Chapter 8

Dementia mimicking Alzheimer's disease due to a tau mutation: CSF and PET findings

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Abstract

Objective: To illustrate the utility of positron emission tomography (PET) imaging using [^{11}C]PIB and [^{18}F]FDDNP, together with cerebrospinal fluid (CSF) measures of amyloid-β1-42 (Aβ42), total tau (t-tau) and tau phosphorylated at threonine 181 (p-tau) in the *in vivo* diagnosis of specific dementia syndromes.

Methods: Two siblings fulfilling diagnostic criteria for familial Alzheimer's disease (AD) were investigated using [^{11}C]PIB and [^{18}F]FDDNP PET, in combination with CSF measures of Aβ42, t-tau and p-tau. PET data were compared with paired [^{11}C]PIB and [^{18}F]FDDNP data from age matched sporadic AD patients (n=9) and healthy controls (n=6).

Results: [^{11}C]PIB retention and CSF levels of Aβ42 in both patients resembled those of controls, suggesting the presence of non-amyloid pathology. Genetic testing confirmed the absence of mutations in the *presenilin 1* gene in one patient; subsequent testing revealed the R406W *tau* mutation in both individuals leading to a diagnosis of frontotemporal dementia (FTD). [^{18}F]FDDNP retention broadly correlated with CSF levels of t-tau and p-tau. Despite both individuals harbouring the same mutation, [^{18}F]FDDNP retention and CSF t-tau and p-tau were elevated in one patient but not in the other.

Conclusion: [^{11}C]PIB imaging and CSF measures of Aβ42 are useful in refuting the presence of underlying amyloid pathology. This, in combination with elevated levels of CSF t-tau and p-tau, has potential value in differential diagnosis of FTD from AD.

Introduction

The prospect of disease modifying drugs for Alzheimer's disease (AD) means that distinguishing AD both from normal ageing and from different forms of dementia is becoming increasingly important. Potential *in vivo* biomarkers of AD pathology including positron emission tomography (PET) with amongst others, [^{11}C]PIB (*1*) and [^{18}F]FDDNP (*2*), and cerebrospinal fluid (CSF) analysis (*3*) are thus the subject of intense study and ongoing validation. Of these, [^{11}C]PIB binding reflects cerebral Aβ load (*1*), and [^{18}F]FDDNP binding is thought to reflect both Aβ plaque and tangle load (*2*). Reduction of amyloid-β1-42 (Aβ42) and increase in levels of total tau (t-tau) and tau phosphorylated at threonine 181 (p-tau) in CSF have been shown to be of diagnostic value in AD (*3*).

Patients with confirmed genetic mutations leading to autosomal dominant inherited dementia syndromes provide a unique opportunity to examine the specificity of such biomarkers *in vivo*. In this report we describe two siblings with progressive cognitive deterioration clinically resembling AD in whom biomarkers suggested the absence of underlying amyloid pathology, a suspicion subsequently confirmed by the identification of the R406W *tau* mutation, leading to a diagnosis of frontotemporal dementia (FTD) (*4*).

Methods

Subjects

Two siblings with an AD clinical phenotype were included in this imaging study. Six patients fulfilling criteria for probable sporadic AD, and nine healthy controls were used to provide normative imaging data (*5*). All subjects received a standard dementia screening including medical history, physical and neurological examinations, screening laboratory tests, brain MRI, and neuropsychological testing. Clinical diagnosis was established according to standard consensus criteria in a multidisciplinary meeting. All AD patients met NINCDS-ADRDA (*6*) criteria for probable AD. Written informed consent was obtained from all subjects. The study was approved by the Medical Ethics Review Committee of the VU University Medical Centre Amsterdam.

CSF analysis

CSF Aβ42, t-tau and p-tau were measured with Innotest (Innogenetics, Ghent, Belgium) sandwich ELISAs as described previously (*3*).

Positron emission tomography

Dynamic 90 minutes [^{11}C]PIB and [^{18}F]FDDNP PET scans were performed as described previously (*5*) after injection of approximately 390 MBq [^{11}C]PIB with a specific activity (SA) of 41 GBq/μmol and 194 MBq [^{18}F]FDDNP with an SA of 35 GBq/μmol. [^{11}C]PIB and [^{18}F]FDDNP parametric images of binding potential (BP$_{ND}$), a quantitative measure of specific binding, were

generated using cerebellar grey matter as reference tissue. For regional analyses, the volume weighted average BP_{ND} of frontal, parietal and temporal cortex, medial temporal lobe (MTL) and posterior cingulate was calculated. A global cortical region of interest (ROI) was defined as the volume weighted average of all aforementioned regions. PET results were compared with paired [11C]PIB and [18F]FDDNP data of age matched AD patients and healthy controls included in a previous study (5).

Genetic testing

Following appropriate counselling, testing for specific mutations in presenilin 1, the gene most frequently associated with familial AD was performed in patient 1; screening for mutations in the tau gene was subsequently performed in both patients. Exon 13 of MAPT including intron/exon boundaries was amplified from genomic DNA according to the following conditions (7): reaction volume was 15 µl, with a final concentration of 10 mM Tris-HCL (pH8.3), 50 mM KCl, 1,5 mM MgCl2, and 250 µM dNTPS; Platinum Taq polymerase at 0,35 units/15µl; primers at 10pmol/µl and 15 ng template genomic DNA. PCR reactions were sequenced in both strands and run on an automated DNA sequencer (ABI 3730).

Results

Patient 1

The patient was a 61-year-old man who complained of progressive episodic memory impairment since seven years. There was a positive family history of dementia: his grandfather, father, two uncles and one aunt on his father's side all had developed dementia prior to the age of 60. The Mini Mental State Examination (MMSE) score was 29/30. Magnetic resonance
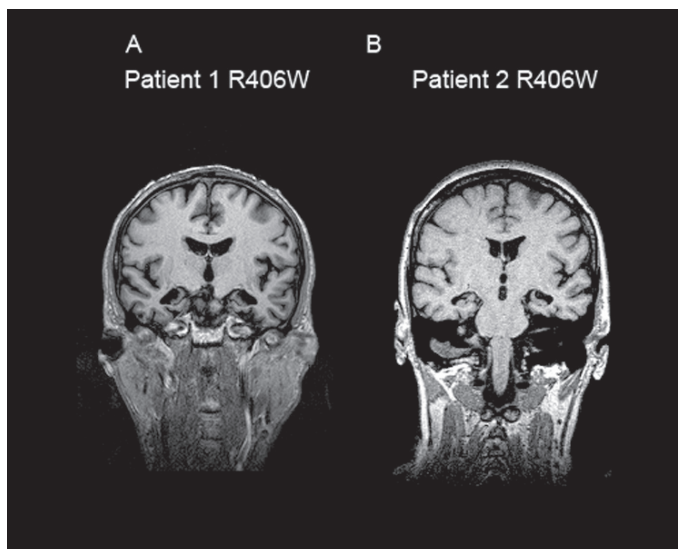

Figure 1: Coronal MRI in R406W mutation patients
Figure 1 illustrates severe, strictly isolated, symmetrical medial temporal lobe atrophy in patients 1 (panel A) and 2 (panel B).

imaging (MRI) of the brain revealed pronounced isolated bilateral, symmetrical medial temporal lobe atrophy, especially in the anterior part (Figure 1 A). Neuropsychological testing revealed problems with registration and retention of verbal information and poor face recognition, with no impairment on executive functions. A clinical diagnosis of amnestic MCI (*8*), probably due to incipient familial AD, was made.

Patient 2

Concurrently, the patient's sister, a 59 year old woman, also sought medical attention for evaluation of cognitive decline. She presented with similar, but more severe complaints than her brother, leading to interference of activities of daily living. The MMSE score was 26/30. MRI of the brain revealed a similar, though more profound, pattern of selective hippocampal atrophy (Figure 1 B). Neuropsychological testing revealed problems with registration and retention
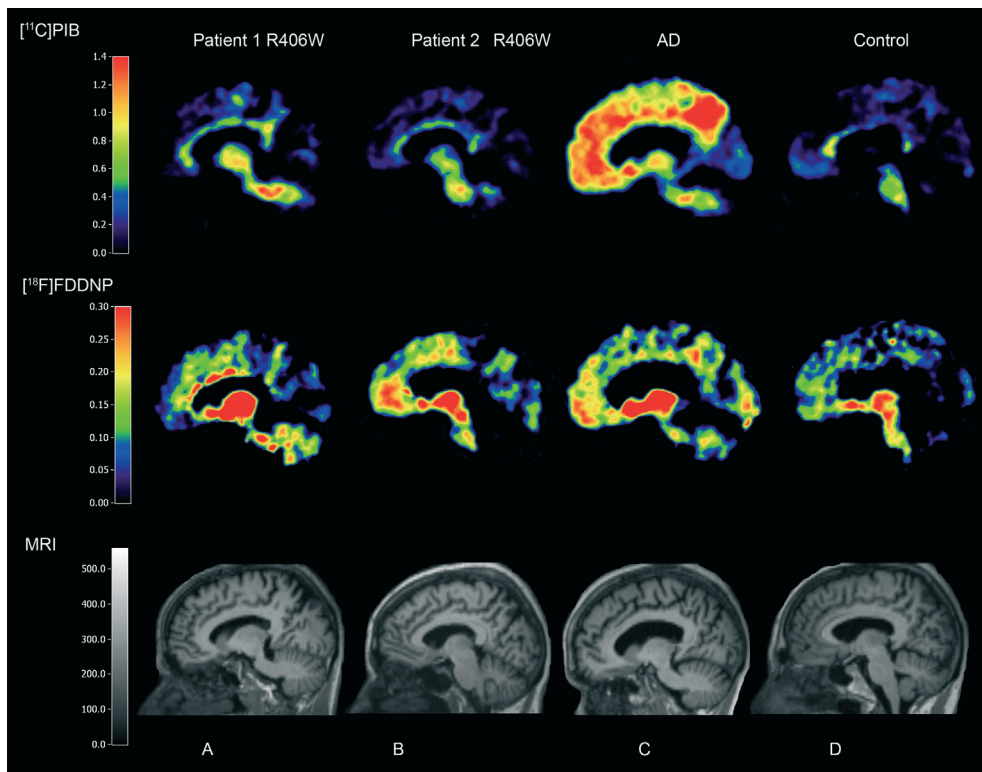

Figure 2: [^{11}C]PIB and [^{18}F]FDDNP PET and MRI in R406W mutation patients together with AD and control

Panel A=patient 1, B=patient 2, C=Alzheimer's disease patient, D=healthy control. Normal [^{11}C]PIB retention in panels A, B and D. Panel C displays high [^{11}C]PIB retention in frontal and parietal regions. Normal [^{18}F]FDDNP retention in panels A and D. Panels B and C display higher frontal [^{18}F]FDDNP retention with more diffuse [^{18}F]FDDNP uptake in panel C.

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of verbal information, with no impairment on executive functions. A clinical diagnosis of AD, probably due to familial AD, was made.

CSF
A lumbar puncture was performed at the initial visit for both patients. CSF Aβ42 levels were within normal limits (patient 1: 933 pg/ml, normal range (*3*) (NR)>495 pg/ml; patient 2: 1026 pg/ml). T-tau and p-tau levels were normal in patient 1 (340 pg/ml, NR<356 pg/ml and 51 pg /ml, NR<54 pg/ml, respectively). Both were elevated in patient 2 (t-tau: 442 pg/ml; p-tau 63 pg /ml)

[^{11}C]PIB and [^{18}F]FDDNP PET
Twenty months after first clinical assessment, patient 1 underwent an [^{11}C]PIB PET scan and thirteen months thereafter, an [^{18}F]FDDNP PET scan was performed. Thirty-three months after first assessment, patient 2 underwent paired [^{11}C]PIB and [^{18}F]FDDNP PET scans. Visual inspection of parametric [^{11}C]PIB images did not reveal abnormal tracer accumulation; inspection of parametric [^{18}F]FDDNP images revealed an indistinct pattern of retention in both siblings (Figure 2, panel A and B). Global and regional [^{11}C]PIB and [^{18}F]FDDNP binding of the 2 siblings was compared with paired [^{11}C]PIB and [^{18}F]FDDNP data of six AD patients (age 62±4 years, MMSE 24±3) and nine healthy controls (age 61±3 years, MMSE 30±1) (*5*). Global and regional [^{11}C]PIB uptake of both patients was similar to that of controls. Patient 1 displayed low [^{18}F]FDDNP uptake, both compared to controls and AD; Patient 2 had an intermediate level of binding, lying within the range of both AD patients and controls (Figure 3). Patient 1 had higher [^{18}F]FDDNP binding than seen in the AD group in the medial temporal lobe; whilst patient 2 displayed increased binding, similar to mean binding in AD, in frontal and parietal lobes and posterior cingulate (Table 1).

Table 1: Regional [^{11}C]PIB and [^{18}F]FDDNP binding data by diagnostic group

Diagnosis	[^{11}C]PIB BP$_{ND}$				[^{18}F]FDDNP BP$_{ND}$			
	Controls	Patient 1	Patient 2	AD	Controls	Patient 1	Patient 2	AD
Brain region								
Global	0.03±0.03	0.02	-0.02	0.90±0.12	0.06±0.02	0.04	0.07	0.09±0.02
Frontal	0.01±0.04	0.01	-0.02	0.97±0.10	0.05±0.02	0.04	0.09	0.09±0.03
Medial temporal	0.04±0.02	-0.03	-0.10	0.17±0.08	0.11±0.02	0.20	0.05	0.15±0.06
Temporal	0.04±0.03	0.04	-0.02	0.82±0.11	0.07±0.03	0.05	0.07	0.10±0.03
Posterior cingulate	0.07±0.04	0.04	0.02	0.87±0.25	0.04±0.05	0.00	0.07	0.07±0.06
Parietal	0.04±0.02	0.00	-0.02	1.01±0.23	0.03±0.01	-0.02	0.05	0.06±0.02

Data are presented as mean±SD.
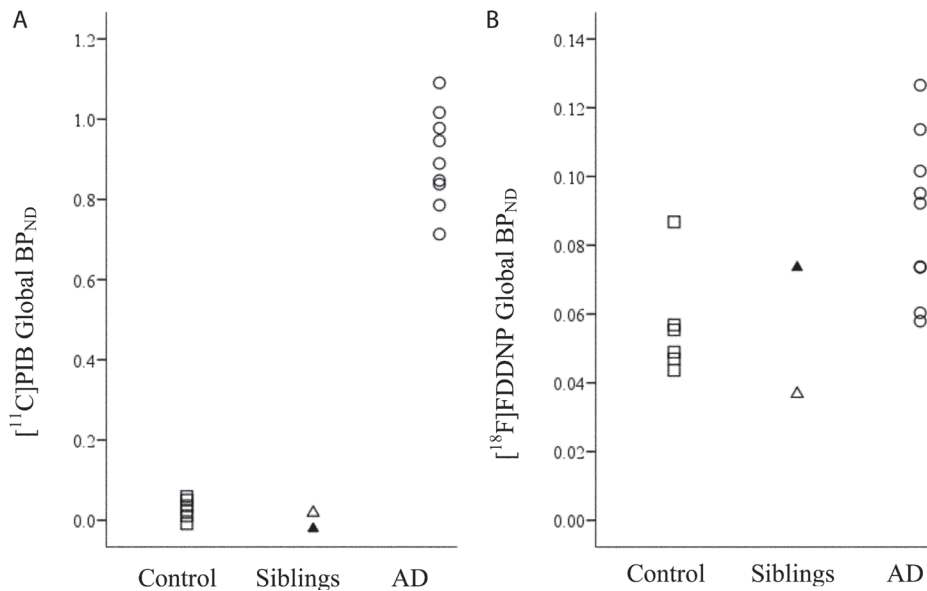AD, Alzheimer's disease; BP$_{ND}$, binding potential

Figure 3: Scatter plots of global cortical [^{11}C]PIB and [^{18}F]FDDNP binding
Scatter plots of global [^{11}C]PIB (A) and [^{18}F]FDDNP (B) BP$_{ND}$, by diagnostic group (controls: open squares; AD=Alzheimer's disease: open circles; siblings: open triangle for patient 1 and closed triangle for patient 2).

Genetic testing

No specific mutations in the presenilin 1 gene were found in patient 1; subsequent screening revealed the R406W *tau* mutation in both patients.

Discussion

By studying patients with rare autosomal dominantly inherited dementias, in whom a definitive diagnosis can be made *in vivo,* the specificity of biomarkers can be tested. This study illustrates the power of CSF and [^{11}C]PIB PET in refuting the presence of amyloid pathology in patients fulfilling the clinical criteria of AD. Moreover, it reveals the potential value of the combination of biomarkers for the differential diagnosis of (sporadic) FTD from AD. Elevated levels of CSF t-tau and p-tau values together with normal [^{11}C]PIB imaging and CSF measures of Aβ42 have proven to be highly suggestive of FTD.

In the two patients described, the clinical phenotype of slowly progressive episodic memory loss with profound hippocampal atrophy, is in line with previous reports on patients with FTD due to the R406W *tau* mutation (*9,10*). Normal [^{11}C]PIB uptake and CSF Aβ42 corresponds with the neuropathology typically associated with this mutation, i.e. neurofibrillary tangles in the absence of Aβ plaques (*11-14*), although concomitant presence of numerous plaques has been reported in two subjects (*9,15*).

Although the [^{18}F]FDDNP results in the two patients were not conclusive, the findings did

provide additional information regarding binding of this ligand. The apparently low levels of cerebral amyloid in these patients suggests that any [^{18}F]FDDNP retention reflects binding to a substrate other than amyloid. Moreover, differences in global and regional [^{18}F]FDDNP binding between the two patients were, at least to some extent, mirrored by CSF p-tau and t-tau levels. The latter is in line with the strong positive association between global [^{18}F]FDDNP binding and increased CSF tau levels in AD (*16*).

Acknowledgements

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