IMAGING OF CENTRAL NERVOUS SYSTEM IN MULTIPLE SCLEROSIS

M. G. AVRAM[1], M. PEREANU[2]

[1] PhD candidate, "Lucian Blaga" University of Sibiu, [2] "Lucian Blaga" University of Sibiu

Keywords: *multiple sclerosis, imaging criteria, magnetic resonance imaging, white matter, grey matter*

Abstract: *The diagnosis and monitoring of patients with Multiple Sclerosis (MS) requires magnetic resonance imaging (MRI), that should be acquaired according to a standardized and reproductible protocol, consistent with international guidelines. Hyperintensities on T2 or FLAIR sequences are a very sensitive finding in patients with MS but is not specific of the underlying pathology. Among patients with clinically isolated syndrome, the presence of spatially disseminated lesions on the initial MRI is highly predictive of the conversion to clinically define MS. New sequences such as MR spectroscopy, diffusin tensor imaging, magnetization transfer imaging allow more sensitive quantification of such alterations. Molecular imaging by Positrons Emission Tomography is a very promising technique with high tissue specificity. It should improve our understanding of the pathophysiologic mechanisms involved in MS.*

Cuvinte cheie: *scleroza multiplă, criterii imagistice, imagistica prin rezonanţă magnetică, substanţa albă, substanţa gri*

Rezumat: *Diagnosticul şi monitorizarea radiologică a pacienţilor cu Scleroză Multiplă (SM) necesită un protocol de achiziţie în imagistica prin rezonanţă magnetică (IRM) standardizat şi reproductibil, în concordanţă cu recomandările internaţionale. Existenţa hipersemnalelor pe secvenţele T2 sau Flair reprezintă o anomalie foarte sensibilă la pacienţii cu SM, dar acest semn nu este specific unui mecanism fiziopatologic demielinizant. La pacienţii cu sindrom clinic izolat, prezenţa leziunilor diseminate în spaţiu pe IRM iniţial este extrem de predictivă pentru conversia la SM clinic definită. Noi secvenţe, cum ar fi spectro-RM, imagistica de difuzie, imagistica prin transfer de magnetizare, permit cuantificarea mai sensibilă a acestor alterări. Imagistica moleculară prin tomografie cu emisie de pozitroni este o tehnică foarte promiţătoare cu înaltă specificitate tisulară. Ea ar trebui să amelioreze înţelegerea noastră asupra mecanismelor fiziopatologice implicate în SM.*

SCIENTIFICAL ARTICLE OF BIBLIOGRAPHIC SYNTHESIS

Central nervous system imaging has become a mandatory procedure in diagnosing and monitoring inflammatory demyelinating disorders, particularly for the most common of them, the Multiple Sclerosis (MS). The most dominant of the techniques is the so-called conventional magnetic resonance imaging (MRI), generally used in hospital practice, but non-conventional imaging sequences are nowadays in full progress and may become interesting means of improving our knowledge on disease physiopathology.

Magnetic resonance imaging and Multiple Sclerosis diagnosis

The central role of MRI in diagnosing and monitoring the activity of the disease and among the therapeutic tests explains the need for a standardized and reproducible acquisition protocol. For this purpose suggestions have been made in order to standardize the methods and to adapt the acquisition techniques to the pathophysiology of the disorder. A magnetic field of at least 1.5 Tesla is recommended and the following sequences also:

- T2 fast spin echo (FSE) in axial sections of 3 mm thick maximum along the bi-callous plan.
- Fast fluid attenuated inversion recovery (FLAIR) in axial and sagittal sections.
- T1 echo spin preceded by at least 5 minutes by injecting a 0.1 mmol/kg standard dose of Gadolinium (severe kidney failure does not allow a gadolinium injection the risk of systemic fibrosis being present) (1).

Medullary MRI is advisable in case of primary medullary symptoms or if the cerebral MRI result is not ambiguous for the MS diagnosis. The Gadolinium injection should not be given systematically therefore it is being recommended only if the medullary MRI has been performed at a distance from the contrast cerebral MRI. Two planes, sagittal and axial should be study. The sections should be close to each other and should not exceed a 3 mm thickness.

The MRI monitoring is not usually systematical but it may become appropriate in cases of inexplicable aggravations, in cases of re-assessing the number of lesions prior to initiating any new treatment, or in case one should suspect a secondary/intercurrent pathology. If a MRI should be indicated in such cases, it should be performed following an identical protocol, in order to obtain an interpretation compared to the previous tests.

T2-weighted or FLAIR are highly sensitive to the plaques appearing as hyperintensity areas. These hyperintensities are not typical to a pathological mechanism and reflect a combination of inflammation, oedema, demyelination, axonal loss, and gliosis. In the supratentorial level these lesions are placed periventricular, subcortical and juxtacortical. At the periventricular level the lesions are usually ovoid, placed perpendicularly to the big axle of the lateral ventricles, and frequently touch the lower side of the callous body. On the T2-weighted it is sometimes difficult to distinguish certain periventricular or juxtacortical lesions, due to the hyperintense adjoining cerebrospinal fluid (CSF). Thus, FLAIR sequences are preferred because the liquid intensity is blocked (2).

Being more visible on T2-weighted images than on FLAIR, the subtentorial lesions usually touch the cerebellum peduncles, the 4th ventricle floor and the pons.

More recently the cortical lesions are being identified in

[1]Corresponding Author: M. G. Avram, Military Hospital of Sibiu, 46 Bl. Victoriei street, Sibiu, România; e-mail: gabriel.avram@gmail.com; tel +40-0745 272819

Article received on 23.03.2010 and accepted for publication on 07.04.2010
ACTA MEDICA TRANSILVANICA September 2010; 2(3)193-196

MS: are find focal leucocortical lesions, intracortical lesions, and subpial lesions. These lesions can be identified in an almost identical proportion as those hystologically documented using high resolution MRI (7T or 9.4T) (3.4).

A variable number (10-20%) of hyperintense lesions in T2-weighted is also visible as a hypointensity in T1-weighted sequences. Moderate hypointensity areas do not persist during the evolution of the disease. These areas would reflect a reversible oedema or a partial demyelination, while persistent hypointensities (with an intensity similar to the CSF) called 'black holes' reflect a tissue destruction combined with a permanent axonal loss.

The intravenous injecting of the paramagnetic contrast substance (gadolinium) and the acquisition of the conventional T1-weighted sequence allow the discovery of areas of blood- brain barrier breakdown, secondary to the inflamation and thus the visualization of the active lesions. The most recent lesions (not more than 3 months old) are contrast-enhanced while older lesions are not.

Where the medullary MRI is concerned, the most accurate sequences are the T2-weighted ones which allow to distinguish the hyperintensity areas in more than 70% of the patients. Such lesions are more often seen at the cervical level, they are found at the height of less than 2 rachidian segments, and they are asymmetrical on the axial sections. At an acute phase one may notice a segmental medullary expansion as well as contrast-enhanced.

Nowadays there are several methods available to measure the cerebral volume. These methods have shown that cerebral atrophy occurs early in MS. The atrophy affects the cortical and subcortical white matter as well as the grey matter: while the atrophy of the white matter seams to evolve on the entire duration of the disease, the atrophy of the grey matter seems to evolve when the disease is more advanced (5).

Due to the appearance of new techniques of processing the images the measuring of the medullary atrophy becomes possible. One should note that in progressive forms of the disease, the medullar atrophy can be detected during the first years, especially on patients presenting a great number of medullary lesions. In this case the atrophy is segmentary conferring to the medulla an irregular caliber (6).

In 1997 Barkhof et al. have advanced the first MRI criteria focused on the number of lesions, their location (periventricular, juxtacortical or subtentorial), and on the presence of active lesions that are contrast-enhanced. Due to their being specific to MS this pattern has been included by MacDonald et al. among the diagnosis criteria in 2001 and stand at the basis of the radiological demonstration of spatial and temporal dissemination (7). According to Barkhof et al. 3 out of the following 4 criteria should be present in order to set a spatial dissemination diagnosis in MRI:

- at least 9 hyperintensity lesions in T2-weighted or a lesion contrast-enhanced;
- a infratentorial lesion;
- a juxtacortical lesion;
- 3 periventricular lesions..

All the lesions should exceed 3 mm in diameter. As for dissemination in time its existence can be proven radiologically through the presence of a new MRI lesion obtained 3 months after the first clinical episode. It may be the case of a contrast appearance or a new lesion in T2. Although they may appear complex at first, these criteria have allowed a more facile determination of the diagnosis in MS having the purpose of offering the patients the most rapid treatment. The 2001 MacDonald et al. criteria have given room to disapproving opinions and consequently they have been revised in 2005 (8).

The limits of the initial criteria are first and foremost interesting as they give a far minor but still very specific to MS importance to medullary lesions. As a result of the 2005 alterations a medullary lesion can be validated as an infratentorial lesion and any Gd-enhancing medullary lesion is equivalent to a cerebral one. A major second change concerns the definition of dissemination in time. A 3 months interval seemed too restrictive. Thus the appearance of a new T2 lesion on a checking MRI taken at any time after a reference MRI taken in its turn 1 month after the clinical episode is relevant enough to define this dissemination in time. Despite all the alterations, these criteria remain moderately sensitive (60 %) and specific (88%).

In 2006 Swanton et al. suggested some simplified criteria according to which dissemination in space is proven by detecting a T2 hyperintensity lesion, suggestive in 2 out of the following 4 locations: juxtacortical, periventricular, subtentorial and medullary. Dissemination in time requires the presence of a new T2 lesion on a distanced MRI, regardless of the time frame between the first imaging and the clinical episode. Compared to the MacDonald et al. criteria in a retrospective multi-central study, these new criteria bear an identical specificity (87%) for the MS diagnosis, but a higher sensitivity (71%) and do not require pathological contrast-enhanced (9,10).

Clinical isolated syndromes (CIS) manifesting themselves as optic neuritis, myelitis, brain stem damaged, are very frequently the first symptoms of MS. Still not every CIS evolves to a definite MS. In a 2008 study D.H.Miller`s team of researchers present their results after 20 years of studying a group of 107 patients with MS. They concluded that 63% of these patients have undoubtedly developed MS.

Patients with an abnormal initial MRI (one or more T2 hyperintensity lesions) present a higher risk than the ones without cerebral abnormalities (82% vs. 21%). Within the group presenting an abnormal MRI the average time frame of evolving to definite MS is of 2 years compared to a 6 year frame in the case of a normal initial MRI (11).

The contribution of the new sequences and techniques:

1. Spectro-MRI:

Magnetic resonance spectroscopy is different from the other MRI techniques as the measured signal does not come from protons found in water molecules but from protons found in organic molecules located in certain tissues like N-acetylaspartate (NAA), coline, lactate, glutamate, or myoinositol. Spectro-MRI provides information on 2 pathological processes within MS: inflammatory demyelination and neural loss in injured or apparently normal tissues.

The increasing of coline, lactate, and macromolecules is associated with active inflammation and demyelination. This local increase may occur a few weeks earlier than T2 hyperintensities do and in some patients can be seen even in white matter areas that appear normal, indicating an inflammatory strike that exceeds by far the plaques visible in conventional imaging.

A special role is held by NAA, a specific metabolite of the neural segment. Thus, a decrease in the NAA signal may be interpreted as a neural disorder. NAA signal abnormalities are distinguished at the level of visible lesion, but also in the apparently normal white matter, suggesting a diffuse neural dysfunction.

The role of the grey matter in the pathophysiology of the disorder can be emphasized with the help of spectro- MRI. A decrease in the NAA level has been observed in the cortical and deep grey matter. This sequence along with the measurement of the thalamic atrophy in T1-weighted allowed the assessment of the neural loss (approx. 30%) within the medio-dorsal nucleus of thalamus in patients with MS: values consistent with the neural loss measured on post-mortem brains.

Still, variations of the NAA level may reflect a diminution in the number of neurons as well as neural atrophy or a metabolic dysfunction (12).

Table no. 1. MRI criteria for dissemination in space (DIS) and time (DIT) for MS. Rovira and Leo

	McDonald 2001	McDonald 2005	Swanton 2007
DIS	3 or more of: - 9 T2 lesions or 1 Gd-enhancing lesion - 3 or more PV lesions - 1 or more JC lesions - 1 or more PF lesions 1cord lesion can replace 1 brain lesion	3 or more of: - 9 T2 lesions or 1 Gd-enhancing lesion - 3 or more PV lesions - 1 or more JC lesions - 1 or more PF lesions A SC lesion can replace an infratentorial lesion An enhancing SC lesion is equivalent to an enhancing brain lesion Any number of SC lesions can be included in total lesion count	≥1 lesion in each of ≥2 characteristic locations: - PV - JC - PF - cord All lesions in symptomatic regions excluded in BS and SC syndromes
DIT	A Gd-enhancing lesion at least three months after CIS onset With reference to a prior scan, a new T2 lesion at least three months after CIS onset	A Gd-enhancing lesion at least three months after CIS onset With reference to a baseline scan, a new T2 lesion obtained at least 30 days after CIS onset	A new T2 lesion on follow up MRI irrespective of timing of baseline scan

2. Magnetization transfer imaging:

This particular technique measures the interaction between free protons (water and fat) and protons attached at macromolecules. The calculation of these exchanges takes the shape of a ratio called ”magnetization transfer ratio” (MTR). Post-mortem studies have shown that MTR, as a parameter suggested by many groups as appropriate to specifically assess demyelination and remyelination, is correlated with the degree of demyelination, but also with the number of residual axons. So this method does not seem specific enough to emphasize the myelin. The decreasing of MTR precedes the appearance of T2 hyperintensities and it is more relevant when the lesion is being visible under the shape of a T1 hypointensity. A decrease of the MTR is also made obvious within the apparently normal white and grey matter in MS patients, consolidating the concept of diffuse pathology (13).

3. Diffusion imaging:

This method measures the microscopic movements of the water molecules at tissue level. Inside the well-organized tissues like white substance or grey substance the water molecules have a reduced mobility. The diffusion process is consequently lower in such tissues. The interruption of the white substance fasciculi as well as the alteration of the axonal membranes permeability cause an increase in the apparent diffusion coefficient (ADC), in the medium diffusivity (MD), and in the fractional anisotropy which measures the leading direction of the diffusion process. These alterations are classically observed inside the demyelination plaques presenting a major increase especially in the ADC at the level of contrast-enhanced lesions. It has also been demonstrated that these parameters are disturbed at the level of the apparently normal cerebral tissue, suggesting that the presence of micro-structural alterations is still undetectable by means of conventional sequences (14).

Using a diffusion sequence for more than one direction allows one to determine the orientation of the axons and to assess the quality of the white matter fasciculi. This technique called tractography is used to determine the cortico-spinal fasciculi trajectory and to quantify the number of T1 and T2 lesions and the alteration of diffusivity at their level.

4. Functional MRI:

This is an indirect imaging method of the cerebral activity at a higher temporal resolution. Its purpose is to detect the transitory hemodynamic response triggered by the neural activity. It gives additional valuable information on the cortical strike in MS. Using the functional MRI while performing a motor, visual, or cognitive task on patients, points out a problem in recruiting the areas normally implicated in achieving such tasks and in activating new cortical areas compared to the healthy-control group. These functional changes, a proof of the existence of compensatory mechanisms, occur early, from the first clinical episode and continue with the evolution of the disease and the extension of the tissue damage. From the pathophysiological point of view, it is not known if this cortical reorganizing is a consequence of the axonal recovery, of the synaptic plasticity, or the preexisting parallel neural circuits (15).

5. Positron emission tomography (PET):

The advantages of this technique consist in the specificity, sensitivity, and the possibility to perform a reliable quantitative imaging. From another point of view, we are dealing with a complex and expensive method.

Neuro-inflammation imaging is possible through the ligands of the peripherical receptors of benzodiazepins, having as reference tracer (11C) - PK 11195. This tracer has already allowed the visualization of the microglial inflammation in MS, and in other degenerative neurological disorders (16).

6. Other sequences:

The sequences able to identify the cortical plaques (“double inversion recovery”, 3T and 7T high resolution MRI) which sensitivity/specificity is being studied or the T2 relaxometry whose early component would then be the reflection of the water contained by the myelin (17).

A special interest is carried by the usage of new contrast agents containing nano-particles (US - PIOs) which are actively phagocyted by monocytes and circulating macrophages, allowing the identification of the macrophage component of the cerebral inflammation at lesion level but also inside the apparently normal white matter (18).

In conclusion, the central nervous system imaging in MS has known a great development in the last 10 years. Nowadays, MRI represents a mandatory examination procedure indispensible in determining an early diagnosis, initiating the appropriate treatment, and monitoring patients. The multiple pathophysiological components of this disorder (lymphocyte and microglial inflammation, demyelination, neural-axonal damage) justify the development of higher tissue specificity techniques, thus revealing a wider research field regarding so-called non-conventional MRI sequences, new contrast agents, and molecular imaging. The following years shall undoubtedly be marked by major developments in this field.

“Cercetari realizate in cadrul proiectului POSDRU/6/1.5/S/26 cofinantat din Fondul Social European prin Programul Operational Sectorial Dezvoltarea Resurselor Umane 2007-2013”

REFERENCES

1. Simon JH, Li D, Traboulsee A. Standardized MR imaging protocol for multiple sclerosis: Consortium of MS centers consensus guidelines. Am J Neuroradiol 2006;27:455-61.
2. Bruck W, Bitsch A, Kolenda. Inflammatory central nervous system demyelination: correlation of magnetic resonance imaging findings with lesion pathology. Ann Neurol 1997;42:783-793.
3. Mainero C, Benner T, Radding A. In vivo imaging of cortical pathology in multiple sclerosis using ultra-high field MRI. Neurology 2009;73:941-948.
4. Schmierer K, Parkes HG, Po-Wah So. High field (9.4 Tesla) magnetic resonance imaging of cortical grey matter lesions in multiple sclerosis. Brain 2010;133:858-867.
5. Fisniku LK, Chard DT, Jackson JS. Gray matter atrophy is related to long term disability in multiple sclerosis. Ann Neurol 2008;64:247-54.
6. Rashid W, Davies GR, Chard DT. Increasing cord atrophy in early relapsing-remitting multiple sclerosis: a 3 year study. J Neurol Neurosurg Psychiatry 2006;77:51-5.
7. McDonald WI, Compston A. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121-7.
8. Polman CH, Reingold SC, Edan G. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 2005;58:840-6.
9. Swanton JK, RoviraA, Tintore M. MRI criteria for multiple sclerosis in patients presenting with clinically isolated syndromes: a multicentre retrospective study. Lancet Neurol 2007;6:677-86.
10. Rovira A, Leon A. MR in the diagnosis and monitoring of multiple sclerosis: an overview. Eur J Radiol 2008;67:409-14.
11. Fisniku LK, Brex PA, Altmann DR. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset multiple scerosis. Brain 2008;131:808-17.
12. Sajja BR, Wolinsky JS, Narayana PA. Proton magnetic resonance spectroscopy in multiple sclerosis. Neuroimaging Clin N Am. 2009 Feb;19(1):45-58.
13. Schiermer K, Scaravilli F, Altmann DR. Magnetization transfer ratio and myelin in post-mortem multiple sclerosis brain. Ann Neurol 2004;56:407-15.
14. Rovaris M, Gass A, Bammer R. Diffusion MRI in multiple sclerosis. Neurology 2005;65:1526-32.
15. Pantano P, Mainero C, Caramia F. Functional brain reorganization in multiple sclerosis: evidence from fMRI studies. Neurology 2007;69:1942-52.
16. Kannan S, Balakrishnan B, MuzikO. Positron emission tomography imaging of neuroinflammation. J Child Neurol. 2009 Sep;24(9):1190-9.
17. Neema M, Goldberg-Zimring D, Guss ZD. 3 T MRI relaxometry detects T2 prolongation in the cerebral normal-appearing white matter in multiple sclerosis. Neuroimage;2009 Jul 1;46(3):633-41.
18. Stoll G, Bendszus M. New approaches to neuroimaging of central nervous system inflammation. Curr Opin Neurol; 2010 Jun;23(3):282-6.