Use of lesion volumes and loads for monitoring patients with multiple sclerosis. Local experience and literature review

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Abstract: Multiple sclerosis (MS) is a common demyelinating disease that involves the central nervous system causing focal lesions in the brain and spinal cord causing diverse neurological development deficits, many of them severe and irreversible, affecting and invaliding a large percentage of young productive-aged patients. MRI exams have improved diagnostic capability compared to computed tomography, but in this decade the development of new magnets, coils and software have allowed the development of quantitative neuroradiology which achieves the evaluation of parameters such as total brain volume, of each of its structures, as well as semi-automated or automated counting of the lesion load, allowing better monitoring of each individual patient in relation to a particular event such as a new neurological deficit in an outbreak of the disease, a previously undetected cognitive impairment or in related to a given treatment. We will show our local experience using the FreeSurfer software in our habitual practice, as well as other post-processing software, this being the first experience of its use in multiple sclerosis published in our country.

Keywords: Brain volume, FreeSurfer, Magnetic resonance imaging, MIPAV software, Multiple sclerosis, Lession load.

Introduction

Multiple sclerosis (MS) is a common demyelinating disease that affects the central nervous system, producing focal lesions that cause diverse neurological deficits with progressive evolution, many of them severe and irreversible. A significant percentage affects young people (between 20 and 40 years of age), more common in women (2:1), which determines a significant economic and social impact. Its etiology has not been exactly defined making it difficult to find a cure. For these reasons, its study is an important source of research in many centers worldwide.
From the diagnostic point of view, one of the significant developments was the incorporation of magnetic resonance imaging in the 1980s, which allows us to visualize the lesions that were missed by computed tomography. Incorporating better magnets, new coils and post processing software has increased the sensitivity in the diagnosis of this disease.

An important feature of MS is the heterogeneity in its clinical expression which correlates with its neuropathological heterogeneity.

Different clinical courses of MS: relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP), and progressive relapsing (PR). RRMS is characterized by self-limited acute neurological dysfunction followed by a variable degree of recovery. To the contrary, PPMS is characterized by a steady decline in neurologic function from the onset, without evident outbreaks in the clinical course of the disease. Approximately 50-80% of the individuals who present a clinically isolated syndrome already have lesions on MRI, which would be previous (hidden) to the activity of the disease. Lucchinetti has proposed four different pathological forms of the disease where there are multifocal lesions with destruction and repair of myelin, axonal loss and reactive astrogliosis.

For the routine clinical diagnosis T2-weighted sequences were used (Figure 1) which allow the radiologist to evaluate the number, position and shape of the lesions in the spinal cord and brain to establish a presumptive diagnosis of multiple sclerosis. In T1 sequences the so called “black holes” can be seen, which indicates extensive tissue damage.

In 2001 the McDonald criteria were incorporated, which established specific diagnostic criteria for multiple sclerosis in MRI both in dissemination in time and in space.

A correlation between MRI findings and inflammatory activity has been observed, which has been used as a biomarker for progression, with a good correlation to the neuropathological findings. Several studies have confirmed the relationship between the uptake of gadolinium (Gd) of the lesions in T1 with inflammatory activity. This has led to the acceptance of MRI as a substitute marker in various clinical trials of anti-inflammatory treatments for MS.

Technical advances in resonance with high-field magnets and new coils, allow us to routinely acquire T1 and T2 enhanced volumetric studies. With this, and the new automatic or semiautomatic post processing techniques allow us to evaluate the total brain volume, as well as different brain regions or structures and to determine the lesion load in each of our patients. The latter is an important element of useful judgment to determine the course of the disease within a short time such as a year, which introduces us to the use of quantitative parameters in multiple sclerosis.

Figure 1. In the MPR reconstructions of volumetric FLAIR sequence (a) multiple hyperintense lesions in the white matter with periventricular demyelinating pattern, were observed, with callososseptal interface commitment, noting the typical morphology of Dawson’s fingers. Similar MPRAGE slice (b) is included.

Quantitative Neuroradiology

The development of new sequences in resonance, new coils, and greater power in the magnet fields (high fields) have yielded images with greater sensitivity in relation to neuropathological changes and improved anatomical resolution.

Furthermore, the development of new software such as FSL (www.fmrib.ox.ac.uk/fsl/) and SPM (www.fil.ion.ucl.ac.uk/spm/), allows the analysis...
and quantitative interpretation of the obtained data. Thus quantitative neuroradiology emerges changing the view that was had of the disease, trying to change the management of MS as it allows the identification of small previously undetectable quantitative variations and, therefore, improves our precision to evaluate the individual responses to a given treatment.

Measurements of lesion load and inflammatory activity of the disease through MRI quantitative techniques are used with increasing frequency in both clinical and research areas. These techniques require an analysis flow to ensure efficiency, reproducibility and quality control of MRI images in MS patients, which requires advanced image processing. Due to advances in computer science with the implementation of PACS (Picture Archiving and Communication Systems) databases have been made available that allow analysis directed at a particular pathology.

Software for determining brain volume uses image segmentation techniques, co-registration and analysis of time-series\(^{(11)}\).

Since the quantitative analysis of MR images is based on relative intensities, as a first step in the process, field inhomogeneity (very important in high-field equipment, greater than T3, and with the use of phased-array coils) must be corrected, and then the registration and segmentation is carried out.

At registration images taken on different equipment overlap in the same anatomical locations\(^{(12)}\). The time between studies can be days or years, allowing a long-term comparative monitoring. Studies can be performed with the same weighting, for example T1 to assess atrophy\(^{(13)}\) or different weighting, even using different imaging methods, e.g. MRI v/s PET.

**Lesional Load Measurement**

An important use of segmentation in the study of MS is to determine the number and volume of T2 hyperintense lesions, which can be quantified in cubic millimeters to compare with future studies. Changes in lesion volume are used in clinical trials of new treatments for MS\(^{(14,15)}\).

The MS lesion segmentation can be done manually slice by slice by an operator, where it is possible to achieve a reasonable reproducibility, but it is slow and requires extensive use of labor. In addition, intra-observer (same operator) or inter-observer (different operators) errors occur.

Multiple studies have addressed the problem of reducing the amount of operator time and to improve the reproducibility of the MS lesion volume measurement, using semi- or fully automated methods (16-18), which include edge detection techniques, contour following, neural networks, fractal image compression, etc.

Probably the most promising approach is based on segmentation using multiple parameters, where information from a number of sequences (e.g. T1, PD and FLAIR) combine to segment lesions based on the position of the pixels in an N-dimensional space, depending on intensity.

The semi-automatic lesion classification can give an adequate sensitivity and a good reproducibility in the detection method of MS lesions, together with the elimination of the variability and subjectivity (intra-observer variability, inter-observer) and cost reduction associated with the manual process. But the operator is still required to manually identify some MS lesions.

Most identification and automatic as well as semi-automatic segmentation methods of lesions are based on a range of intensities for the different tissues of the brain. However, large variations in intensity may violate these assumptions and adversely affect the success of the process. These variations arise from different manufacturers and models of resonators, differences in protocol acquisition (slice thickness, etc.), as well as for being used in different stages of the disease or the presence of concomitant diseases that can significantly affect the tissue intensity behavior\(^{(19,20)}\). Because of this, some software such as TOADS-CRUISE, besides using gray levels for detecting MS lesions use anatomical atlases to eliminate false positives\(^{(21)}\).

**Cerebral atrophy**

Brain atrophy is a normal feature of aging, with progressive loss of brain tissue from early adulthood. To assess brain atrophy, we must take into consideration that brain volume is highly variable between individuals.

It is believed that neuronal tissue loss is a long term indicator of irreversible tissue damage. This is somewhat complex when the pseudoatrophy global phenomenon exists for the anti-inflammatory effect of some MS treatments, where an initial rapid shrinkage of brain volume occurs due to a reduction in the excess fluid in the brain, a phenomenon that should be considered when evaluating the volume\(^{(22)}\).

Brain atrophy can be measured longitudinally or transversely. The transversal is to estimate the total volume of brain tissue. Since the brain volume is variable, results are not readily comparable, except in studies of large populations. One way to standardize the measurements is to provide a “normalized” brain volume. There is a way to do this: dividing the volume of brain parenchyma by intracranial volume, as the intracranial volume remains unchanged during adulthood\(^{(23)}\).

In longitudinal studies it is possible to measure the brain volume reduction normalized with respect to the baseline study. However, sophisticated records of the studies done at different points of time make it possible not only to evaluate the gross change in tissue volume, but also to display the anatomical location of the tissue loss\(^{(24)}\).
Pathological and imaging studies suggest that the development of permanent neurological damage in MS is associated with the progressive atrophy of the brain and spinal cord.

**Material and methods**

With Siemens Avanto and General Electric (GE) 1.5T Optima 450 resonators, volumetric T1 sequences were acquired (MPRAGE sequence on Siemens equipment with parameters: TR 2400 ms, TE: 3.4 ms, Ti: 1000 ms, FOV: 250 x 250. FSPGR sequence (BRAVO) on GE equipment with parameters TR: 9.7 ms, TE: 3.7 ms, Ti: 600 ms, FOV: 256 x 256. FLAIR sequence on Siemens equipment with parameters TR: 7000 ms, TE: 430 ms, Ti: 2200 ms, FOV: 256 x 256. FLAIR sequence on GE equipment with parameters TR: 6000 ms, TE: 146.7 ms, Ti: 1812 ms, FOV: 256 x 256) on 50 patients referred by their treating physicians for routine control of multiple sclerosis, or the occurrence of a clinical outbreak. From these 11 were selected (9 women and 2 men) because they had at least one MRI control over time (average: 12.6 months), whose ages ranged between 23 and 54 years (average: 38 years). Monitoring with resonance was performed between the 5th and 15th months (average: 12.6 months). Volumetric analysis was performed with FreeSurfer v.4.5.0 software (FreeSurfer, http://surfer.nmr.mgh.harvard.edu; segmentation example) and with MIPAV software with TOADS-CRUISE plug-in (http://www.nitrc.org/projects/toads-cruise/) for lesion count, which allows the use of T1-weighted, FLAIR, T2 and PD sequences, but better results are obtained using T1 and FLAIR sequences. These were compared with our normal volumetric database according to age range.

In order to compare images of the different patients it is necessary to transform them to a standard anatomical space\(^{12}\). In our cases we rely on the MNI brain atlas from the Montreal Neurological Institute, which is made up of the registry of studies from a large sample of control subjects, from which an average brain is obtained, which was approximately co-registered to the atlas of Talairach and Tournoux\(^{26}\).

**Results**

In Figure 2, coronal slice segmentation for an MS patient, obtained with FreeSurfer, is shown. In Figure 3 axial slices of MS lesions segmentation for the same previous patient, obtained with TOADS-CRUISE, is shown. In Figure 4 the 3D reconstruction of MS lesions previously segmented with TOADS-CRUISE and reconstructed with 3D Slicer, is shown. In Figure 5, two 3D reconstructions of lesion loads for the same patient in a year of evolution, are compared. Red circles indicate areas with increased lesion load.

In Figure 6 and Table I, is shown the format that gives us the individual volumetric study in our patients with FreeSurfer. In this case we visualize a slight decrease of diffuse cerebral volume within one year.
36% of the patients studied had decreased diffuse cerebral volume (Figure 7), but we must differentiate if the white matter or the cerebral cortex is more affected. Volume decrease of the cortical gray matter (72% of the 11 patients) affects a larger number of patients than the reduction in volume of the white matter (39%, Figure 8).

54% of the patients showed a decrease in volume of one or both hippocampi (Figure 9).

The MIPAV study allows us to compare the lesion load in the same patient, which can be visualized in three dimensions (3D). 63% of patients studied had increased lesion load (Figure 10).

**Discussion**

Atrophy has been suggested as a potential progression marker for the disease. Serial resonance registration provides a useful alternative to assess brain atrophy with this technique, since the measurements are sensitive and reproducible, which allows detection of the progressive atrophy within short periods such as, for example, a year of evolution of a disease and may have potential as a marker of disease progression in the monitoring of therapeutic trials. In the study by Fox et al (2006) (26), baseline brain volumes in the MS group were lower v/s the controls, the rate of brain atrophy in the MS group was 0.8% per year, more than twice that of the controls (0.3%). Ventricular growth rate was five times higher than the controls (28), which we viewed in 36% of the cases.

Cognitive impairment is an important clinical event in the evolution of MS, depending on the stage and type of disease, between 45-65% will develop a variable degree of cognitive dysfunction. Pathological and MRI studies have failed to show a strict relationship between cognitive impairment and pathology in the
subcortical white matter. The correlation is poorer even when considering the global atrophy (white matter plus cortex).

The gray matter commitment in MS is now widely accepted. Demyelinating lesions are common in the cortex and subcortical regions. Subpial demyelinating foci can also spread to the cortex. These are probably related to the B-cell infiltration nodes in the overlying meninges and may reflect the action of antimyelin antibodies. The cortical and subcortical gray matter atrophy is progressive during the course of the disease, which can be attributed to neural dystrophy but in subcortical nuclei, like the thalamus atrophy is associated with neuronal loss. A significant negative correlation between average cortical thickness and total volume of white matter lesions has been observed, which gives support to the use of measurement of lesion load and average cortical thickness. We quantified that 63% presented increased lesion load.

### Table I. Monitoring volumes with a year’s difference using FreeSurfer, in a multiple sclerosis patient with RRMS, where volumetric analysis of brain structures is detailed, showing 5% decreased brain volume.

<table>
<thead>
<tr>
<th></th>
<th>14/10/2010 (cc)</th>
<th>4/10/2011 (cc)</th>
<th>Normal values (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total intracranial volume:</td>
<td>1536</td>
<td>1536</td>
<td>normal: 1485,4 DS: 123,4</td>
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<tr>
<td>Brain volume:</td>
<td>1001</td>
<td>954</td>
<td>normal: 984,1 DS: 88,0</td>
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<tr>
<td>Left hemisphere white matter volume:</td>
<td>227,8</td>
<td>216,4</td>
<td>normal: 217,2 DS: 19,4</td>
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<tr>
<td>Left hemisphere cortical volume:</td>
<td>239,4</td>
<td>227,5</td>
<td>normal: 243,8 DS: 23,6</td>
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<td>Left hippocampus:</td>
<td>4,3</td>
<td>4,2</td>
<td>normal: 4,2cc DS: 0,4</td>
</tr>
<tr>
<td>Left amygdala:</td>
<td>1,5</td>
<td>1,5</td>
<td>normal: 1,7 DS: 0,2</td>
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<tr>
<td>Left lateral ventricle:</td>
<td>8,4</td>
<td>9,0</td>
<td>normal: 7,1 DS: 2,6</td>
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<tr>
<td>Right hemisphere white matter volume:</td>
<td>245,1</td>
<td>223,0</td>
<td>normal: 219,7 DS: 19,1</td>
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<tr>
<td>Right hemisphere cortical volume:</td>
<td>229,2</td>
<td>228,4</td>
<td>normal: 244,6 DS: 24,6</td>
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<tr>
<td>Right hippocampus:</td>
<td>4,0</td>
<td>3,9</td>
<td>normal: 4,5cc DS: 0,5</td>
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<tr>
<td>Right amygdala:</td>
<td>1,6</td>
<td>1,5</td>
<td>normal: 1,7 DS: 0,2</td>
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<tr>
<td>Right lateral ventricle:</td>
<td>10,8</td>
<td>11,3</td>
<td>normal: 6,8 DS: 2,6</td>
</tr>
<tr>
<td>3rd Ventricle:</td>
<td>0,8</td>
<td>0,8</td>
<td>normal: 0,9 DS: 0,1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>14/10/2010</th>
<th>4/10/2011</th>
<th>Normal values</th>
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<tbody>
<tr>
<td>Left hemisphere white matter volume:</td>
<td>0,1483</td>
<td>0,1409</td>
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<td>Left hemisphere cortical volume:</td>
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<td>0,1481</td>
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<td>Left hippocampus:</td>
<td>0,0028</td>
<td>0,0027</td>
<td>normal: 0,0028 DS: 0,0002</td>
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<tr>
<td>Left amygdala:</td>
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<td>0,0010</td>
<td>normal: 0,0012 DS: 0,0001</td>
</tr>
<tr>
<td>Left lateral ventricle:</td>
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<td>0,0058</td>
<td>normal: 0,0048 DS: 0,0015</td>
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<td>Right hemisphere white matter volume:</td>
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<td>0,1452</td>
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<td>Right hemisphere cortical volume:</td>
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<tr>
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<td>0,0026</td>
<td>0,0025</td>
<td>normal: 0,0030 DS: 0,0002</td>
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<tr>
<td>Right amygdala:</td>
<td>0,0010</td>
<td>0,0010</td>
<td>normal: 0,0011 DS: 0,0001</td>
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<tr>
<td>Right lateral ventricle:</td>
<td>0,0071</td>
<td>0,0074</td>
<td>normal: 0,0046 DS: 0,0017</td>
</tr>
<tr>
<td>3rd Ventricle:</td>
<td>0,0005</td>
<td>0,0006</td>
<td>normal: 0,0006 DS: 0,0001</td>
</tr>
</tbody>
</table>
For our analysis we used the FreeSurfer v.4.5.0 software (34-36) to analyze the cortical volume as well as the cortical thickness (this data will be the subject of subsequent publications). This software gives us the values of total cortical volume by default (Figure 2), which is included in the evaluation of MS patients, especially if they have some degree of cognitive deficit.

The primary role of cortical pathology in MS for focal inflammatory lesions and cortical atrophy has been underestimated. These determine focal cognitive deficits (memory impairment, attention deficits, language processing) and global atrophy, which is determined by various studies (37-40).

Our findings, which are similar to those found in published experiences in other centers, make us understand that the technical advances in MRI equipment, as well as new imaging processing techniques, allow us to obtain quantitative parameters such as global brain volume and of the different brain structures, especially the white matter and cortical, as well as lesion load, which allows us to quantitatively evaluate the temporal evolution of patients with multiple sclerosis. This marks a big difference to the standard MRI protocols used in the clinical routine of our country. This has allowed us to determine the morphovolumetric changes during annual MRI controls in those patients without apparent outbreaks of their disease, finding by surprise that despite the treatment(s) used to halt the progression of the disease, the appearance of new lesions with increased lesion load and decreased brain volume have been observed.

The use of quantitative techniques for the assessment of cerebral volume and lesion count in MS patients has not been made public in our country to date.

Within the limitations of this technique we should mention the difficulty of lesion segmentation in the posterior fossa, due to the lower signal difference between the white and gray matter in this region and the difficulty of the technique to differentiate between cerebellar cortex and lesions, therefore the accuracy of the technique is poor for counting lesions in the
posterior fossa, but this limitation does not affect the comparison in the same subject, as the omission of lesions in this region is constant in the different studies of a patient and does not condition a significant lesion load variation, which is determined by the supratentorial lesions that are of greater volume and number and which are well defined by this technique. It would be interesting to have the correlation of our findings with neuropsychological examinations of the patients studied, as well as the exact correlation of treatment that each of them used and its evolution with them, which will be the subject of further studies.

In summary, brain volumetry together with the automated counting of lesions in MS patients allows longitudinal monitoring of the patients, comparing studies from different dates with multiple parameters in a reproducible and reliable manner. If this is done at an early stage in the course of the disease we can expect to improve the management of this condition, in the hope that new therapies in development are able to stop the course of the disease and achieve substantial improvements in the long-term prognosis, preventing the generation of new lesions and the subsequent cerebral atrophy, which are responsible for the irreversible neurological damage we see today.

Bibliography


