

Inflammatory penumbra in multiple sclerosis lesions visualized by MRI: following the time course of focal pathology



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Background

- MRI provides in vivo insights on MS focal pathology as different sequences are sensitive to different underlying biological phenomena¹.
- Here we analyse new MS lesion volumetric changes over time using different MRI techniques and we propose a model of MS lesion formation.

Methods

- Patients:** Patients with RR MS (n= 12) were followed with monthly MRI scans on a 1.5 Tesla MRI scanner (Gyrosan, Philips).
- Inclusion criteria:** New white matter lesions, with visible contrast enhancement on T1-w sequences persistent for at least 2 observations, were included in the study (n=100, 16 ring and 84 nodular)
- Post processing:** Lesion volumes were evaluated monthly, using a semi-automated contouring method on FLAIR and T1w sequences after single (T1wGdSD) and triple (T1wGdTD) dose of the contrast agent Gadolinium (Gd).
- Peak and FLAIR outcome:** In this study we called FLAIR or T1w Gd "peak" the highest volume recorded for each lesion during the monthly follow up and "FLAIR outcome" the volume of a lesion 6 month after the end of T1w enhancement
- Volume kinetic analysis:** Lesion volumes underwent a time-course analysis before and after the interpolation of the experimental data by means of the canonical interpolation equation. **Mathematical model applied to FLAIR volume kinetic:** For each single lesion an analytical curve was derived and a pathophysiologically motivated two *random walks type curves* (RW) mathematical model was applied.

Results

Peak and FLAIR outcome. FLAIR volume at peak was >T1wGdTD volume at peak that was >T1wGdSD at peak. The FLAIR outcome volume was always smaller compared to the T1wGd volume at peak (Tab1 and Fig1)

Volume kinetic analysis. The time course analysis revealed (Fig2):

- An *acute phase* featuring synchronous peak volumes
 - A shrinking *subacute phase* when T1wGd volumes return to zero, with a less steep FLAIR slope compared to T1Gd.
 - A third, *late subacute phase*, featuring a persistent FLAIR outcome.
- these results were observed for both nodular and ring lesions

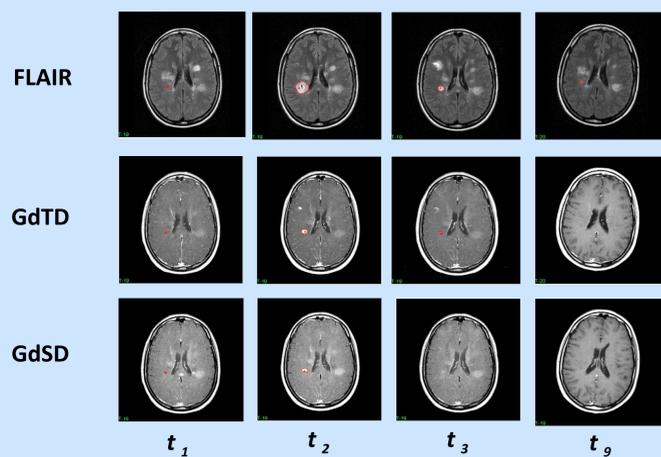
Mathematical model applied to FLAIR volume kinetic identified 2 RW (Fig 3):

- a rapid onset curve (I), with a similar shape compared to the T1wGd curves shown in Fig 2
 - a second curve (II) beginning at the same time but slowly increasing and decreasing.
- both nodular (R2 0.7 ±0.1) and ring (R2 0.81 ±0.08) lesions resulted to be described by the 2 random walks model with a very high fitting quality.

Table 1. Average peak volume (mm³) as measured on FLAIR, T1wGdTD and T1wGdSD sequences and FLAIR outcome volume. Volumes are reported for nodular (n=84) and ring (n=16) enhancing lesions. Values are expressed as mean (± SD).

	FLAIR peak	Gd TD peak	Gd SD peak	FLAIR outcome
Nodular Lesions	968 (±229)	422 (±76)	318 (±68)	161 (±27)
Ring Lesions	2698 (±909)	933 (±278)	-	308 (±81)

Fig. 1. Volume of one representative lesion on FLAIR, T1w Gd-SD and Gd-TD MRI. The time t_2 represents the peak and time t_9 , the FLAIR outcome



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Fig 2. Kinetic curves: Mean volume over time for nodular (A) and ring (B) enhancing lesions, after interpolation. The blue curve represent the mean FLAIR volumes (mm³) over time (months). The red and green curves represent, respectively, T1wGdTD and T1wGdSD volumes over time.

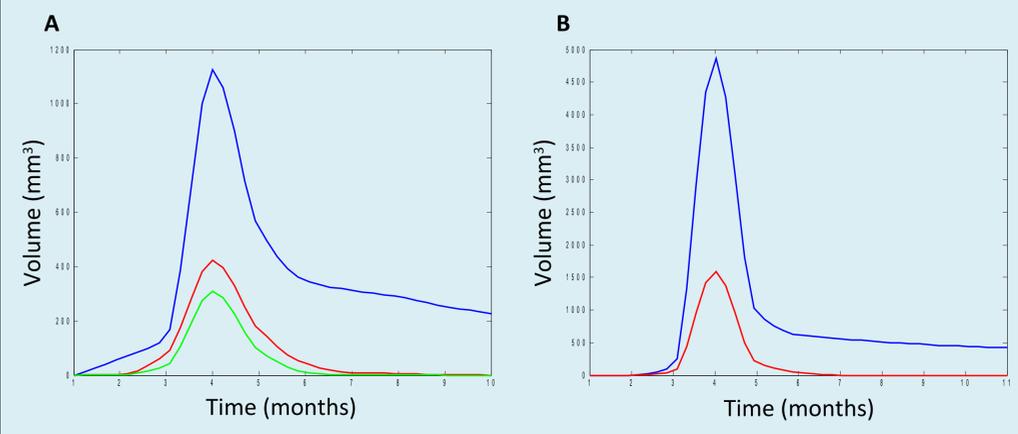


Fig 3. Mathematical model applied to FLAIR volume, for nodular (A) and ring (B) lesions:

Two different subcomponents, random walks type curves (light grey (A) and red dotted curves (B)) were found to contribute to the FLAIR kinetic curve (dark grey (A) and blue (B)). A rapid onset curve (I), that overlaps with the Gd enhancing phase and a second curve (II) beginning at the same time but less rapidly increasing and decreasing. Both nodular (A) and ring (B) lesions resulted to be described by the 2 random walks curves model with a very high fitting quality (R2 0.7 ±0.1 for nodular and R2 0.81 ±0.08 for ring).

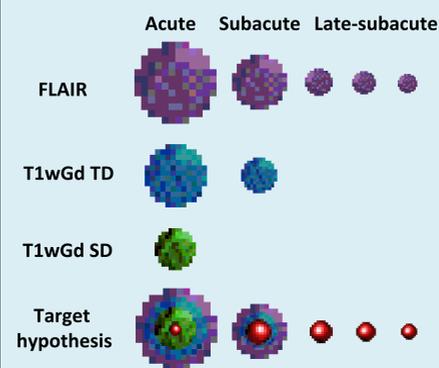
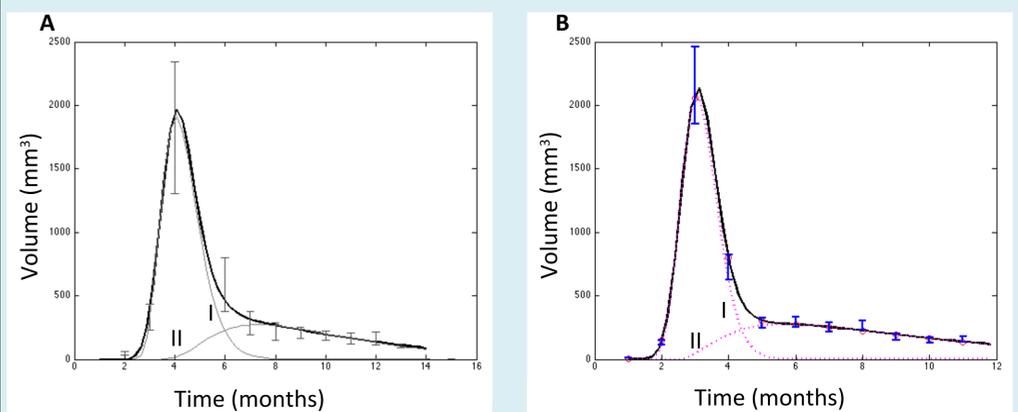
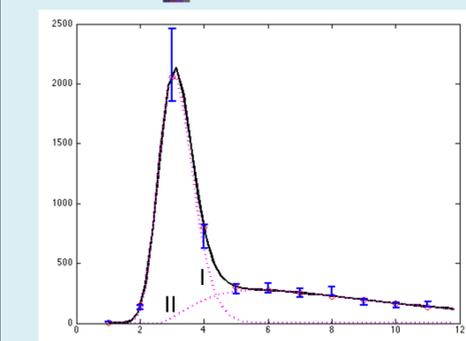


Fig 4. Model of MS lesion formation based on FLAIR and T1wGd volumetric changes over time.

In the first *acute phase* the external part of the lesion, visible only on the FLAIR sequence, corresponds to the inflammatory oedema that rapidly shrinks as the first component of the FLAIR curve (I) well represent. During this acute phase, the difference between the T1wGdSD at T1wGdTD areas of enhancement, represent an internal-external gradient of BBB disruption, the inflammatory process in MS moving from the centre toward the periphery².

The core of the lesion, red circle in "target hypothesis" and represented by the second FLAIR sub-curve (II) in the 2 random walks model, expands with time reaching it's peak during the *subacute phase* and then slowly shrinks, leaving a residual FLAIR hyperintensity during the *late subacute phase*. This core may represent cellular infiltration and, particularly, demyelination³.



Conclusions

- During the acute phase, the difference between the FLAIR lesion volume and the T1wGd volumes probably represents an outside area of oedema without overt BBB disruption.
- The difference between the GdSD et GdTD areas of enhancement in the acute phase, represent an internal-external gradient of BBB disruption suggesting a less severe BBB disruption in the external part of the lesions, where Gd enhancement is visible only on the T1wGdTD.
- The difference between the FLAIR outcome (FLAIR volume 6 months after the end of visible Gd enhancement) and the T1wGd volume at peak suggests that not the whole Gd enhancing area becomes a permanent tissue damage and part of it (the external one) is going to be presumably repaired⁴.
- The physiopathological interpretation of the two random walks FLAIR curves suggests how the first curve (I), that rapidly increases and decreases resembling the T1w Gd curve, represents the inflammatory oedema; the second curve (II), characterized by a slow increase and decrease, probably reflects cellular infiltration and demyelination.
- To conclude, in the acute phase the pathologic substrate of the lesions is made of overlapping layers: a central "core" containing inflammation, severe BBB disruption and tissue damage and an external "penumbra", with reversible BBB disruption and tissue damage surrounded by water diffusing from the inner layers.
- The biological model described above was valid for both nodular and ring enhancing lesions suggesting, in conjunction with literature reports from previous studies², a similar physiopathological substrate.