Appendix

Attendees of the workshop: "Correlation between pathological and MRI findings in MS: an update" (Milan, November, 23-24, 2017)

Chairs- Massimo Filippi (Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy); Wolfgang Brück (Institut für Neuropathologie, Universitätsmedizin Göttingen, Göttingen, Germany)

Speakers- W. Brück (Institut für Neuropathologie, Universitätsmedizin Göttingen, Göttingen, Germany); D. Chard (Institute of Neurology, Faculty of Brain Sciences, University College London, London, UK); C. Enzinger (Department of Neurology, Medical University of Graz, Graz, Austria); F. Fazekas (Department of Neurology, Medical University of Graz, Graz, Austria); M. Filippi (Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy); J.J.G. Geurts (Department of Anatomy and Neurosciences, VU University Medical Center, Amsterdam, Netherlands); S. Hametner (Department of Neuroimmunology, Medical University of Vienna, Vienna, Austria); T. Kuhlmann (Institute of Neuropathology, Universität Münster, Münster, Germany); P. Preziosa (Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy); M.A. Rocca (Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy); A. Rovira (Section of Neuroradiology and Magnetic Resonance Unit, Department of Radiology (IDI), University Hospital Vall d'Hebron, Autonomous University of Barcelona, Barcelona, Spain); K. Schmierer (Blizard Institute, Queen Mary University of London and Barts Health NHS, London, UK); C. Stadelmann (Institut für Neuropathologie, Universitätsmedizin Göttingen, Göttingen, Germany).
Discussants- G. De Luca (Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford, UK); R.G. Henry (Radiology and Biomedical Imaging, UCSF School of Medicine, San Francisco, CA, USA); R. Reynolds (Division of Brain Sciences, Department of Medicine, Imperial College London, London, UK); M. Vercellino (Neurologia I U, AOU Città della Salute e della Scienza di Torino, Torino, Italy).

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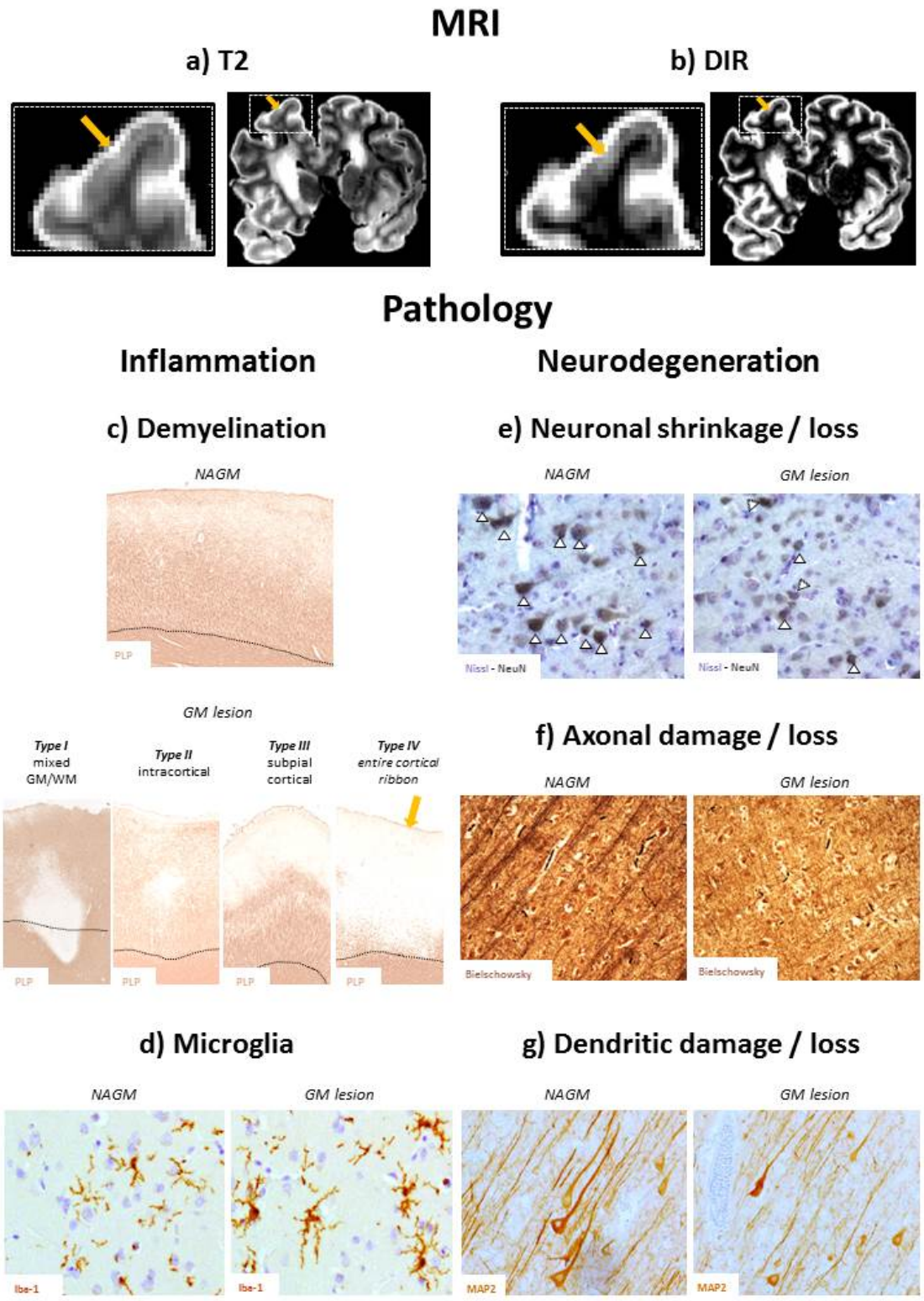
Panel

Atypical forms of demyelination, such as tumefactive demyelinating lesions (TDLs), may also occur in a minority of MS patients. Pathologically, TDLs resemble typical MS lesions with an active inflammatory demyelination, increased cellularity with phagocytes containing myelin debris and lymphocytes, and reactive gliosis.[1,2] A distinctive feature of TDLs is the presence of reactive astrocytes called Creuzfeldt cells.[1,2] TDLs are distinguished from typical demyelinating lesions by size (usually ≥2 cm), the tumor- or mass-like WM dominant involvement and sometimes the presence of a T2-hypointense rim, increased but also restricted diffusivity, edema and open-ring enhancement.[1] Most patients with TDLs typically develop MS during the follow-up, especially if other MS-typical lesions are present.[2,3]



Supplementary Figure. *Post mortem* MRI and histopathological substrates investigated in cortical lesions. (a) Upper part: matched MRI with (a) T_2-weighted, and (b) double inversion recovery (DIR) sequences of a *post mortem* brain slice showing a cortical gray matter (GM) hyperintensity in the left superior frontal gyrus (orange arrows). Lower part: (c) section stained for proteolipid protein (PLP) to quantify myelin confirmed the presence of a type IV cortical GM lesion (affecting the entire cortical ribbon) (orange arrow). Compared to normal appearing gray matter (NAGM), in GM lesion, sections stained for (d) ionized calcium binding adaptor molecule 1 (*Iba1*) showed a higher prevalence of microglia, (e) Nissl and NeuN revealed neuronal shrinkage and loss (white arrowheads), while (f) Bielschowsky staining and (g) microtubule-associated protein 2 (MAP2) demonstrated axonal and dendritic loss, respectively.

Supplementary Table 1. *In vivo* prevalence of cortical lesions and their associations with clinical disability and cognitive impairment in MS patients at different stages of the disease.

Phenotype	CLs prevalence	CLs accumulation	Cognitive impairment	Disability severity and progression (EDSS)	Phenotype evolution	References
RIS	Up to 40%	?	-	-	-	[4]
CIS	Up to 52%	28% patients (3y FU)	-	-	Higher risk to develop CDMS	[5-8]
RRMS	Up to 64%	43-58% patients (3y-5y FU) (≈0.8-0.9 new CLs/patient/yr)	**CLs volume**	**CLs number/volume** Predictors (3y-5y) FU: **baseline CLs volume**	Predictors (5y-7y FU): **baseline CLs number and volume**	[5,9-16]
SPMS	Up to 74%	47-48% patients (3y-5y FU) (≈1.0 new CLs/patient/yr)	-		-	[5,9,11-13,15,16]
PPMS	Up to 84% (DIR) Up to 88% (PSIR)	15-58% patients (1y-2y FU) (≈0.8-1.6 new CLs/patient/yr)	-	Predictors (2y FU): **baseline CLs volume**	-	[17,18]
Pediatric MS	Less than 12%	?	**CLs number/volume** not different between CI and CP patients	-	-	[19,20]

Abbreviations: CLs=cortical lesions; RIS=radiologically isolated syndrome; CIS=clinically isolated syndrome; RR=relapsing remitting; MS=multiple sclerosis; SP=secondary progressive; PP=primary progressive; EDSS=expanded disability status scale; CI=cognitively impaired; CP=cognitively preserved; FU=follow-up.

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