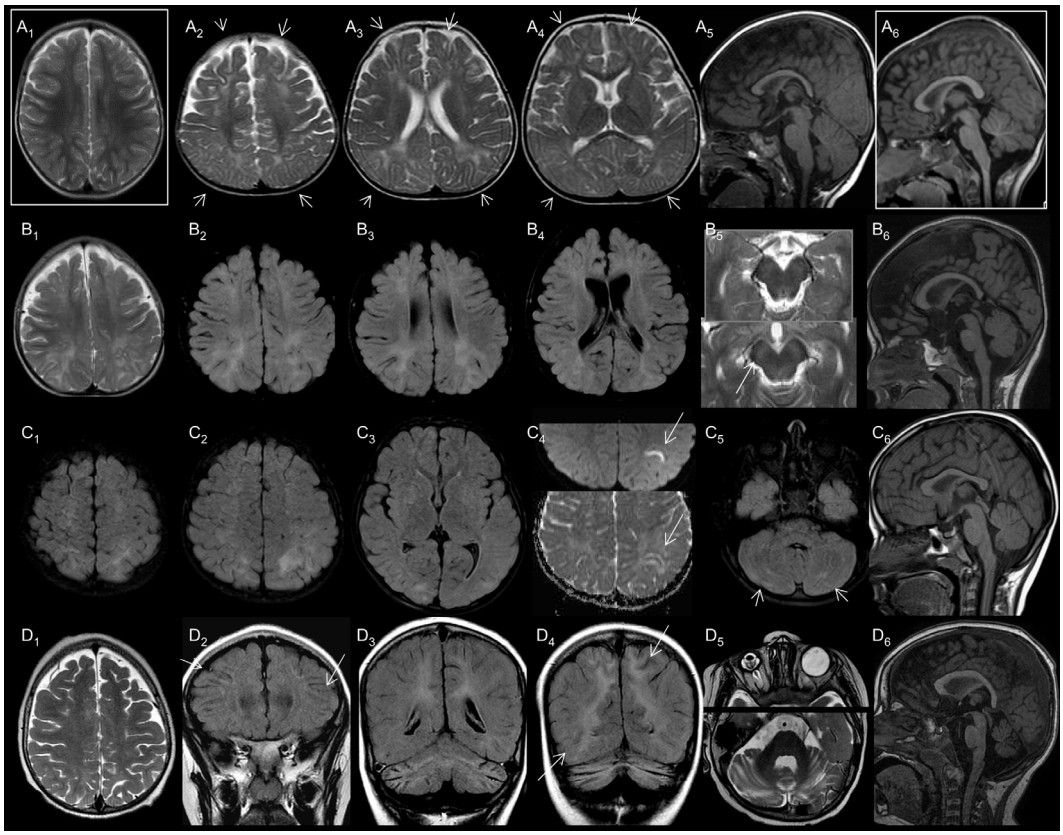

FIGURE 1 Wedge-like watershed injury. A, 15-month-old DHPRD_01 with frontal and parieto-occipital T2-hyperintensity ($A_{2\text{-}4}$, exemplary arrowheads, compare with A_1 from 15-month-old patient with normal imaging). Corpus callosum is too thin for age, in particular in its dorsal portion (A_5, compare with normal image in A_6). B, 20-month-old DHPRD_02 with wedge-like T2/FLAIR-hyperintensities of parieto-occipital and frontal white matter in ($B_{1\text{-}4}$) and mild T2-hyperintensity of substantia nigra (arrow in B_5 below; compare with normal image above from a 20-month-old patient examined at the same scanner using the same sequence). Global atrophy with widened ventricles (B_4) and a dorsally thin corpus callosum (B_6). C, In 6-year-old DHPRD_05 supratentorial changes are focally accentuated in the left parietal lobe (C_2) with restricted diffusion (arrows in C_4: DWI (above), ADC-map (below)). Cerebellar watershed injury (arrows in C_5). Absence of atrophy including normal corpus callosum (C_6). D, 4-year-old patient MAOAD_02 with watershed injury the depth of frontal sulci (D_2) and of parieto-occipital white matter and cortex (D_4), extensive cerebellar watershed injury (D_4), predominantly infratentorial atrophy (D_5) and a dorsally thin corpus callosum (D_6). NB persisting hyperplastic primary vitreus in right orbit (D_5). (T2w: $A_{1\text{-}4}$,$B_{1,5}$,$D_{1,5}$; FLAIR: $B_{2\text{-}4}$,$C_{1\text{-}3,5}$,$D_{2\text{-}4}$; DWI/ADC: C_4 above/below; T1w: A_5,A-D_6; normal images for comparison: $A_{1,6}$,$B_{5\text{above}}$)

changes in cerebral border zones and atrophy in THD_03 and DHPRD_02.

Changes of *substantia nigra* were observed in two patients with DHPRD who also had changes in supratentorial watershed areas. No patient had isolated involvement of gray matter.

3.5 | Atrophy and other findings

Nonspecific, variable *atrophy* was present in 24 patients (29 MRI scans) imaged between 5 months and 25 years. Twenty-three patients had supratentorial atrophy, five had infratentorial atrophy. Supratentorial atrophy in 14 patients was global with widening of ventricles and sulci, often of frontotemporal predominance, and an increased bicaudate ratio with *z*-scores[17] of at least 2. The other patients had more focal signs of volume deficit, namely a thin corpus callosum as an indicator of supratentorial white matter deficit, bilaterally wide frontotemporal sulci, and/or a unilaterally wide temporal horn.

In three patients a slightly wide left anterior temporal horn was not rated as atrophy as it was due to a round, relatively medially positioned hippocampus and a deep, verticalized collateral sulcus, consistent with *incomplete hippocampal inversion* (DHPRD_06, AdGTPCD_02, PTPSD_12; Figure S3). In three other patients, incomplete hippocampal inversion was observed in addition to global atrophy (DHPRD_09 MAOAD_03 and THD_09). With the exception of AdGTPCHD_02, all patients with incomplete hippocampal inversion had epilepsy.

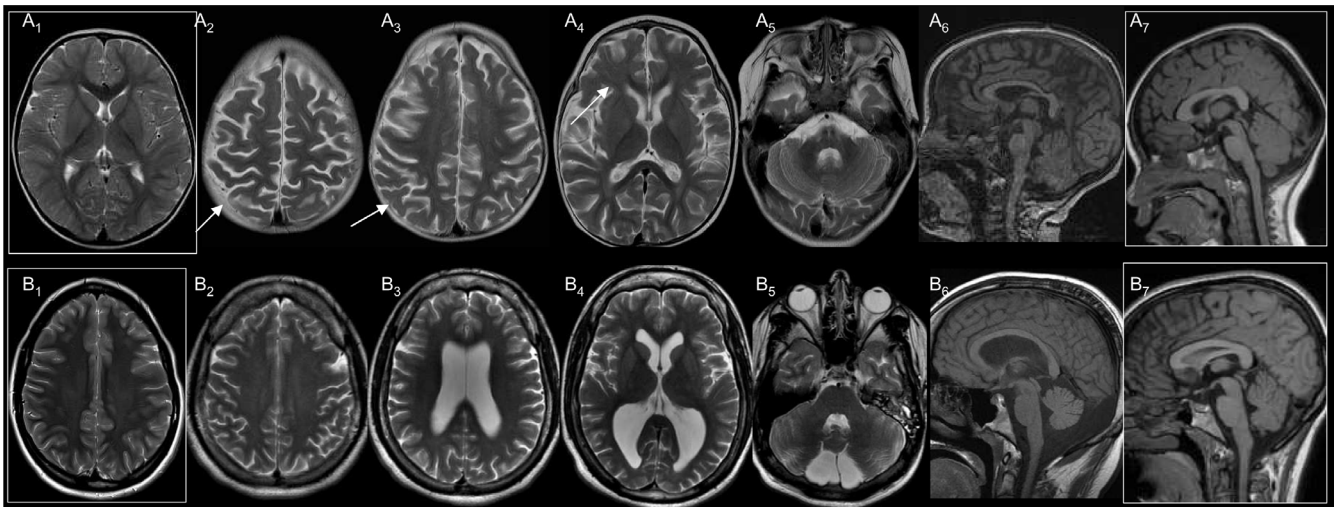

FIGURE 2 Changes consistent with neuronal disease. A, Mildly T2-hyperintense white matter relative to corpus callosum, slightly thin cortex and decreased cortex-white matter-contrast in 17-months-old AADCD_04 ($A_{2\text{-}4}$, compare with normal image in A_1). Atrophy with mildly wide supratentorial CSF spaces and thin corpus callosum (A_6 compare with normal image in A_7). Absent bright spot of posterior pituitary (A_6). B, Similar findings in 25-year-old MAOAD_03 including absent bright spot of posterior pituitary (B_6, compare with normal image in B_7). Mildly T2-hyperintense white matter with decreased contrast between cortex and white matter and less distinct cortex-white matter-junction ($B_{2\text{-}5}$, compare with normal image in B_1). Small cerebellum with a compact vermis and midline falx cerebelli indicating that the CSF widened space corresponds to cisterna magna and not an arachnoid cyst ($B_{5,6}$). (T2w: A,$B_{1\text{-}5}$; T1w: A,$B_{6,7}$)

Malformations of cortical development were not seen in any patient.

Absence of the normally T1-hyperintense posterior pituitary was observed in two patients, namely 25-year-old patient MAOAD_03 with a small pituitary and 1.4-year-old patient AADCD_04, both without documented endocrinological findings. One patient had an incidental, isolated left temporal arachnoid cyst (AdGTPCHD_08). Abnormal *T2-hypointensity suggestive of calcification or blood degradation products* was not observed in any of the 24 patients with T2 gradient-echo sequence or susceptibility weighted imaging (25 MRIs, n = 2 AADCD, n = 4 adGTPCHD, n = 1 arGTPCHD, n = 3 DHPRD, n = 2 MAOA, n = 3 PTPSD, n = 1 SRD, n = 7 THD; n = 4 watershed injury, n = 0 acute deterioration, n = 1 myelination delay).

3.6 | MRI changes in different disorders

MRI was normal in all seven patients with SRD (Table 2). In adGTPCHD it was normal in six of eight patients and in the other two patients MRI revealed an isolated arachnoid cyst as an incidental finding or incomplete hippocampal inversion (without associated epilepsy). Incomplete hippocampal inversion is thought to result from incomplete development and is not unequivocally abnormal on its own since it is can be found in up to 26% of healthy subjects.[21] Both patients with arGTPCHD had isolated hyperintensity of central tegmental tracts. This is a finding of unclear clinical significance that has been suggested to represent a physiological, maturation associated process occurring in children with and without central nervous system disorders and is thus on its own not unequivocally abnormal.[22] Patients with PTPSD either had normal findings (7/13), atrophy (4/13), or isolated central tegmental tract hyperintensity (2/13).

The most consistent imaging changes were observed in DHPRD: Six of nine patients had watershed injury, with incomplete hippocampal inversion in two, while normal imaging, isolated T2-hyperintense central tegmental tracts, or atrophy with central tegmental tract hyperintensity was found in the other three patients.

MRI changes were more variable and less common in THD and AADCD, the two only disorders in which delayed myelination was observed. In AADCD six of twelve patients had normal imaging, two had myelination delay and the other four patients had isolated atrophy, atrophy and central tegmental tract hyperintensity, white matter changes consistent with a neuronal disorder of post-infantile onset, or profound hypoxic-ischemic injury. In THD seven of 16 patients had normal imaging. Changes in watershed areas became visible with progressing myelination in one of two patients with myelination delay. Five patients had isolated atrophy, one had atrophy and

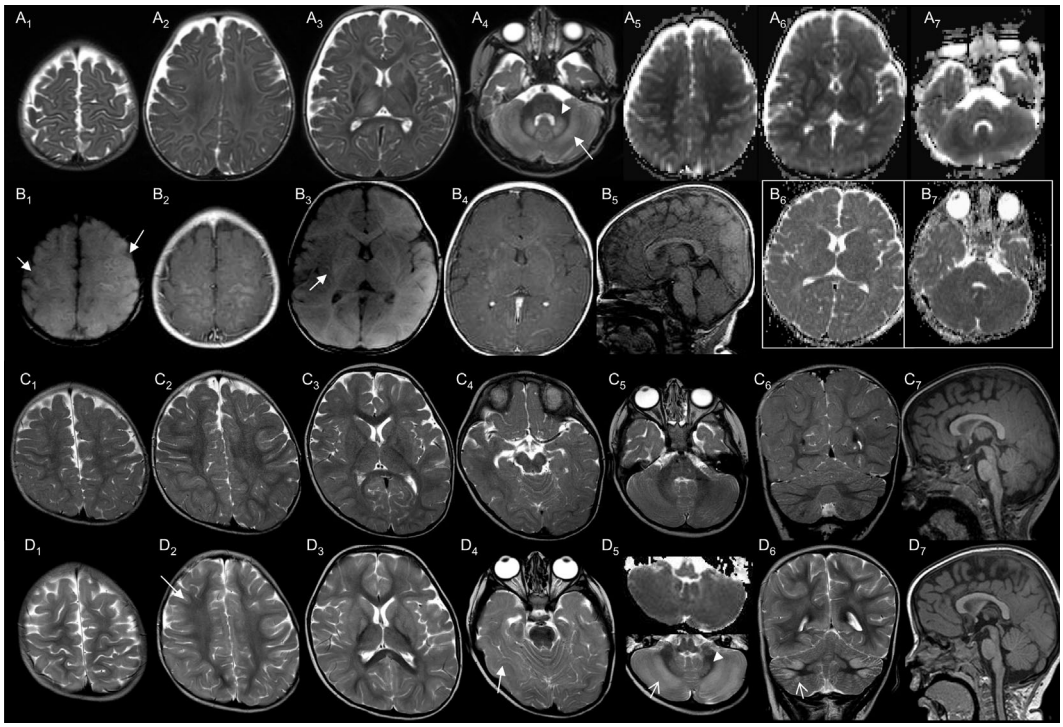

FIGURE 3 MRI in patients with acute, severe encephalopathy. A,B, 9-month-old AADCD_06 with profound hypoxic–ischemic injury: T2-hyperintense thalami, basal ganglia, and dentate nuclei (arrowhead;$A_{3,4,6}$). Focal T1-hyperintensity of cortex and right dorsal putamen ($B_{1,3}$) and more extensive gray matter enhancement ($B_{2,4}$). Extensive T2-hyperintensity of white matter ($A_{1\text{-}3}$) with restricted diffusion ($A_{5,6}$, compare with normal ADC-maps in B_6). Cerebellar watershed injury at depth of fissures (A_4, arrow) with restricted diffusion of cerebellar cortex and adjacent white matter (A_7, compare with B_7). C, Mild widening of supratentorial CSF spaces ($C_{1\text{-}5}$) in 17-month-old THD_10. D, New hypoxic–ischemic injury in THD_10 on follow-up at 25 months in deep gray matter and watershed areas: T2-hyperintensity of basal ganglia (D_3), temporo-occipital (arrow inD_4 compare with C_4), and cerebellar watershed areas (D_5, D_6, below; arrows) with pseudonormalized ADC (D_6, above). New, mild T2-hyperintensity of supratentorial white matter may be related to hypoxic–ischemic injury or represent white matter changes associated with neuronal disease (arrowhead D_2). Atrophy has progressed. (T2w: $A_{1\text{-}4}$, $C_{1\text{-}6}$,$D_{1\text{-}6}$; ADC: $A_{6,7}$,$B_{6,7}$; T1w: D_4; T1w: $B_{1,3,5}$,C_7,D_7; T1w + GAD: $B_{2,4}$)

incomplete hippocampal inversion, and one patient with initially isolated atrophy suffered watershed injury following an acute event with hypotension.

All three patients with MAOAD had imaging changes, ranging from watershed injury, a pattern consistent with neuronal disease and additional incomplete hippocampal inversion to isolated atrophy.

4 | DISCUSSION

Our study is the first to systematically analyze MRI changes in a larger cohort of patients with inherited disorders of monoamine neurotransmitter metabolism. It is limited by the retrospective nature of the study, differently sized groups and age composition due to the rarity of iMNDs as well variable follow-up making comparison between groups difficult. While our results confirm an overall large proportion of normal imaging of approximately 50% in our patients, we also identify different patterns of MRI changes, including (a) chronic changes consistent with a neuronal disorder and (b) changes localized in cerebral and cerebellar watershed areas consistent with mild to moderate hypoxic-ischemic injury. These MR patterns point towards different pathophysiological processes occurring in iMNDs.

4.1 | Chronic changes consistent with a neuronal disorder

Neuronal disorders cause secondary white matter changes by disrupting the normal interplay of axon and myelin necessary for myelination and myelin maintenance.[19,20] MRI changes depend on the time of onset: Early-onset neuronal disorders result in myelination delay or secondary hypomyelination, disorders with later, postinfantile onset in a characteristic pattern of mildly T2-hyperintense white matter, loss of contrast at the cortical-white matter interface, and a variably thinned

cortical ribbon. Non-specific atrophy is seen with early and late onset.[19,20] iMNDs interfere with normal neuronal function by disrupting neurotransmission. Since only a subset of neurons using certain neurotransmitters is affected, the resulting neuronal dysfunction may be less severe compared to disorders with more general and less selective impairment of neuronal function. It nevertheless seems likely that not only the mild, diffuse white matter changes observed in our two patients with AADCD and MAOAD, but also delayed myelination, and possibly atrophy, in our and previously reported patients result from the inherent, chronic neuronal dysfunction in iMNDs.

Myelination delay has been reported for patients with PTPSD,[8] SRD,[23] and DHPRD[24] and in our study it was observed in patients with AADCD and THD. Since THD and AADCD had the highest number of patients imaged up to the age of 26 months (8/10 and 10/16, respectively), followed by PTPSD (7/13), our observation may be biased by age distribution. Moreover progression of myelination, either spontaneously ([23] our patients) or following treatment[8] suggests that myelination is ultimately complete and that initially delayed myelination might have already resolved at the time of imaging. Hypomyelination, reported for patients with AADCD,[14,25] PTPSD,[26] and THD[14], was not observed in any of our patients.

T2-hyperintensity of central tegmental tracts, a finding of unclear clinical significance, was predominantly seen in patients with BH_4 deficiency (7/9), which may be coincidental or suggests that the underlying maturational processes are more likely disturbed[22] in these disorders.

4.2 | Injury in cerebral and cerebellar watershed areas

Changes consistent with varying degrees of cerebral and cerebellar watershed injury were predominantly found in patients with DHPRD (6/9) as well as one patient each with THD and MAOAD. Additional cases with hyperacute injury, which is only apparent on DWI but not on T2/FLAIR images, might have been missed among the 25 patients without DWI and follow-up.

Changes in watershed areas are also present in six previously reported patients with DHPRD in the supratentorial border zones depicted on MRI (n = 5) or CT images (n = 1).[10,12,27-29] In addition, the characteristic pattern of cerebellar watershed injury can be identified as T1-hypointensity in the depth of cerebellar fissures on the parasagittal image of one of these patients, who died after multiple episodes of pneumonia.[27] To the best of our knowledge, similar changes are neither mentioned nor depicted for other iMNDs, in particular not for any of the reported patients with THD and MAOA/BD (as yet no imaging reported for isolated MAOAD).

Bilateral changes in cerebral and cerebellar watershed areas are primarily associated with arterial hypotension. In iMNDs stress situations, for example, infection, may result in hypotension, hypoglycaemia, hypo-/hyperthermia and cardiac complications due to catecholaminergic deficiency and autonomic dysfunction. This is mainly reported in single patients with AADCD and THD.[30-32] The severe clinical deterioration with signs of profound hypoxic-ischemic injury on brain imaging triggered by infection in THD_10 and AADCD_06 in our study is likely favored by the underlying iMND.

The predominant occurrence of watershed injury in DHPRD raises additional questions regarding the causative pathophysiological processes. DHPR regenerates BH_4, which is the essential cofactor for the three human aromatic amino acid hydroxylases (phenylalanine hydroxylase, tyrosine hydroxylase; tryptophan hydroxylases 1/2) and for the three nitric oxide synthases (NOS1-3), from q-dihydrobiopterin (qBH_2). qBH_2 can also be converted non-enzymatically to 7,8-dihydrobiopterin (BH_2). DHPRD thus differs from other iMNDs by the additional accumulation BH_2 and secondary cerebral folate deficiency.[33] Both, absence or lack of BH_4 and increasing BH_2 have been shown to codetermine uncoupling of endothelial NOS, resulting in generation of oxygen radicals instead of the antiatherogenic nitric oxide even in the absence of exogenous oxidative stress.[34] In addition, BH_4 is required for regulation of vascular tone and blood pressure as demonstrated in a mouse model,[35] with microvasculature being apparently predominantly affected.[36] Interestingly, calcification of the walls of small, medium, and large arteries and veins as well as calcification in perivascular spaces has been found on histopathology in two patients with DHPRD.[37,38] Thus, intermittently hampered vascular function and/or premature vessel degeneration due to increased oxygen radicals might exacerbate hypotensive episodes.

In conclusion, we report the first systematic analysis of brain MRIs in a cohort of 70 patients with various iMNDs. Despite absence of a pathognomonic MRI pattern, we identified different patterns of imaging changes that allow some insight into the underlying pathophysiology in iMNDs. We hypothesize that deficiency of catecholamines and/or BH_4 increase the incidence of and the CNS susceptibility to vascular dysfunction, in particular in DHPRD. Apart from the characteristic, though non-specific changes consistent with a neuronal disorder, iMNDs have a propensity to cause cerebral and cerebellar watershed injury. This will be helpful in the (neuroradiological) differential diagnosis of children with unknown

disorders and might become important for monitoring of patients with iMNDs.

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CONFLICT OF INTEREST

O. K. H. received teaching honorarium from PTC Therapeutics GT, Inc. J. F. had trials with Biogen (Angelman's Syndrome) and Stealth Biotherapeutics (Mitochondrial Disorders); J. F.'s spouse is Founder and Principal of Friedman Bioventure, which holds a variety of publicly traded and private biotechnology interests. In addition, he is chief operating officer of DTX Pharma, which is a company developing RNA therapeutics. R. P. has received honoraria as a speaker, consultant and advisory board from Genesis Pharma, PTC therapeutics, Proveca and Brain Therapeutics. S. I.-M. worked as a consultant with PTC Therapeutics. E. L.-L. worked as a consultant with PTC Therapeutics. G. F. H. received consulting and lecture fees from PTC Therapeutics as well as lecture fees from Takeda. V. L. received honoraria as an expert in the field for taking part in 4 Advisory Boards organized by PTC Therapeutics International GT, one Advisory Board organized by BioMarin Pharmaceutical Inc., and one Advisory Board organized by Homology Medicines. A. G.-C. received honoraria as an expert in the field for taking part in three Webinars organized by PTC Therapeutics, one conference organized by Biomarin Pharmaceutical Inc, and a Research Grant (Research Metabolic Fund) from Nutricia. T. O. receives teaching honorarium and research support from PTC Therapeutics GT, Inc. A. M., F. M., G. H., E. C.-S., S. M.-A., Y. Y., J. K., M. O., J. A. K., I. P.-V., R. D.-J., O. A.-F., T. G.-A., P. d. C., C. A., D. I. Z., P. G., R. S., T. H., S. F. G., H. S. S., K. J., and I. H. declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Oya Kuseyri Hübschmann, Thomas Opladen, and Inga Harting designed the study and wrote the initial draft of the manuscript. All authors examined patients and/or collected data. All MRIs were evaluated by Inga Harting and Alexander Mohr. All authors revised the manuscript and approved the submission.

ETHICS APPROVAL

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. The study was approved by the Institutional Ethics Committee of the University of Heidelberg (S-471/2014) and by all contributing clinical partners, and listed in the German Clinical Trials Register, https://www.drks.de, DRKS00007878.

INFORMED CONSENT

Informed consent was obtained from all patients or their legal guardians prior to being included in the study.

DATA AVAILABILITY STATEMENT

The MRI images are not publicly available under data protection laws. Data ownership is by the members of the iNTD. All participating iNTD members approved this study. Data availability for specific research purposes is subject to the consent of the iNTD executive board and iNTD members upon request.

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SUPPORTING INFORMATION

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