PK11195-PET Enhancement in Black Holes Correlates with Disability and Outcome in Progressive Multiple Sclerosis

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FISM Grant 2010/B/7

Introduction

- Multiple sclerosis (MS) is characterized pathologically by focal areas of inflammatory demyelination and variable axonal loss in the central nervous system
- T2 and enhancing T1 MRI lesions have limited utility in predicting MS outcome
- Literature on black holes (T1 hypointense MS lesions, BH) is inconsistent with regards to their pathological features and ultimate clinical role (Sahraian *et al.*, 2009)
- Activated microglia has a major role in the pathology of MS, for both neuroinflammation and degeneration
- The PK11195 (PK) PET tracer has a high affinity for the translocator protein (TSPO), which is localised to and expressed at high levels in mitochondria of activated microglia
- *in vivo* PK-PET has been used to study MS BHs, as an indicator of microglial activity and its correlation with disability

Methods

STUDY POPULATION

- Nineteen MS patients
  - ✓ Relapsing: 10 subjects
  - ✓ Progressive: 9 subjects

INVESTIGATIONS

- History
- Neurological examination (EDSS)
- PK-PET scan
- Co-localising MRI scan

PK-PET QUANTIFICATION

- Binding potential relative to the non-specific volume (BP_{ND}) (Innis *et al.*, 2007)
- Reference tissue model (Gunn *et al.*, 1997)
- Tissue reference input extraction: SUPERPK software (Imperial Innovations; Turkheimer *et al.*, 2007; Boellaard *et al.*, 2009)

BLACK HOLES

BHs were manually drawn, defined as hypointense regions > 3 mm^2 on T1-weighted MRI images corresponding to hyperintense regions on T2-weighted images (Truyen *et al.*, 1996)

Table 1: Study population

Subject	Age	Age at onset	Disease duration	EDSS	Course	Medication[a]
1	29.5	25.8	3.6	9.5	P	CP
2	31.6	18.6	13.0	4.0	R	None
3	46.3	21.2	25.1	8.5	P	None
4	26.1	18.4	7.7	7.0	P	Cop-1
5	42.0	13.9	28.2	7.0	P	None
6	33.1	26.1	7.1	8.0	R	IFNβ-1a
7	47.6	34.4	13.2	4.0	R	None
8	28.9	25.2	3.8	7.0	P	None
9	43.5	20.4	23.1	5.5	P	None
10	57.8	46.5	11.3	6.5	P	None
11	39.1	25.7	13.4	6.5	R	None
12	49.4	20.0	29.4	8.0	P	None
13	25.2	21.8	3.4	4.5	R	None
14	47.1	27.9	19.2	6.5	R	Cop-1
15	46.6	35.0	11.6	6.0	R	None
16	43.7	19.0	24.6	3.5	R	None
17	42.3	23.3	19.0	4.0	R	None
18	29.6	19.7	9.9	7.0	P	None
19	26.8	25.9	1.0	5.5	R	IFNβ-1a
Mean (SD)	38.8 (9.6)	24.7 (7.5)	14.1 (8.9)	6.2 (1.7)	19 Total	
Mean (SD)	38.3 (8.5)	25.8 (5.6)	12.6 (7.3)	5.3 (1.5)	10 R	
Mean (SD)	39.2 (11.1)	23.5 (9.3)	15.8 (10.5)	7.3 (1.2)	9 P	
IST-T	*ns*	*ns*	*ns*	*		

Population demographic and clinical characteristics, in order of PET scan date (from oldest to newest). EDSS: Expanded Disability Status Scale; [a]: medication for MS at the PET scan, CP: cyclophosphamide, Cop-1 Copaxone; IST-T R-P: Independent Samples T-Test between Relapsing and Progressive MS groups; SD: Standard Deviation; *ns: non-significant*; * *p=0.003*.

Table 3: Baseline demographic and clinical characteristics of progressive subjects. Subjects are grouped according to their clinical outcome at 2 year follow up

	Group A Mean (SD)	Group B Mean (SD)	IST-T
Age	41.00 (10.72)	36.95 (9.73)	*ns*
Age at MS onset	25.4 (12.55)	21.0 (2.90)	*ns*
Disease duration	16.26 (9.06)	16.48 (11.21)	*ns*
Years on only relapsing course	4.86 (5.40)	12.73 (9.95)	*ns*
Age at progression onset	29.52 (13.20)	33.40 (9.15)	*ns*
Years on progressive course	11.32 (7.55)	3.55 (1.83)	*ns*
EDSS at baseline (PET scan)	7.70 (1.12)	6.88 (0.89)	*ns*
FU time from baseline (months)	20.80 (4.96)	21.00 (2.74)	*ns*
EDSS change	+ 0.60	- 0.70	

Group A: n = 5 progressive MS patients with stable or increased disability at follow-up; Group B: n = 4 progressive MS patients with decreased disability at follow-up; SD: Standard Deviation; IST-T: Independent Samples T-Test; *ns: non-significant*.

Results

Multiple sclerosis population

Table 1: clinical and demographic difference between the two populations

- progressive vs relapsing patients had a significantly higher disability on the EDSS (*p=0.004*)

MRI T1 black holes exhibit a significant range of PK binding

BHs show either presence ($BHPK^+$) or absence ($BHPK^0$) of PK enhancement (Fig. 1 and Table 2)

There was no difference in number per patient according to the disease subtype (Table 2)

The volume and PK binding in MRI T1 black holes differ between relapsing and progressive patients

Volumetric distribution of BHs (Fig. 2)

- $BHPK^+$: relapsing vs progressive *p=0.907*
- $BHPK^0$ relapsing vs progressive *p=0.387*
- ✓ Relapsing group: $BHPK^+$ vs $BHPK^0$ *p=0.027*
- Progressive group: $BHPK^+$ vs $BHPK^0$ *p=0.347*

$PKBP_{ND}$ in the relapsing patients' BHs was significantly lower than in the progressive patients' (*p=0.00003,* Fig. 3)

In relapsing patients the $BHPK^0$ were smaller relative to the $BHPK^+$ and the PK uptake in the $BHPK^+$ was less than in progressive patients.

Figure 1. Enhancing/non-enhancing black holes

Top row: relapsing MS, arrow: enhancing BH
Bottom row: progressive MS.
Left: MRI-PET
Right: two black holes as seen at MRI.
Middle: the same black holes show different PK binding at PET scan: 1/red) absence of tracer uptake; 2/green) high PK binding.

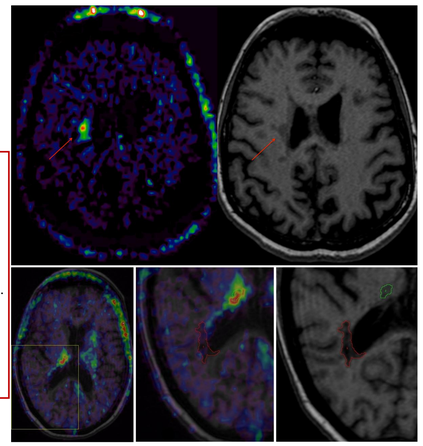
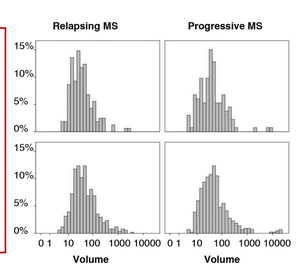


Figure 2

Percentage of black holes (Y axis) according to their volume in mm^3 (X axis, log scale base 10). Top row: non-enhancing black holes ($BHPK^0$); bottom row: enhancing black holes ($BHPK^+$). Left column: relapsing patients; right column: progressive patients.



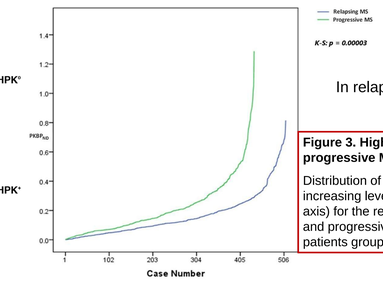


Figure 3. Higher PK binding in progressive MS patients

Distribution of $BHPK^+$ (X axis) with increasing levels of $PKBP_{ND}$ (Y axis) for the relapsing (blue line) and progressive (green line) patients groups.

PK binding in MRI T1 black holes correlates with clinical outcome in progressive patients

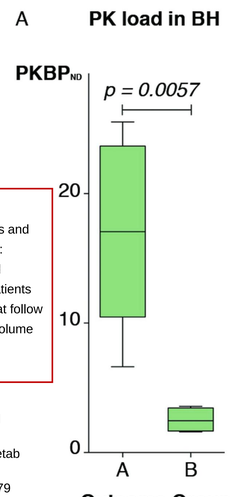
Progressive population FU at 21 months from the initial PK-PET scan (Table 3).

Five patients (Group A) showed a stable or increased disability score

Four patients (Group B) showed a slight improvement in disability score

Retrospective analysis of the PK-PET scans of these two progressive subgroups (Fig. 6):

1. The total amount of $PKBP_{ND}$ in the BHs in group A (mean of 17.07±7.26 per patient) vs group B (mean of 2.52±0.94): ISTT: *p<0.01*
2. The baseline volume load of BHs at MRI: ISTT: *p<0.01*
3. The baseline volume load of $BHPK^+$: ISTT: *p<0.05*



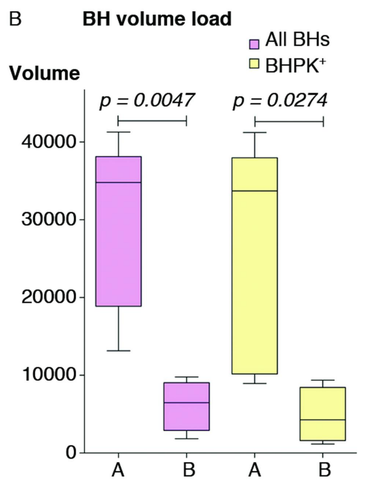


Figure 6

Black holes in progressive patients and clinical outcome (X axis). Group A: patients with a stable or increased disability at follow up. Group B: patients with an improvement of disability at follow up. Y axis: $PKBP_{ND}$ load (a); BH volume load and $BHPK^+$ volume load (b). Independent Samples T-Test.

References

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Innis *et al.*, J Cereb Blood Flow Metab 2007;27:1533-9
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CONCLUSIONS

In this study we used PK-PET heterogeneity within BHs as an *in vivo* marker of microglial/macrophage activation, to refine our understanding of the contribution of BHs to MS disability. We found that microglial/macrophage activation in MS BHs, determined by $PKBP_{ND}$, showed a high degree of heterogeneity and that only in progressive patients did the degree of activation correlate with disability and prognosis. In relapsing MS the level of $PKBP_{ND}$ was higher in the smaller lesions and not associated with disability.

Table 2: Black holes population

Black Holes	$BHPK^+$ Number (% of total) Mean per patient (SD)	$BHPK^0$ Number (% of total) Mean per patient (SD)	Total
Relapsing	510 (41.1) 51.0 (38.2)	162 (13.0) 16.2 (11.9)	672
Progressive	437 (35.2) 48.6 (41.7)	133 (10.7) 14.8 (10.0)	570
Total	947 (76.2)	295 (23.8)	1242
IST-T	*ns*	*ns*	

$BHPK^+$: Black Holes PK enhancing; $BHPK^0$: Black Holes PK non-enhancing; SD: Standard Deviation; EDSS: Expanded Disability Status Scale; IST-T: Independent Samples T-Test; MS: multiple Sclerosis; PET: Positron Emission Tomography; FU: Follow-Up; *ns: non-significant*.

MRI T1 black holes are not associated with disability in this population

Table 2: a total of 1,242 BHs were identified.

The BH lesion load, as measured by MRI, did not correlate with disability, age of onset or disease length in the total population or in relapsing and progressive groups analysed separately

Smaller volume MRI T1 black holes have higher PK binding in relapsing patients

In relapsing group, the correlation between the $PKBP_{ND}$ and $BHPK^+$ lesion load was r=-0.781; *p<0.01* (Fig. 4)

In relapsing group, the correlation between the $PKBP_{ND}$ and $BHPK^+$ volume within the 510 $BHPK^+$ was r=-0.101, *p<0.05*.

PK binding in MRI T1 black holes correlates with disability in progressive patients

A significant positive correlation between the $PKBP_{ND}$ in $BHPK^+$ and EDSS was found only in the progressive population: r = 0.818 (*p<0.01*, Fig. 5)

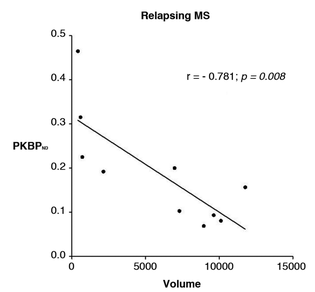

Figure 4

Correlation between $PKBP_{ND}$ and $BHPK^+$ lesion load in relapsing patients.

Figure 5

Correlation between BH $PKBP_{ND}$ and EDSS in progressive patients.