Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/pjnns

Review article

What you cannot get from routine MRI of MS patient and why – The growing need for atrophy assessment and seeing beyond the plaque

Marcin Hartel [a,*], Ewa Kluczewska [a,b], Krystyna Pierzchała [c], Monika Adamczyk-Sowa [c], Jacek Karpe [d]

[a] MDC Voxel, Katowice, Poland
[b] Medical University of Silesia, Department of Radiology and Radiodiagnostics, Zabrze, Poland
[c] Medical University of Silesia, Department of Neurology in Zabrze, Zabrze, Poland
[d] Medical University of Silesia, SK1 Hospital in Zabrze, Poland

ARTICLE INFO

Article history:
Received 17 May 2015
Accepted 13 January 2016
Available online 23 January 2016

Keywords:
Multiple sclerosis
Magnetic resonance imaging
Brain atrophy
Volumetric analysis

ABSTRACT

Multiple sclerosis is a disease that still has not been fully understood and calls for better diagnostic procedures for the improvement of everyday patient care and drug development. Routine magnetic resonance examinations reveal demyelinating focal lesions, but they do not correlate sufficiently with the patients' disability and cognitive impairment. For more than 100 years it has been known that demyelination affects not only white but also grey matter of the brain. Recent research has confirmed the serious consequences of grey matter pathology. Over the last several years, atrophy of the brain and especially of its grey matter has become a most promising marker of the patients' clinical status. The paper discusses the concept and importance of atrophy assessment in relation to the standard magnetic resonance results.

1. Introduction

Multiple sclerosis (MS) affects approximately 2.5 million people worldwide. It is an acquired, chronic inflammatory disease of the central nervous system (CNS) characterised by the presence of inflammatory-demyelinating lesions and progressive loss of brain tissue. The condition was first described over 170 years ago; however, its aetiology is still unclear. Until the 1980s, that is, until partial efficacy of immunosuppressive drugs was demonstrated, MS was considered an incurable disease. Symptoms of MS include progressive impairment of motor and sensory functions, as well as cognitive disorders. The disease is the most common non-traumatic cause of disability in young people [1,2].

Primary lesions in MS are believed to be of inflammatory aetiology. However, due to gradual deterioration of the patients' clinical condition and to lesions found in diagnostic imaging, MS has recently been considered also a degenerative disease. The primary pathological process in MS affects myelin

* *Corresponding author at*: ul. Reta 39G, 43-190 Mikołów, Poland. Tel.: +48 667 666 931; fax: +48 32 790 42 20.
E-mail address: hartel@voxel.pl (M. Hartel).
http://dx.doi.org/10.1016/j.pjnns.2016.01.007
0028-3843/

but there is also secondary atrophy and degeneration of other brain components [3].

In a routine MRI scan, demyelinating lesions are usually found in the white matter. However, since 1880s it has been known from histopathological examinations that the pathological process also takes place in the grey matter (GM) [4]. This has been confirmed by modern diagnostic imaging techniques, and nowadays the classification of MS as solely a white-matter disease is increasingly regarded as obsolete [5].

2. Magnetic resonance imaging in MS

What can be visualised by routine MRI still remains ''the tip of the iceberg''. The amount of lesions revealed, in most cases in the white matter (WM) only, is quite small in comparison to the known extent of CNS damage which remains beyond the capabilities of the standard imaging sequences. This often results in a discrepancy between the clinical symptoms and the findings in routine MRI, i.e. the so-called clinical-radiological paradox [11]. In the relapsing-remitting (RR) form, MRI reveals 10–20 times more new lesions than the number of known clinical relapses. In some patients, active lesions remain visible in MRI for a very long time, and yet the clinical course of the condition is stable. Half of untreated asymptomatic patients present active plaques in MRI [6].

Neuroradiological markers are constantly being sought that would be more clearly correlated with the patient's condition and would be more useful for effective modification of treatment. For this reason, attention has been paid to the damage of normal-appearing white matter (NAWM) and normal-appearing grey matter (NAGM). It is supposed that these areas could be damaged as a result of Wallerian degeneration of the fibres passing through the plaques visible in the MRI image, or due to an independent pathological process. The progression of damage to the normal-appearing brain tissue (NABT), resulting in increasing atrophy, is associated with the progression of the patient's disability. As there is no direct relationship between the clinical symptoms and the number of plaques, it is the atrophy that is considered to reflect MS pathology, being invisible in conventionally assessed MR imaging [12].

Given that MR imaging went into clinical use in 1980, the publication *The evaluation of multiple sclerosis by magnetic resonance imaging, Val M. Runge et al.* is one of the first to describe the application of this method in MS. The today's standard MRI scan protocol is not much different from that presented in the article. Certainly present routine scans are of better quality and are obtained in a shorter time, but they are still unable to show CNS pathology located beyond demyelination lesions. With the use of modern MRI scanners which allow to modify the sequence in research mode, DIR (double inversion recovery) sequences can be activated. Nevertheless, they remain imperfect, revealing up to 20% of GM lesions [13,14]. Only a few centres are able to track the atrophy of the brain and its components, but it is still not a standard procedure to use this information for the purpose of therapy modification.

Atrophy assessment predicts disease progression in the years to come. MRI techniques permit the detection of differences in brain volume in a relatively short period of time – even within 6–12 months. That is why we need software that could be used for daily diagnosis of patients, and not only for research [6]. The increasingly available programmes are relatively easy to use and will soon allow to include an assessment of brain atrophy in multiple sclerosis patients in routine MRI reports [15,16].

3. Grey matter pathology in MS

Basing on histopathological examinations, several types of plaques in the cerebral cortex are distinguished: (1) located at the border between the cortex and the white matter, (2) not reaching the surface of the cerebral cortex, (3) located externally, under the arachnoid (the most common ones). Some authors distinguish type 4: lesions involving the entire thickness of the cerebral cortex.

Microscopic examination has also demonstrated that demyelination is often more pronounced in the grey matter than in the white matter. Its presence correlates better with the patient's clinical condition than the WM pathology but routine MRI performed in MS does not show GM plaques well enough. Grey matter damage involves diffuse and local demyelination, and is often secondary to lesions in the white matter. The percentage of inflammatory lesions in the GM is lower and the process involves other inflammatory cells besides WM. Also, partial BBB damage takes place [6].

Degenerative processes in the grey matter are not always associated with demyelination, and the pathologies of the white and grey matter are independent processes, at least to some extent. However, 80% of lesions examined in microscopy are not visible in the modern sequences (including DIR), applied for visualisation of the grey matter pathology in MS. This is particularly relevant for lesions located under the pia mater. The number of demyelinating lesions in the grey matter is clearly associated with the patient's disability progression and the reduction of his/her intellectual abilities. Besides DIR sequence, the use of diffusion tensor imaging (DTI) can also help detect cortex damage. A decrease in fractional anisotropy (FA) is associated with the plaques volume and worse patient's clinical condition [7].

The grey matter represents 65% of the parenchymal brain volume. Therefore, its atrophy clearly affects the volume of the whole brain. GM atrophy correlates better with the patient's clinical presentation than WM atrophy or the total plaque volume [6,8].

The difficulty in observing grey matter pathology is due to the fact that this process cannot be adequately shown in vivo in routine MRI scans. The visualisation of demyelinating lesions and GM atrophy with advanced MRI techniques could not only supplement routine diagnostics but also allow to better correlate imaging with the clinical status of patients. On the other hand, it suggests that GM damage should be considered as a target for modern MS therapies [9–11].

4. Brain atrophy and its assessment

Atrophy of the brain leading to an irreversible loss of its tissues is a well-known phenomenon, directly related to the clinical