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Volumetric study of brain MRI in a cohort of patients with neurotransmitter disorders

Chiara Alfonsi[1,2] · Christian Stephan-Otto[3,4] · Elisenda Cortès-Saladelafont[5,6] · Natalia Juliá Palacios[1] · Inés Podzamczer-Valls[6,7] · Nuria Gutiérrez Cruz[8] · María Rosario Domingo Jiménez[9] · Salvador Ibáñez Micó[9] · Miguel Tomás Vila[10] · Kathrin Jeltsch[11] · Oya Kuseyri Hübschmann[11] · Thomas Opladen[11] · Ramón Velázquez Fragua[12] · Teresa Gómez[13] · Oscar Alcoverro Fortuny[13] · Inmaculada García Jiménez[14] · Eduardo López Laso[15,16] · Ana Roche Martínez[17] · Jordi Muchart López[18] · Àngels Garcia-Cazorla[1,16]

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Abstract

Purpose Inborn errors of neurotransmitters are rare monogenic diseases. In general, conventional neuroimaging is not useful for diagnosis. Nevertheless, advanced neuroimaging techniques could provide novel diagnosis and prognosis biomarkers. We aim to describe cerebral volumetric findings in a group of Spanish patients with neurotransmitter disorders.

Methods Fifteen 3D T1-weighted brain images from the International Working Group on Neurotransmitter related Disorders Spanish cohort were assessed (eight with monoamine and seven with amino acid disorders). Volumes of cortical and subcortical brain structures were obtained for each patient and then compared with those of two healthy individuals matched by sex and age.

Results Regardless of the underlying disease, patients showed a smaller total cerebral tissue volume, which was apparently associated with clinical severity. A characteristic volumetric deficit pattern, including the right Heschl gyrus and the bilateral occipital gyrus, was identified. In severe cases, a distinctive pattern comprised the middle and posterior portions of the right cingulate, the left superior motor area and the cerebellum. In succinate semialdehyde dehydrogenase deficiency, volumetric affection seems to worsen over life.

Conclusion Despite the heterogeneity and limited size of our cohort, we found novel and relevant data. Total volume deficit appears to be a marker of severity, regardless of the specific neurotransmitter disease and irrespective of the information obtained from conventional neuroimaging. Volumetric assessment of individual brain structures could provide a deeper knowledge about pathophysiology, disease severity and specific clinical traits.

Keywords Inherited neurotransmitter disorders · Monoamines · Amino acids · Neuroimaging · Brain volumetric study · Volumetric deficit

Abbreviations

GABA	Gamma-aminobutyric acid
CSF	Cerebrospinal fluid
MRI	Magnetic resonance imaging
iNTD	International Working Group on Neurotransmitter related Disorders
AADCD	Aromatic amino acid decarboxylase deficiency
ADGTPCHD	Autosomal dominant GTP cyclohydrolase deficiency
ARGTPCHD	Autosomal recessive GTP cyclohydrolase deficiency
MAOA-BD	Monoamine oxidase A and B deficiency
NKH	Non-ketotic hyperglycinemia
PTPSD	6-Pyruvoyl-tetrahydropterin synthase deficiency
SSADHD	Succinate-semialdehyde-dehydroxylase deficiency
THD	Tyrosine hydroxylase deficiency

Chiara Alfonsi and Christian Stephan-Otto contributed equally to this work.

✉ Àngels Garcia-Cazorla
agarcia@sjdhospitalbarcelona.org

Extended author information available on the last page of the article

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Introduction

Inborn errors of neurotransmitters are a group of rare neurometabolic disorders. Two main groups of disorders exist, according to the type of neurotransmitters involved: (I) disorders of monoamine metabolism and (II) defects of amino acid neurotransmitters, such as glycine, serine, glutamate and gamma-aminobutyric acid (GABA) [1]. The monoamine deficiencies result from alterations in the synthesis; breakdown or transport of dopamine, serotonin, norepinephrine and epinephrine or altered availability of tetrahydrobiopterin (BH_4), an important cofactor for monoamine synthesis [2]. First clinical symptoms can appear from the neonatal period until adulthood and include developmental delay, hypotonia, parkinsonism and dystonia. Autonomic disturbances, psychiatric symptoms and epilepsy are also present [3–5]. Cerebrospinal fluid (CSF) findings are crucial for the diagnosis, together with molecular genetic confirmation. Monoamine defects are traditionally considered to have normal brain magnetic resonance imaging (MRI), although unspecific alterations like white matter signal and myelination abnormalities, basal ganglia calcifications and global brain atrophy are reported [3, 6]. Alterations in brain watershed areas consistent with mild to moderate hypoxic-ischemic injury have also been reported recently [6]. Treatment is addressed to enhance dopaminergic and/or serotonergic transmission, either with L-Dopa and decarboxylase inhibitors, 5- hydroxytryptophan, dopamine agonists and/or monoamine oxidase inhibitors. Cofactors such as BH_4 or vitamin B_6 are also administered in some disorders [7], but response to treatment depends on the type and severity of the disorder and ranges from full recovery in some patients to no response and lack of developmental progress in others. Disorders of amino acid neurotransmitters are caused by monogenic defects that impair enzymes in synthesis, catabolism and transport, or cause postsynaptic receptor mutations. Severe infantile epileptic encephalopathy is a common clinical feature of glycine, serine and glutamate disorders. GABA disorders can present with non-specific clinical symptoms including developmental delay, early onset hypotonia, non-progressive ataxia, expressive language disorders and neuropsychiatric manifestations [1, 8–10]. CSF analysis is crucial in the diagnosis of glycine and serine disorders whilst quantification of 4-hydroxybutyrate in urine is pivotal for GABA disorders. Amino acid defects have a repertoire of neuroradiological signs: corpus callosum abnormalities, as well as diffusion restriction on DWI in the already myelinated areas at birth (brainstem, cerebellum, corticospinal tract, the perirolandic area), brain atrophy and malformations have been reported in nonketotic hyperglycinemia (NKH) [10–12]. Pallidum and cerebellum involvement, as well as white matter changes, has been described in succinate semialdehyde dehydroxylase deficiency (SSADHD) [13], whilst signal alterations of thalami, bilateral putamen and caudate nucleus have been occasionally reported [14]. Serine deficiency presents unspecific radiological patterns like brain atrophy, myelination abnormalities or corpus callosum alterations [15, 16]. Besides serine deficiencies, most of the amino acid disorders do not have an effective treatment so far. Attenuated forms of NKH can beneficiate of early medical treatment [17].

This work reports the results of volumetric analyses performed on conventional MRI of patients with monoamine and amino acid neurotransmitter disorders. Our hypothesis is that even in the case of normal conventional brain MRI, a volume-specific neuroimaging study could improve the diagnostic work-up and provide more detailed characterizations of the diseases.

Methods

Participants

Most of the MR images analysed for this study were obtained in a retrospective manner after reviewing the clinical histories of all patients. In general, the available MRI acquisitions that met our inclusion criteria were obtained many years before the volumetric analysis. MRI images for a few of the participants were obtained prospectively. Informed consent was obtained for all patients, for both retrospective and prospective recruitment. The International Working Group on Neurotransmitter related Disorders (iNTD) established the first international and longitudinal patient registry for neurotransmitter disorders. Data is protected on a secure server located at the coordinating centre, Heidelberg University Hospital (study approved by the local ethics committee, application number S-471/2014). Patients enrolled in the iNTD registry from the launching of the database in December 2014 until February 2020 were included in the present work. The diagnoses of the patients were confirmed biochemically and genetically. Only those with an age > 1 month and with 1,5 T brain-MRI images available were included for the analysis. Patients with age < 1 month were excluded due to the lack of control subjects in this age range. The patient cohort included 15 patients with nine different primary neurotransmitter disorders, 12 patients were enrolled in our centre (Sant Joan de Déu Hospital of Barcelona) and 3 patients were enrolled in 3 other Spanish institutions (Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Hospital Nuestra Señora Del Rosario, Madrid and Hospital Universitari i Politècnic La Fe, Valencia). Two patients had each two brain MRIs at different ages that were included in the analysis. The age range of the patients at the time of the MRI study was between 0.5 and 15 years, with mean age 6 years and median age 5 years. An expert paediatric

neuroradiologist reviewed all images to exclude the presence of signs of acute injury (i.e. infarction or edema).

The clinical presentation of the patients in our cohort is widely heterogeneous, but some symptoms occurred more frequently, such as psychomotor delay, intellectual disability, speech delay, neuropsychiatric symptoms, hypotonia or hypertonia, movement disorders and different types of epilepsy (Table 1). Patients were classified in three subgroups according to the degree of clinical severity assessed by neurological examination and, when possible, by neuropsychological scales. The mild phenotype corresponds to patients without psychomotor delay, with normal cognitive functions, with or without mild language impairment and with mild or absent movement disorder. The moderate phenotype corresponds to patients that presented with psychomotor delay, mild or moderate intellectual disability, delayed or absent expressive language and mild or absent movement disorder. The severe phenotype corresponds to patients with severe intellectual disability, absent language function and severe motor impairment with or without movement disorder and, in many cases, epilepsy. Normal brain MRIs of control subjects were acquired at Sant Joan de Déu Hospital, Barcelona. The revision of neuroradiological images by a neuropediatric radiologist was performed to generate the control group, and clinical reports of every control subject were reviewed to exclude any neurological manifestation. Two age-matched and sex-matched control subjects were selected for every patient. The age range of the control group MRI study was from 0.4 to 14.5 years, the mean age was 5.8 years and the median age was 5 years.

Acquisition of brain volumetric images

After an initial review of the study requirements, only some of the images provided were selected, 12 of which were from Sant Joan de Déu Hospital and 3 from other centres. For most of the patients and all of the control subjects, T1-weighted 3D FSPGR IR acquisitions from a clinical protocol were obtained, using the following parameters: pixel spacing = 0.43 mm × 0.43 mm, slice thickness = 2 mm, TR = 12.4 ms, TE = 5.2 ms and FOV = 22 cm. Our volume calculation methodology is designed to provide reliable volumetric measurements independently of image acquisition parameters. Supplementary Table 1 contains detailed information on MRI acquisition parameters for the 4 centres involved. All scanners were built by General Electric and had the same 1.5 T field strength.

Brain tissue segmentation and labelling

The automatic segmentation algorithm was based on various tools provided by the Advanced Normalisation Tools software (ANTs, http://stnava.github.io/ANTs/). This method was used to identify cortical grey matter, subcortical grey matter, white matter and cerebrospinal fluid from T1-weighted images. First, the subject's T1-weighted image was registered to the Montreal Neurological Institute (MNI) standard anatomical space using the diffeomorphic registration tool included in ANTs. Then, the Atropos tool was used to segment cortical and subcortical grey matter as well as white matter and cerebrospinal fluid. Using the labels of the Neuromorphometrics Inc. parcellated brain (http://www.neuromorphometrics.com/) for each structure, the subject's grey matter was labelled and later registered to the subject's native space. Volumes of cortical and subcortical structures were then recorded and relative volumes according to total intracranial volume were calculated. For each patient, these relative structure volumes were compared with those of two sex- and age-paired control subjects. A 15% loss in relative volume was considered to indicate volumetric deficit. Differences in global brain tissue volumes for cortical grey matter, subcortical grey matter and white matter, as well as total intracranial volume, were also considered. In this case, 5%, 10% and 15% volumetric deficits were established as thresholds indicating degrees of severity. In order to easily visualise the results, cerebral patterns of volumetric deficit were obtained by overlapping masks of the affected structures into the standardised anatomical space [18].

Statistical analysis

As this is only a descriptive study with a small number of patients per disease, no statistical analysis was performed.

Results

Global brain tissue segmentation results and conventional MRI findings

Our cohort included 9 female patients (60%) and 6 male patients (40%), which presented nine different primary neurotransmitter disorders. They were all of Indo-European origin, with the exception of 4 of them who were of Arabic origin. The age range of the whole MRI study cohort was 0.5 to 15 years. The degree of volume deficit for total cerebral tissue and volume deficit according to tissue type for each patient, as well as conventional MRI findings, is described in Table 2. Some MRI sequences are reported in Supplementary material Fig. 1 . Most of the patients presented thinned or absent corpus callosum (8/15 patients). Some of them presented other white matter alterations like hypo/demyelination and periventricular white matter volume deficit (patient Nr. 5 at age 3, and patients 8 and 9), pallidum and nucleus dentatus involvement (SSADHD patients), cortical abnormalities (Nr. 7 at both 3 and 11 years of age and Nr. 9) and cerebellar atrophy (Nr. 5 at both ages and Nr. 15) in the conventional MRI study. In general, patients presented a smaller total cerebral

Table 1 Clinical characteristics of our cohort of patients with inborn errors of neurotransmitters

Patient* (Nr.)	Diagnosis	Gender	Age of onset (m or y)	Age of MRI (m or y)	PMD	Hypotonia	Movement disorder	Intellectual disability	Verbal function	Psychiatric symptoms	Other features	Severity
1	THD	F	5 m	15 y	x	x	Limbs rigidity and dystonia, distal choreoathetosis, oculogyric crisis	Severe	Absent expressive language	Irritability, conduct disorder	Glossoptosis, eyelid ptosis, lack of sphincter control	Severe
2	THD	F	5 m	13 y	No	x	Bradykinesia, limbs hypertonia, dystonia, dyskinesia, oculogyric crisis	No	Expressive language delay	NA	No	Mild
3	NKH	M	3 y	5.5 y	x	No	No	Moderate	Moderate language delay, mutism	Suboptimal visual contact, conduct disorder, anxiety, mutism	Developmental coordination disorder	Moderate
4	NKH	F	Birth	2 y	x	x	No	Severe	Absent	No	Epilepsy	Severe
5	SSADHD	M	5 m	3 y; 7 y	x	x	Limbs spasticity, hypomimia, stereotypies	Severe	Absent expressive language	ADHD, ASD	Epilepsy	Severe
6	SSADHD	F	1,5 y	9 y	x	No	Stereotypies, tics	Moderate	Moderate expressive language delay	ADHD, ASD, generalised anxiety	Sleep disorder	Moderate
7	SSADHD	M	5 m	3y; 11 y	x	x	No	Mild	Moderate expressive language delay	ADHD	Learning difficulties	Moderate
8	3-PGDHD	M	1 m	1.5 y	x	x	Dystonia, nystagmus, dyskinesia, oculogyric crisis	Moderate	Absent expressive language	Conduct disorder	Spastic tetraparesis, microcephaly, congenital bilateral cataract, failure to thrive	Severe
9	3-PGDHD	F	7 m	9 y	x	x	Stereotypies	Severe	Absent	No	Epilepsy, spastic tetraparesis, irritability, failure to thrive, feeding difficulties, vomiting	Severe

Table 1 (continued)

Patient* (Nr.)	Diagnosis	Gender	Age of onset (m or y)	Age of MRI (m or y)	PMD	Hypotonia	Movement disorder	Intellectual disability	Verbal function	Psychiatric symptoms	Other features	Severity
10	AADCD	F	10 m	5 y	x	x	Limbs hypertonia, hypomimia, high amplitude tremor, hypokinesia, bradykinesia, oculogyric crisis, episodic strabismus	Severe	Absent expressive language	No	Irritability, retrognathia, ogival palate, thermoregulation disorder (hyperhidrosis), sleep disorder, nasal rinorrea, failure to thrive, episodic hypoglycemia	Severe
11	PTPSD	F	2 m	0.4 y	No	x	Distal dyskinesias	No	Mild expressive language delay	No	Irritability	Mild
12	AR-GTPCHD	M	4 m	1.5 y	No	x	Hypokinetic-rigid syndrome, oculogyric crisis, episodic ptosis	No	Mild expressive language delay	NA	Sleep disorder	Mild
13	AD-GTPCHD	F	6,5 y	8 y	No	No	Ataxia, rigidity, lower limb spasticity and dystonia, paroxysmal upper limb dyskinesia, daily fluctuation	No	N	No	No	Mild
14	AD-GTPCHD	F	2 y	5 y	No	No	Ataxia, rigidity, lower limb spasticity and dystonia, tremor, daily fluctuation	No	N	No	No	Mild
15	MAOA-BD	M	6 m	4.5 y	x	x	No	Severe	Absent	No	Epilepsy, congenital glaucoma, blindness, sleep disorder	Severe

Disease: *THD*, tyrosine hydroxylase deficiency; *NKH*, non-ketotic hyperglycinemia; *SSADHD*, succinate-semialdehyde-dehydroxylase deficiency; *3-PGDHD*, 3-phosphoglycerate dehydrogenase deficiency; *AADCD*, aromatic amino acid decarboxylase deficiency; *PTPSD*, 6-pyruvoyl-tetrahydropterin synthase deficiency; *ARGTPCHD*, autosomal recessive GTP cyclohydrolase deficiency; *ADGTPCHD*, autosomal dominant GTP cyclohydrolase deficiency; *DHPRD*, dihydropteridine reductase deficiency; *MAOAD*, monoamine oxidase A and B deficiency. Symptoms: *PMD*, psychomotor delay; *N*, normal; *NA*, not available. *Medical centres of origin: Sant Joan de Déu Hospital, Barcelona: 1; 2; 3; 5; 6; 8; 9; 10; 11; 12; 13; 14; Hospital Clínico Universitario Virgen de la Arrixaca, Murcia: 4; Hospital Nuestra Señora Del Rosario, Leganés, Madrid: 7; Hospital Universitari i Politècnic La Fe, Valencia: 15

Table 2 Total brain volume deficit, white matter and cortical and subcortical grey matter deficit

Patient Nr. (age in years)	Diagnosis	Conventional MRI findings	Total cerebral tissue volume deficit	Cortical grey matter volume deficit	Subcort. grey matter volume deficit	White matter volume deficit	Phenotype severity
1 (15)	THD	Normal	*				Severe
2 (13)	THD	Corpus callosum agenesis				***	Mild
3 (5.5)	NKH	Ventricles abnormality, corpus callosum hypoplasia	*				Moderate
4 (2)	NKH	Ventricles abnormality, corpus callosum hypoplasia	*		*		Severe
5 (3)	SSADHD	Pallidum T2 hyperintensity, hipo/dysmyelination, cerebellum cortex and nucleus dentatus T2 hyperintensity + atrophy					Severe
5 (7)	SSADHD	Cerebellum atrophy progression	**	**	***	**	Severe
6 (9)	SSADHD	Pallidum T2 hyperintensity, cerebellum nucleus dentatus T2 hyperintensity	**				Moderate
7 (3)	SSADHD	Cortex abnormality, pallidum T2 hyperintensity, corpus callosum hypoplasia	*				Moderate
7 (11)	SSADHD	No changes or abnormalities progression	**				Moderate
8 (1.5)	3-PGDHD	Corpus callosum hypoplasia, periventricular WM volume deficit	**			*	Severe
9 (9)	3-PGDHD	Cortex abnormality, ventricles abnormality, myelination delay, corpus callosum atrophy, internal capsule involvement	*			**	Severe
10 (5)	AADCD	Corpus callosum hypoplasia	***	**	***	***	Severe
11 (0.5)	PTPSD	Normal	*		**	***	Mild
12 (1.5)	ARGTPCHD	Normal					Mild

Table 2 (continued)

Patient Nr. (age in years)	Diagnosis	Conventional MRI findings	Total cerebral tissue volume deficit	Cortical grey matter volume deficit	Subcort. grey matter volume deficit	White matter volume deficit	Phenotype severity
13 (8)	ADGTPCHD	Normal					Mild
14 (5)	ADGTPCHD	Normal	*				Mild
15 (4.5)	MAOA-BD	Corpus callosum hypoplasia, cerebellum cortex T2 hyperintensity + atrophy	***	***	*	**	Severe

* indicates at least 5% volume loss; ** indicates at least 10% volume loss; *** indicates at least 15% volume loss

tissue volume (the sum of cortical and subcortical grey matter and white matter) than control subjects, which appears to be associated with severe phenotypes in some cases. In the single cases of MAOA-BD and aromatic l-amino acid decarboxylase deficiency (AADCD) as well as in one of the SSADHD cases, all tissue types were volumetrically affected (all three patients, Nr. 5 at age 7, Nr. 10 and Nr. 15, presented a severe clinical phenotype, according to our classification scheme). Although conventional MRI for the two NKH patients (Nr. 3 and Nr. 4) showed a hypoplastic corpus callosum, no global white matter deficit was observed in these subjects. Global tissue volume deficit was observed in these two patients, and volumetric deficit of subcortical grey matter was present in the severe NKH case (patient Nr. 4). In SSADHD, major global volumetric deficit was observed in the patient with a severe phenotype (Nr. 5 at age 7). Moreover, in the two patients with longitudinal data (Nr. 5 and Nr. 7), brain tissue volume deficit seems to accelerate with age: volumetric study of patient Nr. 5 at 3 years of age did not show any volume deficit, whilst at 7 years of age showed an important volume deficit of all brain tissues, and patient Nr. 7 presented progressive volume deficit at 3 and at 11 years of age, although less severe than patient Nr. 5. Furthermore, a global brain volumetric deficit combined with different degrees of brain white matter deficit seems to be present in the severe presentation of 3-phosphoglycerate dehydrogenase deficiency in two patients (Nr. 8 and Nr. 9). Both patients showed white matter abnormalities in conventional MRI: thinned corpus callosum and periventricular white matter volume deficit in patient Nr. 8, and myelination delay and internal capsule involvement in the case of patient Nr. 9. This patient also showed cortical abnormalities. In the patient with AADCD (Nr. 10), a markedly smaller total brain tissue was observed compared to control subjects. This patient presented a severe phenotype, characterised by a hypokinetic-rigid syndrome with severe intellectual disability, absence of language function and autonomic dysfunction. A severe volumetric deficit of white matter and subcortical grey matter was observed, whilst cortical grey matter deficit was moderate. None of these volumetric deficits were detected by conventional MRI; only thinned corpus callosum was described. The patient affected by 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency (Nr. 11) showed a significant volumetric deficit of white matter and subcortical grey matter, despite normal conventional brain MRI and a mild phenotype with normal cognitive function, mild movement disorder and mild expressive language delay. Patients affected by AD and ARGTPCHD (Nr. 12, Nr. 13 and Nr. 14) presented mild cerebral volume deficit and mild symptomatology (mild phenotype, presenting movement disorder and normal neuropsychological and motor functions). Conventional MRI revealed normal findings.

Volume deficit patterns

Amongst all the data of 15 patients, some regions were found to be more frequently affected in terms of volume. Figure 1 shows volume deficit patterns that result from overlapping the volume deficit masks of all patients. The most frequently affected brain regions (in 6 of 15 patients) were the right Heschl gyrus and the bilateral occipital gyrus. The left superior motor area, the left middle orbital gyrus and the triangular part of the left inferior frontal gyrus were found to be affected in 5 patients, whilst the bilateral cerebellum and triangular part of the right inferior frontal gyrus were affected in 4 patients. Figure 2 shows the volume deficit patterns of 7 patients considered as having a severe clinical phenotype (see Table 2). Here, 5 patients had an affected left superior motor region whilst up to 4 patients appeared to be affected in the left superior occipital gyrus, the bilateral cerebellum and in structures within the frontal lobe: the right superior medial frontal gyrus and, bilaterally, the frontal pole and the medial frontal gyrus. The subgroups with mild and moderate severity did not present consistent patterns of reduced grey matter volume. The left parietal operculum, the left superior motor region and the bilateral medial frontal gyrus show volumetric deficit in 3 of the 6 patients with psychiatric symptoms, like autism spectrum disorder, attention deficit and hyperactivity disorder, conduct disorder and anxiety (Fig. 3).

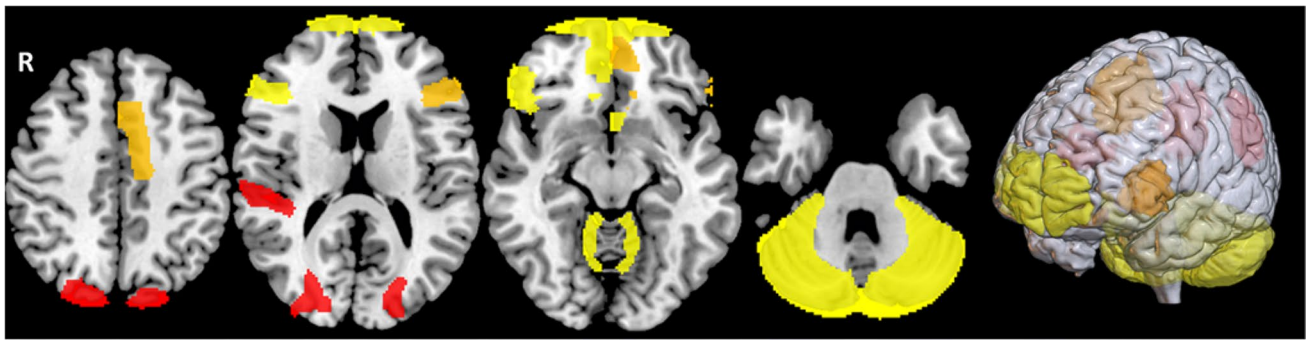

Fig. 1 Schematic representation of the most affected brain regions. For each of the 15 patients, masks were created considering the brain structures that have at least 15% volume reduction when compared to paired controls. In this representation, the colour corresponds to the number of patients that present volume deficit for a certain brain structure: red = 6 patients affected, orange = 5, yellow = 4. For illustration purposes, the adult Montreal Neurological Institute (MNI) standardised brain is used as background (from left to right, the axial planes correspond to coordinate z = 45, 15, − 11 and − 31)

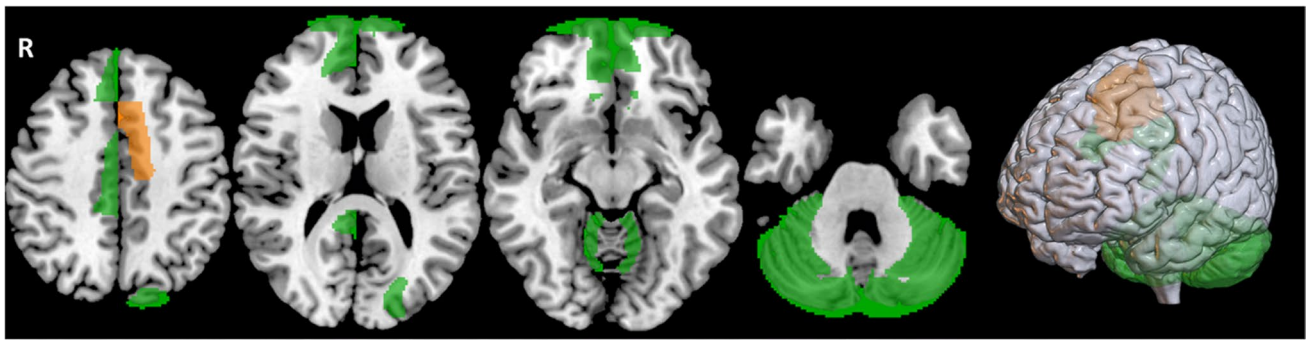

Fig. 2 Schematic representation of the most affected brain regions in patients considered as having a severe phenotype. For each of the 7 patients, masks were created considering the brain structures that have at least 15% volume reduction when compared to paired controls. In this representation, orange colour indicates 5 patients affected in that region, and green corresponds to 4 patients. For illustration purposes, the adult Montreal Neurological Institute (MNI) standardised brain is used as the background (from left to right, the axial planes correspond to z = 45, 15, − 11 and − 31). The following patients were considered to construct this figure: Nr. 1 (THD), Nr. 4 (NKH), Nr. 5 (SSADHD), Nr. 8 and Nr. 9 (3-PGDHD), Nr. 10 (AADCD) and Nr. 15 (MAOA-BD)

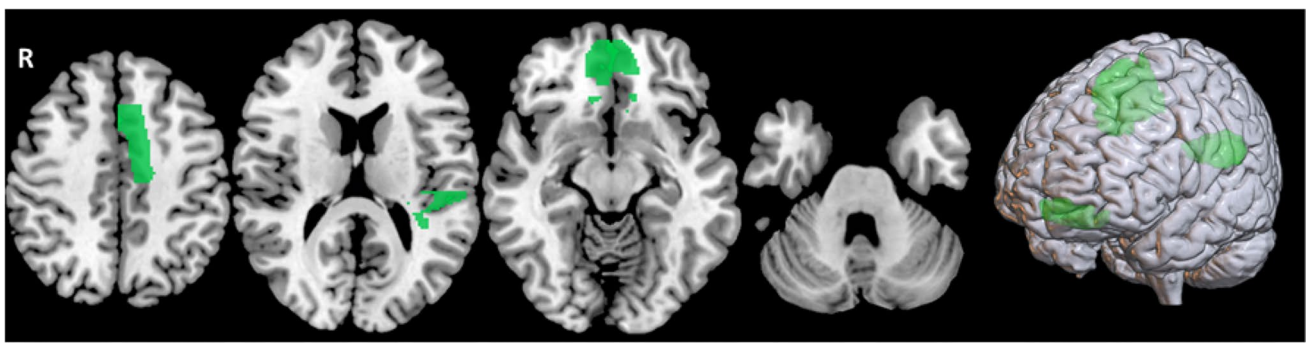

Fig. 3 Schematic representation of the most affected brain regions in patients with psychiatric symptoms. For each of the 6 patients, masks were created considering the brain structures that have at least 15% volume reduction when compared to paired controls. In this representation, the colour green indicates that 3 patients were affected in that region. For illustration purposes, the adult Montreal Neurological Institute (MNI) standardised brain is used as background (from left to right, the axial planes correspond to coordinate z = 45, 15, − 11 and − 31). The following patients were considered to construct this figure: Nr. 1 (THD), Nr. 3 (NKH), Nr. 5, Nr. 6 and Nr. 7 (SSADHD) and Nr. 8 (3-PGDH)

Discussion

By global brain tissue segmentation, we found that total volume deficit appears in some patients with severe phenotype, as in patients with MAOA-B deficiency, AADC deficiency and in a patient with SSADHD (patient Nr. 5). Although these considerations are only preliminary and based in a small cohort of patients, we can hypothesise that total volume deficit (deficit in three types of tissues) can be a possible marker of disease severity, independently of the specific neurotransmitter disorder. In particular, it seems that the grey matter tissue volume deficit could be associated with the severity of the symptomatology: in the 7 severe cases, 4 patients presented subcortical grey matter volume deficit and 3, in addition, cortical grey matter volume deficit. This consideration could be the basis of future studies that could strengthen this hypothesis. Mild cerebral volume deficit and mild symptomatology were observed in patients with AD or ARGTPCHD, having normal or non-pathological findings of conventional MRI in our study, as reported in the literature [6, 13, 19]. Thus, volumetric data could be useful to complete radiological assessment. A mild reduction of the global brain tissue volume (that includes cortical and subcortical grey matter and white matter) has been detected in our two patients with NKH (Nr. 3 and Nr. 4). Furthermore, the only conventional MRI finding for both patients was a hypoplastic corpus callosum. In literature, white matter abnormalities, like diffusion restriction on DWI in myelinated areas and corpus callosum hypoplasia/agenesis, have been reported in patients affected by NKH [10–12]. In one of our two NKH cases, we observed a subcortical grey matter volumetric deficit, in line with previous reports of basal ganglia atrophy and diffusion restriction in the globus pallidus [20]. Furthermore, our case with subcortical volume deficit corresponded to a severe phenotype, which tentatively suggests that the generalised deficit of subcortical brain tissue could be a biomarker of severity. Although volumetric subcortical grey matter loss in NKH has been recently described in literature in patients with chorea [21], this patient in particular did not present any movement disorder at the time of radiological assessment (2 years of age). A global brain tissue volume deficit combined with different degrees of white matter volume deficit appears to be associated with the severe phenotype of patients affected by 3-phosphoglycerate dehydrogenase deficiency. Conventional MRI in these patients showed different alteration degrees of white matter, reflecting the volumetric findings in this specific tissue. These results are in line with previous literature about white matter alterations in defects of serine biosynthesis (evidence of loss of white matter volume with hypo- or demyelination and abnormality/agenesis of corpus callosum) [16]. However, in our patients, the volumetric study added information to the conventional radiological findings, highlighting a global brain volume deficit, indicating a possible complementarity of the two diagnostic tools. The three SSADHD patients presented a total brain volume deficit, in line with previous literature reporting cerebral and cerebellar atrophy [13]. Moreover, clinical severity appeared to be associated with considerable volumetric deficits of the three types of brain tissue. The longitudinal volumetric assessment of SSADHD cases seems to indicate that volumetric affectation worsens throughout a patient's life. Patient Nr. 5 did not present any volumetric brain abnormality at age 3, but a global volume loss (all tissue types) was present at the age 7. Such volumetric pattern corresponds with the severe phenotype observed in this patient (severe intellectual disability with lack of language, epilepsy, movement disorder and psychiatric symptoms). A similar pattern was observed in patient Nr. 7, showing a progressive but milder reduction in the brain total volume, and in agreement with the moderate phenotype of this patient. In terms of conventional MRI findings, only patient Nr. 5, which presented the severe phenotype, shows a progression of abnormalities (cerebellar atrophy). Molecular studies have shown the hyperactivation of the kinase Tor1 inhibitor by elevated levels of GABA that leads to increased degradation of mitochondria and peroxisomes, determining oxidative stress and mitochondrial alterations [22]. This mechanism, that probably determines a progressive cell loss, could partially explain the volume deficit patterns observed for this disease. Therefore, our results could suggest that the volumetric assessment of cerebral tissue could play a role in monitoring the clinical progression of this disease. In the patient affected by AADCD, a severe volumetric involvement of white matter and subcortical grey matter was observed, whilst cortical grey matter deficit was moderate. Cortical atrophy and thinned corpus callosum as well as other white matter manifestations like focal demyelination changes, leukodystrophy-like patterns, hypomyelination, delayed myelination and white matter changes consistent with a neuronal disorder of postinfantile onset, or profound hypoxic-ischemic injury, have been reported in AADCD [6, 13, 26]. Our patient volumetric study also showed an important deficit of subcortical grey matter volume, whilst the conventional MRI study only detected a thinned corpus callosum. In literature, only a few cases with caudate nucleus volume deficit have been described using conventional radiological assessment [24]. The volumetric study of sufficiently large AADCD cohorts is necessary to confirm whether the subcortical volume deficit pattern we observe is characteristic of this disease. The patient affected by PTPS deficiency showed a significative volumetric white matter

deficit and a subcortical grey matter volumetric involvement, although his conventional brain MRI resulted normal. In this disorder, normal conventional MRI findings, atrophy, isolated central tegmental tract hyperintensity or white matter signal abnormalities in T2-weighted images have been described [6, 19]. Our patient presented a mild clinical phenotype, but it would be interesting to study volumetric MRI patterns in a large PTPSD cohort and probe their usefulness as indicators of phenotype severity. Interestingly, three of the five patients that presented a deficit in total subcortical grey matter volume were cases of monoamine diseases (AADCD, PTPSD and MAOA-BD). Despite this, we did not observe volumetric deficits in the basal ganglia whilst considering the individual volumes of these structures, suggesting an unspecific affectation of subcortical grey matter. In terms of grey matter volume deficit in cortical and subcortical structures, our sample presented an interesting pattern. The more affected areas in terms of volume were the right superior temporal gyrus (Heschl gyrus) and the bilateral occipital gyrus, both involved in 6 patients, and respectively related with language and visuospatial functions. These findings corresponded to the cohort patients with severe phenotype and lack of language or language delay. As mentioned earlier, speech impairment is a frequent clinical finding in neurotransmitter disorders, in the context of a global psychomotor retardation or severe intellectual disability [1, 4]. Furthermore, an exploration of affected grey matter regions only in severe cases shows a specific volume deficit pattern. We observed a volume deficit pattern encompassing the left superior motor area, the middle and posterior right cingulate, the left superior occipital gyrus, the bilateral cerebellum and several regions of the frontal lobe. These areas could be associated with the severe intellectual disability and motor involvement found in this subgroup. The presence of psychiatric symptoms does not seem to correspond to specific volume alteration of any of the brain tissues (white matter, cortical and subcortical grey matter), but to the diagnostic group. A volumetric pattern of psychiatric symptoms could be observed only at a preliminary level, given the size of our sample and the heterogeneity in psychiatric symptomatology. It is interesting to note that neurotransmitters, in addition to the main role of regulating synaptic communication, also participate in some developmental processes such as neuron proliferation, differentiation and migration and cell apoptosis [25]. In particular, monoamines seem to promote proliferation of neural precursors [26], GABA seems to play a role in controlling cell division and contributing to neuronal migration and maturation [27] and D-serine, in addition, takes part in the generation and maturation of synaptic contacts [28], whilst glutamate seems to induce neuronal apoptosis [29]. Moreover, L-serine, that is the precursor of D-serine, also takes a role in the synthesis of myelin components (sphingolipids) and contributes to cellular development and apoptosis [30]. These multiple functions could provide an explanation for the differing and additional radiological findings detected by volumetric studies in some diseases.

Some limitations of this study are worth mentioning. We enrolled patients from various centres, although most of them were recruited in our centre (12). For patients from other centres, we relied on clinical reports by the corresponding paediatric neurologists. On top of working with diseases that are markedly rare, technical requirements in terms of resolution/quality of MRI acquisitions resulted in a small sample size with a heterogeneous disease distribution. Also, the ages at which MRI images were acquired varied widely within our cohort, and we were able to recruit only 2 control subjects for each patient, mainly for ethical concerns regarding the sedation of healthy children during MRI procedures. Despite this, the age differences between patients and their two matched control subjects were very small. In certain pathologies, for example in THD, clinical severity in some cases was not associated with large effects on brain tissue volumes, which could be an inherent characteristic of the disease or due to the fact that only a few cases of each disease were available for this study. The lack of patients in the neonatal stage of the disease is also a limitation, since some of these disorders present during neonatal period. In some cases, the MRI data were obtained at an early stage of the disease and, unfortunately, we have no information about volumetric progression. In conclusion, a larger sample with many patients in each disease group and at each stage of clinical evolution could help establish more accurate results in terms of the use of brain tissue volumetry as an indicator of disease severity.

Conclusions

We report the first brain MRI volumetric study in a cohort of patients affected by different neurotransmitter disorders. Our results may inspire new radiological approaches that consider volume alterations in clinical follow-up investigations. Although the small size and heterogeneity of our sample only allow a first approach to establish the potential clinical applications of the proposed methodology, precise volumetric information appears to be useful in the characterisation of neurotransmitter diseases.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00234-022-02989-8.

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Author contribution Chiara Alfonsi: conceptualization; data curation; resources; formal analysis; investigation; methodology; writing—original draft.

Christian Stephan-Otto: conceptualization; formal analysis; investigation; methodology; resources; software; validation; writing—original draft.

Elisenda Cortès-Saladelafont: conceptualization; data curation; writing—original draft.

Inés Podzamczer-Valls: data curation.

Natalia Juliá Palacios, Nuria Gutiérrez Cruz, María Rosario Domingo Jiménez, Salvador Ibáñez Micó, Miguel Tomás Vila, Ramón Velázquez Fragua, Teresa Gómez, Oscar Alcoverro Fortuny, Inmaculada García Jiménez, Eduardo López Laso, Ana Roche Martínez: data curation; resources; writing—review and editing.

Kathrin Jeltsch, Oya Kuseyri Hübschmann, Thomas Opladen: writing—review and editing.

Muchart Jordi López: data curation; software; resources; writing—review and editing.

Àngels Garcia-Cazorla: conceptualization; funding acquisition; investigation; project administration; resources; supervision; validation; visualisation; writing—review and editing.

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Declarations

Ethics approval The study was approved by the local ethics committee (ID number: PIC-131–18). All the procedures 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.

Consent to participate Oral and written informed consent was obtained from all subjects or their parents/legal guardians regarding publishing their data. Images from control subjects were obtained from a local anonymized MRI database, for which the patients or their parents/legal guardians gave informed consent.

Conflict of interest Dr. Cortès-Saladelafont reports personal fees from Takeda, outside the submitted work. Dr. Kuseyri Hübschmann reports personal fees from PTC Therapeutics GT, outside the submitted work. Dr. López-Laso has received honoraria as an invited speaker and has also received consultation fees from PTC Therapeutics, outside the submitted work. Dr. Ibáñez-Micó reports grants and personal fees from PTC Therapeutics, during the conduct of the study. Dr. Alfonsi, Dr. Stephan-Otto, Dr. Juliá Palacios, Dr. Podzamczer-Valls, Dr. Nuria Gutiérrez, Dr. Kathrin Jeltsch, Dr. Velázquez Fragua, Dr. Alcoverro-Fortuny, Dr. Teresa Gómez, Dr. Roche Martínez and Dr. Muchart López have nothing to disclose.

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Authors and Affiliations

Chiara Alfonsi[1,2] · Christian Stephan-Otto[3,4] · Elisenda Cortès-Saladelafont[5,6] · Natalia Juliá Palacios[1] · Inés Podzamczer-Valls[6,7] · Nuria Gutiérrez Cruz[8] · María Rosario Domingo Jiménez[9] · Salvador Ibáñez Micó[9] · Miguel Tomás Vila[10] · Kathrin Jeltsch[11] · Oya Kuseyri Hübschmann[11] · Thomas Opladen[11] · Ramón Velázquez Fragua[12] · Teresa Gómez[13] · Oscar Alcoverro Fortuny[13] · Inmaculada García Jiménez[14] · Eduardo López Laso[15,16] · Ana Roche Martínez[17] · Jordi Muchart López[18] · Àngels Garcia-Cazorla[1,16]

1 Inborn Errors of Metabolism Unit, Pediatric Neurology Department, Institut de Recerca Sant Joan de Déu, and MetabERN, Hospital Sant Joan de Déu, Passeig Sant Joan De Deu Nº 2, 08950 Esplugues De Llobregat, Barcelona, Spain

2 Department of Human Neuroscience, Sapienza, University of Rome, Via dei Sabelli n.108, 00185 Rome, Italy

3 Institut de Recerca Sant Joan de Déu, Pg Sant Joan De Deu Nº 2, 08950 Esplugues De Llobregat, Barcelona, Spain

4 Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Av. Monforte de Lemos, 3-5. Pabellón 11. Planta 0, 28029 Madrid, Spain

5 Unit of Inherited Metabolic Diseases and Neuropediatrics, Hospital German Trias I Pujol, Carretera de Canyet s/n, 08916 Badalona, Spain

6 Universitat Autònoma de Barcelona, Plaza Cívica, Bellaterra, Cerdanyola del Vallès, 08193 Barcelona, Spain

7 Hospital de La Santa Creu I Sant Pau, Carrer de Sant Antoni Maria Claret n. 167, 08025 Barcelona, Spain

8 Department of Pediatrics, Hospital Universitario Severo Ochoa, Av. de Orellana s/n, 28911 Leganés, Spain

9 Department of Pediatric Neurology, Hospital Universitario Virgen de La Arrixaca, Ctra. Madrid-Cartagena s/n, 30120 El Palmar, Murcia, Murcia, Spain

10 Department of Neurology, Hospital La Fe, Avinguda de Fernando Abril Martorell n.106, 46026 Valencia, Spain

11 Division of Child Neurology and Metabolic Disorders, University Children's Hospital Heidelberg and MetabERN, Im Neuenheimer Feld 430, 69120 Heidelberg, Germany

12 Department of Pediatric Neurology, Hospital La Paz, C. de Pedro Rico n. 6, 28029 Madrid, Spain

13 Department of Psychiatry, Hospital General de Granollers, Carrer de Francesc Ribas s/n, 08402 Granollers, Spain

14 Metabolic Disorders Unit, Hospital Universitario Miguel Servet, P.º Isabel La Católica, 1-3, 50009 Saragossa, Spain

15 Pediatric Neurology Unit, Department of Pediatrics, University Hospital Reina Sofía, IMIBIC, Av. Menendez Pidal S/N, 14004 Córdoba, Spain

16 Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), C. de Melchor Fernández Almagro n. 3, 28029 Madrid, Spain

17 Department of Pediatrics, Hospital Parc Tauli, Parc Taulí n. 1, 08208 Sabadell, Spain

18 Department of Radiology, Hospital Sant Joan de Déu, Pg Sant Joan De Deu Nº 2, 08950 Esplugues De Llobregat, Barcelona, Spain