Detection of amyloid plaques in patients with post-stroke dementia

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KEY MESSAGES

1. Using ^{11}C-Pittsburgh Compound B (PiB) positron emission tomography (PET), Alzheimer's disease pathology was found in one-fifth of patients with post-stroke dementia.
2. Patients with Alzheimer's disease pathology had a more progressive cognitive decline over 3 years after stroke or transient ischaemic attack.
3. In patients with post-stroke dementia, PiB PET may be used to guide treatment decision, as those with significant Alzheimer's disease pathology may be more responsive to anti–Alzheimer's disease drugs than those without.

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Introduction

Cognitive impairment is a common sequel to stroke; the rate of post-stroke dementia is 6% to 30%. As a predictor of long-term mortality and functional disability (independent of physical impairment), post-stroke dementia poses a huge economic and social burden in developed countries. Cerebrovascular disease may not be the only factor responsible for the cognitive decline following stroke/transient ischaemic attack. Alzheimer's disease pathology may also play a role in post-stroke dementia. Amyloid plaques are a pathological hallmark of Alzheimer's disease. Cerebrovascular lesions and amyloid frequency co-exist with ageing. ^{11}C-Pittsburgh Compound B (PiB) positron emission tomography (PET) can detect amyloid plaques in Alzheimer's disease patients with high sensitivity and specificity.[1] Alzheimer's disease treatment (eg acetylcholinesterase inhibitors) may be more beneficial in patients with mixed dementia than in those with pure vascular dementia. Therefore, determining the presence of concurrent Alzheimer's disease among patients with post-stroke dementia has clinical implications.

This study aimed to determine the frequency of amyloid plaques in patients with post-stroke dementia, and whether the cognition of post-stroke dementia patients with amyloid plaques declines faster than those without.

Methods

This study was conducted from January 2010 to June 2013. A total of 75 patients with stroke or transient ischaemic attack 3 months after hospital admission were recruited and followed up annually for 3 years.[2] Patients underwent PiB PET at 3 months and were classified as PiB+ (characteristic of Alzheimer's disease) or PiB-. Cognition was assessed yearly using the Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-cog).

Results

Of the 75 patients, 14 (18.7%) were PiB+. At baseline (3 months after stroke), three patients could not complete the ADAS-cog assessment. After 1 year, eight patients died, and nine patients could not complete the ADAS-cog assessment due to poor health, and two patients refused further follow-up. Eventually, 53 subjects completed serial ADAS-cog assessments at year 1. Overall, subjects who withdrew had more impaired cognitive function than those who completed the study. The PiB+ patients had a lower education level but a higher rate of having a genotype of the APOEε4 allele (a genetic risk factor for Alzheimer's disease) [Table 1].

The PiB+ and PiB- groups did not differ significantly in ADAS-cog score (P=0.069) at different time points (P=0.562) after adjustment for education level and genotype of ApoE, or in the cognitive decline rate at 1 year (P=0.499), or in MMSE score at 1 year.

In 60 patients, cognitive change over 3 years was assessed using MMSE. The PiB+ and PiB- groups were comparable in the rates of lost to follow-up (7.1% vs 24.2%, P=0.277) and death (7.1% vs 16.1%, P=0.678). Overall, subjects who withdrew had comparable clinical characteristics with those who completed the study. The PiB+ patients were older (P=0.037) and had a lower education level

(P=0.013) and a higher rate of genotype of ApoE ε4 allele (P=0.023). Because the age and education level had potential effects on cognition, they were treated as covariates in longitudinal analysis to evaluate changes between the two groups.

During 3 years of follow-up, cognition declined over time in the PiB+ and PiB- groups (Table 2 and Fig). The change in MMSE score at different stages differed significantly between PiB+ and PiB- groups (P=0.025, Table 2). In the PiB+ group, the MMSE score continued to decline over time at a relatively consistent rate. In contrast, the score in the PiB- group declined initially from baseline to year 1, but levelled off during the following 2 years (Fig). The rate of decline of MMSE score in the PiB+ and PiB- groups was comparable between baseline and year 1 (P=0.324), but the PiB+ group had a faster rate of decline between year 1 and year 2 (P=0.068), and significantly greater between year 2 and year 3 (P=0.005). Therefore, the mean MMSE score at 3 years was lower in PiB+ than PiB- patients (11.8±5.9 vs 17.2±6.8, P=0.049), and the total decline in MMSE score at 3 years was greater in PiB+ than PiB- patients (-5±6 vs -1.8±4.3, P=0.044).

Discussion

Abnormal amyloid deposits may play a role in determining the long-term progression of cognitive impairment in patients with stroke or transient ischaemic attack. In the early stage after stroke, cognition of both PiB+ and PiB- patients declined. Yet, cognition of PiB+ patients continued to decline in the long term, while that of PiB- patients remained relatively stable. In addition, the prevalence of concurrent amyloid deposits in post-stroke dementia patients was 18.7%.

The use of PiB PET enables valid diagnosis in living persons and overcomes the limitations of post-mortem studies with their retrospective nature, long time lag from dementia onset, and uncertainty about the temporal relationship between the development of brain lesions and dementia onset.

Limitations of this study included a high attrition rate during the 1-year study period. There were 22 (29.3%) patients who failed to return for

TABLE 1. Demographic and clinical characteristics of patients with positive or negative PiB positron emission tomography outcome at 1 year

Parameter	Mean±SD or No. (%) of patients		P value
	PiB+ (n=12)	PiB- (n=41)	
Age (years)	78.7±3.8	75.7±8.3	0.084
No. (%) of females	5 (41.7)	18 (43.9)	0.891
Education (years)	1.7±2.1	4.9±4.7	0.026
With APOEε4 allele*	7 (58.3)	4 (11.4)	0.003
Mortality	1/14 (7.1)	6/61 (9.8)	1
Dropout rate	2/14 (14.3)	20/61 (32.8)	0.21

* Data were not available for six subjects

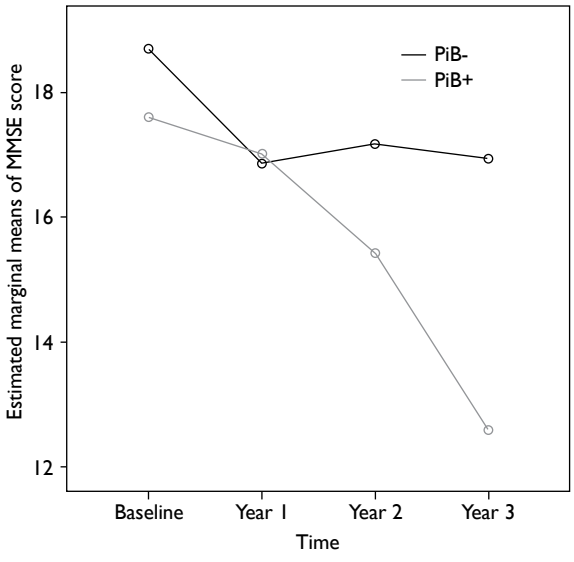

FIG. Cognitive decline over 3 years in terms of Mini-Mental State Examination (MMSE) score in patients with positive or negative PiB positron emission tomography outcome

TABLE 2. Change in Mini-Mental State Examination (MMSE) score in patients with positive or negative PiB positron emission tomography outcome

MMSE score	Mean±SD (adjusted mean±SD)		P value
	PiB+ (n=13)	PiB- (n=47)	
Baseline	16.7±5 (17.6±6.5)	19±6.6 (18.7±6.3)	0.599
Year 1	16.1±5 (17±5.9)	17.1±6.1 (16.9±5.7)	0.934
Year 2	14.5±5.8 (15.4±6.6)	17.4±6.6 (17.2±6.4)	0.406
Year 3	11.8±5.9 (12.6±6.8)	17.2±6.8 (16.9±6.6)	0.049
Change			
Baseline to year 1	-0.6±4.5 (-0.6±4)	-1.8±3.6 (-1.8±3.8)	0.324
P value	1	0.006	
Year 1 to year 2	-1.6±2.3 (-1.6±3.2)	0.3±3.2 (0.3±3.1)	0.068
P value	0.211	1	
Year 2 to year 3	-2.7±2.5 (-2.8±2.8)	-0.3±2.7 (-0.2±2.7)	0.005
P value	0.028	1	
Baseline to year 2	-2.2±5.3 (-2.2±4.4)	-1.5±3.8 (-1.5±4.3)	0.64
P value	0.872	0.059	
Year 1 to year 3	-4.3±2.9 (-4.4±3.6)	0.04±3.6 (0.08±3.5)	<0.001
P value	0.002	1	
Baseline to year 3	-5±6 (-5±5)	-1.8±4.3 (-1.8±4.8)	0.044
P value	0.078	0.045	

a second ADAS-cog assessment. We could not infer the cognitive progression of the 19 patients who did not attend follow-up. It is probable that their cognitive symptoms were too severe to communicate, but the possibility of other physical pathology causing aphasia could not be omitted. In addition, because the prevalence of PiB+ was lower than our preliminary estimation, the final number of PiB+ patients was small. Hence, a larger study is needed to verify the findings of our study.

Conclusions

Concurrent amyloid pathology is found in about one-fifth of patients with stroke or transient ischaemic attack and dementia; it can exert a negative long-term impact upon cognitive progression. The use of PiB PET enables detection of amyloid plaques in patients with post-stroke dementia. In those with concurrent amyloid plaques, Alzheimer's disease treatment may help to slow cognitive decline in the long term.

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