Multiple sclerosis in 2020: un bon cru

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Multiple Sclerosis 2020 : a "bon cru"

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Despite no major therapeutic trial results in 2020, the landscape of multiple sclerosis (MS) is changing, with better insight on prognosis, entry of artificial intelligence in MS brain imaging, technological advances challenging knowledge on disease pathogenesis, identification of novel therapeutic pathways. But 2020 will certainly be remembered as the year of outbreak of COVID-19 pandemic. In this context, the possibility of an increased vulnerability to severe COVID-19 in MS patients has rapidly become a burning question. Higher age, an EDSS $\geq$ 6, and obesity were identified as independent risk factors for severe COVID-19 in a French multicentric observational cohort.[1] Whereas in this study including 347 patients, there was no significant association between disease modifying treatment exposure and COVID-19 severity, some evidence is now emerging that therapies targeting CD20 (ocrelizumab and rituximab) may be linked to an increased risk of severe form of COVID, and several programmes are ongoing.[2]

How to manage patients with Radiologically Isolated Syndrome (RIS) - patients with brain MRI abnormalities compatible with CNS inflammation but lacking neurological symptoms- remains challenging, as long term evolution is unknown. The multicentric RIS consortium[3] - the largest and longest to date - included 277 RIS subjects from the 2014 original cohort. The cumulative probability of a clinical event at 10 years was 51.2%. Consistent with previous publications, young age, presence of oligoclonal bands or elevated IgG index in the CSF, infratentorial lesions and spinal cord lesions were identified as independent predictors of a first clinical event. The novelty here is the demonstration of a stepwise increase of risk associated with the number of factors (with a probability ranging from 29% for subjects with $\geq$ one risk factor to 87% with the 4 risk factors). Nevertheless, as long as the results of ongoing trials are not obtained, there is no recommendation to treat patients with RIS.

Artificial intelligence has opened new avenues for medical imaging in general. In MS, one interesting example is the deep learning approach applying convolutional neural networks[4], evaluating the possibility to predict brain lesional activity without the need for contrast injection. In this study, conventional MRI data from 519 patients, with a total number of 1390 enhancing lesions, were used to train and test the network performance. Participants with enhancing lesions were classified with 70% accuracy. In the same vein, the method proposed by Wei et al.[5] might offer an alternative to positron emission tomography (PET) - myelin imaging with ^{11}C-PIB PET allows quantification of myelin content changes in vivo, but is invasive, with injection of a radioactive tracer, and poorly suitable to multicentric studies - to predict myelin content changes using multisequence quantitative MRI. This deep learning approach allowed to generate synthetic images predicting myelin content changes in a longitudinal analysis of patients with MS. By providing accessible MRI-based algorithms, deep learning methods will likely modify, in the near future, the management of MS patients, as well as the design of therapeutic studies.

Concerning disease pathogenesis, single cell RNA sequencing methods have recently revealed oligodendroglia, neurons and microglia heterogeneity in healthy and MS tissue.[6,7] The single cell genetic and epigenetic study by Wheeler et al[8] unravelled astrocytes heterogeneity in MS tissue and MS model, and identified a subpopulation of astrocytes, characterized by decreased expression of the antioxidant transcription factor NRF2 and increased expression of the transcription factor MAFG, leading to repression of anti-oxidant and anti-inflammatory transcriptional programs. Such pro-inflammatory astrocytes are also detected within active MS white matter lesions. These results, which identify how astrocytes might contribute to inflammation and tissue damage, open perspectives for therapeutic candidates targeting neurotoxic astrocytic activity in MS.

Promoting neuroprotection in MS is a major challenge, as irreversible disability is highly correlated to accumulation of neuronal damage. Several trials of pro-remyelinating candidates are ongoing (see review in [9]). Very recently, negative results of AFFINITY (opicinumab) trial on disability improvement were released, while some promising results –unpublished- were communicated for bexarotene in relapsing MS, (ACTRIMS-ECTRIMS 2020). Concerning « direct » neuroprotection, the negative results of MS-SMART were disappointing.[10] This phase 2b, multiarm, parallel group, double-blind, randomised placebo-controlled trial aimed

at evaluating simultaneously 3 neuroprotective drugs (amiloride, fluoxetine, riluzole) selected from preclinical and clinical research search. The trial included 445 patients with secondary progressive MS. None of the therapeutic arms reached the primary outcome - volumetric MRI percentage brain volume change from baseline to 96 weeks-. Despite this negative result, the study demonstrated convincingly the value and feasibility of a multiarm phase 2 trial designed to take a go/no go decision for phase 3 trials targeting neuroprotection.

Finally, exciting preclinical data accumulate on behavioural interventions. Cutting edge live imaging methods were used to follow oligodendrocytes and individual myelin sheaths in murine demyelinated motor cortex, to assess the impact of learning a motor task on remyelination. Training indeed led to increased remyelination, by both new and surviving oligodendrocytes – an important result in the current debate on the identity of remyelinating cells in the adult CNS.[11] This study not only strengthens the evidence on the role of neuronal activity on myelination,[12] but also provides a convincing demonstration that timely (after the onset of remyelination) behavioural intervention accelerates functional recovery through enhanced remyelination.

References

1- Louapre C, Collongues N, Stankoff B, et al. Clinical Characteristics and Outcomes in Patients With Coronavirus Disease 2019 and Multiple Sclerosis. *JAMA Neurol.* 2020;**77**:1079-88.
2- Sormani MP; Italian Study Group on COVID-19 infection in multiple sclerosis An Italian programme for COVID-19 infection in multiple sclerosis. Lancet Neurol. 2020 Jun;19(6):481-482. doi: 10.1016/S1474-4422(20)30147-2.
3- Lebrun-Frenay C, Kantarci O, Siva A, et al. Radiologically Isolated Syndrome: 10-Year Risk Estimate of a Clinical Event. *Ann Neurol*. 2020 Jun 4. doi: 10.1002/ana.25799
4- Narayana PA, Coronado I, Sujit SJ, Wolinsky JS, Lublin FD, Gabr RE. Deep Learning for Predicting Enhancing Lesions in Multiple Sclerosis from Noncontrast MRI. *Radiology* 2020;**294**:398-404.
5- Wei W, Poirion E, Bodini B, et al. Predicting PET-derived myelin content from multisequence MRI for individual longitudinal analysis in multiple sclerosis. *Neuroimage*. 2020;**223**:117308.
6- Jäkel S, Agirre E, Mendanha Falcão A, et al. Altered human oligodendrocyte heterogeneity in multiple sclerosis. *Nature*. 2019;**566**:543-7.

7- Masuda T, Sankowski R, Staszewski O, et al. Spatial and temporal heterogeneity of mouse and human microglia at single-cell resolution. *Nature*. 2019;**566**:388-92.
8- Wheeler MA, Clark IC, Tjon EC, et al. MAFG-driven astrocytes promote CNS inflammation. *Nature*. 2020;**578**:593-9.
9- Lubetzki C, Zalc B, Williams A, Stadelmann C, Stankoff B. Remyelination in multiple sclerosis: from basic science to clinical translation. *Lancet Neurol.* 2020;**19**:678-88.
10- Chataway J, De Angelis F, Connick P, et al. Efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis (MS-SMART): a phase 2b, multiarm, double-blind, randomised placebo-controlled trial. *Lancet Neurol.* 2020;**19**:214-25.
11- Bacmeister CM, Barr HJ, McClain CR, et al. Motor learning promotes remyelination via new and surviving oligodendrocytes. *Nat Neurosci* 2020;**23**:819-31.
12- Gibson EM, Purger D, Mount CW, et al. Neuronal activity promotes oligodendrogenesis and adaptive myelination in the mammalian brain. *Science*. 2014;**344**:1252304.