Natural history of multiple sclerosis inflammatory brain lesions: a FLAIR and T1w post constrast volumetric analysis

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Background

• MRI provides in vivo insights on MS focal pathology as different sequences are sensitive to different underlying biological phenomena[1].
• 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 (Gyroscan, 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 (Fig. 1)
•**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 (Shannon theorem).
•**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 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 (Fig.2)

•**Volume kinetic analysis.** The time course analysis (Fig.2) revealed:

1. An *acute phase* featuring synchronous peak volumes
2. A shrinking *subacute phase* when T1wGd volumes return to zero, with a less steep FLAIR slope compared to T1Gd.
3. A third, *late subacute phase*, featuring a persistent FLAIR outcome.

➔ these results were observed for both nodular and ring lesions (data not shown)

•**Mathematical model applied to FLAIR volume kinetic.** Two random walks curves (Fig 3):

1. Curve (I), with a similar shape compared to the T1wGd curves (Fig 2)
2. Curve (II) beginning at the same time but slowly increasing and decreasing.

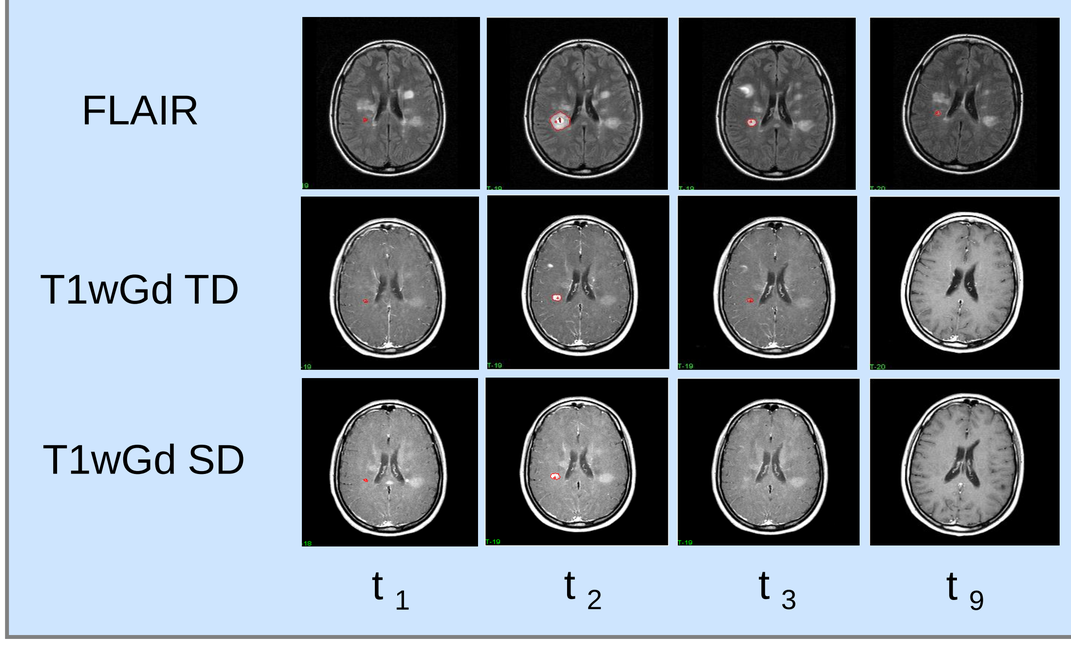
➔ both nodular (R2 0.7 ±0.1) and ring (R2 0.81 ±0.08) lesions resulted to be described by the 2 random walks model with a very high fitting quality (data not shown).

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 GdTD et GdSD 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 repaired[4].
•The physiophathological 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 (purple circle in Fig. 3).
•To conclude, in the acute phase the pathologic substrate of the lesions is made of overlapping layers: a central "core" containing inflammation, overt BBB opening and irreversible tissue damage and an external "penumbra", with reversible BBB 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 studies[2], a similar physiopathological substrate.
•Modification of the second RW curve profile (the curve that in our view mirrors the demyelinating process) could help to monitor remyelinating treatments efficacy in MS.

1. Absinta M et al. Seven-tesla phase imaging of acute multiple sclerosis lesions: a new window into the inflamma- tory process. Ann Neurol 2013;74:669–678.
2. Gaita☐ n MI et al. Evolution of the blood- brain barrier in newly forming multiple sclerosis lesions. Ann Neurol 2011;70:22–29.
3. Maggi P et al. The formation of inflammatory demyelinated lesions in cerebral white matter. Ann Neurol 2014;76:594–608.

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



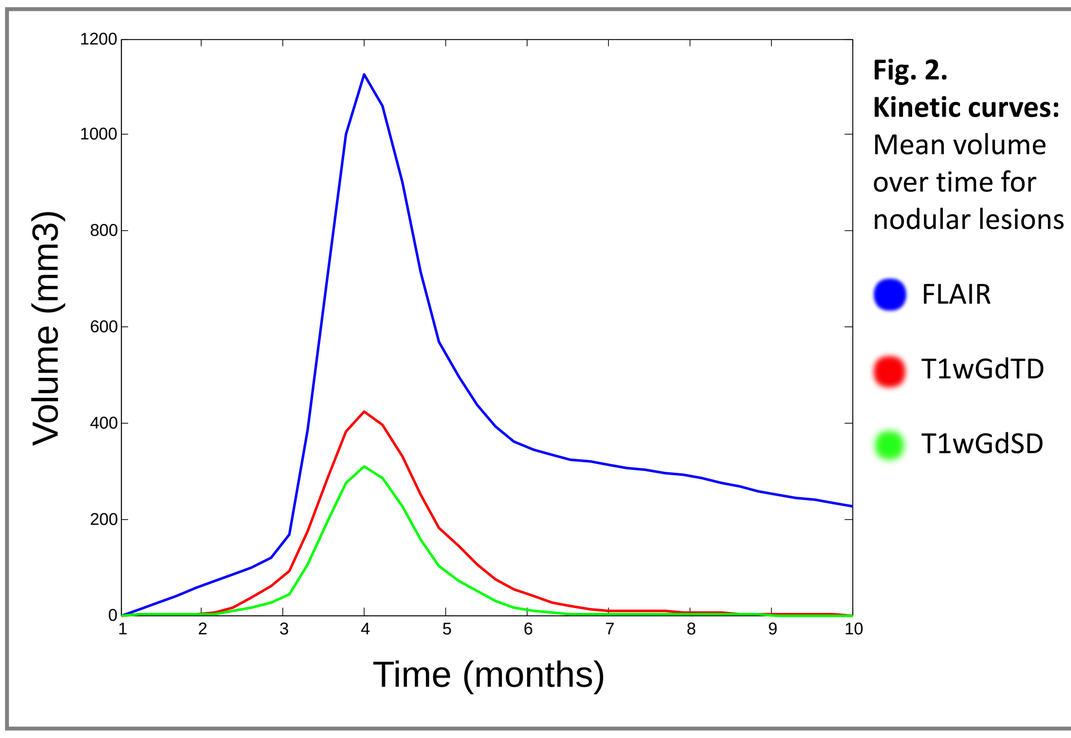


Fig. 2. Kinetic curves: Mean volume over time for nodular lesions

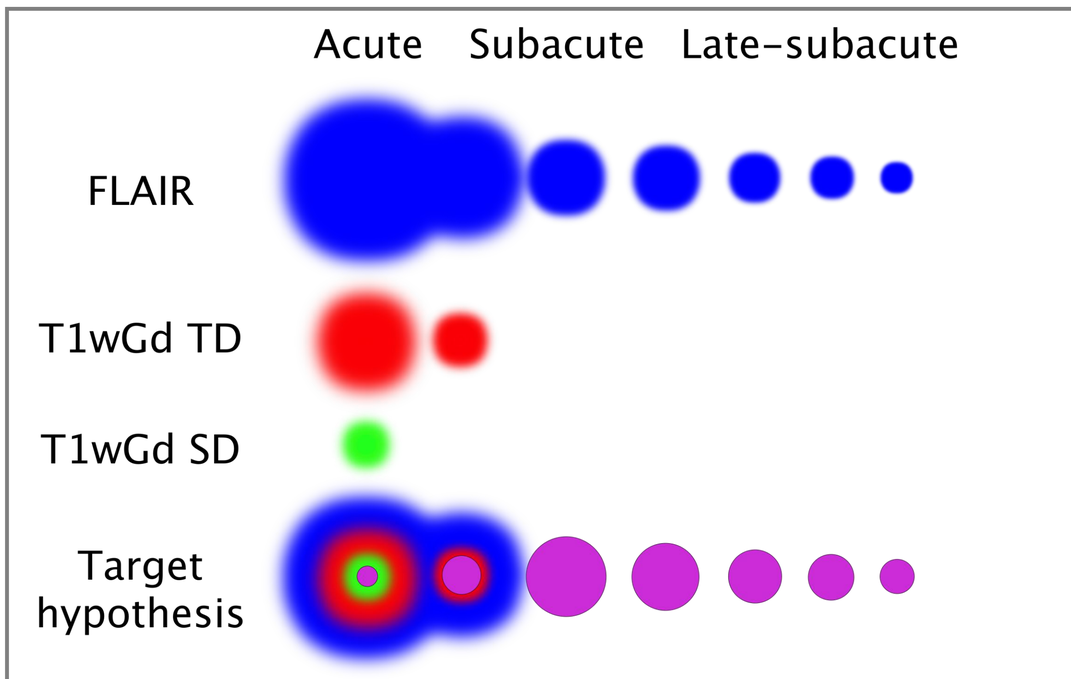


Fig. 3. Random walks