Cognitive functions and inflammation in multiple sclerosis: mechanisms and concepts

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OBSERVATIONS ON ATTEMPTS TO PRODUCE ACUTE DISSEMINATED ENCEPHALOMYELITIS IN MONKEYS

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PLATES 1 TO 3

(Received for publication, February 21, 1933)
How to define multiple sclerosis?

- First cause of neurological disability in young adults
  (100 000 patients in France, onset usually 15-35)

Motor disability (pyramidal, cerebellar)
Sensory disturbances (vision, sensitive...)
Vegetative symptoms
Fatigue, pain
Cognitive impairment

2 main clinical phenotypes
- Relapsing-remitting
- Progressive
How to define multiple sclerosis?

- Multifocal inflammatory demyelinating disease of the central nervous system

Focal inflammatory lesions associated with clinical relapses
How to define multiple sclerosis?

- Neurodegenerative disease characterized by progressive brain and spinal cord atrophy

Lassmann, 2012
SPMS
Marked atrophy with dilatation of cerebral ventricles and outer cerebrospinal fluid spaces
MS pathology

- Focal lesions
  - axonal degeneration
    Diffuse WM injury

- Cortical demyelination and deep GM injury

→ Atrophy
Main cognitive functions affected in MS

- Information processing speed (IPS)
- Learning/Memory
- Attention, working memory
- Executive functions, Verbal fluency
- Reasoning, conceptualisation

Rao et al., 1991
Main cognitive functions affected in MS

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Percentage of MS group scoring <5th percentile for healthy controls:
- Language: 8–9%
- Visuospatial abilities: 12–19%
- Attention span: 7–8%
- Information processing: 22–25%
- Memory: 22–31%
- Problem solving: 13–19%

Role of inflammation and neurodegeneration in cognitive impairment in MS?

Rao et al., 1991
Mechanisms of CI in MS

**IPS**
- Early symptom
- Main CI in RRMS
- Associated with diffuse white matter injury, focal inflammation and brain atrophy

**Memory**
- Early symptom
- More severe in PMS
- Hippocampal atrophy

Ruet, 2013  Benedict, 2005
Lesions located in the cingulum, parieto-frontal pathways and thalamo-cortical projections, with a left-sided predominance, as well as the right cerebellar white matter correlated moderately with NP test performances.

Voxelwise analysis of lesions probability maps (T2)

Sepulcre et al. Neuroimage, 2009
Contribution of normal appearing brain tissue pathology to IPS deficits

Cognitive impairment as marker of diffuse brain abnormalities in early relapsing remitting multiple sclerosis

M S A Deloire, E Salort, M Bonnet, Y Arimone, M Boudineau, H Amieva, B Barroso, J-C Ouallet, C Pachai, E Galliaud, K G Petry, V Dousset, C Fabrigoule, B Brochet


56 early RRMS
IPS vs lesion volume, brain atrophy or magnetization transfer ratio of normal appearing brain tissue (outside lesions) (reflecting axonal pathology)

Multivariate analysis:
Correlation of magnetization transfer ratio in normal appearing brain parenchyma with NP test
Contribution of normal appearing brain tissue pathology

**NABT MTR** in patients with early RRMS (2 years) predicts the progression of cognitive impairment during the subsequent **seven year** period (*Deloire et al, Neurology 2011*)
Mechanisms of neurodegeneration in WM

Trapp et al. NEJM 1998
Blood

Activation

Migration

Traficking

Inflammation

Demyelination, axonal injury, and degeneration

BBB

CNS

Macrophage

Microglia

Macrophage

Neurons

Oligodendrocyte

Axonal section

(Pelletier, 2006)
Mechanisms of IPS slowness

Peripheral Inflammation crossing the BBB (plaques) → Axonal degeneration → CNS Atrophy
Hippocampus and memory deficits in MS

Correlation between hippocampal atrophy and memory

Table 2 Correlation between total and subregional hippocampal volumes and cognitive test performance

<table>
<thead>
<tr>
<th>Hippocampal region</th>
<th>Spearman’s rank correlation coefficient</th>
<th>PASAT</th>
<th>Significance</th>
<th>Word list learning</th>
<th>Significance</th>
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<td>−0.34</td>
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<td>NS</td>
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<tr>
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</table>

Results shown are for RRMS and SPMS patients combined.
NS = not significant.

RRMS (DD=3.5) and SPMS (DD=13)

Koubiyer et al., ECTRIMS 2017: GM atrophy in CIS
Memory and hippocampal microstructure in early MS

Diffusion tensor imaging (DTI) was performed using Maps.

FA maps registered in the MNI space with hippocampal masks.

Planche et al.; MSJ 2016
Correlation microstructural abnormalities (DTI)/memory

Planche et al; MSJ 2016
Experimental Autoimmune Encephalomyelitis
Model: fear conditionning

Contextual fear conditionning (A Desmedt)

Planche et al., Brain Behav Immun. 2017

EAE-mice showed an early hippocampal-dependent memory deficit
Hippocampal volume

Planche et al., Brain Behav Imm un. 2017

4.7T scanner

no difference between EAE and CFA-mice 20 d.p.i.
20.58mm$^3$ vs 20.67mm$^3$, p=0.90,

No atrophy
Diffusion tensor imaging: microstructural injury in hippocampus

Planche et al., Brain Behav Immun. 2017

*In vivo* DTI revealed selective microstructural modifications in the molecular layer of the dentate gyrus of EAE-mice
EAE-mice showed a selective and early neurodegenerative process in the dentate gyrus
The loss of neurites was correlated with FA and AD in the molecular layer of the dentate gyrus.

EAE-mice showed a selective and early neurodegenerative process in the dentate gyrus.
Microglial activation in hippocampus

- Activated microglia (without neither lymphocyte infiltrates nor demyelination)
- Minocycline (systemic or in situ) prevent memory deficit, DTI abnormalities and pathological lesions by stopping microglial activation.

Planche et al., Brain Behav Immun. 2017
Inflammation in the brain is linked to axonal injury

T cells
HLAD+ microglial cells and macrophages
Lymphoïd folicles in meninges

Maggliozi et al.,
Brain 2007: 130;
1089-1104

Fig. 1. Characterization of ectopic B-cell follicles and inflammatory cell infiltrates in post-mortem brain tissue from cases with SPMS and PPMS. Immunostaining of serial brain sections from a F-SPMS case (A–D) shows an intraventricular ectopic B-cell follicle in a cerebrospinal subcortical white matter lesion expressing CD20 (red) and polyclonal anti-CD20 (green) antibodies and plasmablast/plasma cells stained with an anti-IgG, A, M polyclonal antibody (D). The inset shows two intraventricular plasma cells at high-power magnification. Panel E shows prominent perivascular accumulation of CD20+ B cells in a periventricular WML from a F-SPMS case. Several scattered CD20+ B cells are present in the severely inflamed meninges entering a cerebrospinal subcortical white matter lesion in a PPMS case (F). The lower, composite panel illustrates the localization of ectopic B-cell follicles in the multiple sclerosis brain. The schematic drawing shows that ectopic B-cell follicles develop along (H) and in the depth (I) of the cerebral white matter, whereas scattered B lymphocytes (J) are detected in the meninges covering the external brain surface. The micrographs in panels H–J show representative fields from a F-SPMS case out of the 12 examined. Original magnifications: E–G = 200 x; A, D, H–J = 200 x, B, C and inset in A and D = 100 x.
Conclusion

Deficit of speed of information processing

Early connectivity disturbance
Diffuse and focal (WM)

Gray matter injury

Memory impairment,

Conclusion
Relapses

Peripheral Inflammation crossing the BBB (plaques)

Axonal degeneration

IPS

Progression Memory

CNS Atrophy

GM pathology

Chronic in situ inflammation

?