Alzheimer's & Dementia: Translational Research & Clinical Interventions 3 (2017) 107-113

Alzheimer's & Dementia

Featured Article

The prevalence and biomarkers' characteristic of rapidly progressive Alzheimer's disease from the Alzheimer's Disease Neuroimaging Initiative database

Maowen Ba[a,b], Xiaofeng Li[b,c], Kok Pin Ng[b,d], Tharick A. Pascoal[b], Sulantha Mathotaarachchi[b], Pedro Rosa-Neto[b], Serge Gauthier[b,*], and the Alzheimer's Disease Neuroimaging Initiative[1]

[a]*Department of Neurology, Yantai Yuhuangding Hospital Affiliated to Qingdao Medical University, Shandong, People's Republic of China*
[b]*Alzheimer's Disease Research Unit, McGill Centre for Studies in Aging, McGill University, Douglas Institute, Montreal, Quebec, Canada*
[c]*Department of Neurology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, People's Republic of China*
[d]*Department of Neurology, National Neuroscience Institute, Singapore*

Abstract

Introduction: The prevalence and detailed biomarkers' characteristic of rapidly progressive Alzheimer's disease (rpAD) remain incompletely understood.
Methods: A total of 312 mild AD patients from the Alzheimer's Disease Neuroimaging Initiative database were chosen and dichotomized into rpAD and non-rpAD groups. We performed the prevalence and comprehensive biomarker evaluation.
Results: The prevalence of rpAD was 17.6% in mild AD. Compared with non-rpAD, there were no differences in *APOE* ε4/ε4, *APOE* ε3/ε4, and *APOE* ε2/ε4 genotype distribution, cerebrospinal fluid tau, phosphorylated tau (p-tau), amyloid-β, hippocampus volume, and amyloid deposition in rpAD. Yet, a lower p-tau/tau ratio was observed in rpAD ($P = .04$). rpAD showed region-specific hypometabolism ([18F]fluorodeoxyglucose-positron emission tomography [FDG-PET]) ($P = .001$). Receiver-operating characteristic analysis of FDG-PET demonstrated that left angular and left temporal cortices were the regions with higher area under the curve and predictive value for identifying clinical at-risk rpAD.
Discussion: We identified that rpAD commonly existed in mild AD. Cerebral hypometabolism could provide potential clinical differential value for rpAD in the short-term follow-up period.

Keywords: Alzheimer's disease; Biomarkers; Rapidly progressive dementia

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative dementia, which severely affects daily life [1,2]. The rapidly progressive Alzheimer's disease (rpAD) can be defined by a steeply decline on psychometric test [1–5], such as Mini-Mental State Examination (MMSE) score, (e.g., ≥4 points within 6 months) [1,5]. This definition is generally thought to select AD patients with more rapid pathophysiological and functional activity declines and high mortality rate [1–5]. The prevalence of rpAD found in the literature varied greatly across different studies and conceptual definitions [2,3]. Therefore, reliable results in large-scale populations are crucial to better characterize these set of individuals for future clinical trials designed to test interventions able to mitigate the aggressive disease progression in this population. So, studies of prevalence of rpAD in a

The authors have no conflicts of interest to report.

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

*Corresponding author. Tel.: 1-514-766-2010; Fax: 1-514-888-4050.
E-mail address: serge.gauthier@mcgill.ca

http://dx.doi.org/10.1016/j.trci.2016.12.005

larger study population such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) database are highly desirable [6].

Recent studies have shown that several biomarker modalities can predict cognitive decline in AD populations, including glucose hypometabolism measured by uptake of [18F]fluorodeoxyglucose in positron emission tomography (FDG-PET) [7,8], hippocampal atrophy in magnetic resonance imaging (MRI) [9], decreased cerebrospinal fluid (CSF) amyloid-β ($A\beta_{1–42}$), increased CSF total tau (t-tau) and phosphorylated tau (p-tau) [8,10–12], and the *APOE* genotype [1,13–15]. However, parts of these results remain inconsistent. Moreover, these biomarkers were separately tested in different study during longer follow-up period. Therefore, when AD patients were dichotomized into rpAD and non-rpAD based on MMSE score loss $\geq$4 points within 6 months, for such a given population of rpAD, which biomarkers more correlate with the rapidly cognitive decline during the short-term follow-up period still need to be verified in the same AD population. Based on this idea, we decided to investigate the prevalence and comprehensive biomarkers' characteristic of rpAD patients from ADNI database in the same population, which could contribute to a better understanding of the disease in this population.

2. Methods

2.1. Study samples

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early Alzheimer's disease (AD). Further information can be found at http://www.adni-info.org/.

2.2. Participants

The operational definition of mild AD were patients with MMSE score of 20–26, clinical dementia rating >0.5, absence of any other neuropsychiatric disorders, and who meet the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD [16]. Further information about the inclusion/exclusion criteria of AD adopted by the ADNI is described in detail at www.adni-info.org. According to the definition of MMSE score loss $\geq$4 points within 6 months [1,5], the mild AD patients were allocated to the rpAD and non-rpAD groups. Alzheimer's Disease Assessment Scale—Cognitive Subscale consisting of 13 items (ADAS-Cog 13) and Functional Activity Questionnaire (FAQ), as gold standard comparisons of cognition and function measures, were also checked over 12 months in the present study.

2.3. CSF data

CSF $A\beta_{1–42}$, t-tau, and p-tau at threonine 181 were measured by using Innogenetics (INNO-BIA AlzBio3) immunoassay kit–based reagents in the multiplex xMAPLuminex platform (Luminex) as previously described [17]. The CSF data used in this study were obtained from the ADNI files "UPENNBIOMK5-8.csv." Further details of ADNI methods for CSF acquisition and measurements and quality control procedures can be found at www.adni-info.org.

2.4. Neuroimaging data

The neuroimaging data, including regional volume on MRI, white matter hyperintensity (WMH) on MRI, cerebral glucose metabolism on FDG uptake (FDG-PET), and cortical amyloid burden via standardized uptake values ratios (SUVRs) on Florbetapir-PET, were obtained from the ADNI files "UCSFFSL_11_02_15," "UCSFFSX51_11_02_15_V2," "UCD_ADNI1_WMH.csv," "UCD_ADNI2_WMH_10_26_15.csv," "UCBERKELEY FDG_07_30_15.csv," and "UCBERKELEYAV45_06_15_16.csv." The neuroimaging techniques used by ADNI have been reported previously [18,19]. To investigate neurodegeneration, we used the hippocampal volume and FDG-PET uptake from five brain regions (left angular gyrus, right angular gyrus, bilateral posterior cingular, left inferior temporal gyrus, and right inferior temporal gyrus). The WMH volume, a cerebrovascular disease marker, was also obtained. We also obtained the SUVR means of Florbetapir-PET from four regions (frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal) and global Florbetapir-PET SUVR (average precuneus, prefrontal, orbitofrontal, parietal, temporal, anterior, and posterior cingulate cortices) to calculate the amyloid burden. Further details regarding ADNI image acquisition and processing can be found at www.adni-info.org/methods.

2.5. Statistical analysis

Demographic, clinical, and biological data were compared between study groups using two-tailed Student *t* test for continuous variables and chi-square (χ^2) tests for categorical variables, respectively. The original data of CSF biomarkers were presented. However, the statistical analyses were further replicated after log conversion to get normal distribution. Post hoc pairwise comparisons were also performed using a general linear model. The effects of age, gender, education, and *APOE* genotype were adjusted for all pairwise comparisons. Bivariate logistic regression analysis was also performed to regress group status on CSF biomarkers. Receiver-operating characteristic (ROC) analysis was performed to find the cut-off value of biomarker. The highest area under the curve (AUC) and Youden index (Youden index = sensitivity + specificity − 1) were used to select the cut-off value of biomarker's measurement. In general, a test is acceptable in clinical efficacy if its

AUC of ROC is not <0.70 [20]. The "*k*-fold" cross-validation was used to evaluate the performance of the prediction model. The original sample is randomly partitioned into *k* equal-sized subsamples. Of the *k* subsamples, a single subsample is retained as the validation data for testing the model, and the remaining $k - 1$ subsamples are used as training data. The cross-validation process is then repeated *k* times (the folds), with each of the *k* subsamples used exactly once as the validation data. The *k* results from the folds can then be averaged to produce a single estimation.

Statistical analyses were performed using SPSS (version 19.0), and a *P*-value <.05 was taken as statistically significant.

3. Results

3.1. Demographic and clinical characteristics

The present study included 312 mild AD participants. Table 1 lists the detailed characteristics of all these AD participants. According to the definition of MMSE score loss ≥4 points within 6 months, we divided the mild AD group to the rpAD and non-rpAD. There were no differences in gender, age, education, baseline MMSE score, and *APOE* ε4/ε4, *APOE* ε3/ε4, and *APOE* ε2/ε4 genotype distribution between groups. In addition, the percentage of *APOE* ε4/ε4 homozygotes were 14.5% and 20.6% in rpAD and non-rpAD group, respectively. The prevalence of rpAD patients ($n = 55$) was 17.6% in ADNI mild AD population. During the 6-month follow-up period, mean MMSE score loss for rpAD was 5.9455 ± 2.4975 and 0.1128 ± 2.1394 for non-rpAD ($P < .000$). Meanwhile, baseline ADAS-Cog 13 and ADAS-Cog 13 loss were higher in rpAD group. In addition, over the 12-month follow-up period, rpAD subjects continued their rapidly cognitive and functional decline, as reflected in ADAS-Cog 13 and FAQ measures (Fig. 1).

Yet, there were no differences in MMSE and ADAS-Cog 13 score loss between positive *APOE* ε4/ε4, *APOE* ε3/ε4, *APOE* ε2/ε4, and negative *APOE* ε3/ε3 rpAD patients (Table 2).

3.2. CSF biomarkers

Among the 312 AD participants, there were 216 with available CSF tau, p-tau, and $A\beta_{1–42}$ data. The final data for CSF analyses included 37 rpAD and 179 non-rpAD participants. CSF biomarker levels by study groups were also demonstrated in Table 1. There were no differences in baseline concentration of CSF tau, p-tau, and $A\beta_{1–42}$ between two groups. For tau/$A\beta_{1–42}$ ratio, there was a trend for higher levels in rpAD in comparison with non-rpAD ($P = .099$). CSF p-tau/tau ratio was lower in rpAD patients compared with non-rpAD (0.37 ± 0.15 vs. 0.44 ± 0.21, $P = .04$). Further, we analyzed the association between baseline CSF biomarkers and group status. Yet, the associations were absent in CSF biomarkers such as $A\beta_{1–42}$ (slope

Table 1
Demographics and key sample characteristics

Characteristics	rpAD	Non-rpAD	*P* value
Numbers	55	257	
Age, y	74.7386 ± 7.1265	75.0004 ± 7.8062	.819
Males, *n* (%)	28 (50.9%)	145 (56.4%)	.551
Education, y	15.3455 ± 2.7502	15.1323 ± 3.0075	.629
APOE, *n* (%)	39 (70.9%)	174 (67.7%)	.761
APOE ε4/ε4	14.5%	20.6%	.353
APOE ε3/ε4	56.4%	47.1%	.236
APOE ε2/ε4			
MMSE score (baseline)	23.1091 ± 2.0337	23.3385 ± 2.0421	.45
MMSE loss in 6 mo	5.9455 ± 2.4975	0.1128 ± 2.1394	.000*
ADAS-Cog13 (baseline)	36.25 ± 8.52	28.19 ± 7.03	.000*
ADAS-Cog13 loss in 6 mo	5.40 ± 6.63	1.93 ± 4.61	.000*
CSF t-tau (pg/mL)	128.31 ± 55.90	126.69 ± 63.40	.887
CSF p-tau (pg/mL)	44.91 ± 24.15	52.69 ± 31.63	.159
CSF Aβ1–42 (pg/mL)	135.44 ± 27.99	141.05 ± 41.66	.434
p-tau/tau	0.37 ± 0.15	0.44 ± 0.21	.04*
tau/Aβ1–42	1.005 ± 0.54	0.83 ± 0.57	.099
p-tau/Aβ–142	0.36 ± 0.29	0.34 ± 0.33	.63
Left hippocampal volume, mm^3	2831.86 ± 516.16	2836.16 ± 517.77	.955
Right hippocampal volume, mm^3	2785.04 ± 589.79	2907.81 ± 556.19	.143
WMH	4.13 ± 7.43	4.02 ± 6.31	.911
Florbetapir-PET global SUVR	1.3974 ± 0.2568	1.3945 ± 0.2043	.955

Abbreviations: rpAD, rapidly progressive Alzheimer's disease; *APOE*, apolipoprotein E; MMSE, Mini-Mental State Examination; ADAS-Cog 13, Alzheimer's Disease Assessment Scale—Cognitive Subscale consisting of 13 items; CSF tau, cerebrospinal fluid tau; CSF p-tau, cerebrospinal fluid phosphorylated tau; CSF Aβ, cerebrospinal fluid β-amyloid; Florbetapir-PET cortical SUVR, summary Florbetapir cortical standardized uptake value ratio by positron emission tomography; WMH, white matter hyperintensity; FDG-PET, [18F]fluorodeoxyglucose-positron emission tomography.

NOTE. Results are mean ± standard deviation.

**P* values are statistically significant.

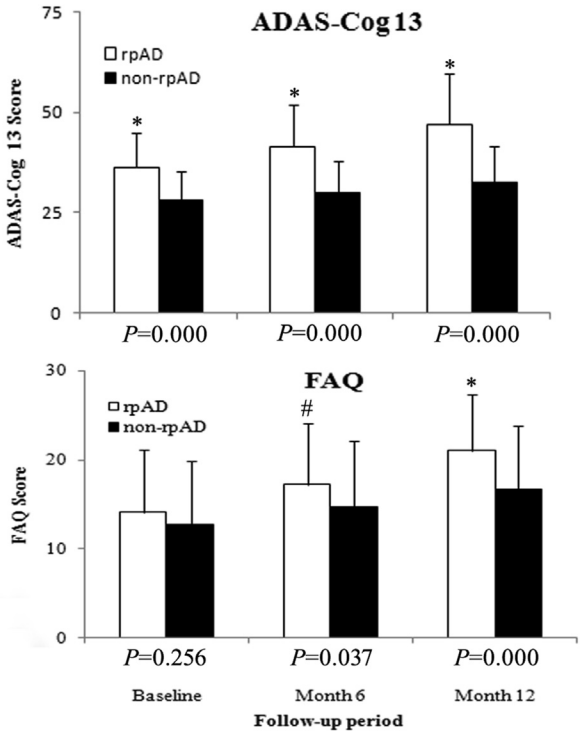

Fig. 1. Changes of ADAS-Cog 13 and FAQ measures over the 12 months in rpAD and non-rpAD. Results are mean ± standard deviation. *P* value was assessed using two-tailed Student *t* test for each variable; # and * denote that *P* values are statistically significant. Abbreviations: rpAD, rapidly progressive Alzheimer's disease; ADAS-Cog 13, Alzheimer's Disease Assessment Scale—Cognitive Subscale consisting of 13 items; FAQ, Functional Activity Questionnaire.

coefficient [β] = 0.009, P = .137), tau (β = –0.006, P = .206), and p-tau (β = 0.024, P = .051).

3.3. Neuroimaging biomarker analysis

Among the 312 AD participants, there were 308 with available data on hippocampus volume and WMH (MRI). The final data for MRI analyses included 55 rpAD and 253 non-rpAD participants. There were no differences in baseline hippocampus volume and WMH between two groups (Table 1).

Table 2
MMSE and ADAS-Cog 13 characteristics of rpAD by *APOE* genotype

Measure	*APOE* εX/ε4	*APOE* ε3/ε3	*P* value
Numbers	39	16	
MMSE	23.08 ± 2.16	23.19 ± 1.76	.857
MMSE loss in 6 mo	6.05 ± 2.71	5.69 ± 1.92	.628
ADAS-Cog 13	35.86 ± 9.13	38.06 ± 7.36	.397
ADAS-Cog 13 loss in 6 mo	5.79 ± 7.06	5.30 ± 4.25	.795

Abbreviations: rpAD, rapidly progressive Alzheimer's disease; *APOE*, apolipoprotein E; *APOE* εX/ε4, *APOE* ε4/ε4, *APOE* ε3/ε4, and *APOE* ε2/ε4; MMSE, Mini-Mental State Examination; ADAS-Cog 13, Alzheimer's Disease Assessment Scale—Cognitive Subscale consisting of 13 items.

NOTE. Results are mean ± standard deviation.

Among the 312 AD participants, there were 203 with available FDG-PET data. The final data for FDG-PET analyses included 39 rpAD and 164 non-rpAD participants. In the further analysis of hypometabolic regions via FDG-PET in baseline and 6-month follow-up period, the significant differences between rpAD and non-rpAD were especially located in left angular and left temporal cortices ($P < .05$, Table 3).

By the use of "9-fold" cross-validation, the FDG-PET of left angular and left temporal obtained significant prediction value for rpAD (AUC > 0.70, $P = .000$, Table 4). AUC of the left angular FDG-PET was 0.73 with both high sensitivity (71.8%) and specificity (60.2%), and the corresponding cut-off value was 1.01. AUC of the left temporal FDG-PET was 0.71 with both high sensitivity (68.6%) and specificity (61.9%), and the corresponding cut-off value was 0.98.

Among the 312 AD participants, there were 131 with available data on cortical amyloid deposition (Florbetapir-PET). The final data for Florbetapir-PET analyses included 23 rpAD and 108 non-rpAD participants. There were no differences in baseline Florbetapir-PET from global and four regions (frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal) between two groups (Tables 1 and 5).

4. Discussion

The present study demonstrates a comprehensive assessment about the prevalence and multiple biomarkers' characteristic of rpAD patients from the ADNI database. We have four important findings: (1) the prevalence of rpAD patients was 17.6% in mild AD according to the definition of MMSE score loss ≥ 4 points within 6 months, (2) *APOE* genotype seemed to have no effect on rpAD, (3) there was lower p-tau/tau ratio in rpAD, and (4) rpAD patients showed significant region-specific hypometabolism (FDG-PET) especially in left angular and left temporal cortices.

The present study confirmed that rpAD commonly existed in mild AD with 17.6% prevalence. This findings is consistent with the previous reports showing that 10% to 30% of mild AD patients manifest rpAD [1,2]. It is important to mention that different prevalence of rpAD among studies might be caused by different definitions of rapidly cognitive decline, as reflected in the MMSE score loss. A general but clinically useful definition of rapidly progressive course of AD may be "an obvious deterioration in patient status with a short period (6–12 months)." We defined rpAD according to MMSE score loss ≥4 points within 6 months, which represented a higher risk of institutionalization and mortality rate as reported previously [1,5]. The rapid cognitive and functional changes were also well captured by the ADAS-Cog 13 and FAQ over 12 months. Thus, we confirmed that the rapid changes observed in the MMSE were reflected in different cognitive and functional measures. The rpAD definition of MMSE score loss≥ 4 points within 6 months could be very informative. Meanwhile, the 6-month follow-up

Table 3
FDG-PET characteristics of rpAD in different regions

	Baseline			Month 6		
Measure	rpAD	Non-rpAD	*P* value	rpAD	Non-rpAD	*P* value
Angular left	0.9792 ± 0.1716	1.0829 ± 0.1739	.000*	0.9349 ± 0.1699	1.0594 ± 0.1740	.005*
Angular right	1.0063 ± 0.1678	1.0942 ± 0.1785	.003*	0.9756 ± 0.1559	1.0542 ± 0.1716	.065
Cingulum (post)	1.1071 ± 0.1567	1.1484 ± 0.1604	.125	1.0554 ± 0.1324	1.0990 ± 0.1502	.236
Temporal left	0.9462 ± 0.1710	1.0438 ± 0.1540	.000*	0.9266 ± 0.1649	1.0324 ± 0.1647	.012*
Temporal right	1.0089 ± 0.0.1763	1.0864 ± 0.1560	.004*	0.9947 ± 0.1682	1.0572 ± 0.1672	.139

Abbreviations: rpAD, rapidly progressive Alzheimer's disease; FDG-PET, [18F]fluorodeoxyglucose-positron emission tomography.
NOTE. Results are mean ± standard deviation.
**P* values are statistically significant.

period seemed to be a practical interval in clinical practice in deciding to use and change drug treatment. Thus, based on 6-month cut-off value, a proportion of AD patients really have a rapid course of disease.

The *APOE* is the most important genetic risk factor for sporadic AD. *APOE* genotype influences onset age of AD [21–23]. Yet, it is still a matter of debate whether *APOE* genotype would predict the progression of AD [1]. Many studies have failed to connect the presence of *APOE* genotype to cognitive decline because of the fact that it is dependent on disease severity [14]. Our results support this notion showing that in mild AD there was no difference in frequency of *APOE* ε4/ε4, *APOE* ε3/ε4, and *APOE* ε2/ε4 occurrence between rpAD and non-rpAD. In addition, there was no difference in MMSE and ADAS-Cog 13 score loss in *APOE* ε4/ε4, *APOE* ε3/ε4, *APOE* ε2/ε4 positive, and *APOE* ε3/ε3 negative rpAD patients. Thus, our data demonstrate that *APOE* genotype does not increase the risk and severity of rpAD in the mild stage of disease. However, a positive association of cognitive decline with *APOE* genotype was found in several studies [15,24]. Yet, we must point out that there are still many differences in the selected measures, the number of patients, duration of follow-up, and visiting interval between the present study and others. In this study, we focused on rapidly cognitive decline in 6 month short-term duration of follow-up. In the future, one more frequent and prolonged evaluation should occur to understand *APOE* genotype effect on the rapidly progressive course in mild AD.

CSF biomarkers, such as increased tau and p-tau and decreased $A\beta_{1–42}$, are useful diagnostic marker for AD. Yet, the results remain inconsistent in predicting progression of AD by CSF biomarkers [10–12]. Recent longitudinal studies have found a relation between CSF biomarkers and disease progression, which indicated that a combination of high CSF t-tau without proportionally elevated p-tau, and high tau/$A\beta_{1–42}$ ratio is related to a rapidly cognitive decline [10]. We must point out that the conclusions about CSF biomarkers as predictors of disease progression were more suitable with longer follow-up period. In the present study, AD patients were dichotomized into rpAD and non-rpAD based on MMSE score loss $\geq$4 points within 6 months. During the short-term follow-up period, we found that there were no obvious differences in baseline concentration of CSF tau, p-tau, and $A\beta_{1–42}$ in rpAD and non-rpAD group. Regression analysis also did not showed causal relationship between group status and CSF tau, p-tau, and $A\beta_{1–42}$. Interestingly, in comparison with non-rpAD, a trend for higher tau/$A\beta_{1–42}$ ratio and lower p-tau/tau ratio in rpAD was observed, which could reflect adjoint relationship and offer differential value for rpAD during the short-term follow-up period. In the literature, higher tau/$A\beta_{1–42}$ ratio reflected the pathology of AD with increased tau and decreased $A\beta_{1–42}$. CSF t-tau represents one common biomarker for neuronal degeneration [25–29]. P-tau is one more specific biomarker for AD and is related to neurofibrillary tangles [30–32]. The lower p-tau/tau ratio indicated a low rate of p-tau and seemed contrary to general knowledge for high p-tau, which was associated with main AD pathology. Recent evidence demonstrated that p-tau can benefit the neurons via preventing against an acute apoptosis, instead resulting in neurodegeneration [33–35]. This could suggest

Table 4
Efficacy of FDG-PET in predicting rpAD

Measures	AUC	95% CI	*P*	Cut-off	Sensitivity	Specificity	Accuracy
Angular left	0.73	0.71–0.74	.000*	1.01	71.8	60.2	69.6
Angular right	0.65	0.64–0.66	.000*	1.09	57.4	67.5	60
Cingulum (post)	0.59	0.57–0.61	.013*	1.03	81.5	43.6	72.8
Temporal left	0.71	0.69–0.73	.000*	0.98	68.6	61.9	68
Temporal right	0.63	0.61–0.64	.001*	0.96	79.9	46.6	72.5

Abbreviations: rpAD, rapidly progressive Alzheimer's disease; FDG-PET, [18F]fluorodeoxyglucose-positron emission tomography; AUC, area under the curve; CI, confidence interval.
NOTE. Results are mean ± standard deviation.
**P* values are statistically significant.

Table 5
Florbetapir-PET characteristics of rpAD in different regions

Measures	rpAD	Non-rpAD	*P* value
Frontal	1.5995 ± 0.3435	1.5780 ± 0.2702	.746
Cingulate	1.6807 ± 0.3477	1.6785 ± 0.2701	.974
Parietal	1.6149 ± 0.3601	1.5776 ± 0.2598	.568
Temporal	1.4923 ± 0.3262	1.4706 ± 0.2525	.728

Abbreviations: rpAD, rapidly progressive Alzheimer's disease; Florbetapir-PET cortical SUVR, summary Florbetapir cortical standardized uptake value ratio by positron emission tomography.

NOTE. Results are mean ± standard deviation.

that p-tau has compensatory or protective effect. From this point of view, lower p-tau/tau ratio suggests higher neurodegeneration and more rapidly cognitive decline.

Previous research reported that hippocampus atrophy rate correlated with cognitive decline rate over time in AD [9,36]. Yet, during the short-term follow-up period, the change of MRI hippocampus volume did not offer differential value for rpAD. Similarly, baseline cortical amyloid deposition (Florbetapir-PET) in mild AD did not show useful information for rpAD in the relative short-term follow-up period. Our research revealed that the baseline hypometabolism (FDG-PET) was lower in rpAD patients compared with non-rpAD, which persisted in the 6-month follow-up period. Hypometabolism difference was region specific and located in left angular and left temporal cortices. Our ROC analysis of FDG-PET also clearly demonstrated that left angular and left temporal cortices were the regions with higher AUC and predictive value for the diagnosis of rpAD. Thus, hypometabolism in FDG-PET in AD-related regions might be a sensitive neuroimaging marker for the early detection of rpAD before MRI hippocampus atrophy and cortical amyloid deposition.

Taken together, by using the high-quality ADNI database, we identified that rpAD commonly existed in mild AD. Cerebral hypometabolism and lower p-tau/tau ratio could provide potential clinical differential value for rpAD in the short-term follow-up period. Our findings could have significance for clinical practice and randomized clinical trial.

Acknowledgments

This work was supported by the Canadian Institutes of Health Research (CIHR, MOP-11-51-31), Prevent-AD scholarship (T.A.P.), Canadian Consortium of Neurodegeneration in Aging (CIHR-CCNA), the Weston Brain Institute, and the Alzheimer's Association (NIRG-08-92090). S.G. and P.R-N. are members of the CIHR-CCNA Canadian Consortium of Neurodegeneration in Aging. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer, Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuroimaging at the University of Southern California.

RESEARCH IN CONTEXT

1. Systematic review: We reviewed the literature using PubMed and reference lists from relevant articles. The prevalence and detailed biomarkers' characteristic of rapidly progressive Alzheimer's disease (rpAD) remain incompletely understood. There have been several recent publications describing rpAD. These relevant citations are appropriately cited.
2. Interpretation: Our study demonstrated a comprehensive assessment about the prevalence and multiple biomarkers' characteristic of rpAD patients in short-term follow-up period. We found that rpAD commonly existed and cerebral region-specific hypometabolism could provide clinical predictive value for identifying rpAD.
3. Future directions: Our study contributed to a better understanding of rpAD. These findings are crucial to better characterize these set of individuals for future clinical trials designed to test interventions able to mitigate the aggressive disease progression in this population.

References

[1] Soto ME, Andrieu S, Arbus C, Ceccaldi M, Couratier P, Dantoine T, et al. Rapid cognitive decline in Alzheimer's disease. Consensus paper. J Nutr Health Aging 2008;12:703–13.

[2] Sona A, Ellis KA, Ames D. Rapid cognitive decline in Alzheimer's disease: a literature review. Int Rev Psychiatry 2013;25:650–8.

[3] Schmidt C, Wolff M, Weitz M, Bartlau T, Korth C, Zerr I. Rapidly progressive Alzheimer disease. Arch Neurol 2011;68:1124–30.

[4] Gauthier S, Vellas B, Farlow M, Burn D. Aggressive course of disease in dementia. Alzheimers Dement 2006;2:210–7.

[5] Soto ME, Andrieu S, Cantet C, Reynish E, Ousset PJ, Arbus C, et al. Predictive value of rapid decline in mini mental state examination in clinical practice for prognosis in Alzheimer's disease. Dement Geriatr Cogn Disord 2008;26:109–16.

[6] Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack CR, Jagust W, et al. Ways toward an early diagnosis in Alzheimer's disease: the Alzheimer's Disease Neuroimaging Initiative (ADNI). Alzheimers Dement 2005;1:55–66.

[7] Mosconi L. Brain glucose metabolism in the early and specific diagnosis of Alzheimer's disease. FDG-PET studies in MCI and AD. Eur J Nucl Med Mol Imaging 2005;32:486–510.

[8] Andriuta D, Moullart V, Schraen S, Devendeville A, Meyer ME, Godefroy O, et al. What are the most frequently impaired markers of neurodegeneration in ADNI subjects? J Alzheimers Dis 2016; 51:793–800.

[9] Jack CR Jr, Shiung MM, Gunter JL, O'Brien PC, Weigand SD, Knopman DS, et al. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. Neurology 2004; 62:591–600.

[10] Kester MI, van der Vlies AE, Blankenstein MA, Pijnenburg YA, van Elk EJ, Scheltens P, et al. CSF biomarkers predict rate of cognitive decline in Alzheimer disease. Neurology 2009;73:1353–8.

[11] Snider BJ, Fagan AM, Roe C, Shah AR, Grant EA, Xiong C, et al. Cerebrospinal fluid biomarkers and rate of cognitive decline in very mild dementia of the Alzheimer type. Arch Neurol 2009;66:638–45.

[12] Stefani A, Martorana A, Bernardini S, Panella M, Mercati F, Orlacchio A, et al. CSF markers in Alzheimer disease patients are not related to the different degree of cognitive impairment. J Neurol Sci 2006;251:124–8.

[13] Cosentino S, Scarmeas N, Helzner E, Glymour MM, Brandt J, Albert M, et al. APOE epsilon 4 allele predicts faster cognitive decline in mild Alzheimer disease. Neurology 2008;70:1842–9.

[14] Holmes C. Genotype and phenotype in Alzheimer's disease. Br J Psychiatry 2002;180:131–4.

[15] Martins CA, Oulhaj A, de Jager CA, Williams JH. APOE alleles predict the rate of cognitive decline in Alzheimer disease: a nonlinear model. Neurology 2005;65:1888–93.

[16] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–44.

[17] Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol 2009; 65:403–13.

[18] Risacher SL, Saykin AJ. Neuroimaging and other biomarkers for Alzheimer's disease: the changing landscape of early detection. Annu Rev Clin Psychol 2013;9:621–48.

[19] Zhang D, Wang Y, Zhou L, Yuan H, Shen D. Alzheimer's Disease Neuroimaging Initiative. Multimodal classification of Alzheimer's disease and mild cognitive impairment. Neuroimage 2011; 55:856–67.

[20] Viccaro LJ, Perera S, Studenski SA. Is timed up and go better than gait speed in predicting health, function, and falls in older adults? J Am Geriatr Soc 2011;59:887–92.

[21] Yu JT, Tan L, Hardy J. Apolipoprotein E in Alzheimer's disease: an update. Annu Rev Neurosci 2014;37:79–100.

[22] Kim J, Basak JM, Holtzman DM. The role of apolipoprotein E in Alzheimer's disease. Neuron 2009;63:287–303.

[23] Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 1997;278:1349–56.

[24] Hirono N, Hashimoto M, Yasuda M, Kazui H, Mori E. Accelerated memory decline in Alzheimer's disease with apolipoprotein epsilon4 allele. J Neuropsychiatry Clin Neurosci 2003;15:354–8.

[25] Riemenschneider M, Wagenpfeil S, Vanderstichele H, Otto M, Wiltfang J, Kretzschmar H, et al. Phospho-tau/total tau ratio in cerebrospinal fluid discriminates Creutzfeldt-Jakob disease from other dementias. Mol Psychiatry 2003;8:343–7.

[26] Buerger K, Otto M, Teipel SJ, Zinkowski R, Blennow K, DeBernardis J, et al. Dissociation between CSF total tau and tau protein phosphorylated at threonine 231 in Creutzfeldt-Jakob disease. Neurobiol Aging 2006;27:10–5.

[27] Hesse C, Rosengren L, Andreasen N, Davidsson P, Vanderstichele H, Vanmechelen E, et al. Transient increase in total tau but not phospho-tau in human cerebrospinal fluid after acute stroke. Neurosci Lett 2001;297:187–90.

[28] van der Vlies AE, Verwey NA, Bouwman FH, Blankenstein MA, Klein M, Scheltens P, et al. CSF biomarkers in relationship to cognitive profiles in Alzheimer disease. Neurology 2009;72:1056–61.

[29] Arai H, Morikawa Y, Higuchi M, Matsui T, Clark CM, Miura M, et al. Cerebrospinal fluid tau levels in neurodegenerative diseases with distinct tau-related pathology. Biochem Biophys Res Commun 1997; 236:262–4.

[30] Itoh N, Arai H, Urakami K, Ishiguro K, Ohno H, Hampel H, et al. Large-scale, multicenter study of cerebrospinal fluid tau protein phosphorylated at serine 199 for the antemortem diagnosis of Alzheimer's disease. Ann Neurol 2001;50:150–6.

[31] Buerger K, Ewers M, Pirttilä T, Zinkowski R, Alafuzoff I, Teipel SJ, et al. CSF phosphorylated tau protein correlates with neocortical neurofibrillary pathology in Alzheimer's disease. Brain 2006; 129:3035–41.

[32] Schoonenboom NS, Pijnenburg YA, Mulder C, Rosso SM, Van Elk EJ, Van Kamp GJ, et al. Amyloid beta(1-42) and phosphorylated tau in CSF as markers for early-onset Alzheimer disease. Neurology 2004; 62:1580–4.

[33] Li HL, Wang HH, Liu SJ, Deng YQ, Zhang YJ, Tian Q, et al. Phosphorylation of tau antagonizes apoptosis by stabilizing beta-catenin, a mechanism involved in Alzheimer's neurodegeneration. Proc Natl Acad Sci U S A 2007;104:3591–6.

[34] Rametti A, Esclaire F, Yardin C, Terro F. Linking alterations in tau phosphorylation and cleavage during neuronal apoptosis. J Biol Chem 2004;279:54518–28.

[35] Andorfer C, Acker CM, Kress Y, Hof PR, Duff K, Davies P. Cell-cycle reentry and cell death in transgenic mice expressing nonmutant human tau isoforms. J Neurosci 2005;25:5446–54.

[36] Li B, Shi J, Gutman BA, Baxter LC, Thompson PM, Caselli RJ, et al. Influence of APOE Genotype on Hippocampal Atrophy over Time—An N=1925 Surface-Based ADNI Study. PLoS One 2016; 11:e0152901.