Pathological characterization of Broad Rim Lesions: A New Biomarker for Rapid Disease Progression in Multiple Sclerosis

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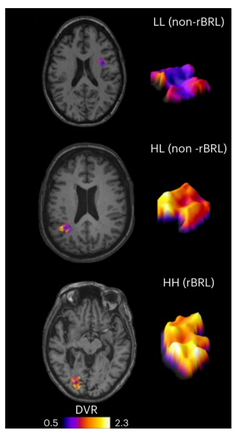
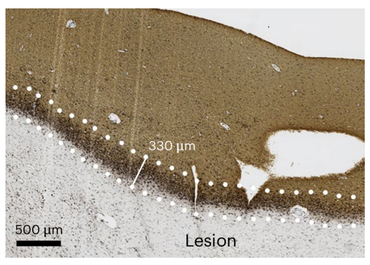
INTRODUCTION

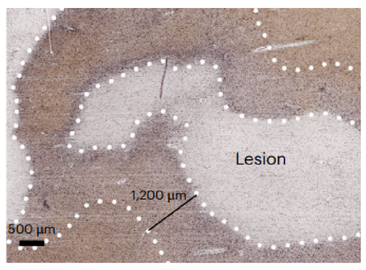
Broad Rim Lesions (BRLs) are a recently identified chronic MS lesion subtype marked by a rim of activated microglia/macrophages exceeding 1 mm in thickness around a demyelinated core. They occur more frequently in patients with rapidly progressive disease and can be detected *in vivo* using TSPO-PET, suggesting their potential as biomarkers of aggressive MS[1].
This study investigated the relationship between rim broadness and disease severity, explored pathological factors influencing rim expansion and quantified associated tissue damage to assess neurodegeneration. The analysis was conducted on **post-mortem MS brain samples** from the **Netherlands Brain Bank (NBB)**.



Detection of BRL using TSPO-PET



Classical mixed active/ inactive lesion (CL)

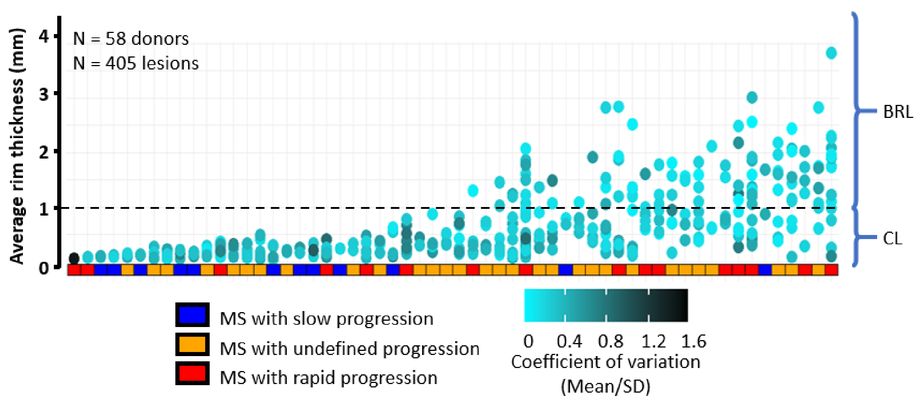


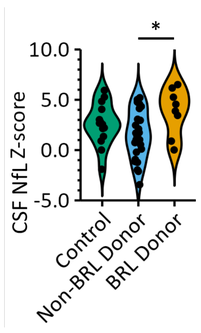
Broad Rim Lesion (BRL)

METHODS

- **58 NBB MS** donors were classified as having slow or rapid progressive disease based on the swiftness of disability milestones accumulation.
- Lesions were classified as classical mixed active/inactive lesions (**CL**) or **BRLs**, based on the average rim thickness outlined on HLA/PLP stained tissue **(N= 405 lesions of N=58 NBB MS donors).**
- Lesional (**core and rim**) and non-lesional (**perilesion** white matter and **normal appearing white matter**) compartments were outlined on each section.
- Cerebrospinal fluid (CSF) samples from 8 BRL, 27 non-BRL MS donors and 12 non-neurological controls were analyzed for neurofilament light chain (**NfL**) z-scores.
- **Cuffing of perivascular lymphocytes** and **ventricle adjecence** were registered.
  T and B lymphocyte densities were quantified by immunohistochemistry using markers CD3 and CD79a , respectively.
- Acute axonal damage was assessed by quantifying **APP+** events and gliosis was evaluated on **GFAP** staining using the R SCORE[2] . A total of **18 NBB MS donors** were included in this analysis.

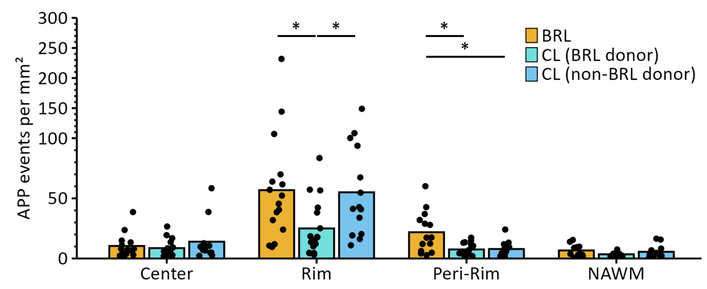
RESULTS

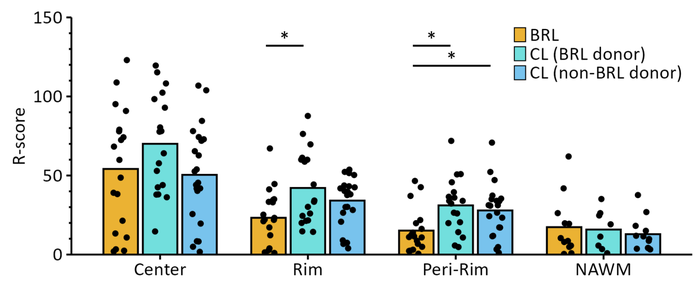


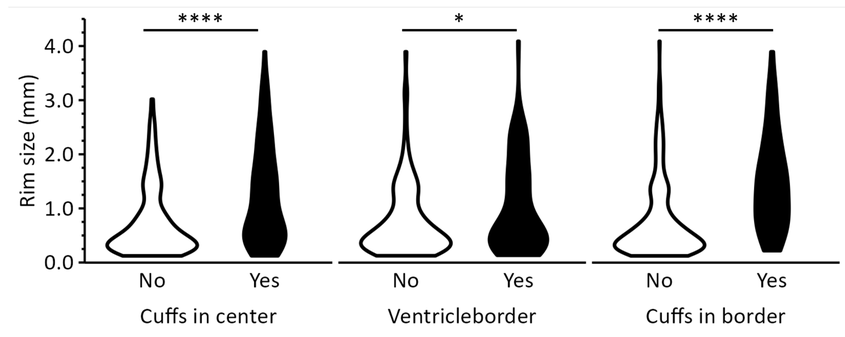


1. MS patients with rapid disease progression display on average thicker lesion rims. While rarely seen in patients with slow progressive disease, BRLs are more frequently seen in donors with more rapid disability accumulation. Analysis of CSF revealed increased NfL levels in BRL donors compared with non-BRL donors ($p < 0.05$). These findings support a link between rim broadness and disease severity in MS.

2. The rim and the perilesion white matter of BRLs display more acute axonal damage and reduced astrogliosis.
In lesion rims, acute axonal damage and the astrogliosis score in BRL was comparable to CL from non-BRL **(CL-nBRL)** donors but higher than in CL from BRL donors **(CL-BRL)**. In the perilesional white matter, BRL showed increased acute axonal damage and reduced astrogliosis compared to CL from both BRL and non-BRL donors.

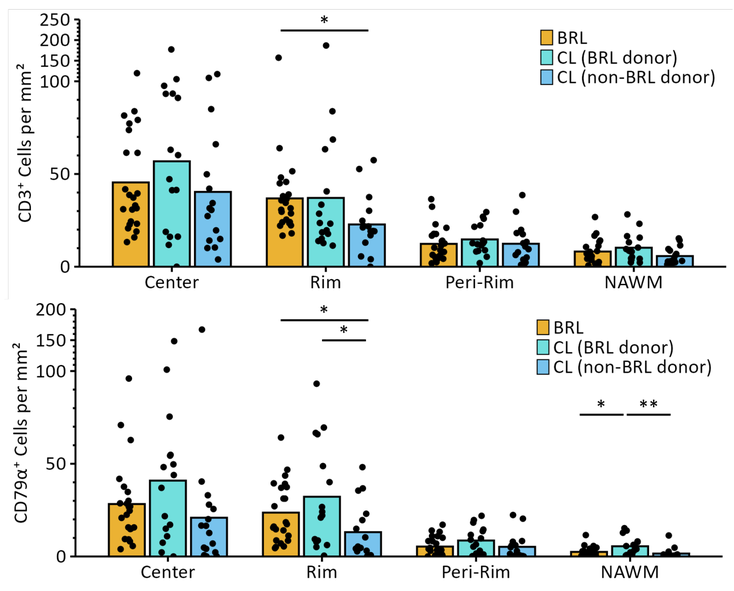






3. Lesion bordering ventricles or containing perivascular cuffs display broader rims. Lesions adjacent to the ventricles and those containing perivascular lymphocytic cuffs—accumulations of lymphocytes around blood vessels— exhibit significantly broader rims. Proximity to the cerebrospinal fluid (CSF) may expose periventricular tissue to soluble inflammatory mediators that activate resident innate immune cells, while perivascular cuffs likely represent focal sites of ongoing immune infiltration and activation. Together, these factors contribute to a compartmentalized inflammatory milieu that promotes and sustains broad-rim lesion formation.

4. Broad rims display increased lymphocytes densities .
BRL showed higher densities of $CD3^+$ T cells and $CD79\alpha^+$ B cells compared with classical lesions (CL) from non-BRL donors. These findings indicate enhanced lymphocytic infiltration at lesion rims in donors exhibiting BRL pathology, potentially contributing to increased rim thickness.



CONCLUSION & FUTURE PERSPECTIVES

We demonstrated that rim broadness is a pathological feature associated with severe disease outcomes in MS, elevated CSF NfL levels, and widespread neuropathological tissue damage extending into the perilesional white matter, indicative of extensive secondary axonal degeneration.
Inflammatory mediators released in perivascular and periventricular regions may contribute to broad-rim lesion formation. Future **large-scale CSF proteomic analyses** using Olink and HuProt platforms could help identify specific soluble antigen and antibody signatures involved in BRL pathogenesis.

REFERENCES

1 .Klotz, L., Smolders, J., Lehto, J. *et al.* Broad rim lesions are a new pathological and imaging biomarker for rapid disease progression in multiple sclerosis. *Nat Med* (2025).
2. Luijerink L, Rodriguez M, Machaalani R. Quantifying GFAP immunohistochemistry in the brain - Introduction of the Reactivity score (R-score) and how it compares to other methodologies. J Neurosci Methods. 2024 Feb;402:110025.