**Appendix e-1**

*Qualitative and quantitative assessment of CHI3L1 expression*

Detailed lesion maps were prepared from each section to select the area for quantification to include different brain regions and lesion types identified on the basis of hematoxylin/eosin and Luxol fast blue myelin stainings, and Bielschowsky silver impregnation for axons. Basic characterization of the lesions also included immunohistochemistry for different myelin proteins (PLP, MOG and MAG) as well as markers for T-cells (CD3) and macrophages/microglia (CD68). On the basis of these lesion maps, the areas for quantitative evaluation were selected. Positive CHI3L1 cells were counted in four fields with 40x objective (0.95 mm2) in different brain regions and lesions (cortex, NAWM, active lesion, inactive lesion and SEL) and in each MS subtype. According to the number of cells, we assigned the following: 0 if there were no positive cells, +/- if there were no more than 10 cells per field, + if there were between 10 to 20 positive cells, ++ if there were between 20 to 50 positive cells and +++ if we counted more than 50 positive cells. For co-localization studies, the same immunohistochemistry protocol was followed with the exception that, in this case, buffer Dako antibody diluent (Dako 53022) was used to dilute primary antibodies. To-Pro 3 (MW 642-661) was used for nuclear staining. Samples were mounted with Prolong Gold antifade reagent (Invitrogen P36930).

For quantitative assessment, digital optical densitometry (OD) was performed for CHI3L1 staining, according to a previously published protocol (Hametner *et al.*, 2013; Zrzavy *et al.*, 2017). Quantification of CHI3L1 expression was carried out employing ImageJ to calculate the positive DAB signal area fraction. Three images per region of interest were taken with the 10x objective (0.45 mm2). Images were saved as JPEG. A color deconvolution plugin was run to remove haematoxylin counterstaining, Further RGB images were converted into 8-bit greyscale images and inverted. A threshold was set in resulting images and the area fraction was calculated.

*Correlation of CHI3L1 expression and meningeal or perivascular inflammation*

Sections labeled with anti-CHI3L1 and anti-CD68 antibodies were used. Images were taken (Cases MS9, MS10, M14, MS15, MS22) from meninges and blood vessels of NAWM in the vicinity of grey matter cortical lesions, respectively (objective 10x). Cell count was performed using the Photoshop calculation command. To isolate CD68 or CHI3L1 positive cells the threshold and noise parameters were manually adjusted and applied to each image. Cell density was calculated as the mean number of CD68 positive cells per millimetre length. We also analyzed inactive lesions in white matter and cortex and SEL (edge and core). Perivascular CD68+ cells were excluded in the counts.

The density of lymphocytes was quantified in the same regions. Four non-overlapping areas were measured; all of them captured at 10x magnification in haematoxylin and eosin-stained sections. A gradient of inflammation was established as a measure of meningeal inflammation: the absence of lymphocytes (0), presence of one cluster of 5-50 cells (+), one or more clusters with more than 200 cells (++) and one or more clusters with more than 300 cells (+++). Another gradient was established in the case of perivascular inflammation: mild inflammation with less than 20 lymphocytes (0+), moderate inflammation with 20-50 lymphocytes (+), high inflammation with more than 50 lymphocytes (++), and severe inflammation with more than 100 lymphocytes (+++). The maximum degree of inflammation, both in examined meninges and blood vessels, was used to establish the inflammatory level in each case. Distance from measured area in cortex to meningeal follicle or to perivascular infiltrates in NAWM did not correlate to cell counts (r= 0.158; *P* = 0.300 and r= -0.044; *P* =0.768, respectively).