Chapter 13

Serial Magnetic Resonance Imaging in Patients with a First Clinical Episode Suggestive of Multiple Sclerosis:
Outline of a Research Protocol

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Introduction

The application of magnetic resonance imaging (MRI) in multiple sclerosis (MS) has provided powerful insights into the evolution of the disease process over time. MRI has an established role in the diagnosis and has also been used to investigate the natural course of the disease and to monitor treatment effects in clinical trials [1].

In patients with clinically isolated syndrome (CIS) suggestive of MS, brain MRI revealed multifocal white matter abnormalities indistinguishable from MS in 50%-80% [2-5]. Previous studies have shown that such lesions at presentation can predict the risk of progression to clinically definite MS (CDMS) in the next 1-5 years [6-8]. The results of a 10-year clinical follow-up study showed that the progression to CDMS occurred in 83% of CIS patients with an abnormal brain MRI and in 11% of those with normal MRI [9]. Furthermore, the lesion load detected by T2-weighted brain MRI images at the earliest clinical stage is strongly predictive of clinical course and level of disability 10 years later [10]. The presence of gadolinium (Gd) enhancement at baseline in patients with CIS is also one of the most-predictive features of the early development of MS [5, 11].

The role of serial MRI studies in assessing the natural history of the disease and the outcome of clinical trials in relapsing-remitting (RR) MS patients was first suggested by the Bethesda group [12]. In follow-up studies performed with monthly Gd-enhanced MRI, 75% of mild RRMS patients showed more than one new enhancing lesion per month, thus indicating that the disease is active even in the clinically silent phase of the illness. Furthermore, it was also found that the frequency of the lesions was not constant and there was marked fluctuation in lesion number from month to month.

In a recent meta-analysis of longitudinal MRI studies performed on both RR and secondary progressive (SP) MS patients, the relapse rate in the 1st year was predicted by the mean number of Gd-enhancing lesions in monthly scans during the first 6 months. The best predictor for relapse rate in the subsequent 1st and 2nd year was the variation of lesion counts in the first 6-monthly scans [13].

Little is known about the natural history of disease activity in CIS patients measured by serial MRI scans. A prospective study based on serial T2-weighted...
and Gd-enhanced MRI at 2-month intervals for 12-15 months has been performed in seven patients with CIS [14]. Although based on a small sample, this study suggested that the presence of enhancing lesions was potentially an important prognostic measure in these patients.

**Objectives**

The primary aim of this research protocol is to investigate the dynamics of disease activity in a cohort of patients with CIS and baseline MRI strongly suggestive of MS.

Longitudinal monthly Gd-enhanced MRI performed in MS patients, either in studies on natural history or in the placebo group of clinical trials, showed that MRI activity was slightly lower in SP than RRMS [13]. Whether MRI activity in the early phase of the disease is similar to, lower or higher than in CDMS is not well known.

In this serial MRI study we also investigate the evolution of brain volume changes, the outcome of new enhancing lesions to hypointense T1 lesions, and the water diffusion changes in the lesions and in the normal-appearing white matter (NAWM). These more-sophisticated MRI measures have the potential to detect more-specific pathological changes than conventional techniques but have not been explored to date in patients with CIS [1].

Furthermore, we would like to determine whether serial MRI scans may have a useful role in predicting the subsequent clinical and MRI disease activity. This information may have relevance in establishing the proper time to start a preventive treatment. Treatment has frequently been withheld from patients who do not meet the criteria of CDMS. The results of two recent multicenter trials (CHAMPS and ETOMS), however, demonstrated that a treatment with disease-modifying agents initiated at the time of the first demyelinating event delays the development of the second clinical event [15, 16]. Therefore, it should be useful to identify patients at high risk for MS who are appropriate candidates for an early treatment.

MRI criteria showing a high positive predictive value for the development of CDMS include the presence of enhancing lesions at baseline and both new T2 lesions and new enhancing lesions at an MRI follow-up performed 3 months later, indicating dissemination in space and time [5]. However, further elements should be considered in order to build a model that can better predict the conversion to CDMS. These elements may include the best timing at which MRI should be repeated after the clinical onset, and the number, location and type of new lesions at follow-up.

**Trial Design and Study Population**

The trial is a longitudinal 36-month study on 60 consecutive CIS patients referred to the MS Center of the University of Rome “La Sapienza”. All patients