MRI-detectable cortical lesions in the cerebellum and their clinical relevance in multiple sclerosis

*Andrea Lazzarotto, MD, *Alice Favaretto, MD, *Davide Poggiali, Math, PhD, ^Giuseppe Rolma, MD, ^Francesco Causin, MD, *Francesca Rinaldi, MD, *Paola Perini, MD and *Paolo Gallo, MD, PhD.

*The Multiple Sclerosis Centre – Veneto Region (CeSMuV), Department of Neurosciences SNPSRR
^Neuroradiology Unit, University Hospital of Padova, via Giustiniani 5, Padova, Italy.*

Background

Histological and MRI studies have disclosed a major role of cerebellar pathology in determining physical and cognitive disability in all disease phases of multiple sclerosis (MS). However, the correlation between the MRI-detectable focal inflammatory lesions in the cerebellar cortex and the progressive accumulation of cerebellar-related disability remains undefined. This is mainly due to the limitations of the MRI sequences currently used to depict focal lesions in the cerebellum.

Objectives

We investigated the occurrence of cerebellar cortical lesions (CL) and white matter lesions (WML) and their correlation with cerebellar-related disability by combining Double Inversion Recovery (DIR) and Phase Sensitive Inversion Recovery (PSIR) MRI images in MS patients.

Patients and Methods

Patients

A cohort of 40 patients (Table 1) were enrolled in the study: 10 clinically isolated syndromes suggestive of MS (CIS, 7 patients) or early relapsing remitting MS with a very short disease duration (<3 years, eRRMS, 3 patients); 24 relapsing-remitting MS (RRMS); 6 secondary progressive MS (SPMS).

Image acquisition

3DT1, Fluid Attenuated Inversion Recovery (FLAIR), 2D-DIR and 2D-PSIR images were acquired on a 3T Achieva TX system (Philips Healthcare, Best, The Netherlands) with a 64-channel coil. The acquisition parameters for DIR and PSIR were the following: DIR=resolution 1x1x3mm, FOV 230x200mm, TR 13000ms, TE 10ms, TI 3400/325ms, Slices n40, time 3.5mins; PSIR: resolution 1x1x3mm, FOV 230x200mm, TR 7000ms, TE 13ms, TI 400ms, Slices n40, time 7mins.

Image Analysis

CL and WML were first identified separately on DIR and PSIR scans by consensus of three examiners (AF, DP, PG), then the images were re-analyzed in parallel. Finally, all lesions and artifacts were discussed in detail with two experienced neuroradiologists (FC, GR). Since the structure of the cerebellum cortex makes very hard the classification of CL, all the lesions that involved the cortex (i.e., purely intracortical, those encompassing several folia and those extending in the subcortical white matter) were pooled together in the analysis.

		F/M	Age	Disease Duration	EDSS
CIS/eRRMS	10	7/3	30.0±7.2 [23-46]	0.9±0.6 [0.33-2.4]	1.6 ± 0.5 [1-3]
RRMS	24	13/11	40.9±7.4 [25-53]	9.7 ± 7.2 [1-24.5]	2.5±1.4 [1-6,5]
SPMS	6	5/1	44.5±9.8 [27-56]	18.6 ± 10.6 [8.7-41.5]	6.6±0.5 [6-7.5]

Table 1. Demographic and clinical characteristics of the patients included in the study. Data are expressed as mean±SD and range (into brackets). Age and disease duration are expressed in years. EDSS= expanded disability status scale.

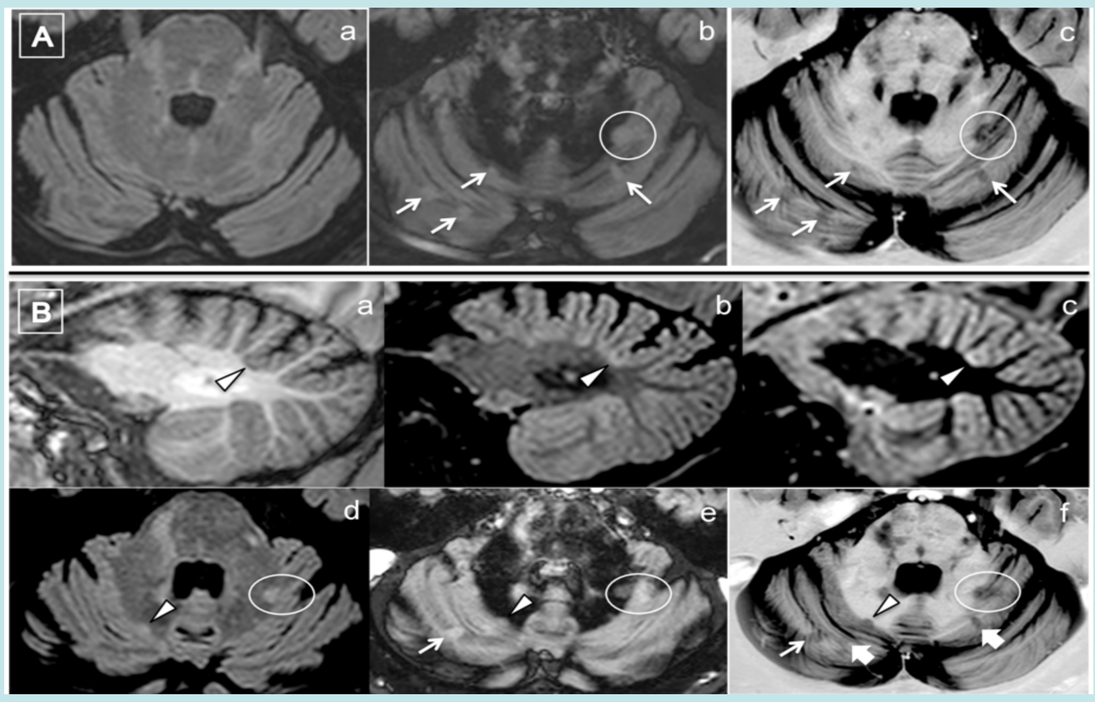

Fig. 1. A. Patient with RRMS. No GM lesion can be identified on the FLAIR (a) image, while at least 5 CL (mixed) can be recognized both on DIR (b) and PSIR (c) images (arrows and circle). Both sequences are needed to clearly identify and delimitate the lesion in the circle that encompasses multiple folia.
B. Patient with RRMS. Sagittal T1 (a), FLAIR (b) and DIR (c) images and axial FLAIR (d), DIR (e) and PSIR (f) images of a mixed white/grey matter lesion (arrow-head). This lesion seems confined in the subcortical white matter on FLAIR images, but is definitely classified as mixed on PSIR images. A CL (thin arrow) is clearly visible on both DIR (e) and PSIR (f) axial images, while two CL detectable by PSIR, but not by DIR, are indicated by the thick arrows. In the circle, a lesion that was considered a subcortical WML on FLAIR, was reclassified as mixed on the base of the combined examination of DIR and PSIR images. PSIR allowed a better morphological characterization of WM lesions compared to FLAIR.

Results

Table 2 summarizes the mean number of CL and WML observed in the three groups of patients. PSIR allowed the disclosure of higher numbers of CL compared to DIR in all groups of patients, and the differences were significant in RRMS (p=0.0008) and SPMS (p=0.002) (Figures 1, 2 and 3). In some cases, the combined analyses of DIR and PSIR images allowed the correct identification and classification of CL (Figure 1/A and Figure 2/C). Only in one case (Figure 3, A, circle), a lesion that was identified by all the three examiners on DIR images was not confirm on PSIR. PSIR images allowed also a better morphological characterization of the WML identified on FLAIR images (Figure 1). Only rarely CL could be identified on FLAIR scans, while WML were well identified by PSIR as markedly hypo-intense lesions. Taken all the patients together, the correlation between WML and CL observed by PSIR was low (r=0.54; p= 0.003).

Although CL could be observed in patients with CIS/eRRMS having no symptom/sign of cerebellar dysfunction, a high correlation was found between numbers of CL and the EDSS score in the cerebellar functional system with both DIR (r=0.69, p<0.0001) and PSIR (r=0.72, p<0.0001). A mild correlation was found between the number of CL observed on PSIR, but not on DIR, and the global EDSS score (r= 0.55, P<0.01), the brainstem functional system (r=0.5, p<0.01) and the pyramidal functional system (r=0.56, p<0.01).

With regards to the possible correlation existing between the number of supra-tentorial CL (data not shown) and the cerebellar CL, when CIS, RRMS and in SPMS were analyzed separately, no correlation could be demonstrated. When all the patients were pooled, a very weak correlation was obtained with DIR (p<0.05), but not confirmed with PSIR (p=0.9).

	DIR		PSIR		I%	
	CL	WML	CL	WML	CL	p (CL)
CIS/eRRSM (10)	0.8±1.2	0.7±1.0	1.5±1.1	0.7±1.0	87.5%	0.2
RRSM (24)	2.1±2.6	1.5±2.3	3.9±4.7	1.5±2.6	90%	0.0008
SPSM (6)	4.7±2.3	0.8±1.2	8.5±3.4	2.5±2.4	82.1%	0.002
ALL (40)	2.1±2.6	1.2±1.9	4.0±4.5	1.5±2.3	87.2%	<0.0001

Table 2: number of cerebellar cortical and white matter lesions (CL, WML) detected by means of DIR and PSIR (mean ± standard deviation), and increase of PSIR CL with respect to DIR CL (I%).

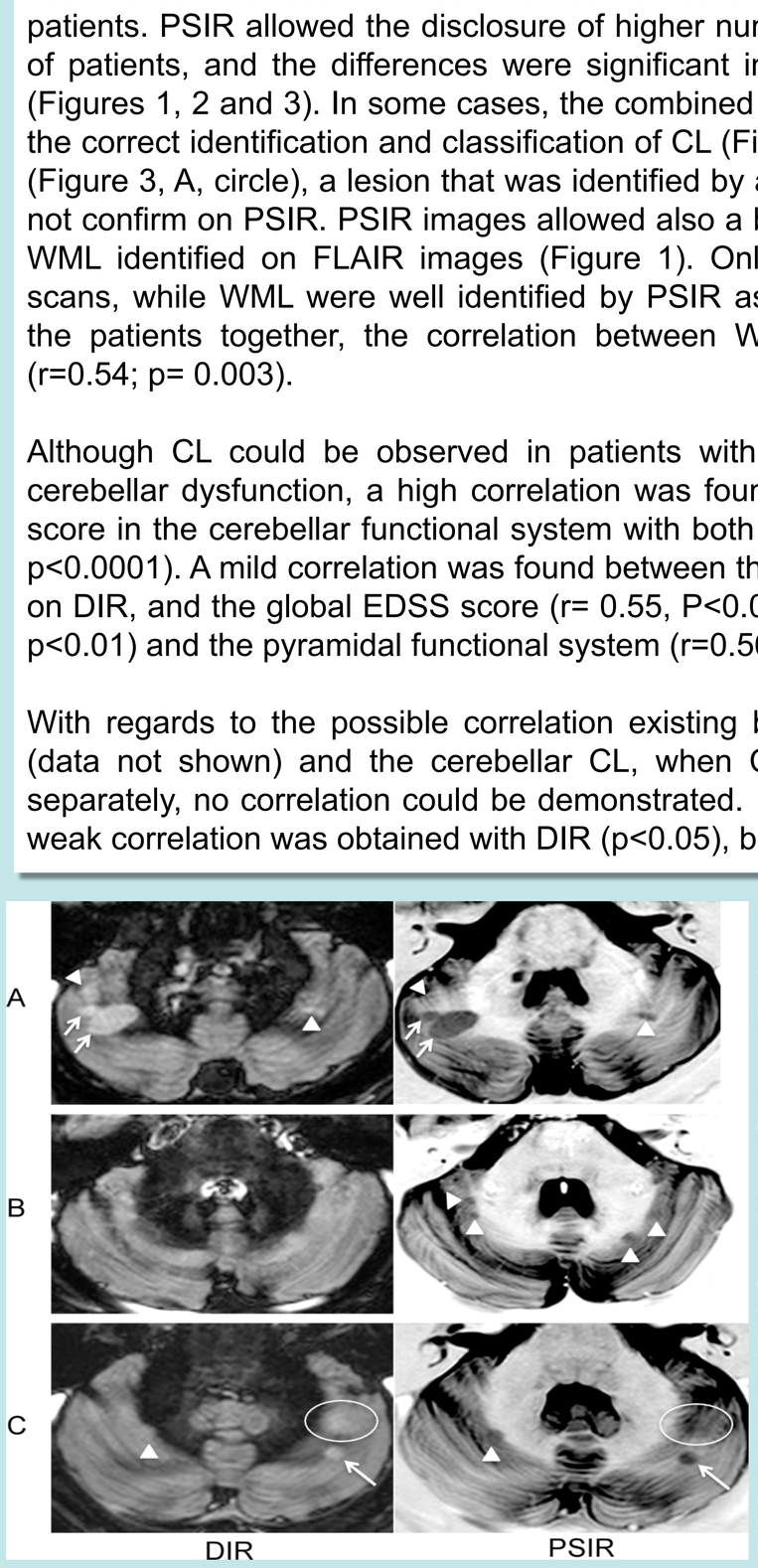

Fig. 2. A. Patient with SPMS. Arrows indicate 2 lesions in the right cerebellum hemisphere that were identified by both DIR and PSIR. The arrow-head in the left hemisphere points out a lesion that did not obtained the consensus of the examiners on DIR, but that was definitely considered by consensus a true lesion after PSIR analysis and combined observation. The arrow-head in the right hemisphere shows a round faint shade of grey (hyper-intense on DIR and hypo-intense on PSIR) that was object of careful analysis and considered a 'probable' CL.
B. Patient with eRRMS. Arrow-heads indicate 4 CL that were scored by consensus on PSIR images, but not on DIR images. Indeed, on DIR images, the two small spot-like lesions observed in the right hemisphere were considered artifacts, while the two lesions in the left hemisphere did not show a signal intensity change to allow their consideration as lesions.
C. Patient with RRMS. The arrow indicate a GM lesion in the left hemisphere that was identified both on DIR and PSIR images. The arrow-head in the right hemisphere points to a mixed lesion that was undoubtedly identified on PSIR, and suspected on DIR image only because of its protrusion that changes the profile of the boundary line between the grey and the white matter, since its signal was identical of that of the surrounding normal-appearing grey matter. The ovoid circle surrounds a CL that encompasses multiple folia and that was definitely identified by comparing the two images.

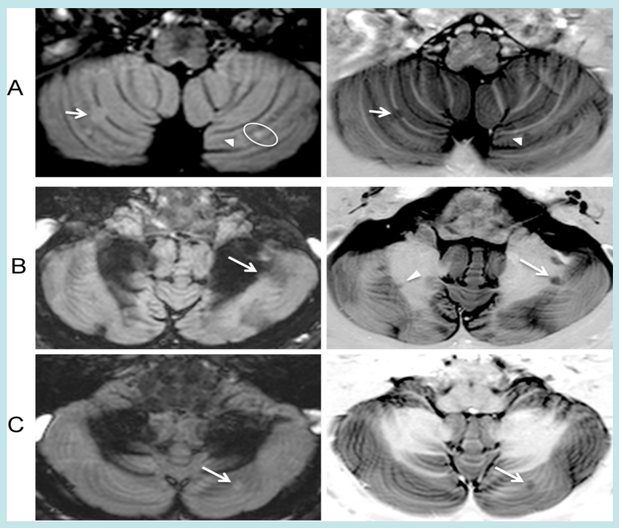

Fig. 3. A. Patient with RRMS. The arrow indicates a CL that was identified on both DIR and PSIR sequences. The arrow-head indicates a very small lesion that was not identified by consensus on DIR, but was recognized on PSIR image as a mixed white/grey matter lesion. In the circle, a signal change that was scored (by consensus) as a CL on DIR, but that was not visible on PSIR.
B. Patient with CIS. The arrow indicates a mixed white/grey matter lesion that was only 'suspected' on DIR, but definitely identified on PSIR image. The arrow-head points to a small lesion identified only on PSIR image.
C. Patient with CIS.

Conclusions

We demonstrate that cerebellar CL can be disclosed by means of PSIR in the great majority of MS patients, including those at clinical onset with no symptom/sign of cerebellar dysfunction. CL increase with disease progression, are above WML in number and frequency, and, in some patients, could develop before the appearance of WML, thus suggesting that MS-related inflammation may start in the grey matter. Although our study shows a correlation between CL and cerebellar-related disability, longitudinal studies, currently in progress in larger number of patients, are necessary to evaluate their prognostic value.

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