

MRI FINDINGS IN THE DIAGNOSIS AND MONITORING OF RASMUSSEN'S ENCEPHALITIS

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Abstract – Rasmussen's encephalitis is a devastating syndrome of multifocal brain dysfunction and focal seizures. Magnetic resonance (MR) findings, associated with clinical data and electroencephalogram (EEG), may indicate the diagnosis and could be an indicative of prognosis. We studied 5 patients with Rasmussen's encephalitis, assessing clinical history and MR images. All patients had refractory focal seizures with a predominant motor component associated with hemispheric atrophy, that was proportional to severity of disease and neurological deficits in these patients. Gray and white matter abnormal signal on T2 MR images were found in patients who had hemiparesis. It was not related to the duration of the disease but to aggressiveness. MR proton spectroscopy in severe disease showed lactate and choline increase and decreased NAA, reflecting neuronal and axonal loss, gliosis and elevated membrane turnover and recent - crisis (not controlled). MR studies, in addition to help in diagnosis, may be useful for monitoring metabolic changes and progression of disease in Rasmussen's encephalitis.

KEY WORDS: Rasmussen's encephalitis, MRI, spectroscopy, epilepsy.

Achados de RM no diagnóstico e monitorização da encefalite de Rasmussen

Resumo – A encefalite de Rasmussen é uma devastadora síndrome com disfunção cerebral multifocal e convulsões focais. Achados de ressonância magnética (RM), associados aos dados clínicos e de eletrencefalograma (EEG), podem indicar o diagnóstico e podem ser indicativos de prognóstico. Foram estudados 5 pacientes com encefalite de Rasmussen, avaliando a história clínica e imagens de RM. Todos os pacientes apresentavam crises epiléticas focais refratárias com componente predominantemente motor associadas à atrofia hemisférica, que foi proporcional à gravidade da doença e déficits neurológicos nestes pacientes. Alteração da intensidade de sinal nas substâncias branca e cinzenta, nas sequências ponderadas em T2, foram encontradas nos pacientes com hemiparesia. Ela não estava relacionada com a duração da doença, mas à severidade. A espectroscopia de prótons por RM na doença severa demonstrou aumento dos níveis de colina e lactato e diminuição de N-acetilaspártato, refletindo perda neuronal e axonal, gliose e aumento de *turnover* de membrana e crise recente (não controlada). Estudos de RM, além de ajudar no diagnóstico, podem ser úteis para acompanhar alterações metabólicas e progressão da doença na encefalite de Rasmussen.

PALAVRAS-CHAVE: encefalite de Rasmussen, RM, espectroscopia, epilepsia.

The syndrome of chronic encephalitis and intractable focal epilepsy was first reported by Rasmussen in 1958 and consists in severe epilepsy associated with slow progressive neurologic deterioration and progressive lateralized brain destruction¹. Previous studies indicated that anti-GluR3 autoantibodies might be involved in pathogenesis of the disease². However, other investigators did not find these autoantibodies³. More recently, other mechanisms as a cytotoxic T-cell reaction against neurons were dem-

onstrated to play a causative role in Rasmussen encephalitis (RE)⁴. Despite the fact that an etiologically significant viral antigen has not yet been found; the early immunosuppressive and antiviral treatment may be effective for a period of time⁵.

Although in rare situations RE may present without epilepsy⁶, seizures mark the clinical features and their severity and evidence of progressive neurological deterioration usually led to early consideration of surgical therapy.

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Surgical specimens and biopsy show typical encephalitis with widespread perivascular cuffs and round cells, gliosis and scattered microglial nodules. However, the morphologic picture of active chronic encephalitis is nonspecific. Resected specimens in the more advanced clinical stages have demonstrated diffuse cortical atrophy with neuronal loss and a lack of inflammatory cells⁷. Magnetic resonance imaging (MRI) in combination with clinical data and slow focal activity on EEG, contralateral to the motor manifestations may indicate the diagnosis^{8,9} and hasten brain biopsy. The progression of lesions on MRI seems to reflect the course of this disease and prognosis, although the extent of the lesions not necessarily correlates with the frequency of seizures¹⁰.

Thus, the purpose of this study was to determine if MRI may indicate prognosis in patients with RE.

METHOD

Local research ethics committees granted ethical approval for the study.

Magnetic resonance exams were performed in five patients with clinical and neuroimaging evidences of RE. In three of them the diagnosis of RE was confirmed by pathological examination of the surgical specimen. In the other two, clinical and imaging of two year follow-up confirmed the diagnosis. MRIs were

performed in a 2T scanner (Elscent Prestige®, Haifa, Israel), with T1 and T2 acquisitions in three orthogonal planes, including T1-weighted SE gadolinium enhanced images. MRI acquisition parameters were: sagittal T1 spin echo, 6 mm thick, flip angle=180°; repetition time (TR)=430 ms, echo time (TE)=12 ms, matrix 200 × 350, field of view (FOV)=25 × 25cm, T2-weighted and proton density “fast spin echo” (FSE), 3 mm thick, flip angle=160°; TR=4800 ms, TE=108/18 ms, matrix 256 × 256, FOV=22 × 22 cm; T1-weighted spin echo (SE); TR=540 ms, TE=28 ms; T1-weighted inversion recovery (IR), 3 mm thick, flip angle=200° TR=2700 ms, inversion time (TI)=860 ms, TE=14 ms, matrix 130 × 256, field of view (FOV)=16 × 18 cm, and T2-weighted fluid-attenuated inversion recovery (FLAIR) images TR=8500 and 2000 ms or 100 and 2200 ms, TE=72 or 90 ms, matrix of 256 × 296 and FOV of 22 × 22 cm. The analysis of exams, including establishment of atrophy grade, were performed by visual parameters, by three different observers.

Single voxel hydrogen magnetic resonance spectroscopy (¹H-MRS) was acquired in four of the patients, using PRESS sequence (TR/TE =1500/135 ms, number of excitation ((NEX)=200) with two regions of interest (ROIs) of 8 cm³, one in each parietal deep white matter. Prior to the acquisition, a localized shimming at the ROI was performed, followed by water suppression adjustment. Localized shimming was repeated to ensure good field homogeneity and until the ¹H signal from water within the ROI

Table. Patient's data.

Patient n°	Sex	Age (years)	Affected hemisphere	Antecedents	Age of onset first symptoms (years)	Seizures in evolution	Neurological outcome	Hyper signal at T2 MRI	Hemispheric and caudate atrophy	Surgery
1	M	17	R	Meningitis, immediately before the onset seizures	6	EPC (left superior limb, motor)	hemiparesis	Yes	Yes	Yes
2	F	15	R	Not important	10	EPC (left limbs, motor) +GTC	Left foot paresis and coordination deficits	No	Yes	No
3	F	16	L	Mother's cousin with epilepsy	9	GTC and SPMS (right limbs, motor) +GTC	Facial and oral automatisms and right coordination deficits	No	Yes	No
4	F	7	R	Varicella, 2 months before the onset seizures	2	SPMS (left superior limb)	Hemiparesis	Yes	Yes	Yes
5	M	6	L	Twin brother with myoclonus	5	SPMS (right limbs) +GTC	Hemiparesis	Yes	Yes	Yes

M: male; F: female; R: right; L: left; GTC: generalized tonic clonic seizure; SPMS: simple partial motor seizure; EPC: epilepsia partialis continua.

became as narrow as possible. The spectra were post-processed using software supplied by the machine manufacturer (Elscent Prestige 2T, Haifa, Israel).

RESULTS

Table summarizes clinical, EEG and image findings. The age at onset ranged from 2 to 10 years (mean 6.4 years). In the six months before the first symptom, two patients had infections (measles and meningitis). Tonic-clonic generalized seizures marked disease onset in 4 patients and partial seizures in one patient. Seizure frequency varied, however all five patients presented *epilepsia partialis continua* (EPC) at some point of the disease. Convulsive status epilepticus occurred in two patients. Three patients developed hemiparesis. In two patients, who developed symptoms at oldest age, the neurological examination remains normal despite slow progression of the hemispheric atrophy. Although cognitive decline is difficult to assess be-

cause polypharmacy and frequent seizures, four patients showed some degree of cognitive impairment.

Figure 1 summarizes image findings. All patients had cortical atrophy associated with ipsilateral ventricular enlargement and caudate atrophy, more severe in those with hemiparesis. The most affected areas were insular, temporal and parietal regions. Gray and white matter focal signal intensity abnormalities (hyperintense signal in long TR-weighted images) were found in the three patients with hemiparesis.

¹H-MRS performed in one patient (1) showed increased lactate and choline and decreased NAA in atrophic regions (Fig 2). In another patient (3), ¹H-MRS did not show differences between hemispheres (Fig 3).

Antiepileptic drugs were only partially effective for seizure control. Plasma exchange was performed in two patients with transient improvement. Three patients with hemiparesis underwent hemispherectomy.

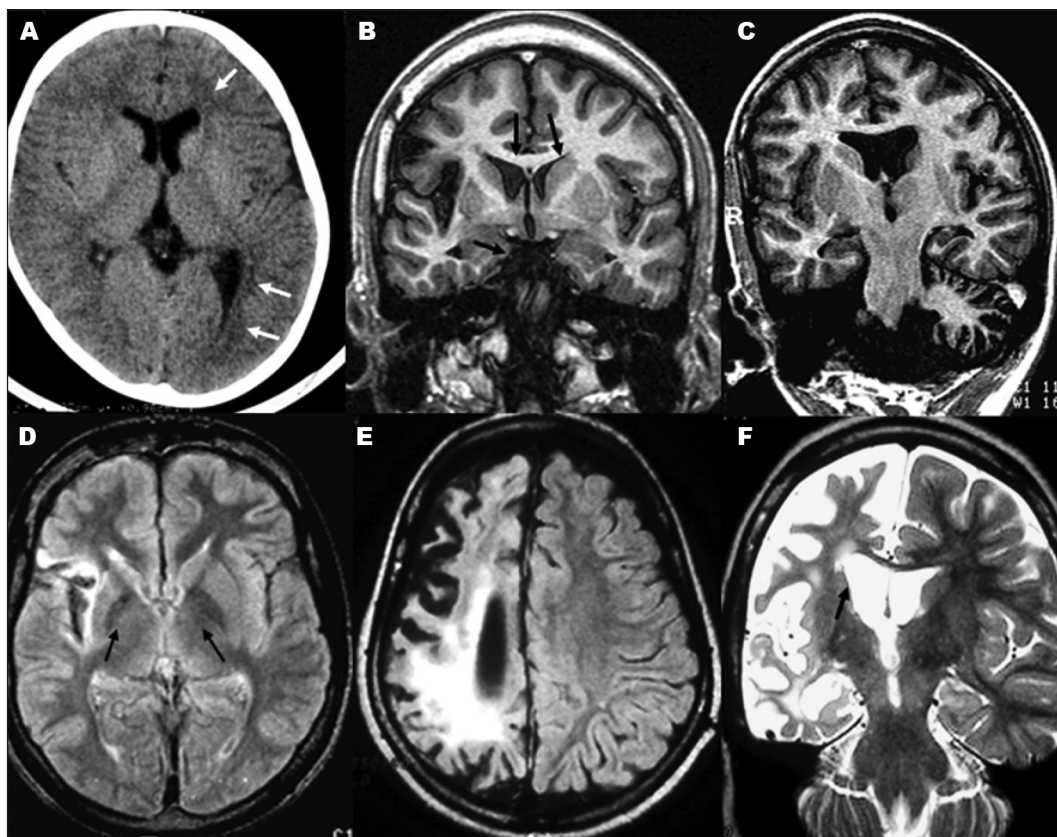


Fig 1. [A] CT. Left hemispheric atrophy with ventricular and cortical sulci enlargement. Note hypodense areas in the white matter of the affected hemisphere (arrow). [B] Coronal T1-weighted image at the level of the anterior commissure. Right hemispheric atrophy. Note the width of right Sylvian fissure, frontal horn and temporal horn of right lateral ventricle (arrow). [C] Coronal IR-weighted image. Asymmetry between head of caudate nucleus, atrophic on the left side (arrow). Note the width of frontal horn of ipsilateral ventricle in consequence of atrophy. [D] Axial T2-weighted image. Hyperintense signal in right insular cortex with discrete width of Sylvian fissure at this level. Note the head caudate nucleus asymmetry (arrows). [E] Axial FLAIR image. Marked right hemiatrophy with hyperintense signal in the white matter of parietal region. [F] Coronal T2-weighted image. Marked right hemiatrophy with focal areas of hyperintense signal in the white matter of frontal, parietal and temporal regions. Note the ipsilateral caudate nucleus atrophy (arrow).

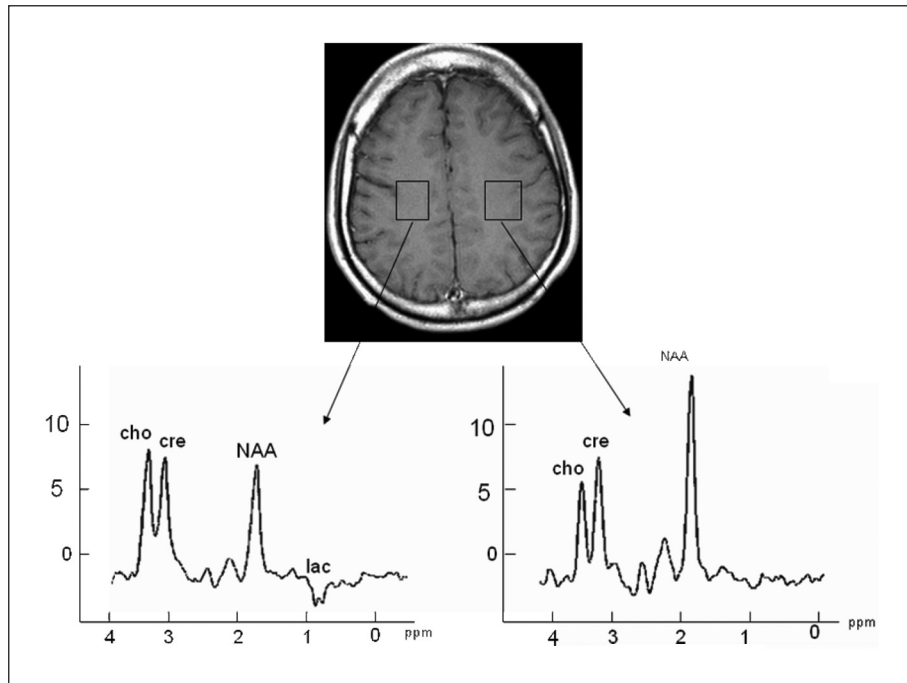


Fig 2. MRS, performed at white matter of frontal regions in patient 1. Note the decreased NAA, increased choline (Cho) and lactate (lac) peak in the atrophic hemisphere (right) compared with the normal one. Cre: creatine.

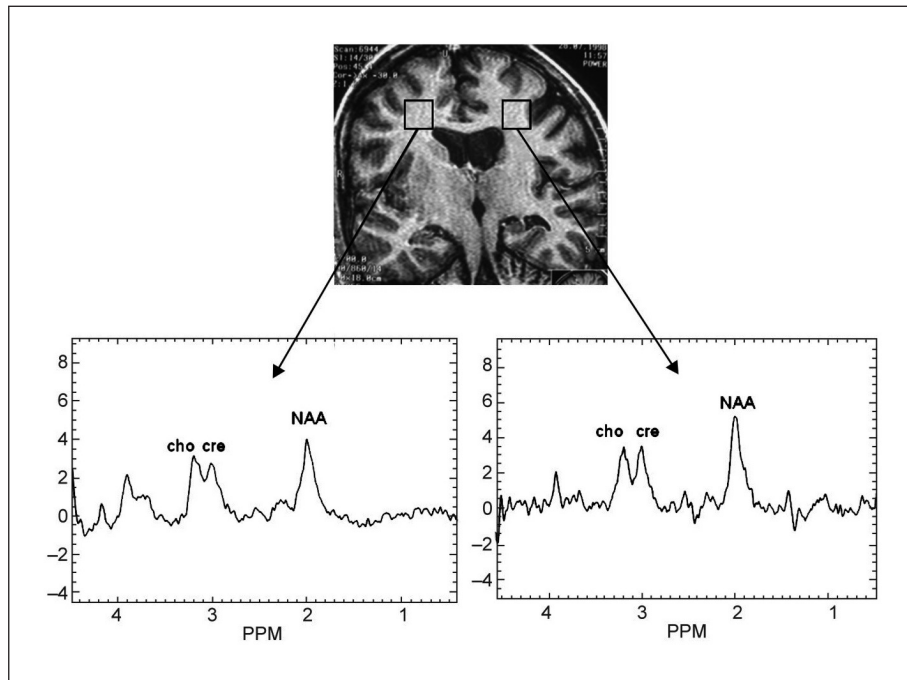


Fig 3. MRS, performed at white matter of frontal regions. There were not differences between the normal side and atrophic hemispheres: right, in patient 3.

DISCUSSION

Progressive cerebral hemiatrophy associated with clinical deterioration and focal EEG features, was the key to the diagnosis of RE, avoiding brain biopsy in all our pa-

tients. The age of onset, the first seizure (generalized tonic-clonic seizure) and a preceding inflammatory or infectious event (that occurred in 2 of 5 of patients), are in agreement with previous studies¹¹.

As occur in RE, seizures were focal, involving exclusively one hemibody, and refractory to antiepileptic drugs. In the initial phase the diagnosis of chronic encephalitis may be difficult, particularly in the absence of EPC. There is a progressive increase in seizure frequency and severity and patients develop permanent neurological deficits contralateral to the affected cerebral hemisphere. The initial MRI scans shows that the inflammatory lesion (hyperintense T2/FLAIR signal) had a monofocal onset^{12,13}. The next phase of disease is marked by neurological deterioration and may persist for more than 10 years. In the last phase, characterized by hemiparesis, seizures are not so frequent but motor and mental deterioration continues⁵ sometimes in spite of surgery^{14,15}. MRI typically shows hemiatrophy with enlargement of ipsilateral ventricles and subarachnoid spaces¹⁶⁻¹⁸.

Cortical atrophy occurred in all our patients, probably secondary to the long course of disease. It was visual proportional to the severity of symptoms, most likely reflecting the severity of disease. However, even patients without hemiparesis presented diffuse hemispheric atrophy. We suppose that this can be an example of brain functional plasticity in chronic insults, frequently observed in RE, pre- and post- operatively^{19,20}. It is possible that reorganization of somatosensory cortex helps to maintain functions, in spite of the anatomical damage. Caudate atrophy occurred in all our patients, although this has been rarely reported²¹⁻²³.

Patients with hemiparesis and more frequent seizures presented also gray and focal white matter hyperintensity in T2-weighted images. Bien et al. demonstrated that this signal change is correlated with the number of T cells in brain parenchyma and reactive gliosis, indicating ongoing damage^{4,24}. In our study, patients with hyperintense T2 lesions and hemiparesis had the most devastating forms of RE.

¹H MRS contributes to evaluation and progression of metabolic changes in RE^{9,25-27}. Although the patterns of metabolites observed are nonspecific. Compared with normal hemisphere, the atrophic regions showed increased lactate, a consequence of repetitive focal epileptic neuronal activity^{28,29}, as well as increased choline (related to gliosis, microglial proliferation and elevated membrane turnover³⁰) and reduced NAA. As NAA plays a role as neuron-glia signaling system³¹, this reduction reflects neuronal loss and axonal dysfunction/depletion³² and possibly also changes in neurotransmitter system, altered in RE³³. This reduction in NAA suggests ongoing neuronal and axonal damage and loss in RE. Patients 1 and 4, with more severe disease and atrophy, showed these abnormalities (Fig 2, related to patient 1). Particularly, the lactate increase was related with recent crisis (not controlled) and not to the disease itself.

In the two patients (patients 2 and 3, Table) whose ¹H MRS did not showed differences between hemispheres (patient 3, Fig 3), the MRI did not show abnormal signal but only atrophy, the age of onset was more advanced and the crisis were controlled with drugs, without surgery, showing a positive correlation between metabolic and structural changes and severity of disease.

Parenchyma atrophy was a common finding of RE in our group and even patients without hemiparesis had some degree of hemispheric atrophy. Our hypothesis is this disconnection is related with the plasticity of child's brain, but a greater number of cases and application of functional techniques, as fMRI, are needed to confirm it. In spite of the few number of patients, we noticed a tendency of patients with more severe disease to present signal changes on MRI and abnormal MRS. This finding may thus favor the possible existence of biochemical changes underlying structural damage, not necessarily visible on conventional MRI. These data are preliminary and these theses will be verified expanding the group and the follow-up timing.

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