BLACK HOLES MICROGLIA ACTIVATION IN RELAPSING AND PROGRESSIVE MULTIPLE SCLEROSIS: A PET STUDY

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BACKGROUND

Black Holes in Multiple Sclerosis

DEFINITION

- Black holes (BHs) are multiple sclerosis (MS) lesions appearing hypointense at T1-weighted and hyperintense in T2-weighted magnetic resonance imaging (MRI).

METHODOLOGY

1. BHs were associated with axonal reduction, extracellular edema and demyelination in 6 CNS biopsied demyelinating lesions (Bruck et al., 2007).
2. In 19 post-mortem MS lesions BHs did not correlate with degree of demyelination or reactive astrocytes but inversely correlated with axonal density (van Walderveen et al., 1998).
3. BHs did not correlate with axonal loss in 14 early MS biopsies. At the MRI follow up the higher the axonal loss and demyelination in the initial biopsy, the more hypointense the lesion became; remyelination was associated with reduction of hypointensity; whether a lesion becomes remyelinated or not, it seems to take place immediately following active demyelination (Bruck et al., 2007).
4. In EAE, BHs hypointensity correlated with increased cellular infiltrates and reduced myelin content in the lesion centre, with microglial and astroglial infiltrates in the perilesional area (Noser et al., 2007).
5. Using N-Acetyl-Aspartate spectroscopy, axonal damage was found in severely hypointense T1 lesions (Van Walderveen et al., 1998).

BH AND DISABILITY

- BHs have been associated with irreversible disability (Truyen et al., 1996, Pasdill et al., 1999, van Walderveen et al., 1998; Simon et al., 2000).
- But this is a not a consistent finding (Szego et al., 1997; O'Farren et al., 1999; Maek et al., 2000).

Current imaging techniques have a limited ability to measure the complete spectrum of pathology in MS; BH lesions represent one of the most evident examples.

Microglia

- Microglia is the first line for central nervous system homeostasis (against any kind of injury).
- Microglia is essential for the onset of progressive neurodegeneration.

Microglia can assume different phenotypes according to the microenvironment in which it resides:

1. When induced by IL-1, IFN-γ or amyloid-β aggregates, microglial acquire features such as Phagocytosis, release of inflammatory mediators and do not support cell renewal, which can even be impeded.
2. When induced by IL-4, microglia acquire features such as Release of inflammatory mediators, release of pro-inflammatory factors, support oligodendrogenesis, support neuroprotection.

PK-PET Imaging

Positron emission tomography (PET) ligand [(11C)]R-PK11195 (PK) has high affinity for the translocator protein (TSPS), which is highly expressed in mitochondria of activated microglia. This ligand has been used in several neurological conditions as marker of inflammation and degeneration, as well as in MS to identify white and grey matter abnormalities beyond anatomical lesions shown at MRI.

Table 1: Study population

<table>
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<tr>
<th>Group</th>
<th>T1 Relapsing</th>
<th>T1 Progressive</th>
<th>T2 Relapsing</th>
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RESULTS

Aims

In light of the variable relationship of MRI T1 BHs with disability and the variable pathological findings we aim to examine the in-vivo functional microglial activity of T1 BHs and the possible correlation with disability.

Microglia activation is here expressed by the PK binding potential of the specifically bound radioligand relative to the non-displaceable radioligand in T1 black holes.

Subjects

Subjects enrolled (Tab.1)
- 10 relapsing MS
- 9 progressive MS

The following investigations were performed
- History and EDSS
- PET [(11C)]R-PK11195 scan
- Colocalization of potassium enhancing MRI scan

Discussion

The results of this study show that relapsing and progressive patients have heterogeneous patterns of [(11C)]R-PK11195 uptake in T1 black holes. In progressive subjects PK uptake in BHs was associated with disability suggesting a role for microglia in mediating axonal loss. In relapsing patients PK uptake in BHs was not associated with disability and there was an inverse correlation between PK uptake and black holes lesion load indicating an early inflammatory role for activated microglia.

It is possible that a microglia phenotype switch occurs during the course of MS.

Our data could represent the in vivo imaging of two alternative microglia phenotypes in our MS populations.

In particular at the lesion onset during an acute inflammatory state a microglia phenotype aiming to recover the lesion seems to be predominant, while in later stages in a chronically over-activated microenvironment, another microglia phenotype is predominant and contributes to the tissue damage.

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