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Re-evaluation of clinical dementia diagnoses with pittsburgh compound B positron emission tomography.

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Link to publication

Original Research Article

Re-Evaluation of Clinical Dementia Diagnoses with Pittsburgh Compound B Positron Emission Tomography

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Key Words

Alzheimer's disease · Dementia with Lewy bodies · Frontotemporal dementia · β-Amyloid · Amyloid biomarker · Pittsburgh compound B positron emission tomography · [18F]Fluoro-2-deoxy-D-glucose positron emission tomography · Neuropsychological tests · Trail Making Test, part A · Episodic memory

Abstract

Objectives: There is an overlap regarding Pittsburgh compound B (PIB) retention in patients clinically diagnosed as Alzheimer's disease (AD) and non-AD dementia. The aim of the present study was to investigate whether there are any differences between PIB-positive and PIB-negative patients in a mixed cohort of patients with neurodegenerative dementia of mild severity regarding neuropsychological test performance and regional cerebral glucose metabolism measured with [18F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET). ***Methods:*** Eighteen patients clinically diagnosed as probable AD or frontotemporal dementia were examined with PIB PET, FDG PET and neuropsychological tests and followed for 5–9 years in a clinical setting. ***Results:*** The PIB-positive patients (7 out of 18) had slower psychomotor speed and more impaired visual episodic memory than the PIB-negative patients; otherwise performance did not differ between the groups. The initial clinical diagnoses were changed in one third of the patients (6 out of 18) during follow-up. ***Conclusions:*** The subtle differences in neuropsychological performance, the overlap of hypometabolic patterns and clinical features between AD and non-AD dementia highlight the need for amyloid biomarkers and a readiness to re-evaluate the initial diagnosis.

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Dement Geriatr Cogn Disord Extra 2013;3:472–481

DOI: 10.1159/000356273

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Introduction

Alzheimer's disease (AD) is characterised by gradual-onset and slowly progressive decline of memory, language, praxis, perception, logical thinking and executive function [1, 2]. Decline in episodic memory is an early symptom in AD [3], but as the disease progresses, all memory systems deteriorate, including short-term memory, semantic memory and procedural memory. However, AD varies widely in clinical course and rate of cognitive decline [4–6]. There is a significant proportion of AD cases identified using strict clinical diagnostic criteria that show non-AD pathology, most commonly dementia with Lewy bodies (DLB) but also frontotemporal dementia (FTD) or other dementia disorders [7]. Reductions in regional cerebral glucose metabolism (rCMRglu) measured with [^{18}F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) reflect affected areas of the brain. AD is typically associated with hypometabolism in the posterior cingulate and parietotemporal cortices and in the frontal lobes in advanced disease [8]. In cohort studies with post mortem diagnosis on AD and non-AD dementia patients, FDG PET identified the AD cases with a sensitivity of about 90% and a specificity of 80% [9]. There is a large overlap in the clinical features, structural and functional imaging between different dementia disorders, and it is sometimes a challenge for the clinician to differentiate ante mortem between AD and non-AD dementia disorders. The clinical diagnosis of probable AD according to current diagnostic criteria has a sensitivity of approximately 80% and a specificity of 70% [10].

Deposition of β-amyloid (Aβ) in senile plaques is a key characteristic in AD together with intraneuronal accumulation of neurofibrillary tangles. N-methyl[^{11}C]2-(40-methylaminophenyl)-6-hydroxybenzothiazole (Pittsburgh compound B; PIB) is an amyloid-binding PET tracer used to detect amyloid depositions in vivo in the human brain [11]. Enhanced PIB retention is believed to be an early event in AD, and the uptake does not increase substantially as the disease deteriorates [12]. PIB retention is not specific for AD. Patients with DLB often have high cortical PIB binding, since senile plaques frequently accompany the α-synuclein aggregations [13]. Further, even substantial proportions of cognitively healthy older subjects and patients with mild cognitive impairment are PIB positive (PIB+), especially APOE ε4 carriers [14], probably indicating preclinical AD.

rCMRglu as measured by FDG PET as well as neuropsychological performance in PIB+ and PIB-negative (PIB–) patients, suffering from different neurodegenerative dementia disorders, are less well described. The aim of the present study was to address this topic and re-evaluate the clinical diagnoses after long-term follow-up.

Methods

Study Design

Eighteen outpatients at the Memory Clinic, Department of Geriatrics, Uppsala University Hospital, who previously had participated in trials with PIB PET and FDG PET scans during 2003–2007 and had evidence of neurodegenerative disease were included [15, 16]. The study protocol received ethical committee's approval and all participants or their legally acceptable representatives provided written informed consent. At baseline, 10 of the patients were diagnosed as AD according to the NINCDS-ADRDA [1] and DSM-IV criteria [2], 6 patients were diagnosed as behavioural variant FTD (bvFTD) and 2 as semantic dementia (SD) according to Neary et al.'s criteria [17]. All patients had CT scans consistent with their clinical diagnosis. They were examined with PIB PET and FDG PET, and an experienced neuropsychologist carried out and assessed all neuropsychological investigations. Mini-Mental State Examination (MMSE) scores at baseline and follow-ups, last available dementia stage and diagnosis,

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and date of death were collected from medical records. All patients were followed for 5–9 years, or to death. DLB patients were diagnosed according to McKeith et al.'s criteria [18]. Unspecified dementia (dementia UNS) was defined as dementia (International Statistical Classification of Diseases-10; ICD-10) without fulfilling any specific dementia diagnosis despite a comprehensive evaluation.

Positron Emission Tomography

Patients were examined with radiotracers in the order PIB and FDG on the same day after at least a 4-hour fasting period before PET. The PET scans were performed using Siemens ECAT EXACT HR+ scanners (CTI PET Systems, Inc., with an axial field of view of 155 mm, providing 63 contiguous 2.46-mm slices with 5.6-mm transaxial and 5.4-mm axial resolution). The orbitomeatal line was used to centre the subject's head. The scanner protocol for transmission, emission and reconstructions as well as tracer doses were the same as used in previous studies at Uppsala Imanet [11, 12]. The subjects were given 238 ± 31 MBq of FDG and 238 ± 71 MBq of PIB. Production of FDG and PIB was carried out according to the standard good manufacturing process at Uppsala Imanet. Synthesis of PIB was performed by means of the method described previously [11].

All PET investigations were analysed using identical standardised regions of interest (ROIs) in the brain and each subject had its set of ROIs individually delineated. All scans were visually characterised as either PIB+ or PIB− by an experienced PIB PET radiologist. The set of ROIs applied for statistical analyses and data management has been described in detail in earlier studies [15, 16]. The CMRglu values were normalised to the pons value (ROI/ref.). For PIB, the mean uptake values of the ROIs obtained in the late time interval (40–60 min) were normalised to the corresponding uptake in the cerebellar cortex, which was chosen as reference region (ROI/ref.) [19]. Scans were characterised as PIB+ both by visual inspection and by a mean ratio >1.6 nCi/ml, obtained by calculating a mean value of the following areas: the frontal, parietal, temporal and posterior cingulum (ROI/ref.). PIB− scans were also characterised both on visual inspection and by a mean ratio <1.6 nCi/ml of the same areas (ROI/ref.). This threshold value is based on the values from healthy controls (mean value + 1 standard deviation) in previous studies [12]. Four FDG PET scans of PIB− FTD patients (2 bvFTD and 2 SD) were characterised by visual inspection only due to technical failure.

Neuropsychological Protocol

Fourteen psychometric tests were used to assess the following skills: *logical thinking:* Arithmetic [Wechsler Adult Intelligence Scale-Revised (WAIS-R) [20] and WAIS 3rd edition (WAIS-III)] [21]; *verbal function:* word fluency test (FAS), object naming (Boston Naming Test), Similarities (WAIS-R, WAIS-III) and Information (WAIS-R, WAIS-III); *visuospatial function:* Clock Drawing with pre-drawn clock faces according to Luria [22] and Block Design (WAIS-R, WAIS-III); *psychomotor speed/attention:* Trail Making Test, part A (TMT A) and Digit Span (WAIS-R, WAIS III) and *memory:* episodic verbal memory: Claeson-Dahl Test for Learning and Memory, 5 out of 10 trials with respect to the patients' limited learning capacity [23] and visual episodic memory: Rey-Osterrieth Complex Figure, immediate recall.

Statistical Analyses

Comparisons of data from the psychometric tests and rCMRglu between PIB+ and PIB− patients were performed by the Mann-Whitney U test. Since some of the participants in the study were assessed with the WAIS-R and others with the WAIS-III, quotas were calculated in order to be able to compare the results. The quotas were calculated as obtained score on the subtest divided by the total possible test score on the subtest. The analyses of correlations between FDG PET data, PIB PET data and neuropsychological test results were conducted

Dement Geriatr Cogn Disord Extra 2013;3:472–481

DOI: 10.1159/000356273

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Table 1. Baseline characteristics

Patient No.	Gender	Age at baseline, years	Education, years	PIB retention[a]	CT: atrophy	FDG PET: parietotemporal hypometabolism[b]	Baseline clinical diagnosis
1	f	73	14	+	temporal atrophy, bilateral	+	AD
2	m	69	14	+	mild frontotemporal atrophy, bilateral	+	AD
3	m	66	15	+	within normal limits	+	AD
4	m	70	7	+	mild temporal atrophy, bilateral	+	AD
5	m	74	15	+	within normal limits	+	AD
6	m	69	15	+	within normal limits	+	AD
7	f	68	7	+	mild frontal atrophy, bilateral	–	bvFTD
8	m	67	12	–	within normal limits	+	AD
9	m	65	10	–	within normal limits	–	AD
10	f	71	7	–	frontoparietal atrophy, bilateral	+	AD
11	m	78	12	–	within normal limits	–	AD
12	m	64	10	–	prominent frontotemporal atrophy, bilateral	+	bvFTD
13	m	60	18	–	within normal limits	–	bvFTD
14	m	72	8	–	within normal limits	–	bvFTD
15	f	62	9	–	moderate temporal atrophy, bilateral	+	SD
16	f	52	12	–	mild frontal atrophy, bilateral	–	bvFTD
17	m	71	7	–	temporal atrophy, most prominent on right side	+	bvFTD
18	f	68	9	–	unspecified mild atrophy	–	SD

[a] Scans were characterised as PIB+ both on visual inspection and by a mean ratio >1.6 nCi/ml obtained by calculating a mean value of the following areas: the frontal, parietal, temporal and posterior cingulum (ROI/ref.).
[b] Typical pattern of regional glucose metabolism in AD.

using Spearman coefficient of correlation. The α level was set to 0.05. Adjustments for multiple comparisons were not made since this was an exploratory study with a small number of patients.

Results

Baseline characteristics are shown in table 1. The PIB+ and the PIB– groups were well matched concerning gender, age and performance on the MMSE. The median length of education was 4 years longer in the PIB+ subjects. One PIB– SD patient scored only 10 points on the MMSE, but was classified as having a mild dementia since she was still able to perform complex activities of daily living. Parietotemporal hypometabolism was present in 6 of 7 PIB+ and in 5 of 11 PIB– patients. During follow-up, the clinical diagnoses were changed in 6 patients out of which 3 patients were re-diagnosed from AD to DLB (table 2). Two of these patients were PIB– and had normal cerebrospinal fluid (CSF) Aβ, tau and p-tau at baseline. Another 2 PIB– patients with a baseline AD diagnosis had high CSF tau and p-tau, but normal levels of CSF Aβ. Autopsy confirmed the FTD diagnosis in 1 PIB– patient, AD diagnosis in 2 PIB+ patients and DLB diagnosis combined with presence of senile plaques in another PIB+ patient.

PIB+ patients had significantly lower psychomotor speed measured by time to completion on TMT A compared to PIB– patients and more impaired visual episodic memory. The median score on verbal episodic memory was lower in the PIB+ group compared to the PIB– group, although not significantly. Otherwise, the results did not differ between groups (table 3).

rCMRglu was approximately 30% lower in the parietal cortices in PIB+ patients compared to PIB– patients, although not significantly. rCMRglu in the frontal and temporal cortices was similar in the two groups (table 4). Patients with a long education (>10 years) had more

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Table 2. Baseline diagnoses and follow-up data (5–9 years)

Patient No.	Baseline clinical diagnosis[a]	Final clinical diagnosis	Dementia stage at baseline (MMSE score)	Dementia stage 1–2 years (MMSE score)	Dementia stage 3–5 years (MMSE score)	Dementia stage ≥6 years (MMSE score)
1	AD +	AD[b]	Mi (23)	Mo (23)	Se (16)	†
2	AD +	AD	Mi (24)	Mi (25)	Mo (16)	Mo (10)
3	AD +	DLB[b]	Mi (27)	Mo (10)	Se (–)	†
4	AD +	AD[b]	Mi (22)	Mi (18)	Se (9)	†
5	AD +	AD	Mi (28)	Mi (29)	Mi (26)	Mo (20)
6	AD +	AD	Mi (19)	Mo (15)	–	–
7	bvFTD +	dementia UNS	Mi (27)	Mi (23)	Mo (–)	Se (–)
8	AD –	DLB	Mi (30)	Mi (30)	Mi (24)	Mo (20)
9	AD –	DLB	Mi (28)	Mo (22)	Se (–)	†
10	AD –	dementia UNS	Mi (28)	Mi (24)	Mi (23)	Mo (18)
11	AD –	dementia UNS	Mi (23)	Mi (22)	Mo (20)	–
12	bvFTD –	bvFTD	Mi (27)	Mi (29)	Mi (29)	Mi (–)
13	bvFTD –	bvFTD	Mi (29)	Mi (–)	Mo (–)	Se (–)
14	bvFTD –	bvFTD	Mi (30)	Mi (29)	†	†
15	SD –	SD	Mi (29)	Mi (22)	Mo (–)	Se (–)
16	bvFTD –	bvFTD	Mi (29)	Mi (30)	Mi (26)	Mi (–)
17	bvFTD –	bvFTD[b]	Mi (19)	Se (–)	†	†
18	SD –	SD	Mi (10)	Mo (–)	Se (–)	†

Mi = Mild dementia; Mo = moderate dementia; Se = severe dementia.
[a] + or – indicate PIB+ or PIB–. [b] Diagnosis confirmed at autopsy. † Dead at follow-up.

Table 3. Neuropsychological test results in PIB+ and PIB– patients (n = 18)

Neuropsychological tests	PIB+ (n = 7)	PIB– (n = 11)	p level
Logical thinking			
Arithmetic[a, b]	0.45 (0.32–0.91)	0.47 (0.07–0.79)	0.84
Verbal function			
FAS[b]	34 (3–56)	26 (3–39)	0.29
Boston Naming Test[b]	17.5 (12–24)	19 (0–26)	0.72
Information[a, b]	0.61 (0.36–0.79)	0.68 (0.07–0.83)	0.89
Similarities[a]	0.42 (0.03–0.76)	0.33 (0–0.81)	0.62
Visuospatial function			
Clock Drawing	2.5 (1.5–4)	2 (0.5–5)	0.27
Block Design[a]	0.32 (0.01–0.56)	0.40 (0.16–0.67)	0.52
Psychomotor speed/attention			
TMT A time to completion, s	95 (61–145)	65 (34–99)	0.03*
Digit Span forward	5 (5–6)	6 (4–7)	0.53
Digit Span backward	4 (2–6)	4 (0–6)	0.38
Memory			
Verbal episodic memory[b, c]	16 (0–30)	24 (9–39)	0.16
Visual episodic memory[d]	0 (0–4.5)	9 (0–25)	0.04*

Data are medians with ranges in parentheses. * Significant difference between PIB+ and PIB– patients, Mann-Whitney U test.
[a] Test result quota (score/maximal score). [b] Seventeen patients due to missing data. [c] Claeson-Dahl's test. [d] Rey-Osterrieth Complex Figure memory.

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Table 4. Mean rCMRglu values in the pons in PIB+ and PIB– patients (n = 14)

	PIB+ (n = 7)	PIB– (n = 7)
Frontal ctx dx	1.34 (1.03–1.51)	1.46 (1.01–1.66)
Frontal ctx sin	1.36 (1.12–1.50)	1.54 (1.03–2.09)
Parietal ctx dx	1.05 (0.93–1.59)	1.54 (0.72–1.76)
Parietal ctx sin	1.13 (0.88–1.55)	1.59 (0.74–1.81)
Temporal ctx dx	0.92 (0.88–1.23)	1.06 (0.74–1.39)
Temporal ctx sin	0.97 (0.84–1.21)	1.15 (1.00–1.39)

Data are medians with ranges in parentheses indicated as µmol/min/100 ml. ctx = Cortex; dx = dexter; sin = sinister.

Table 5. Spearman rank order correlation between rCMRglu on FDG PET and neuropsychological tests in 14 patients

Neuropsychological tests	Fr ctx dx	Fr ctx sin	Par ctx dx	Par ctx sin	Tmp ctx dx	Tmp ctx sin
Arithmetic[a]	0.53	0.32	0.69**	0.48	0.05	0.08
FAS[a]	–0.02	–0.11	0.03	–0.10	–0.20	–0.46
Boston Naming Test[a]	0.05	0.02	0.17	0.24	0.48	0.49
Information	0.07	–0.12	0.08	0.13	0.06	–0.04
Similarities	0.27	0.23	0.56*	0.47	0.17	0.33
Clock Drawing	–0.12	–0.20	–0.08	–0.14	0.07	–0.19
Block Design	0.37	0.26	0.35	0.44	–0.11	0.44
TMT A time to completion	–0.56*	–0.44	–0.62*	–0.66**	–0.14	–0.54*
Digit Span forward	0.44	0.28	0.41	0.47	0.31	0.50
Digit Span backward	0.22	0.18	0.40	0.26	0.09	0.23
Verbal episodic memory[a, b]	0.51	0.39	0.66**	0.61*	0.21	0.44
Visual episodic memory[c]	0.31	0.18	0.11	0.25	0.25	0.26

ctx = Cortex; dx = dexter; fr = frontal; par = parietal; sin = sinister; tmp = temporal. * p < 0.05; ** p < 0.01. [a] Thirteen patients due to missing data. [b] Claeson-Dahl's test. [c] Rey-Osterrieth Complex Figure memory.

pronounced hypometabolism in the temporal lobes and scored higher on Information, but did not differ in performance on any other psychometric test compared to subjects with a short education (≤10 years) (data not shown).

Performances on Arithmetic and Similarities were both positively correlated with CMRglu in the right parietal cortex. Mental speed measured by time to complete TMT A was inversely correlated with CMRglu in the right and left parietal cortices, the right frontal cortex and the left temporal cortex. Performance on the verbal episodic memory test correlated with CMRglu in the right and left parietal cortices; otherwise, the test results did not differ between groups (table 5). Correlation analyses revealed no relations between PIB and rCMRglu.

Discussion

In this study, PIB+ dementia patients, i.e. with evidence of AD pathology consisting of fibrillised Aβ, were more impaired regarding psychomotor speed and visual episodic memory compared to PIB– dementia patients, in spite of a higher educational attainment. Poor perfor-

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mance on the TMT A time to completion is not exclusively seen in AD but is also seen in subjects with high age and low educational level [24] as well as in different psychiatric and other dementia disorders [25, 26]. Our significant result is probably due to slower psychomotor speed in the AD patients compared to the FTD patients. Previous studies have shown conflicting results, with equal [27], worse [28–30] or better [31] performance on psychomotor speed tests in AD compared to FTD. The performance on TMT A differs between various subtypes of FTD, and patients with bvFTD seem to be faster than those with temporal variants, i.e. SD and progressive non-fluent aphasia [28]. Further, performance on TMT A also depends on disease stage. In one study, AD subjects in a group with more severe dementia performed better on TMT A compared with FTD, but were significantly slower than FTD patients in the mildly demented group (MMSE ≥20) [32].

Impaired episodic memory is the most specific early symptom of AD, and performance on memory tests differs from other neurodegenerative dementia disorders such as FTD [33] and DLB [34] on a group level. As expected, we could demonstrate a difference between PIB+ and PIB– patients in visual episodic memory and a tendency to a difference in verbal episodic memory. In contrast, results in tests assessing verbal function, arithmetic and visuospatial function were the same.

Parietal lobe lesions are associated with impaired object recognition and inability to use topographic information, dyscalculia, apraxia and right-left confusion. Our results are in concordance with the involvement of the parietal lobes in calculation, abstract verbal thinking, logical reasoning [35, 36] and processing numerical tasks as in the TMT [37]. They are also involved in episodic memory retrieval [38]. Performance on the TMT has mainly been linked to a left-sided frontal activation [39]. We found correlations between performance on TMT A and CMRglu in the frontal cortices, but without left-side dominance.

Although not significant, PIB+ patients had 30% lower CMRglu in the parietal cortices compared to PIB– patients, i.e. the typical hypometabolic pattern in AD. As expected, there were no relations between PIB and rCMRglu due to the mixture of diagnoses and since PIB retention early reaches a plateau in AD [40]. There is a good correspondence between in vivo PIB PET and post mortem region-matched assessment of plaques [41]. Moreover, there is a high concordance between high PIB retention and low CSF Aβ [16, 42]. However, high PIB retention is not exclusively seen in AD and is, for example, common in LBD [13], and 1 out of 3 LBD patients in our study was PIB+. Further, the proportion of PIB+ subjects increases with age, and about a third of cognitively healthy older volunteers have PIB+ scans [43], probably indicating preclinical AD. Consequently, the presence of biomarkers indicating brain amyloidosis should not be considered as a conclusive evidence of the cause of cognitive impairment in a dementia disorder [44].

Especially in the early stages of different dementia diseases, the assessment of the clinical diagnosis is a challenge. There are large variations in the cognitive profiles of AD dementia.

FTD sometimes presents similarly to AD with primarily impaired episodic memory and spatial disorientation [45]. The parkinsonism in LBD is not always prominent, and the patients and their caregivers do not always report either hallucinations or fluctuating attention. Other dementia disorders such as argyrophilic grain disease and neurofibrillary tangle-predominant dementia cause 5–10% of dementia in high age but are not possible to diagnose ante mortem [46–48]. Further, mixed pathologies are common in AD patients, especially among the oldest [49, 50]. In the present study, the diagnosis was changed for 6 out of 18 patients after PIB PET, FDG PET and repeated clinical examinations, in accordance with previous studies [51, 52].

One obvious limitation of our study was the small number of patients, and larger studies would most likely identify more subtle differences between PIB+ and PIB– patients concerning performance on psychometric tests and rCMRglu. Another limitation is that the design did not

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DOI: 10.1159/000356273

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allow adjustment for differences in educational level and degree of cognitive impairment. According to the cognitive reserve hypothesis, patients with a longer education cope better with pathologic changes in dementia because of a higher IQ and premorbid cognitive resources [53], and this probably interferes with the test performance in the present study. Further, although all patients had a mild dementia at baseline, further adjustments for differences in disease state were not possible.

In conclusion, we followed 18 patients with mild neurodegenerative, non-vascular dementia who underwent PIB PET, FDG PET and a neuropsychological test battery. The initial clinical diagnoses were changed during follow-up in one third of the patients. Immunotherapies for the Aβ protein are under investigation at several sites all over the world, and the possibility of a specific Aβ load-reducing treatment enhances the need for accurate diagnosis and detection of underlying AD pathology. The small differences in neuropsychological performance and the overlap of hypometabolic patterns on FDG PET and clinical features between different clinically diagnosed AD and non-AD dementias highlight the need for amyloid biomarkers (amyloid PET or CSF Aβ) and a readiness to re-evaluate the initial diagnosis.

Acknowledgments

Disclosure Statement

The authors report no conflict of interest.

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