CSF biomarkers in posterior cortical atrophy

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ABSTRACT

Objective: To describe CSF biomarker profiles in posterior cortical atrophy (PCA), which induces high-order visual deficits often associated with Alzheimer disease (AD) pathology, and relate these findings to clinical and neuropsychological assessment.

Methods: This prospective observational study included 22 patients with PCA who underwent CSF biomarker analysis of total tau (t-tau), phosphorylated tau on amino acid 181 (p-tau181), and amyloid β ($A\beta_{42}$). At group level, the CSF profiles of patients with PCA were compared to those of patients with typical AD and patients with other dementia (OD). Individually, the clinical presentation of patients with PCA was correlated to their CSF profile to assess the predictability of clinical features for diagnosis of underlying AD pathology.

Results: At group level, the PCA biomarker profile was not different from that of the AD group, but very different from that of the OD group ($p < 0.001$). More than 90% of patients with PCA had CSF profiles consistent with AD. All patients with PCA with either isolated higher-order visual deficit (n = 8) or visual deficit associated with memory impairment (n = 11) had CSF profiles consistent with AD. Only one of the 3 patients with PCA with asymmetric motor signs fulfilled biological CSF criteria for AD.

Conclusions: PCA syndrome is usually associated with CSF biomarkers suggestive of AD, as shown by previous neuropathologic studies. This does not apply in case of motor signs suggesting associated corticobasal syndrome. CSF biomarkers help to discriminate AD from non-AD processes associated with this condition. *Neurology*® 2011;76:1782–1788

GLOSSARY

Aβ = amyloid β peptide; **AD** = Alzheimer disease; **CBS** = corticobasal syndrome; **CJD** = Creutzfeldt-Jakob disease; **CVLT** = California Verbal Learning Test; **DLB** = dementia with Lewy bodies; **FTD** = frontotemporal dementia; **MMSE** = Mini-Mental State Examination; **OD** = other dementias; **p-PCA** = pure posterior cortical atrophy; **p-tau** = phosphorylated tau protein; **PCA** = posterior cortical atrophy; **t-tau** = total tau proteins.

Posterior cortical atrophy (PCA) is a rare syndrome characterized by predominant progressive higher-order visuoperceptual deficits associated with occipito-parieto-temporal brain dysfunction.[1] Visual symptoms include simultanagnosia, hemispatial neglect, optic ataxia, and visual agnosia. Neuroimaging usually shows atrophic or metabolic changes in posterior brain regions.[2] Evolution generally leads to dementia.

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Supplemental data at www.neurology.org

e-Pub ahead of print on April 27, 2011, at www.neurology.org.

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Study funding: Supported by the "Programme Hospitalier de Recherche Clinique Régional 2004 D50353" and "EU FP6 Project Neuroscreen LSHB-CZ-2006-037719 contract no. 037719."

Disclosure: Author disclosures are provided at the end of the article.

This syndrome is usually related to Alzheimer disease (AD) but can also result from corticobasal degeneration, Creutzfeldt-Jakob disease (CJD), dementia with Lewy bodies (DLB), or subcortical gliosis.[3-8] Etiologic diagnosis remains uncertain until postmortem examination.

CSF biomarkers have become a significant help for in vivo AD diagnosis.[9] In AD they are characterized by a combination of increased total tau proteins (t-tau) and phosphorylated tau on amino acid 181 (p-tau181) and decreased 42 amino acid amyloid β peptide ($A\beta_{42}$).[9-12] These tau and Aβprofiles are related to elementary AD lesions: respectively, neurofibrillary tangles and amyloid plaques. Thus, CSF biomarker examination appears relevant to etiologic diagnosis of PCA, since the prevalence of AD pathology is high in this condition.

The objective of the present study was to describe the CSF biomarker profile in a prospective series of well-defined patients with PCA. The PCA CSF profile was compared to that of typical AD and other dementia groups. The interest for clinicians of CSF determination in PCA was assessed by comparison between clinically based and CSF-based classifications of etiologic diagnosis.

METHODS

PCA subjects. Twenty-two patients with PCA (14 men, 8 women; 65 ± 7.7 years) were recruited from the memory clinics of Lyon, Dijon, Saint-Etienne, Grenoble, Montbéliard, and Roanne (France) between 2005 and 2010. All underwent lumbar puncture. CSF biomarker analysis was performed in the neurobiology department of Lyon.

Diagnostic criteria. PCA diagnosis was based on medical history, caregiver interview, neurologic examination, a neuropsychological test battery, and brain imaging (table 1). The following diagnostic criteria for PCA[4] were applied: 1) history of progressive visual impairment not explained by ophthalmologic abnormality; 2) demonstration of complex visual disorder such as visual agnosia, prosopagnosia, visuospatial neglect, Balint syndrome (ocular apraxia, optic ataxia, and simultanagnosia), often

Table 1 Clinical and neuropsychological features of patients with PCA[a]

Case no.	MMSE score (/30)	Elements of Balint syndrome	Elements of Gerstmann syndrome	Ideomotor apraxia	Parkinsonism	Limb dystonia	Visual hallucinations	Memory
1	21	+	−	+	−	−	+	↓
2	20	+	+	+	−	−	−	↓
3	19	+	+	+	−	−	−	↓
4	26	+	+	−	−	−	−	X
5	22	+	−	−	−	−	−	X
6	10	+	−	+	−	−	−	↓
7	19	+	+	+ R	+	−	−	X
8	29	+	−	+	+	−	−	X
9	19	+	+	+ R	+ R	+ R	−	X
10	18	−	+	+	+	−	−	↓
11	15	+	−	−	−	−	−	↓
12	22	+	−	+	−	−	−	X
13	27	+	−	+ L	+ L	+ L	−	X
14	23	+	−	+	−	−	−	X
15	21	+	+	+	+	−	−	X
16	28	+	+	+	−	−	−	↓
17	13	−	+	+	−	−	−	X
18	12	−	−	−	−	−	−	↓
19	14	+	−	−	−	−	−	↓
20	24	+	−	+	−	−	−	X
21	17	+	+	+	−	−	+	↓
22	20	+	−	+	−	−	−	↓

Abbreviations: + = Clinical signs present; − = clinical sign absent; ↓ = low performance; L = lateralized on the left side; MMSE = Mini-Mental State Examination; NT = not testable; PCA = posterior cortical atrophy; R = lateralized on the right side; X = not affected.
[a] Clinical assessment of PCA for each case.

associated with Gerstmann syndrome (alexia, agraphia, finger agnosia, and right-left disorientation) or visuoconstructional apraxia; 3) no or minor memory impairment, executive dysfunction, or language deficit; 4) posterior atrophic or metabolic alteration on MRI or metabolic imaging.

Neuropsychological examination. The Mini-Mental State Examination (MMSE)[13] was systematically carried out to rate global cognitive ability. Episodic verbal memory was assessed by the Free and Cued Selective Recall Reminding Test,[14] California Verbal Learning Test (CVLT, French version),[15] or MEM-III.[16] Visuospatial and visuoperceptive abilities were explored by the Visual Object and Space Perception battery,[17] the Benton Facial Recognition test,[18] or the Judgment of Line Orientation test.[18] Neglect and constructional praxis were explored by the Crossing-out and Clock Drawing tests.

Clinically based classification. Patients with PCA were classified into 3 groups according to initial clinical presentation and neuropsychological profile, by neurologists blind to the biological results:

1. Pure PCA (p-PCA): isolated visual complaint with visual impairment and no episodic verbal memory impairment.
2. PCA-AD: predominant visual complaint and visual impairment with mild episodic verbal memory impairment.
3. PCA–corticobasal syndrome (CBS): predominant visual complaint and visual impairment with no verbal memory impairment, associated with asymmetric or unilateral parkinsonism and ipsilateral gestural apraxia or dystonia.

Some minor attention, executive, or language deficits could be present in all 3 groups.

Control groups. One population with clinical diagnosis of AD and another with clinical diagnosis of other dementia (OD, comprising DLB and frontotemporal dementia [FTD]) were selected on both consensus clinical criteria and CSF biomarker analysis, for comparison with the PCA group. These patients from our laboratory cohort were matched with the PCA groups for gender, for age at lumbar puncture (±5 years), and for duration of illness (±2 years). The AD control group comprised 160 patients with AD (83 men, 77 women), all meeting National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD.[19] The OD group comprised 138 patients (81 men, 57 women) with a clinical diagnosis of possible (n = 31) or probable (n = 38) DLB based on the consensus diagnostic criteria[20] and possible (n = 23) or probable (n = 45) FTD based on the Lund and Manchester criteria.[21] There was no significant difference in sex ratio (M/F) between PCA (14/8) and AD (83/77) and OD control (81/57) patients (χ^2 test, n = 318, $p = 0.34$).

Standard protocol approval, registration, and patient consent. The study was conducted under the "Programme Hospitalier de Recherche Clinique Régional 2004 D50353" and "EU FP6 Project Neuroscreen LSHB-CZ-2006-037719 contract No. 037719." It was approved by the local Ethics Committee (CPP). All patients (PCA and controls) gave written informed consent to participate.

CSF biomarker assessment. ***CSF sampling and storage.*** CSF was obtained from inpatients by lumbar puncture. CSF sampling was performed according to a standard protocol with tracking sheets to prevent technical problems. In total, 10 mL were collected in polypropylene vials (VWR, PA) and then centrifuged within 2 hours (10 minutes at 4,000 × *g*). Supernatants were distributed in polypropylene vials and aliquots were directly stored at −80°C until analysis.

Since preanalytical steps were critical to the interpretation of results, the following strict CSF exclusion criteria were applied: freezing later than 4 hours after sampling, freezing at −20°C, CSF white cell count >5/mm^3, CSF red cell count >2,000/mm^3, or CSF protein level >1.5 g/L.

CSF analysis. CSF levels of t-tau, p-tau181, and Aβ_{42} were prospectively determined using a commercially available ELISA kit (INNOTEST htau-Ag, INNOTEST Phospho-Tau$_{(181)}$, INNOTEST β-amyloid$_{(1-42)}$, Innogenetics®, Gent, Belgium) according to the manufacturer's instructions.

All biomarker levels were measured in duplicate. Furthermore, all series included quality control using an aliquot of frozen ventricular CSF containing t-tau, p-tau181, and Aβ_{42} at mean concentrations of 550 pg/mL, 60 pg/mL, and 500 pg/mL, respectively. Since the intra-assay coefficient of variation was less than 10% and the concentrations obtained were in the linear range, samples were not retested.

Cutoff values for AD reported in the literature were adopted by the department of biochemistry, as follows: t-tau >350 pg/mL, p-tau181 >60 pg/mL, and Aβ_{42} <500 pg/mL.[22-24]

Western blot immunoassay for 14-3-3 protein was routinely performed. Both positive and doubtful (weakly positive) standard samples were used in all experiments. Immunostaining used anti-14.3.3β polyclonal rabbit antibody (Santa Cruz Biotechnology Sc-629, Santa Cruz, CA) and then alkaline phosphatase-conjugated goat anti-rabbit immunoglobulin G antibody (Santa Cruz Biotechnology Sc-2057, Santa Cruz, CA). The antigen was detected by colorimetric reaction and scored for presence or absence of the majority band and compared to positive and doubtful control bands.

CSF-based classification. Patients with PCA were classified into 3 groups according to t-tau, p-tau, and Aβ_{42} CSF levels, by biologists blind to the clinical results:

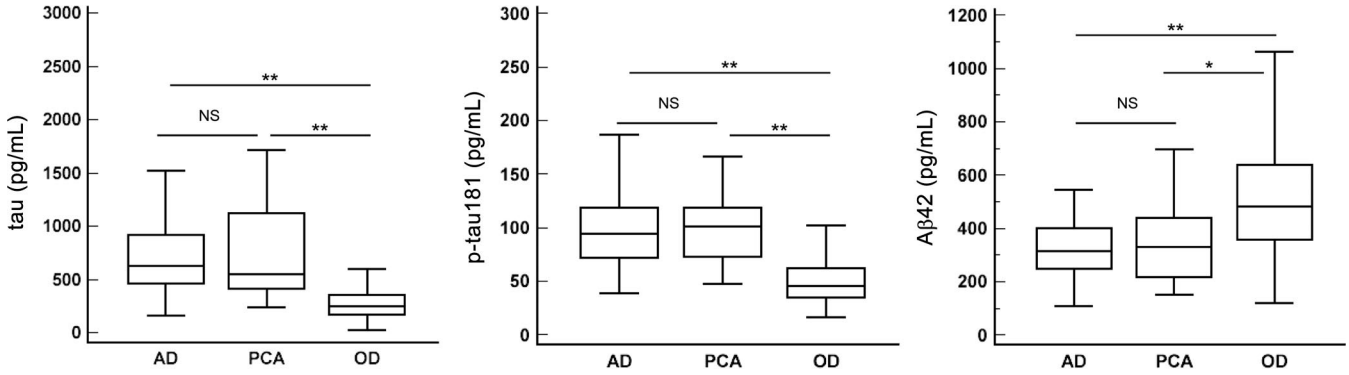
1. Typical AD: both t-tau >350 pg/mL, p-tau181 >60 pg/mL and Aβ_{42} <500 pg/mL.
2. Atypical AD: either t-tau >350 pg/mL and p-tau181 >60 pg/mL, or Aβ_{42} <500 pg/mL.
3. Non-AD: t-tau <350 pg/mL, p-tau181 <60 pg/mL, and Aβ_{42} >500 pg/mL.

Statistical analyses. Age differences among PCA, AD, and OD groups were assessed on one-way analysis of variance and sex differences on 2 × 3 contingency analysis (χ^2 test). Differences in CSF biomarkers among the 3 groups were analyzed on the Mann-Whitney test. p Values below 0.05 and 0.001 were considered to be significant and highly significant, respectively. Analysis was performed on MedCalc® version 11.1.1.0 software (Frank Schoonjans, MedCalc Software, Mariakerke, Belgium).

RESULTS

Clinical features of patients with PCA. Simultanagnosia, alexia, acalculia, agraphia, and ideomotor and constructional apraxia were the most frequent signs (see tables e-1 and e-2 on the *Neurology*® Web site at www.neurology.org). Six patients had mild parkinsonism, which was asymmetric in 3 patients who also presented with unilateral ideomotor apraxia (table 1). Two patients with asymmetric parkinsonism also showed limb dystonia. Two patients reported visual hallucinations. None showed

Figure 1 Comparison of total tau proteins (t-tau), phosphorylated tau on amino acid 181 (p-tau181), and amyloid β peptide (Aβ42) CSF patterns among patients with Alzheimer disease (AD), patients with posterior cortical atrophy (PCA), and patients with other dementias (OD)



Box plot showing median CSF levels of t-tau, p-tau181, and Aβ42 in AD, PCA, and OD subgroups (**$p < 0.0001$; *$p < 0.0016$; NS = nonsignificant).

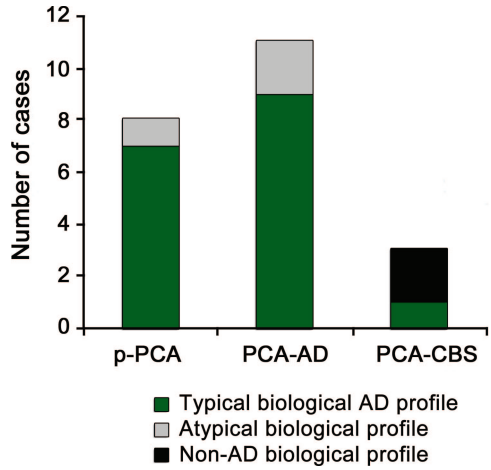
fluctuation of cognitive or motor symptoms. Cognitive functions were variably affected, with a mean MMSE of 20/30 (±5.14), ranging from 10 to 29. Visuoperceptive and visuospatial abilities were affected in all patients, and attention and executive functions in most. Patients with PCA symptoms had been progressing for 1 to 6 years at the first clinical assessment. Eight patients without memory impairment were clinically classified as pure PCA (patients 4, 5, 8, 12, 14, 15, 17, and 20), 11 as PCA-AD (patients 1, 2, 3, 6, 10, 11, 16, 18, 19, 21, and 22), and the remaining 3 as PCA-CBS due to their motor symptoms (patients 7, 9, and 13). MRI showed asymmetric cortical or subcortical atrophy in the parietal and occipital regions in 17/22 and symmetric atrophy in 5/22 patients with PCA. There were no visible differences in MRI abnormality profiles among the 3 clinical subgroups.

CSF biomarker profiles in the PCA compared to the AD and OD groups. Mean t-tau, p-tau181, and $A\beta_{42}$ CSF levels in the PCA group were 742 ± 247, 102 ± 43, and 369 ± 187 pg/mL, respectively. Mean CSF levels in the control groups were t-tau (AD: 749 ± 412; OD: 309 ± 230 pg/mL), p-tau181 (AD: 102 ± 41; OD: 52 ± 25 pg/mL), and $A\beta_{42}$ (AD: 334 ± 127; OD: 508 ± 216 pg/mL). Median CSF t-tau, p-tau181, and $A\beta_{42}$ levels (figure 1) were highly significantly different between the PCA and OD groups ($p < 0.0001$, <0.0001, and 0.0016, respectively) and did not significantly differ between the PCA and AD groups ($p = 0.7$, 0.8, and 0.7, respectively).

CSF biomarker profiles in individual patients with PCA. Seventeen of the 22 patients with PCA (77%) (table e-3) fulfilled the biological criteria for typical AD, with abnormal levels of the 3 CSF markers. Three PCA patient profiles (14%) were classified as atypical AD due to abnormalities in either tau or Aβ protein levels. Two patients (9%) had normal CSF biomarkers. Thus 20 out of 22 patients showed a biological profile consistent with either typical or atypical AD. Although 4 patients had CSF t-tau levels higher than 1,200 pg/mL, none showed positive CSF 14.3.3 protein.

Comparison between clinically and biologically based diagnostic classifications. Seven of the 8 patients with p-PCA had a typical and one an atypical AD CSF profile (figure 2). Nine of the 11 patients with PCA-AD had a typical and 2 an atypical AD CSF profile. Finally, one of the 3 patients with PCA-CBS met biological criteria for AD and 2 had a CSF profile classified as non-AD.

Figure 2 Number of cases with the 3 different CSF patterns in each posterior cortical atrophy (PCA) clinical subgroup



AD = Alzheimer disease; CBS = corticobasal syndrome; p-PCA = pure posterior cortical atrophy.

DISCUSSION CSF analysis in the present PCA cohort was consistent with the high prevalence of underlying AD pathology. At group level, $A\beta_{42}$, t-tau, and p-tau181 levels in patients with PCA differed significantly from those for other dementias and were indistinguishable from those for typical AD. Individually, 17 of the 22 patients presented a typical and 3 an atypical AD CSF profile. These results indicate a high proportion (77%) of patients with PCA with underlying AD pathology with both amyloid and tau pathologies. The 3 atypical AD CSF profiles were consistent with the presence of amyloid plaques or neurofibrillary tangles.[25] More than 90% of the PCA cases thus exhibited a CSF profile consistent with AD and were likely to have underlying AD pathology.

It is now well-established that CSF biomarkers improve the accuracy of in vivo AD diagnosis.[25,26] CSF biomarker changes are related to underlying histologic lesions specific to AD.[25] The combination of the 3 abnormal CSF biomarkers predicts AD neuropathology with sensitivity and specificity exceeding 90% and 85%, respectively.[26] Based on these data, determination of CSF biomarkers may be of diagnostic interest for identifying AD in patients with atypical focal dementia. In PCA, the present study clearly identified a dominant AD-type biological profile. To our knowledge, only 3 studies have been published on this condition. Decreased CSF $A\beta_{42}$ and elevated levels of phosphorylated tau at threonine 199 were reported in a single case of PCA.[27] Elevated t-tau and p-tau181 and low $A\beta_{42}$ CSF levels, similar to those of typical AD, were reported in a cohort of 9 patients with PCA.[28] Elevated CSF p-tau181 levels, although significantly lower than in AD, were also reported in a sample of 15 patients with PCA.[29] The present study likewise showed, in a larger well-defined PCA population, that an overwhelming majority of patients with PCA display CSF profiles suggestive of AD.

These findings are in accordance with the few neuropathologic studies, reporting a high but variable prevalence of underlying AD pathology in PCA syndrome. The largest study reported AD pathology in 62% of 21 autopsied PCA cases.[4] AD lesions were also reported in 7 out of 9 patients in one study,[3] and in all 7 cases of a study with a smaller sample of patients.[7] Other reported etiologies include CBD, AD associated with PD or DLB, CJD, and subcortical gliosis.

In the present cohort, patients were diagnosed with PCA based on a clinical aspect of progressive posterior cortical dysfunction. Rather broad diagnostic criteria were used in order to avoid a priori exclusion of non-AD PCA syndrome.[4] To take the analysis further, patients with PCA were classified in 3 clinically distinct subgroups (pure PCA, PCA-AD, or PCA-CBS) according to clinical status, degree of memory deficit, and presence of motor signs, in order to compare biological profile with episodic memory deficit and motor signs. Although the diagnostic criteria considered in the present study did not exclude patients with parkinsonism, fluctuations, or hallucinations, none of our patients developed more than one of these symptoms so as to be listed as PCA-DLB. None of them, including the 4 cases with elevated t-tau levels above 1,200 pg/mL, showed positive CSF 14.3.3 protein level[30] or symptoms consistent with CJD. Although both elevated t-tau and p-tau181 are associated with AD severity in the AD literature, these patients with PCA were not different from the others in terms of global cognitive ability as rated by MMSE: their cognitive deficits were not more impaired than the others.[31] Interestingly, despite the broad diagnostic criteria used, most patients with PCA still tended to have AD lesions.

All patients with pure PCA presented a CSF profile consistent with either typical (7/8) or atypical AD (1/8). Likewise, all patients with PCA-AD also had a CSF profile consistent with either typical (9/11) or atypical AD (2/11). Atypical profiles were defined by either increased t-tau and p-tau181 and normal $A\beta_{42}$ CSF levels or decreased $A\beta_{42}$ and normal t-tau and p-tau181 CSF concentrations. Such CSF patterns have already been described in patients with autopsy-based diagnosis of AD[25] and remain consistent with underlying AD pathology. However, these CSF profiles are less specific to AD and can be found in other neurodegenerative diseases, sometimes associated with AD. CSF profiles with low $A\beta_{42}$ and normal t-tau levels in particular have been found in patients showing AD lesions associated with diffuse Lewy bodies,[32] PD with dementia, or vascular dementia.[25] Similarly, CSF profiles with normal $A\beta_{42}$ and elevated t-tau and p-tau181 levels have been described in autopsy cases of vascular dementia or DLB.[25] None of the patients in the present study fulfilled diagnostic criteria for probable DLB in our study, and elevated CSF p-tau181 is more specific in AD than in DLB pathology; DLB, however, appears to be the main differential diagnosis.[33,34]

In the present study, a normal CSF profile was observed in only 2 out of 22 cases of PCA, in the small subgroup of 3 PCA-CBS. The third patient with PCA-CBS presented a typical AD CSF profile. The clinical presentation of these 3 PCA-CBS cases was similar at the time of lumbar puncture, in that they all had asymmetric parkinsonism and gestural apraxia, elements of Balint and Gerstmann syndrome, and higher-order visual and attention deficits without memory impairment. None had cortical somatosensory impairment. Mild focal limb dystonia ipsilateral to the

side with predominant parkinsonism clinically differentiated the 2 patients with normal CSF profiles from patients with an AD CSF profile. It has recently been shown that CBS can reveal AD pathology.[35,36] One of the 3 patients with PCA-CBS in the present study is thus likely to have had underlying AD pathology. The normal CSF profiles of the other 2 patients with PCA-CBS were consistent with the hypothesis of underlying corticobasal degeneration pathology or other tauopathy such as progressive supranuclear palsy or even non-tau pathologies, which are also possible in this clinical condition.[36]

Although histologic data were not available in the present study, the CSF results are consistent with those of previous neuropathologic studies in PCA. CSF biomarker analysis suggests prominent underlying AD pathology in PCA and enables in vivo AD diagnosis in this condition. On CSF analysis, only the clinical PCA-CBS subtype seemed to be predominantly related to non-AD pathology. Further studies with CSF analysis and postmortem examination in larger cohorts of PCA with motor signs are needed to describe the underlying pathology in this clinical subtype.

DISCLOSURE

J. Seguin was funded by EU FP6 Project Neuroscreen LSHB-CZ-2006-037719 contract no. 037719. Dr. Formaglio reports no disclosures. Dr. Perret-Liaudet has served on scientific advisory boards for Innogenetics and ExonHit Therapeutics and has received speaker honoraria from the Eisai Inc. and Lundbeck Inc. Dr. Quadrio was funded by EU FP6 Project Neuroscreen LSHB-CZ-2006-037719 contract no. 037719. Y. Tholance reports no disclosures. Dr. Rouaud has served on a scientific advisory board for Eisai Inc. and has received speaker honoraria from Eisai Inc. and Novartis. Dr. Thomas-Anterion reports no disclosures. Dr. Croisile has served on scientific advisory boards for Eisai Inc. and Lundbeck Inc.; has received speaker honoraria from Eisai Inc., Janssen, Novartis, and Lundbeck Inc.; serves on the editorial board of *Neurologies Mémoire Actualités Revue de Gériatrie*; receives publishing royalties for *Votre Mémoire* (Larousse, 2004), *Alzheimer et les Maladies Apparentées* (Larousse, 2007), *Tout sur la Mémoire* (Odile Jacob, 2009), and *Maladie d'Alzheimer* (Larousse, 2010); and has contractual rights in Scientific Brain Training for receipt of future royalty payments. Dr. Mollion serves on a scientific advisory board for Novartis. Dr. Moreaud served on the editorial board of *Psychologie et Neuropsychiatrie du Vieillissement* and has received speaker honoraria from Eisai Inc., Novartis, and Janssen. Dr. Salzmann, Dr. Dorey, Dr. Bataillard, Dr. Coste, and Dr. Vighetto report no disclosures. Dr. Krolak-Salmon serves on scientific advisory boards for Eisai Inc. and Novartis; has received speaker honoraria from Eisai Inc., Novartis, Janssen, and Lundbeck Inc.; and receives research support from Janssen and Programme Hospitalier de Recherche Clinique.

Received September 1, 2010. Accepted in final form November 23, 2010.

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