ACUTE DEMYELINATION: AN INSIGHT INTO THE EFFECT OF MITOXANTRONE ON CNS LESIONS

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SUMMARY

We report the cases of 2 severely disabled patients with large inflammatory lesions suggestive of demyelination treated with mitoxantrone. Clinical condition was improved and brain lesions volume was reduced. On serial MR spectroscopy, there were variations in peaks between 0.9 and 1.4 ppm, suggestive of free lipids and amino acids. These variations may represent neurochemical markers of clinical recovery of large inflammatory lesions in multiple sclerosis.

Key words: multiple sclerosis, spectroscopy, MRI, mitoxantrone.

RÉSUMÉ

Demyelinisation aiguë : effet de la mitoxantrone

Nous rapportons les observations de deux patients présentant une atteinte neurologique sévère liée à de volumineuses lésions inflammatoires. Le traitement par mitoxantrone fut suivi d’une amélioration clinique et d’une diminution du volume lésionnel. Le suivi en spectroscopie par résonance magnétique mit en évidence des variations de pics situés entre 0,9 et 1,4 ppm correspondant aux lipides et aux acides aminés libres. Ces variations pourraient représenter les marqueurs de l’amélioration clinique des volumineuses lésions inflammatoires observées dans la sclérose en plaques.

Mots-clés : sclérose en plaques, spectroscopie, IRM, mitoxantrone.

Multiple sclerosis (MS) is characterized by episodes of demyelination in the central nervous system (CNS), usually preceded by an increase in blood-brain barrier permeability, and subsequent inflammation. Magnetic resonance imaging (MRI) has greatly contributed to the diagnosis of MS and to the understanding of its natural history [6]. However, weak correlations have been reported between total T2 weighted MRI lesions and clinical disability [6], except in the case of large demyelinating lesion in the spinal cord and brain stem. MR spectroscopy (MRS) is a non invasive technique which supplements conventional neuroimaging with neurochemical information [5]. It provides an index of neuronal integrity with the resonance intensity of N-acetylaspartate (NAA), which is localized almost exclusively in neurons in the mature brain [8]. Other peaks correspond to choline compounds, which are associated with membranes, myoinositol, a marker of gliosis, and free moieties corresponding to free lipids and aminoacids [3]. In cases with large demyelinating lesions and correspondingly severe clinical disability, repeated MRI/MRS examinations provide insight into the neurochemical changes of the inflammatory process associated with clinical status.

METHODS

We describe two patients presenting with a severe neurological deficit and large inflammatory lesions on MRI. They were transferred to the neurological department because of a worsening clinical picture despite treatment with IV methylprednisolone. Both were treated with intravenous (IV) combination of mitoxantrone (20mg/month) and methylprednisolone (1g/month) according to the procedure described by Edan et al. [4] in very active MS patients. MRI and MRS were performed immediately before each monthly course of mitoxantrone for six months, and then 3 and 12 months after the last course of mitoxantrone. For both patients, MRI scans included T2 weighted, fast-FLAIR (fluid attenuated inversion recovery), pre- and post-gadolinium (0.2ml/kg) T1 weighted sequences. MRS spectra were acquired with the PROBE-SV module (GE Medical Systems, Milwaukee, Wis), using a stimulated echo acquisition mode (STEAM) sequence. The acquisition technique and spectrum analysis have been described elsewhere [9]. A single volume of interest (VOI), was selected in Patient 1 (posterior lesion: 6.34ml) and 2 VOIs in Patient 2, (parieto-occipital region and centrum semiovale; 6.50ml). The VOI was kept constant in size and location after the first examination. Areas of NAA (ppm=2.02), creatine (Cr, ppm=3.03) and choline (Cho, ppm=3.22) peaks were recorded for each echo-time (TE).
the peak of myoinositol (Myo, ppm=3.56) and peaks between 0.8 and 1.4 ppm, amplitudes were recorded. No baseline correction or other post-processing procedure was used.

Case reports

The first patient was a 31-year-old woman who presented in April 1997 with isolated subacute left hemiparesis sparing the face. Brain MRI showed two large lesions in the right hemisphere (figure 1) with patchy and peripheral gadolinium enhancement. An MRI guided biopsy was obtained from the most anterior frontal lesion and histological examination was suggestive of demyelination. Her clinical condition continued to worsen despite the administration of 12g of methylprednisolone followed by one month oral taper. Treatment with mitoxantrone was initiated and clinical improvement started after the third infusion. No motor deficit was present on neurological examination 2 years after the first presentation (EDSS=1), and no new relapse was recorded.

The second patient was a 30-year-old man who presented in October 1997 with left hemianopsia and hemiparesis. Brain MRI showed a right-sided large parieto-occipital lesion, extending to the centrum semiovale with patchy and peripheral gadolinium enhancement. His clinical condition did not improve despite the administration of 6g of methylprednisolone. Treatment with mitoxantrone was initiated and clinical improvement started after the second infusion. A residual left hemianopsia was present at 2 years after the first presentation without new relapses (EDSS=1).

In both cases, medical and familial history was unremarkable. Routine hematological and biochemical tests were normal. CSF analysis, including oligoclonal band determination, was normal.

MRI and MRS follow-up

Lesion volume decreased by more than 50% during mitoxantrone therapy (figures 1 and 2). In Patient one, two new active lesions appeared during mitoxantrone therapy (figures 1 and 2).

Initially, a considerable decrease in the NAA/Cr ratio and increase in the Cho/Cr ratio were noted (TE=136ms). Both improved but remained abnormal at month 18 (figures 2 and 3). The NAA/Cr ratio fluctuated during evolution: e.g.increase of 21% at month 3 and 16% at month 18 in comparison to the first examination in Patient 1. The Cho/Cr ratio progressively decreased (49% decrease at month 18). Both ratios remained abnormal. The Myo/Cr ratio (short TE) started to increase at month 3, with an increase of more than 40% observed at month 9 and at month 18. Peaks at 1.3 and 1.4ppm decreased progressively (59 and 48% decrease respectively) while peaks centered at 0.9ppm showed a 30% increase starting at month 4 (figure 3).

DISCUSSION

In these 2 patients with large active demyelinating lesions, a monthly course of mitoxantrone was associated with dramatic clinical improvement starting

Fig. 1. – Lesion volume evolution in Patient 1 reconstructed using fast-FLAIR sequences (AW 3D analysis software package). It shows an increase in volume of the right posterior lesion at M-1 and M0, followed by a progressive decrease. Note the appearance of new lesions at months 2 and 5 (under mitoxantrone therapy), and at month 18 (after mitoxantrone therapy).

Fig. 1. – Évolution du volume lésionnel du Patient 1. Le volume est reconstruit à partir des séquences FLAIR rapides (AW 3D). Le volume de la lésion postérieure augmente à M-1 et M0, puis diminue. Noter l’apparition de nouvelles lésions à M2 et M5 (traitement par mitoxantrone en cours) et à M18 (après le traitement par mitoxantrone).
within the period of treatment, and a decrease in lesion volume and gadolinium activity on MRI, a decrease of peaks at 1.3-1.4ppm and increase of peak at 0.9 ppm on MRS. However, two new active lesions appeared in one patient.

Active MS plaques are characterized by perivascular inflammation, the presence of macrophages, local edema [7] and the reduction in the number and diameter of axons [10]. MRS studies have shown a marked decreases in NAA in acute and chronic plaques [2, 3, 9], which was only partially reversible over 4 to 8 months [3]. The decrease in NAA may be related to impaired function of mitochondria during inflammation, or alteration of the relaxation time of NAA by the chemical environment of the lesion.

The progressive increase of the ratio Myo/Cr may indicate the development of gliosis in the lesions. Peaks at 1.3 ppm correspond to lactates, free CH3 lipids and amino acids. The peak at 1.4ppm may represent thymosin4, a possible marker of activated macrophages and of a subset of oligodendrocytes [3]. Histopathological studies of demyelination have shown lipids in the form of triglyceride and cholesterol ester in MS lesions that have been symptomatic for up to 26 weeks, which was compatible with the determined time course of disappearance of lipid laden macrophages from areas of acute myelin destruction [1]. The decrease of peaks at 1.3-1.4ppm during follow-up may indicate decreased macrophage activity in the lesion. Peaks centered at

FIG. 2. – Graphs showing in Patient 1 the volume evolution of the right posterior lesion (normalized by 10), and at TE=136ms NAA/Cr and Cho/Cr ratios (a), and at TE=18ms Myo/Cr, peaks at 1.3, 1.4 and peaks centered at 0.9ppm. Note the fluctuations of NAA/Cr and Cho/Cr, the progressive decrease of lesion volume and peaks at 1.3 and 1.4ppm, and the progressive increase of peaks centered at 0.9ppm and of the ratio Myo/Cr. The volume of interest (6.34ml) was centered on the lesion and kept constant during the study. Mitoxantrone therapy was started after M0 MRI/MRS.

FIG. 2. – Évolution du volume lésionnel (normalisé par 10), et des pics de NAA/Cr et Cho/Cr à TE = 136 ms et de Myo/Cr et des pics centrés à 1,3-1,4 et 0,9 ppm à TE = 18 ms chez le patient 1. Noter les fluctuations de NAA/Cr et Cho/Cr, la diminution progressive du volume lésionnel et des pics à 1,3-1,4 ppm et l’augmentation progressive des pics centrés à 0,9 ppm et de myo/Cr. Le volume d’intérêt (6,34 ml), centré sur la lésion, est resté constant durant l’étude. Le traitement par mitoxantrone a débuté après l’IRM/SRM de M0.

FIG. 3. – Spectra evolution with time from the bottom (M-2) to the top (M18) in Patient 1 at TE=18ms and TE=136ms (STEAM sequences; TR=1500ms; mixing time 13.7ms). Mitoxantrone therapy was started after M0 MRI/MRS.

FIG. 3. – Évolution des spectres au cours du temps du bas (M-2) vers le haut (M18) chez le patient 1 à TE = 18 ms et TE = 136 ms (Séquences STEAM; TR = 1 500 ms; TM = 13,7 ms). Le traitement par mitoxantrone a débuté après l’IRM/SRM de M0.
0.9 ppm correspond to free CH2-lipids and amino acids. Their increase in the context of clinical recovery may be related to synthesis of myelin membranes and may suggest a possible remyelination. The balance between decreased peaks at 1.3-1.4 ppm and increased peaks centered at 0.9 ppm may represent a good in vivo biochemical marker for the reestablishment of sufficient neuronal conduction for clinical recovery.

As these large lesions were studied before and after the initiation of the treatment, our study may also provide insights into the mechanisms of action of mitoxantrone, which seems to decrease macrophage demyelinating activity at the edge of the lesions.

In the early phase of such demyelinating lesions, macrophage infiltration is responsible for demyelination and conduction block. Clinical symptoms persist if the process is ongoing, or if repair mechanisms are inadequate or completely absent. In the early phase, some axons are irreversibly impaired, and others, only suffering, may recover if the demyelinating process stops and/or repair mechanisms are initiated. Mitoxantrone therapy may contribute in this direction.

Monitoring large demyelinating lesions with MRI/MRS provides insight into the pathophysiology of lesions in relation to clinical features. The biochemical variables indicate the chronology of axonal disturbance. MRI/MRS may in these cases contribute to a rapid initiation of immunosuppressive treatment and early detection of markers of repair mechanisms leading to recovery.

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RÉFÉRENCES