Correlation of Regional Proton Magnetic Resonance Spectroscopic Metabolic Changes With Cognitive Deficits in Mild Alzheimer Disease

Sophie Chantal, MPs; Martin Labelle, MSc; Rémi W. Bouchard, MD, MSc, FRCPC; Claude M. J. Braun, PhD; Yvan Boulanger, PhD

Context: The staging of Alzheimer disease (AD) dementia could be improved by a neurometabolic analysis using magnetic resonance spectroscopy.

Objective: To examine the correlation between regional cerebral metabolic alterations measured by proton magnetic resonance spectroscopy and neuropsychological dysfunctions in patients with early AD.

Design: A case-control study.

Setting: University hospital neurology clinic and radiology department.

Participants: A cohort of 14 patients with mild AD and 14 control subjects paired for age and sex.

Interventions: Single-voxel proton magnetic resonance spectroscopic brain examination (60 minutes) and a comprehensive battery of psychometric tests (2 hours).

Main Outcome Measures: Metabolite ratios relative to unsuppressed water were calculated for magnetic resonance spectroscopic metabolites (N-acetylaspartate, choline, creatine-phosphocreatine, and myo-inositol) in the medial temporal lobes (MTLs), parietotemporal cortices (PTCs), and frontal cortices of both hemispheres. Correlations were examined between metabolic changes in an area and psychometric scores of its known regional function: MTL and verbal memory, PTC and language and visuconstructional abilities, and frontal cortices and executive functions.

Results: A significant reduction of N-acetylaspartate/water (H2O) in the left MTL and of choline/H2O in both MTLs, as well as a significant increase of myo-inositol/H2O in the right PTC were observed. Metabolic alterations in the left MTL were correlated with a loss of verbal memory, in the left PTC with language impairment, and in the right PTC with a loss of visuconstructional abilities in the group with AD.

Conclusion: These findings are consistent with regional distribution of neuropathologic changes and cognitive symptoms characterizing early phases of AD, and with the pattern of lateralization of normal brain function.

Arch Neurol. 2002;59:955-962

Alzheimer disease (AD) is a neurodegenerative disorder associated with a gradual deterioration of cognitive functions, personality, and behavior. Impairment of recent memory is commonly the first symptom of the disease attributable to neurochemical and pathologic changes in the medial temporal lobe (MTL). As AD progresses, language, attention, calculation, visuospatial, visuconstructional, and executive functions become impaired because of a dysfunction of the associative cortices in both cerebral hemispheres. The cause and pathogenesis of AD remain complex but it is always associated with gray matter atrophy, disruption of neuronal function, and formation of neurofibrillary tangles and neuritic plaques in the medial temporal limbic regions and isocortex. Cerebral imaging studies have revealed hippocampal atrophy consistent with neuronal loss and predictive of memory performance, and reduced metabolism in the posterior association areas of the neocortex as well as in the posterior cingulate gyrus and pericingular cortex in the early stages of AD. However, heterogeneous metabolic patterns have been reported among patients, reflecting either frontal or parietotemporal abnormalities and right- or left-sided metabolic asymmetries correlated with visuconstructional and language discrepancies. Neuropsychological studies of patients with AD have also revealed selective and heterogeneous patterns of cognitive impairments. For example, some patients present severe language dysfunction along with milder visuconstructional dysfunction, whereas other patients present with the opposite pattern. Such differences in the pat-
PATIENTS AND METHODS

PATIENTS

Fourteen right-handed patients diagnosed as having probable AD of mild severity according to criteria for dementia of the Alzheimer type of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition were compared with 14 right-handed control subjects who had no history of cognitive decline or previous neurologic or psychiatric disorder. They were submitted to physical and neurologic examinations, including laboratory tests and brain imaging (ie, magnetic resonance imaging or computed topography). Clinical assessment of dementia included neurocognitive, behavioral, and psychiatric interviews conducted by the behavioral neurologist (R.W.B.), administration of the Mini-Mental State Examination, and a neuropsychological evaluation. Controls were evaluated with the same neuropsychological tests to ensure healthy cognitive functions. Patients presented with no focal brain lesions detectable by computed tomography or magnetic resonance imaging, had a global staging score of 1 or less on the Clinical Dementia Rating scale and of less than 4 on the Hachinski Ischemia Scale. They were not treated with acetylcholinesterase inhibitors or other investigational drugs to enhance brain cognitive function and were not currently or previously suffering from significant systemic (including diabetes mellitus) or psychiatric conditions or traumatic brain injuries that could compromise brain functions. All controls and patients were individually paired for age and sex.

PROTON MRS

Controls and patients with AD underwent a brain 1H MRS examination performed using a 1.5-T whole-body scanner (GE Signa; General Electric Medical Systems, Waukesha, Wis) operating at 63.85 MHz. Proton MRS data were obtained from 7- to 8-cm3 voxels localized in the left and right MTLs (ie, amygdala, the anterior half of the hippocampus, and part of the underlying subiculum), left and right frontal cortices (FCs) (ie, mixed gray and white matter, 3.1 × 2.3 × 1.0 cm3), and left and right parietotemporal cortices (PTCs) (ie, mixed gray and white matter, 3.7 × 1.9 × 1.0 cm3). The voxel shapes of the FC

abnormalities and cognitive dysfunctions in neurologic and psychiatric disorders and in healthy individuals.

In patients with AD, conflicting results have been reported concerning the correlation between the metabolite levels and the degree of cognitive alteration. The relevance of the correlations is, however, questionable since either conclusions were based on nonspecific brief mental evaluations, such as the Mini-Mental State Examination or global scores from the AD Assessment Scale, thereby not reflecting specific cognitive deficits caused by regional cerebral deterioration, or the cerebral region examined is not functionally involved in early clinical symptoms of AD. To our knowledge, no investigation examined specifically the relation-

and PTC regions were chosen to maximize their gray matter content as shown in Figure 1. The point-resolved spectroscopy pulse sequence was used with the following acquisition parameters: repetition time, 1200 milliseconds; echo time, 50 milliseconds; number of acquisitions, 64; spectral width, 2000 Hz; number of points, 1024; and total acquisition time per voxel, 1.7 minutes. The MRS data were analyzed using the Magnetic Resonance User Interface (Barcelona, Spain) software and signal intensities were calculated directly from time-domain data, using the singular value decomposition 1-dimensional model function fitting. The intensity of the water (H2O) signal was determined from the area of the H2O peak in the H2O-suppressed spectra and metabolite/unsuppressed water ratios were calculated. Owing to the significant overlap with neighboring signals, the ml signal intensity was estimated from the peak height measured manually. The ml/H2O ratios were then calculated by dividing the ml peak height by the NAA peak height and multiplying by the NAA/H2O ratio. Mean and SD values were calculated for all metabolite ratios.

NEUROPSYCHOLOGICAL TESTS

Cognitive domains of verbal memory, language, visuoconstructional abilities, and executive functions were examined using a battery of standard neuropsychological tests as listed in Table 1. The French versions of the original tests were used and the raw test scores were used for statistical analysis. For all tests, except Trail Making Test Part A, higher scores indicate better performance.

STATISTICAL ANALYSIS

Metabolite ratios relative to unsuppressed H2O (NAA/H2O, Cho/H2O, Cr/H2O, and ml/H2O) were compared in all regions between patients with AD and controls by a 2-way repeated measures analysis of variance followed by a Tukey post hoc test for multiple comparisons, when allowed. Differences in metabolite ratios between the 2 groups were considered statistically significant when P < .05. The Pearson correlation coefficients followed by a Bonferroni correction for multiple correlations were used for assessment of the association between scores in the 4 cognitive domains and metabolite ratios. Correlations were considered significant at P < .05 (corrected for 2 neuropsychological tests per functional brain region) with r > 0.50. Statistical analyses were performed using SPSS Version 9.0.1 (SPSS Inc, Chicago, Ill) and SIGMASTAT Version 2.03 (Systat, Golden, Colo).
ship between local metabolism measured by MRS and associated patterns of cognitive impairment.

In the present study, MRS data were acquired in 6 cortical regions known to be affected in patients with AD to evaluate the spatial specificity of the metabolic impairments. Correlations were established between neurometabolic variations and specific neuropsychological performances (ie, verbal memory, executive, language, and visuoconstructional abilities) associated with these regions. To determine the specificity of correlations, cognitive functions were tested in the contralateral functional region as control or in the posterior associative regions in the case of executive functions. The results indicate that pertinent lateralized correlations can be established in several regions.

**RESULTS**

**DEMOGRAPHICS**

The demographic and clinical data of patients with AD and controls paired for age and sex are summarized in **Table 2**. Significant differences in Mini-Mental State Examination scores are measured between patients with AD and controls.

**MRS DATA**

**Table 3** lists the mean metabolite ratios of NAA, Cho, ml, and Cr relative to unsuppressed H2O for all 6 brain regions in patients with AD and controls. The NAA/H2O ratio was significantly decreased for patients with AD in the left MTL only. A decrease was also measured in the left FC but the change did not reach statistical sig-

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**Table 1. Cognitive Tests Administered to Patients With Alzheimer Disease and Control Subjects**

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Test Name</th>
<th>Associated Brain Region*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal memory</td>
<td>California Verbal Learning Test (verbal learning and word recall)</td>
<td>Left MTL</td>
</tr>
<tr>
<td>Language</td>
<td>Boston Naming Test and Verbal Fluency Test</td>
<td>Left FC and/or left PTC</td>
</tr>
<tr>
<td>Visuoconstructional abilities</td>
<td>Block Design subtest of Wechsler Adult Intelligence Scale-Revised and Copy</td>
<td>Right PTC</td>
</tr>
<tr>
<td>Executive functions</td>
<td>of Rey Complex Figure Test</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Part A of Trail Making Test and Verbal Fluency Test</td>
<td>Left, right, or both FC(s)</td>
</tr>
</tbody>
</table>

*MTL indicates medial temporal lobe; PTC, parietotemporal cortex; and FC, frontal cortex.

**Table 2. Demographic and Clinical Characteristics of Patients With Alzheimer Disease (AD) and Control Subjects***

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With AD (n = 14)</th>
<th>Control Subjects (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.5 (7.2)</td>
<td>71.1 (7.5)</td>
</tr>
<tr>
<td>M/F</td>
<td>9/5</td>
<td>9/5</td>
</tr>
<tr>
<td>Educational level, y</td>
<td>11.1 (6.1)</td>
<td>12.8 (4.8)</td>
</tr>
<tr>
<td>MMSE score†‡</td>
<td>22.9 (4.0)</td>
<td>29.3 (0.9)</td>
</tr>
<tr>
<td>MMSE score§</td>
<td>21.4 (3.9)</td>
<td>28.4 (2.1)</td>
</tr>
</tbody>
</table>

*Data are given as mean (SD) unless otherwise noted. MMSE indicates Mini-Mental State Examination.
†Score for spelling the French word “MONDE” backward.
‡P<.001, t test; patients with AD vs control subjects.
§Score for counting backward by 7 beginning with 100.
nificance. In the other regions, the NAA/H\textsubscript{2}O ratios were unchanged. The Cho/H\textsubscript{2}O ratios of patients with AD were significantly reduced relative to controls in both the left and right MTLs (Table 3). No statistically significant Cho/H\textsubscript{2}O changes were measured in the other regions. In the case of ml/H\textsubscript{2}O, increases were measured in all 6 regions, but the changes were statistically significant in the right PTC only and showed a statistical tendency in the left MTL and the left PTC. Finally, both increases and decreases were measured for the Cr/H\textsubscript{2}O ratio in patients with AD relative to the controls. Statistically significant decreases were measured in the left MTL and the left PTC. Figure 2 presents spectra illustrating the major effects of AD on brain metabolites. No correlation could be established between metabolite ratios and age for patients with AD and controls.

### CORRELATIONS BETWEEN MRS AND NEUROPSYCHOLOGICAL DATA

Statistically significant Pearson correlations between individual cognitive test scores and metabolite ratios in specific brain regions in patients with AD are listed in Table 4 and shown in Figure 3. Correlations were obtained between the NAA/H\textsubscript{2}O ratios measured in the left MTL and the learning scores and the word recall memory scores measured by the California Verbal Learning Test (Figure 3A). There was no significant correlation between these verbal memory scores and other metabolite ratios and no correlations were found in the right MTL. In Figure 3B, the negative correlation between language performance measured by the Boston Naming Test (confrontation naming) and the ml/H\textsubscript{2}O ratios in the left PTC is shown. No other correlation was found between Boston Naming Test or verbal fluency scores and any other metabolite ratio in the left or right PTC. Figure 3C shows the negative correlation between scores obtained for the copy of Rey Complex Figure Test and ml/H\textsubscript{2}O ratios in the right PTC. No correlation was found in the left PTC and no other metabolite ratio was correlated with visuo-constructional abilities. Executive functions were evaluated with verbal fluency test and Trail Making Test Part A. Correlations were examined between scores from these 2 tests and all metabolite ratios in the left FC, right FC, bilateral FCs, and posterior associative cortices as control. A correlation was found between Trail Making Test Part A and ml/H\textsubscript{2}O ratios in the right FC (r=0.55, P=.04, n=14), the longer the time spent to complete the test, the higher the ml/H\textsubscript{2}O ratio, but this correlation was not statistically significant when the Bonferroni correction was applied. For all tests, no significant correlation between neuropsychological performances and age or educational level could be found for patients with AD.

### COMMENT

A strong correlation was found between NAA/H\textsubscript{2}O ratios and both the learning and word recall parts of the California Verbal Learning Test in the left MTL (Figure 4).
These results are consistent with the fact that the left MTL is the site of the verbal memory function. Although nonverbal visual memory processing has not been assessed in this study, our results agree with the known laterality of the mnemonic function. In patients with epilepsy, a focus in the left hippocampus was demonstrated to lead to a verbal memory deficit whereas a focus in the right hippocampus was associated with a deficit of the nonverbal visual memory.36 More interestingly, verbal memory deficits were observed in patients with temporal lobe epilepsy following a right-sided excision but only in those patients who had $^3$H MRS abnormalities in the contralateral (ie, left) side.37 Together, these studies and our results suggest that MRS provides a sensitive measure of neuronal damage in the MTL that might be undetectable by standard imaging techniques so early in the disease course. This helps to explain anomalous memory performances that are most characteristic of the disease.

Table 4. Statistically Significant Pearson Correlation Data Between Brain Metabolite Ratios and Cognitive Scores in Specific Regions and in Their Contralateral Regions for Patients With Alzheimer Disease (AD)*

<table>
<thead>
<tr>
<th>Metabolite Ratio</th>
<th>Cognitive Function</th>
<th>Cognitive Test</th>
<th>Brain Region</th>
<th>No. of Patients With AD</th>
<th>$r$ Value</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA/H$_2$O</td>
<td>Verbal memory</td>
<td>CVLT (Learning)</td>
<td>Left MTL</td>
<td>14</td>
<td>0.82</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right MTL</td>
<td>0.66</td>
<td>.83</td>
<td></td>
</tr>
<tr>
<td>NAA/H$_2$O</td>
<td>Verbal memory</td>
<td>CVLT (Word Recall)</td>
<td>Left MTL</td>
<td>14</td>
<td>0.70</td>
<td>.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right MTL</td>
<td>0.11</td>
<td>.73</td>
<td></td>
</tr>
<tr>
<td>ml/H$_2$O</td>
<td>Language</td>
<td>BNT</td>
<td>Left PTC</td>
<td>14</td>
<td>−0.60</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right PTC</td>
<td>−0.12</td>
<td>.69</td>
<td></td>
</tr>
<tr>
<td>ml/H$_2$O</td>
<td>Visuoconstructional functions</td>
<td>Rey CFT</td>
<td>Right PTC</td>
<td>13</td>
<td>−0.68</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Left PTC</td>
<td>−0.09</td>
<td>.75</td>
<td></td>
</tr>
</tbody>
</table>

*All other correlations were found not to be statistically significant. NAA indicates N-acetylaspartate; H$_2$O, water; CVLT, California Verbal Learning Test; MTL, medial temporal lobe; ml, myo-inositol; BNT, Boston Naming Test; PTC, parietotemporal cortex; and Rey CFT, Rey Complex Figure Test.
sphere language dominance. Visuoconstructional dys-
hand, thus increasing the probability of left hemi-
partly explained by the fact that all our patients were right-
learning Test, and the
learning (triangles) and word recall (squares) scores of the California Verbal
DISEASE PROGRESSION MODEL

Recent data suggest that initial changes in the patho-
logic progression of AD involve an increase in the ml level
and that a decrease in the NAA level and an increase in the
Cho level occur later in the disease course. A similar
hypothesis was made for Down syndrome, a pro-
gressive neurochemical disorder in which an ml level in-
crease was found to precede a NAA level loss, suggesting
similar pathologic pathways for both diseases. Our data
support these previously reported studies. The NAA and
Cho level reductions along with an ml level increase, al-
though not always statistically significant, were mea-
sured in MTL regions known to be affected early in AD (Table 3). These results seem to suggest that these re-
gions are affected to a point where the initial ml level in-
crease is no longer a significant marker of AD but where
neuropathologic processes caused by AD are well estab-
ilished. Interestingly, a significant ml level increase was
observed in the right PTC region and a strong tendency
toward statistical significance of an ml augmentation was
measured in the left PTC. These observations are con-
sistent with Braak and Braak’s model of AD pathophys-
ology being initiated in the MTL and then spreading to
upper levels of cortical regions. In accord with this
model, MRS studies have suggested that biochemical
changes in AD are sequential, starting with an ml level in-
crease and followed by decreases of both NAA and Cho
levels. Further investigations will be necessary to de-
terminate if the NAA and Cho level modifications are ob-
servable in the moderate AD stage following the ml level in-
crease in the mild stage. Data suggest that the Cr may
also be reduced in the MTL and PTC regions (Table 3).

The regional metabolite pattern observed in pa-
ients with AD, compatible with Braak and Braak’s model of
pathologic evolution, is also consistent with the pro-
gression of cognitive impairment and reflects a gradual
process of brain degeneration. Deficits of episodic
memory, that is, the ability to acquire and retain new in-
formation associated with the medial structures of the
temporal lobe (which includes the hippocampus and the
An increased ml/H2O correlates with lower Boston
Naming Test scores in the left PTC, reflecting impaired
language performance (Figure 3B). This correlation is con-
sistent with the known lateralized language function in
the left PTC. Although that naming function is not ex-
clusively localized in the left posterior associative cor-
text and anomia may be observed following frontal dys-
function of the left dominant hemisphere, the absence
of correlation with other brain regions lead us to con-
clude that the language association shown is highly spe-
cific to left PTC. Moreover, the stronger relationship be-
tween confrontation naming and ml/H2O ratios may be
partly explained by the fact that all our patients were right-
handed, thus increasing the probability of left hemi-
sphere language dominance. Visuoconstructional dys-
function measured with the Rey Complex Figure Test
was correlated with ml/H2O increases (Figure 3C) in the right
PTC, in agreement with the known neurophysiological
function of the right PTC.

In the case of executive functions, no relevant cor-
relation was found between neuropsychological perform-
ances and metabolite ratios. Even if the Trail Making
Test Part A and the verbal fluency test are considered to
assess executive capabilities, the entire executive system
cannot only be evaluated by these 2 tests. Indeed, in
contrast to limbic cortex and posterior association areas, the concept of executive functions in the frontal
lobe refers to several cognitive abilities such as planning,
judgment, problem solving, abstraction, etc, that
cannot be assessed by a single test. For that reason, the
use of an executive composite z score constructed from
specific tests such as sorting and category tests, the Port-
teus Maze Test, and the Tower of London Puzzle would
be more accurate to test the executive functions against
metabolite measures.

DISEASE PROGRESSION MODEL

Figure 3. Graphs showing statistically significant Pearson correlations
between cognitive scores and 1H magnetic resonance spectroscopic
metabolite ratios in specific brain regions for patients with Alzheimer
disease. A, Between verbal memory performance as measured by the
learning (triangles) and word recall (squares) scores of the California Verbal
Learning Test, and the mI/H2O ratio in the left medial temporal lobe. B, Between language performance as measured by the
Boston Naming Test and the myo-inositol (ml)/H2O ratio in the left
parietotemporal cortex. C, Between visuoconstructional abilities as measured
by the Rey Complex Figure Test and the ml/H2O ratio in the right
parietotemporal cortex. Statistical parameters are listed in Table 4.
Metabolite ratios are multiplied by 1000 and broken lines serve merely to
guide the eye.

(960) ARCH NEUROL / VOL 59, JUNE 2002 WWW.ARCHNEUROL.COM

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adjacent neocortex), usually mark the onset of clinical symptoms of AD. The correlation observed between decreased NAA/H$_2$O ratios measured in the left MTL and verbal memory deficits (learning and word recall memory scores, Figure 3A) in patients with AD supports the role of the MTL in recent memory function. Moreover, since NAA is a neuronal marker, our results suggest a correlation between memory dysfunction and the degree of neuronal loss or damage in the left MTL of patients with AD. This is consistent with previously reported correlations between memory impairment and hippocampal pathology determined by neurofibrillary tangle counts as well as hippocampal atrophy estimated by volumetric magnetic resonance imaging in patients with AD. Higher cortical functions such as language, visuoconstructional and executive functions that decline later in the disease course, are associated with destruction of neocortical association areas. Although neuronal integrity of the associative cortices seems preserved, as suggested by the absence of significant changes in NAA/H$_2$O levels in both the PTC and the right FC, the ml/H$_2$O increases in the left and right PTCs correlated inversely with language and visuoconstructional performances, respectively, in accord with an early AD phase. In Braak and Braak’s staging model of AD, the neocortical stages (V and VI) that correspond to the conventional neuropathologic criteria for clinical AD diagnosis, are marked by severe destruction of neocortical association areas while limbic stages (III and IV) show a much less extensive destruction of the neocortex with no macroscopically detectable atrophy. Since cognitive functions are impaired, as demonstrated by correlations with increased ml/H$_2$O ratios (Figures 3B, C), and since the disease is still in its early stages, as evidenced by the relatively high Mini-Mental State Examination scores (Table 2) and Clinical Dementia Rating global staging scores, it seems as if the disease of our patients corresponds to a clinical incipient AD presumably with mild changes in the associative cortices. Indeed, it is well known that patients in the early stages of AD present heterogeneous patterns of cognitive impairment with considerable between-patients score discrepancies for language, visuoconstructional, and executive dysfunction assessment. This cognitive dysfunction variability among patients tends to fade with the evolution of the disease. Our metabolic-functional correlations reinforce the hypothesis that the ml level increase characterizes the initial stages of the disease and precedes the NAA level loss.

The results of this study demonstrate that clear correlations can be observed when MRS data are compared with scores from specific cognitive tests associated with AD-relevant regions. The use of tests measuring specific cognitive functions instead of a screening test of the general mental status, which has been used in most reported studies, provides a more detailed characterization of functional brain abnormalities in AD. Because of the substantial overlap for some metabolite ratios between the 2 groups, our findings have limited value for clinical diagnosis in individual patients. However, our data on specific brain regions support established models of disease progression within the brain and are consistent with functional laterality of the brain. More support for understanding the course of neurochemical changes in AD could be provided by a longitudinal follow-up study of the same cohort of patients.

Accepted for publication February 11, 2002.

**Author contributions:** Study concept and design (Ms Chantal, Mr Labelle, and Drs Bouchard, Braun, and Boulander); acquisition of data (Ms Chantal, Mr Labelle, and Dr Boulander); analysis and interpretation of data (Ms Chantal, Mr Labelle, and Dr Boulander); drafting of the manuscript (Ms Chantal and Dr Boulander); critical revision of the manuscript for important intellectual content (Ms Chantal, Mr Labelle, and Drs Bouchard, Braun, and Boulander); statistical expertise (Ms Chantal); obtained funding (Ms Chantal and Dr Bouchard); administrative, technical, and material support (Mr Labelle and Drs Braun and Boulander); study supervision (Drs Bouchard, Braun, and Boulander).

This work was supported by grants from the Fondation et Département de la Recherche, Hôpital de l’Enfant-Jésus du CHA, Québec City, and by a scholarship from the Alzheimer Society of Canada, Toronto, Ontario (Ms Chantal).

We thank Andrée Morin, RN, for her assistance with patient recruitment and Abdesslem Khiat, PhD, for helpful discussions.

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