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# Heterogeneity in Longitudinal Evolution of Ring-Enhancing MS Lesions:

## In response to: Gaitán MI, Shea CD, Dphil IEE, et al. Evolution of the blood-brain barrier in newly forming multiple sclerosis lesions. Annals of Neurology 2011:n/a-n/a

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We enjoyed reflecting upon the article by Gaitán and colleagues, "Evolution of the Blood-Brain Barrier in Newly Forming MS Lesions".[1, 2] While the cause of MS remains unknown, a better understanding of lesion formation may provide critical clues as to the inciting event. This group has helped rekindle the debate concerning the role of blood vessels in short term lesion evolution for the 21st century. Neuropathologists have found that not all lesions have a central vessel, and lesions can be eccentric from one or multiple vessels.[3, 4] Lesions may emanate from a single central nidus, grow by coalescence of periphlebitic branches, or a combination.[4, 5]

Our own observations based upon monthly, co-registered MRI scans using triple-dosed gadolinium (Gd, 0.3 mmol/kg, 40 min delay, 3T, 3 mm slice thickness) suggest several patterns of ring enhancing lesion (REL) development and resolution over weeks to months.[6] Preceding ring formation, a nodule may appear which will later become the non-enhanced region in the ring's center (Figure A1–5). This may be consistent with Gaitán's suggestion of an expanding wave of inflammation recruiting additional vessels, with subsequent closure of the blood-brain barrier (BBB) within the lesion center.

Different patterns of ring resolution may suggest heterogeneity in the subsequent cascade of immunologic events. Often, the ring will fade over months until it is no longer apparent (Figure A1–5). However, we have also observed a ring returning to a nodule (Figure B1–5, C1–3), a ring fading from the inside to the outer rim (Figure D1–3), an expanding ring

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(Figure E1–4), and a ring that develops several months after nodule resolution (Figure F1–5). Interestingly, multiple resolution patterns can occur within the same individual.

Important questions remain as to why some MS lesions in some patients form rings. Why is the Gd concentration restricted from the lesion center? Are vessels becoming occluded as Gaitan and colleagues suggest? Or can this be coordinated reconstitution of the BBB? Is the ring an expanding wave of indiscriminate inflammation, or may it represent a strategy to limit inflammatory infiltration with continued surveillance and even repair. Most critically, why does a lesion form in the first place? Is it due to an intrinsic process within the brain parenchyma ("inside in"), or from immune cells entering from the periphery ("outside in")?[7]

Multiple unanswered questions about lesion origin continue to plague the MS community. We agree that imaging should continue to help answer more of these questions.[8]

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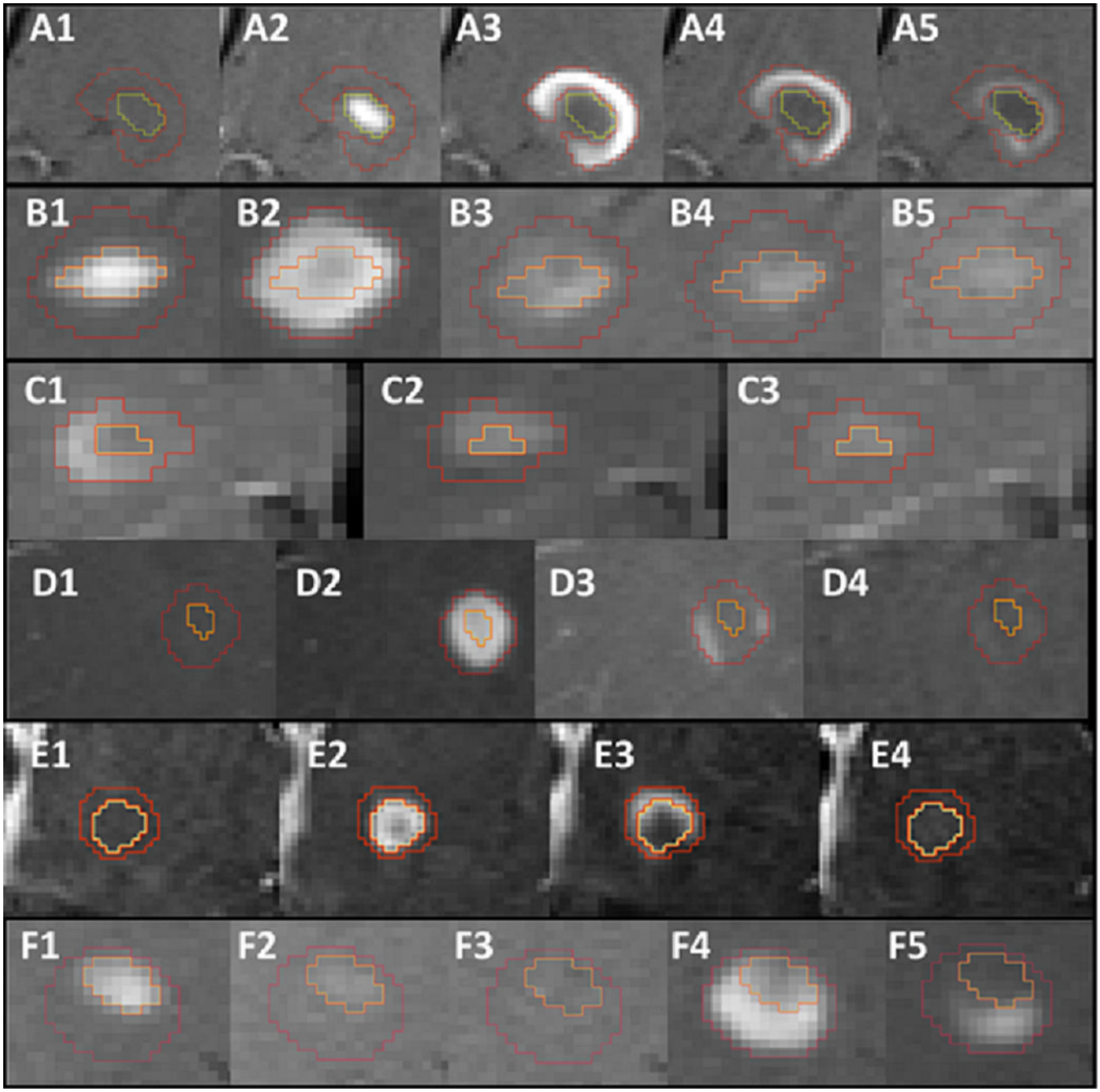


**Figure.**

All enhancing lesions are new, based upon normal prior month scan. **A.** Nodular lesion (A2) evolves the next month into the hypointense center of a REL (A3). The ring progressively fades over 2 months (A3–A5) and disappears the following month (not shown). **B.** Nodular lesion (B1) develops into a REL with a relatively hypointense center, and resolves over 3 months as a central nodule (B3–B5). **C.** Open REL (C1) resolves as a central nodule over 2 months (C2–3). **D.** REL with relatively hypointense center (D2) resolves by fading into the periphery (D2–3). **E.** REL (E2) develops an expanding ring (E3) before disappearing. **F.** Nodular lesion (F1) disappears (F2–3) to develop a ring after central nodule resolution (F4) 4 months later.