

Astrogliosis and microgliosis patterns in diffuse and focal white matter lesions of preterm infants

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INTRODUCTION. White matter damage and myelination defect are key hallmarks of brain lesions observed in preterm infants. Pre-oligodendrocyte cell death has been identified as a major component of white matter damage. Nevertheless, the specific roles of astrogliosis and microglial-macrophages activation in the pathophysiology of white matter damage and/or repair remain a matter of debate.

AIM. To further address the potential link between glia and white matter damage, we studied astrogliosis, microgliosis, vessel growth and myelination processes by immunohistochemistry performed on brain tissue obtained from preterm infants (<37gestational week at birth).

METHODS. Protocols were approved by the Inserm ethical committee. Three groups of brains were included: brains with diffuse white matter damage (n = 4), brains with focal white matter necrosis (n = 4), and control brains (n = 4) with no detectable abnormalities. Different antibodies were used on serial sections, labelling astrocytes [GFAP, monoaminoxidase-B (MAO-B), monocarboxylate transporter-1 (MCT1) and PS100 β], microglia-macrophages [Iba-1, CD68, CD45, LN3 (MCHII)], vessels (CD34 and MCT1), and oligodendrocytes-myelin (Olig2, APC, MBP). Markers were quantified according to a semi-quantitative score ranging from 0 to +++++, controls displaying scores between 0 and + for all markers.

RESULTS.

- 1/ In all pathological cases, astrogliosis was observed both in focal and diffuse white matter damage, as revealed by GFAP immunostaining. MAO-B labelling paralleled GFAP labelling.
- 2/ In controls, MCT1 is expressed at a very low level in astrocytes. In pathological cases, MCT1 was expressed in some astrocytes which did not display yet the typical reactive morphology on sections immunolabelled with GFAP. This was especially observed in diffuse white matter lesions. MCT1 could therefore identify a subpopulation of reactive astrocytes at an early stage with an active energy transport.
- 3/ In diffuse and focal cases, Iba-1 labelled microglia-macrophages at all stages of activation, including subpopulations expressing CD68 and CD45. Of note, microgliosis (whatever the marker used) was an inconstant feature in diffuse white matter lesions.
- 4/ Double labelling with astrocytic and microglia-macrophage markers showed a mismatch pattern of distribution of activated astrocytes and activated microglia-macrophages.
- 5/ The density of Olig2-labelled cells was decreased in diffuse white matter lesions and Olig2 labelling was almost undetectable in focal white matter lesions.
- 6/ Using MCT1 labelling as a marker of vessel walls, areas of hyper vascularization could be observed in both focal and diffuse white matter lesions as well as in some areas of the surrounding cortex.

DISCUSSION. This study identifies new markers for assessing different glial populations in white matter damage of preterm infants. Of particular interest, MCT1 seems to be a metabolic marker of reactive astrocytes. Also, the calcium-binding protein specific of microglia, Iba-1, appears as the best marker to label the largest proportion of brain microglia, from ramified microglia to activated macrophages. Finally, in our samples, astrogliosis seemed to be more prominent than microgliosis, with a mismatch distribution between the two cell populations.