Official Journal of the European Paediatric Neurology Society

Original article

Brain injury in glutaric aciduria type I: The value of functional techniques in magnetic resonance imaging

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ARTICLE INFO

Article history:
Received 30 June 2008
Received in revised form
29 September 2008
Accepted 16 December 2008

Keywords:
Acute striatal necrosis
Substantia nigra
Diffusion-weighted imaging
Glutaric aciduria type I
Glutaryl-CoA dehydrogenase deficiency
Proton magnetic resonance spectroscopy

ABSTRACT

Background: Acute striatal necrosis is a devastating consequence of encephalopathic crisis in patients with glutaric aciduria type I (GA-I), but the mechanisms underlying brain injury are not completely understood.
Objective: To approach pathophysiological aspects of brain injury in GA-I by means of functional techniques in magnetic resonance imaging (MRI).
Patients and methods: Four patients during an acute encephalopathic crisis and three asymptomatic siblings with GA-I underwent single-voxel hydrogen magnetic resonance spectroscopy (MRS) and brain MRI including gradient echo T1-weighted, FLAIR, T2-weighted and diffusion-weighted imaging.
Results: The study was performed between three and eight days after the onset of acute encephalopathic crisis. Isotropic diffusion images showed high signal changes with corresponding low apparent diffusion coefficient values within the putamen, caudate nuclei and globus pallidus (four patients), and the cerebral peduncles including the substantia nigra (one patient). The study disclosed normal findings in asymptomatic siblings. MRS showed decreased N-acetyl-aspartate/creatine ratio at the basal ganglia in encephalopathic patients when compared to a group of sex- and age-matched controls.
Conclusions: Brain injury in GA-I is characterized by the presence of cytotoxic edema and reduced neuronal integrity by functional imaging techniques. Involvement of the basal ganglia may be asymmetrical in patients with unilateral motor disorder and may extent to the cerebral peduncles and substantia nigra, which may be responsible for the acute onset dystonia in some patients. Functional techniques failed to demonstrate any abnormalities in asymptomatic patients, which is in agreement with the integrity of basal ganglia structures observed by conventional MRI sequences.

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doi:10.1016/j.ejpn.2008.12.002

1. Introduction

Glutaric aciduria type I (GA-I) is an inborn error of metabolism, resulting from a defect of glutaryl-CoA dehydrogenase (GCDH). This enzyme is essential for the degradation of lysine, hydroxylysine and tryptophan.[1] After neonatal screening by tandem mass spectrometry, early therapy with a lysine-restricted diet and carnitine supplementation highly reduces morbidity and mortality in GA-I patients.[1,2] Still, patients with a low excretion biochemical phenotype are at high risk of being missed by newborn screening programmes.[3] When GA-I patients do not take the advantage of an early therapy, they may develop encephalopathic crisis and acute striatal necrosis after febrile illness, surgery or immunisations.[1,2,4] Acute striatal necrosis in GA-I has been extensively characterized from a structural point of view by means of conventional magnetic resonance.[1,5,6] However, functional techniques in magnetic resonance imaging, such as diffusion-weighted imaging (DWI) and spectroscopy, have been applied in a few patients with GA-I and heterogeneous phenotypes.[7–14] Our aim was to study brain injury with DWI and magnetic resonance spectroscopy (MRE) in a homogeneous group of infants with GA-I suffering an encephalopathic crisis. Asymptomatic siblings with GA-I were also analysed in order to detect subtle abnormalities that could not be detected by conventional MRI methods.

2. Patients and methods

2.1. Patients

Seven patients were diagnosed with GA-I in our center during the period 2005–2007. MRI studies were performed on four patients during an encephalopathic crisis (mean age: 10.5 months; range 9–12 months) and on three asymptomatic siblings (mean age: 3.6 years; range: 1–6 years).

2.2. Biochemical and molecular analysis

Diagnosis of GA-I consisted of the quantification of glutaric acid (GA) and 3-hydroxyglutaric acid (3-OH-GA) in urine by gas chromatography-mass spectrometry, and mutation analysis in the GCDH gene, as previously reported.[15]

2.3. Brain MRI

MRI examinations were performed on a 1.5-T magnet system (Signa Excite HD, Milwaukee, WI, USA), obtaining sagittal T1-weighted, axial fast-spin echo with fluid-attenuated inversion recovery (FLAIR) and T2-weighted imaging. Axial EPI diffusion-weighted imaging (DWI) sequences were performed with diffusion gradients applied along three orthogonal axes and a b factor of 1000 mm^2/seg. The data obtained were used to construct isotropic DW images and apparent diffusion coefficient (ADC) maps. ADC maps were made with Advantage Windows, using Functool (General Electric, Milwaukee, WI, USA). ADC measurements were directly obtained by drawing ROI (regions of interest) on ADC maps. ROI were manually drawn in the caudate nucleus, putamen and pallidus. ROI size of 17 mm^2 were calculated in all cases.

Single-voxel hydrogen MR spectroscopy (PROBE, GE, Milwaukee, WI, USA) was performed after MRI using the point resolved spectroscopy (PRESS) technology with repetition time TR = 1600 ms and echo time TE = 135 ms. Volumes of 1 cm^3 were selected from putaminal high hyperintensity signal in three encephalopathic patients. These results were compared with a control group of three age- and sex-matched subjects with normal MRI findings examined with the same protocol who underwent examinations for seizures and unspecific developmental delay. Informed consent was obtained in all cases.

3. Results

3.1. Clinical and biochemical results

A summary of the most relevant clinical, radiological, biochemical and molecular data for patients who suffered an acute encephalopathic crisis is shown in Table 1. They were referred to our center with the suspected diagnosis of viral encephalitis. Craneal CT was performed during the first 24 h of neurological deterioration in all patients at their reference centers. Only in patient 3 did the CT disclose decreased signal attenuation in the left striatum. However, a retrospective analysis of the CT in patient 1 detected hypodensity of the basal ganglia.

Familiar molecular studies revealed that two siblings of patient 1 (patients 5 and 6) and a twin sister of patient 3 (patient 7) had the same genotype than their symptomatic siblings. Biochemical studies showed that they were low excretors, with normal glutaric acid (GA) excretion: median 4-mmol/mol creatinine (C.V. 2–10) and slightly raised excretion of 3-OH-GA, median 32 mmol/mol creatinine (C.V. 2–15). These patients, together with the four encephalopathic patients, showed plasma glutarylcarnitine concentrations within the control values. Neurological examination of the three asymptomatic siblings was normal with a head circumference between the 50th and 90th percentile.

After the metabolic decompensation, the four encephalopathic patients and their asymptomatic siblings followed a lysine-restricted diet and carnitine supplementation. No metabolic decompensations were detected afterwards.

3.2. MRI results

The median time from acute neurological signs to MRI examinations in encephalopathic patients was 4.5 days (Table 1). In patients who manifested a generalized motor disorder, *FLAIR* and T2-weighted sequences revealed bilateral and symmetric hyperintensity within the putamen, caudate nuclei, globus pallidus (patients 1, 2 and 4) and cerebral peduncles (patient 4) (Fig. 1). On DWI, high signal changes with corresponding low ADC values were evident in the same areas. The ADC values in the basal ganglia were lower compared to the same areas of asymptomatic patients (Fig. 2). In patient 3, an acute right flaccid hemiparesis appeared after

Table 1 – Clinical, radiological, biochemical and molecular data of GA-I encephalopathic patients.

	Patient 1	Patient 2	Patient 3	Patient 4
Clinical data				
Age at onset (months)	10	9	12	11
Sex	Male	Male	Female	Male
Head circumference	Percentile 90	Percentile > 90	Percentile 75-90	Percentile > 90
Mental and motor development	Normal	Normal	Normal	Normal
Intercurrent illness	Acute wheezing	Acute otitis media	Rotavirus gastroenteritis and dehydratation	Acute gastroenteritis of unknown etiology
Seizures	Yes	Yes	Yes	Yes
Movement disorder	Oromandibular dyskinesias and generalized choreoathetosis	Oromandibular dyskinesias and dystonic tetraparesia	Oromandibular dyskinesias and right dystonic hemiparesia	Oromandibular dyskinesias and dystonic tetraparesia
Magnetic resonance studies				
Time of MR studies from neurological onset	Fifth day	Third day	Fourth day	Eighth day
T_1 findings	Normal	Frontotemporal hypoplasia	Increased volume of left basal ganglia	Frontotemporal hypoplasia
T_2 and *FLAIR* hyperintensities	Symmetrical in pallidus, putamen and caudate	Symmetrical in pallidus, putamen and caudate	Left: pallidus, putamen, caudate Right: putamen, caudate	Symmetrical in pallidus, putamen, caudate and substantia nigra
Isotropic Diffusion hyperintensities	Symmetrical in pallidus, putamen and caudate	Symmetrical in pallidus, putamen and caudate	Left: pallidus, putamen and caudate	Symmetrical in pallidus, putamen, caudate and substantia nigra
Diffusion ADC	Decreased ADC in basal ganglia	Decreased ADC in basal ganglia	Decreased ADC in left basal ganglia	Decreased ADC in basal ganglia and substantia nigra
Spectroscopy in basal ganglia	Decreased NAA and NAA/Cr ratio	Decreased NAA and NAA/Cr ratio	Not done	Decreased NAA and NAA/Cr ratio
Biochemical and molecular studies				
Urinary excretion of GA (C.V. 2–10)	4	79	7	25
Urinary excretion of 3-OH-GA (C.V. 2–15)	226	404	90	85
Molecular diagnosis	M405V/M405V	V400M/V400M	A421V/M405V	V400M/V400M

Values for GA and 3-OH-GA are expressed as mmol/mol creatinine.

three days of irritability, low consciousness and seizures. Twenty-four hours later, DWI showed restricted diffusion of the left basal ganglia (Fig. 3).

Conventional MRI and DWI in asymptomatic siblings disclosed normal findings.

3.3. *MRS results*

MR spectroscopy showed a decreased N-acetyl-aspartate (NAA) peak and NAA/creatinine (Cr) ratio at the basal ganglia in three encephalopathic patients. The values of NAA/Cr ratios in encephalopathic patients (range: 0.97–1.12) were below the NAA/Cr values in control subjects (range: 1.61–1.97) (Fig. 4).

4. Discussion

In Spain, 40% of the GA-I patients present the biochemical phenotype of low excretion.[15] This phenotype consists of a high residual GCDH activity and low excretion of GA and 3-OH-GA in urine. By chance, this study was performed on seven patients with this phenotype that included normal glutarylcarnitine in plasma. Molecular analysis identified three mutations V400M, A421V and M405V (Table 1) that have been associated with the low excretor phenotype.[3,16,17] These patients are at high risk of being missed by newborn screening programmes,[3] and hence, their prognosis depends on an accurate clinical diagnosis for which functional techniques in neuroimaging, such as DWI and spectroscopy, are proposed in this study.

Craneal CT detected signal abnormalities in the basal ganglia of two out of four encephalopathic patients. These results indicate that craneal CT is not a reliable technique for the diagnosis of acute striatal necrosis, as previously noted by other authors.[6,7]

On brain MRIs, *FLAIR* and T2-weighted sequences disclosed an increased signal within the putamen, caudate and globus pallidus in four encephalopathic patients. Lesions were

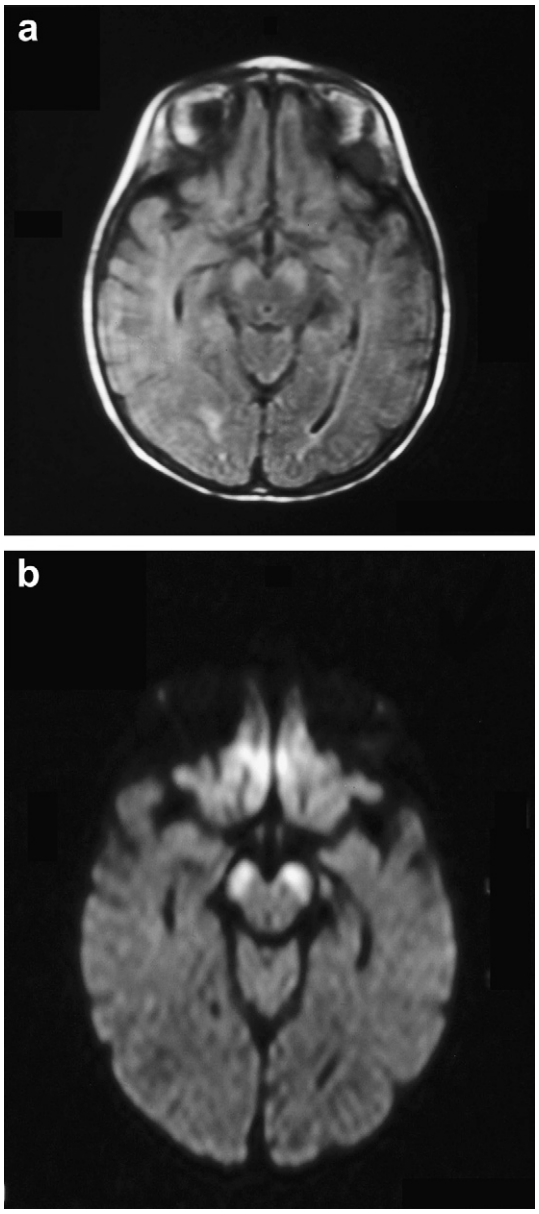

Fig. 1 – (a) Axial *FLAIR* image and (b) axial diffusion-weighted image of patient 4 showing bilateral increased signal in the cerebral peduncles (crus cerebri and substantia nigra).

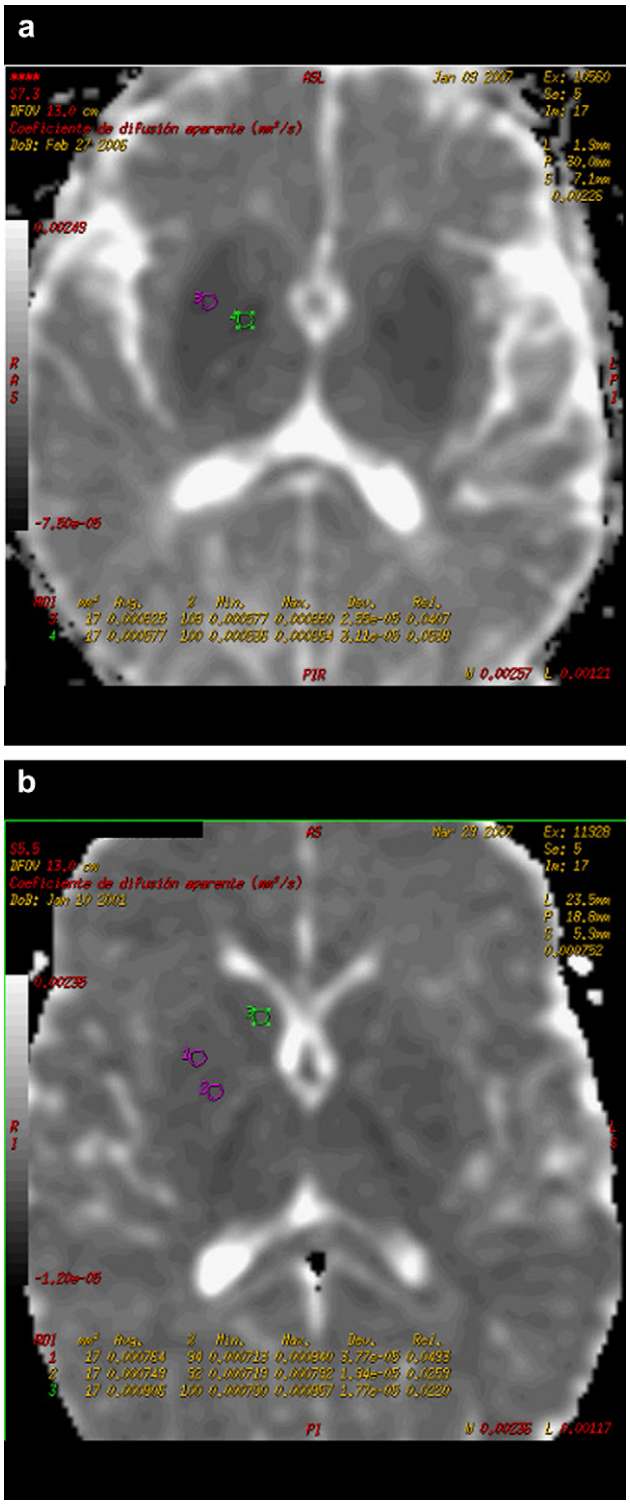

Fig. 2 – Regions of interest (ROIs) of size 17 mm^2 are drawn on ADC maps of patient 1 (a) and 5 (b). ADC values in patient 1 (putamen: 62.5; globus pallidus: 57.7) are decreased when compared with ADC values in patient 5 (putamen: 76.4; globus pallidus: 74.9). ADC values are expressed as 10–5 mm^2/s.

bilateral and symmetric in patients who presented a generalized motor disorder affecting the four limbs. By contrast, the MRI study of patient 3 that was performed twenty-four hours after the onset of an acute right flaccid hemiparesia, disclosed a more extensive signal abnormality in the left basal ganglia. Although striatal necrosis in GAI characteristically shows a symmetric pattern, unilateral or markedly asymmetric basal ganglia involvement has been previously described, especially in GA-I patients with a progressive motor disorder of infancy.[18]

DWI was performed between three and eight days after the onset of neurological deterioration and showed high signal changes with corresponding low ADC values within the basal ganglia in the four encephalopathic patients. By restricted diffusion, the extension of basal ganglia involvement was similar to that observed on conventional MRI sequences. However, we think that restricted diffusion showed more enhanced lesion conspicuity than conventional sequences in all cases.

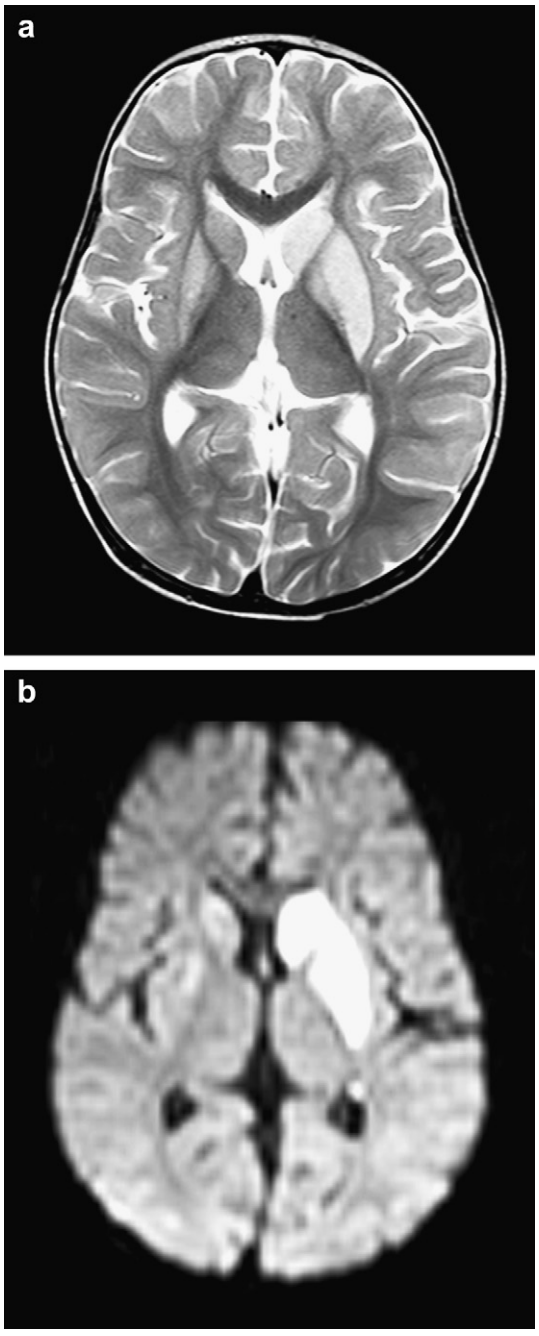

Fig. 3 – (a) Axial T2-weighted image and (b) diffusion-weighted image of patient 3. (a) shows bilateral but asymmetric involvement of the basal ganglia: the left putamen and head of caudate show swelling and extensive increased signal. (b) demonstrates restricted diffusion in the left basal ganglia.

DWI has been previously applied in GA-I patients with striatal necrosis during different stages of evolution[1,7–9,12,14] but, to our knowledge, this is the unique series of GA-I patients studied during an acute encephalopathic crisis. Strauss et al.[14] reported a retrospective study of MRI diffusion and ADC mapping in a series of Amish patients with GA-I. Authors found a 24–34% reduction in diffusion through the basal ganglia in one patient 10 h after the onset of motor regression (acute stage); physical swelling and ''normalization'' of ADC values within the striatum were observed in one patient 56 h after acute regression (sub-acute stage) and a reduced tissue volume and high diffusion values within the striatum were detected in 9 patients several months after the decompensation (chronic stage).

ADC values in our patients were markedly reduced and similar to those values reported by Strauss et al.[14] during the acute stage of striatal necrosis. However, the timing of MRI after the onset of symptoms and the presence of focal swelling within the basal ganglia on conventional MRI sequences led us to classify our patients in the sub-acute stage of evolution.

Previous studies focusing on the time course of ADC values in ischemic stroke patients have shown that ADC values reach a minimum within the first 24 h of cerebral infarction; subsequently, they gradually increase to pseudo-normalisation at 8–12 days post-infarction and reach values four times those encountered in normal tissue in the chronic stage.[19] These changes on ADC values reflect a sequence of histopathological changes beginning with the shift of water from the extracellular space into cells (cytotoxic edema), supervening vasogenic (extracellular) edema and progression through loss of cell membrane integrity and gliosis.

The mechanisms underlying brain injury and age-dependent susceptibility in GA-I are not completely understood. A novel diet-induced mouse model for GA-I showed that high lysine intake in GCDH-deficient (GCDH−/−) mice resulted in vasogenic edema and blood–brain barrier (BBB) breakdown within the striatum.[20] The presence of focal swelling and vasogenic edema in combination with a decreased striatal perfusion during the sub-acute stage of striatal necrosis[14] also support the hypothesis of a disturbance of BBB. However, no evidence of BBB breakdown has been observed in *in vitro* and *in vivo* animal models of GCDH deficiency.[21,22] These studies have demonstrated that the permeability of BBB for GA and 3-OH-GA is not affected, suggesting that intra-cerebral *de novo* synthesis and subsequent trapping of these dicarboxylic acids in the brain are responsible for neuropathological alterations rather than metabolites formed in peripheral organs.

In three asymptomatic patients with GA-I and a similar biochemical phenotype, DWI did not detect abnormal signal in the basal ganglia, and ADC values were higher than those obtained from the same regions in encephalopathic patients. The normal diffusivity of water molecular displacement within the basal ganglia in these metabolic stable patients is in agreement with the integrity of basal ganglia structures observed by conventional MRI sequences.

In patient 4, DWI showed bilateral bright lesions in the cerebral peduncles, partially affecting the substantia nigra. This finding could be important in the pathophysiology of acute generalized dystonia in this patient, as it could be the consequence of dopaminergic neurons' loss in the substantia nigra. In fact, a cerebrospinal fluid analysis of this patient detected slightly decreased levels of homovanilic acid when compared with control values (340 nmol/L, C.V. 344–906).[23]

Involvement of the substantia nigra has been previously described in GA-I patients studied with conventional MRI,[6] but neuropathological studies in GA-I autopsy cases have not detected loss of dopaminergic neurons in the brain of these patients.[24] Although the basal ganglia and substantia nigra are

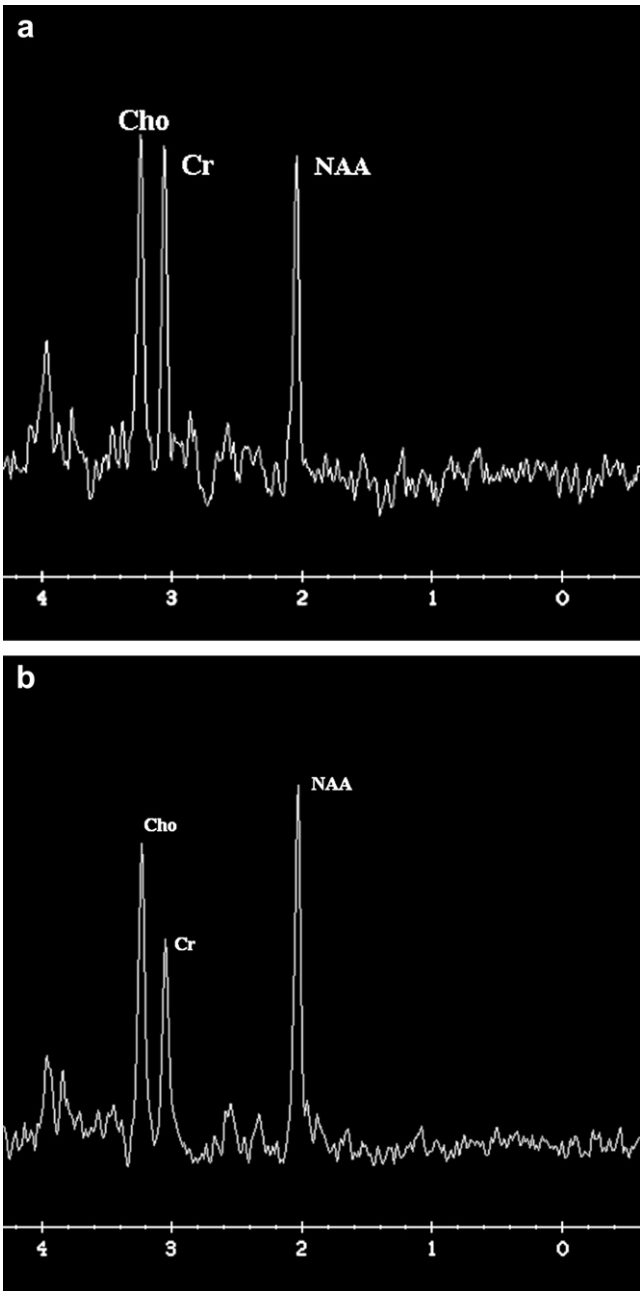

Fig. 4 – Single-voxel hydrogen magnetic resonance spectroscopy (TE = 135) obtained through the putamen nucleus. Compare (a) decreased NAA peak in patient 1 during acute encephalopathic crisis (ratio NAA/Cr: 0.97) with (b) normal spectra in a sex- and age-matched control (ratio NAA/Cr: 1.76). Cho (choline); Cr (creatine); NAA (N-acetyl-aspartate).

the regions of higher presynaptic dopamine turnover in the healthy brain,[25] more studies are needed to confirm the role of dopamine in the degenerative process of GA-I.

MR spectroscopy showed decreased N-acetyl-aspartate (NAA) with respect to creatine peaks in three encephalopathic patients, indicating a reduction of neuronal integrity within the basal ganglia during acute encephalopathic crisis. Three single patients with GA-I and acute striatal necrosis were previously studied with proton MR spectroscopy,[7,8,13] but the reported results are heterogeneous and non-conclusive. Elster[7] and Santos[8] described a normal spectra over the basal ganglia in two infants during an acute striatal necrosis. By contrast, decreased NAA/Cr ratios of 1.069 and 1.14 were detected at the basal ganglia in a 19 months-old infant studied two months after an acute encephalopathic crisis[13] and in an 11-months-old boy with a progressive dyskinetic motor disorder and striatal necrosis,[9] respectively. The values of the NAA/Cr ratio in our patients (range: 0.97–1.12) were very similar to those reported by these authors and markedly below the range of normal values obtained from control patients. Therefore, our results confirm those findings reported by Kurul[13] and Oguz[9] and support the hypothesis that

acute striatal necrosis is associated with a reduction of neuronal integrity within the basal ganglia.

In conclusion, functional imaging techniques demonstrate the presence of cytotoxic edema and a reduction of neuronal integrity during acute striatal necrosis. Involvement of the basal ganglia may be asymmetrical in patients with unilateral motor disorder and may extent to the cerebral peduncles and substantia nigra, which may be responsible for the acute onset dystonia in some patients. Finally, these techniques failed to demonstrate any abnormality within the basal ganglia of asymptomatic patients, which is in agreement with the integrity of these structures observed by conventional MRI sequences.

Acknowledgement

This work was supported by Fondo de Investigaciones Sanitarias (FIS) grants PI070548 and PI051318.

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