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REGULAR ARTICL

Pineal volume reduction in patients with mild cognitive impairment who converted to Alzheimer's disease

Teruyuki Matsuoka, MD, PhD [1]* Nozomu Oya, MD,[1] Hajime Yokota, MD, PhD,[2] Kentaro Akazawa, MD, PhD,[3] Kei Yamada, MD, PhD,[3] Jin Narumoto, MD, PhD[1] and for the Alzheimer's Disease Neuroimaging Initiative[†]

Aim: Pineal parenchymal volume (PPV) reduction is one of the predisposing factors for Alzheimer's disease (AD). Therefore, PPV could be used as a predictor of developing AD in clinical settings. We investigated whether PPV in patients with mild cognitive impairment (MCI) was correlated with conversion of these patients to AD.

Methods: A total of 237 patients with MCI underwent brain magnetic resonance imaging. A two-sample *t*-test was used to compare PPV at baseline in MCI patients who converted to AD (MCI-C) with those who did not convert (MCI-NC). Logistic regression analysis with forced entry was used to identify predictors of AD, with variables of PPV, age, sex, education, APOE-ε4 alleles, Mini Mental State Examination score, and total intracranial volume at baseline. Two-way repeated-measures analysis of variance was conducted to compare PPV at baseline and at the last examination in the MCI-C and MCI-NC groups.

Results: PPV in the MCI-C group was significantly lower than that in the MCI-NC group. In logistic regression analysis, two independent predictors of AD were identified: Mini Mental State Examination and PPV. Two-way repeated-measures analysis of variance revealed a significant group effect, but no time effect.

Conclusion: The pineal volume is a predictor of AD conversion, and pineal volume reduction in AD starts early when patients are still in the MCI stage. Thus, pineal volume reduction might be useful as a predictor of developing AD in clinical settings.

Keywords: *Alzheimer's Disease Neuroimaging Initiative, Alzheimer's disease, mild cognitive impairment, MRI, pineal gland.*

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Many studies of Alzheimer's disease (AD) have been conducted based on the amyloid hypothesis. It is well known that neuropathological changes in AD occur before emergence of clinical symptoms.[1] Specifically, elevation of $A\beta_{1\text{-}42}$ in cerebrospinal fluid (CSF) occurs first in AD, followed by Aβ deposition in the brain, increased tau protein in CSF, brain atrophy, decreased glucose metabolism, and cognitive impairment.[1] Thus, the concepts of a preclinical stage of AD[2] and mild cognitive impairment (MCI) due to AD[3] were proposed by the National Institute on Aging and Alzheimer's Association. Subjects in the preclinical stage have AD pathology, but do not meet clinical criteria for MCI or dementia.[2] Since MCI has a heterogeneous pathological background,[4] MCI due to AD has been proposed as the symptomatic predementia phase of AD.[3] The preclinical stage of AD, MCI due to AD, and AD are considered to be a continuum.[5]

Early measurements of Aβ can be performed using CSF testing, Aβ positron emission tomography (PET), and plasma Aβ biomarkers,[6–8] but these methods are not used routinely in clinical settings. Therefore, it is important to find factors that predict future cognitive decline in clinical settings. Neuroimaging studies have shown the brain regions associated with conversion from MCI to AD. Structural magnetic resonance imaging (MRI) has detected the temporal lobe,[7,9] medial temporal lobe,[7,10,11] hippocampus,[7, 12–15] and parahippocampal gyrus[16] as predictors of conversion, while functional neuroimaging has implied that the precuneus,[9,14] frontal cortex,[9] and temporoparietal cortex[15] are involved in conversion.

Recently, melatonin was suggested to be associated with AD pathology. Melatonin attenuates tau protein hyperphosphorylation and has anti-amyloid, anti-apoptosis, antioxidant, and anti-inflammatory effects.[17–19] Melatonin also affects circadian rhythm and sleep regulation[17]; thus, reduction of melatonin causes sleep disturbance, and sleep disturbance is correlated with AD pathology via dysfunction of the glymphatic pathway.[20,21] Indeed, CSF melatonin levels decrease even in preclinical stages, and therefore, a reduction in CSF melatonin may be one of the early signs of AD.[17] Melatonin might thus play an important role in preventing progression to AD.

Melatonin is secreted by the pineal gland, and pineal gland volume is known to be reduced in AD.[22] Measurement of melatonin is difficult in clinical settings, but the pineal gland volume measured by structural MRI could be used as a predictor of developing AD in these settings. Hence, the purpose of this study was to investigate the pineal volume cross-sectionally and longitudinally in patients with MCI, and to examine whether the pineal volume can serve as a predictor of AD conversion.

[1] Department of Psychiatry, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan
[2] Diagnostic Radiology and Radiation Oncology, Graduate School of Medicine, Chiba University, Chiba, Japan
[3] Department of Radiology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan
* Correspondence: Email: tmms2004@koto.kpu-m.ac.jp

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Methods

Alzheimer's Disease Neuroimaging Initiative

Data used in 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. The primary goal of ADNI has been to test whether MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure progression of MCI and early AD. For up-to-date information, see www.adni-info.org. The study was approved by the institutional review boards at all participating sites, and written informed consent was obtained from all subjects at the time of enrollment.

Subjects

A total of 237 subjects were included in the study. Clinical data were downloaded in July 2018. The inclusion criteria were: (i) brain MRI data using T1-weighted 3-D magnetization-prepared rapid gradient-echo (MP-RAGE) at 3.0 T; (ii) follow-up of at least 12 months; (iii) meeting the diagnosis of MCI; (iv) no significant history of psychiatric or neurological disorders (except MCI), including depressive and anxiety symptoms, sleep disorder, delirium, parkinsonism, vitamin B12 deficit, amyloid angiopathy; and (v) evaluation using the Mini Mental State Examination (MMSE). In the ADNI study, MCI was diagnosed using the following criteria: MMSE score of 24–30, having a memory complaint, objective memory loss measured by education-adjusted scores on Wechsler Memory Scale Logical Memory II, a clinical dementia rating of 0.5, absence of significant levels of impairment in other cognitive domains, largely preserved activities of daily living, and an absence of dementia. AD was defined as an MSME score of 20–26, clinical dementia rating of 0.5 to 1.0, and meeting National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD.[23] Subjects were assessed every 6 to 12 months. MCI subjects who converted to AD were classified as MCI converted (MCI-C), and those who had not converted by the last examination as MCI not converted (MCI-NC).

Image Acquisition

MRI data for T1-weighted 3-D MP-RAGE at 3.0 T from the ADNI-1, ADNI-GO, and ADNI-2 databases were used. The parameters were: flip angle 9.0°, matrix X 240.0 pixels, Y 256.0 pixels, Z 176.0, pixel spacing X 1.0 mm, Y 1.0 mm, slice thickness 1.2 mm, echo time (TE) 2.98 ms, inversion time (TI) 900 ms, repetition time (TR) 2300 ms (Siemens, Erlangen, Germany); flip angle 9.0°, matrix X 256.0 pixels, Y 256.0 pixels, Z 170.0, pixel spacing X 1.0 mm, Y 1.0 mm, slice thickness 1.2 mm, TE 3.13 ms, TI 0.0 ms, TR 6.77 ms (Philips Medical Systems, Best, Netherlands); and flip angle 8.0°, matrix X 256.0 pixels, Y 256.0 pixels, Z 166.0, pixel spacing X 1.0 mm, Y 1.0 mm, slice thickness 1.2 mm, TE 3.05 ms, TI 900.0 ms, TR 7.50 ms (GE Medical Systems, Milwaukee, WI, USA). MRI at baseline and at the last examination were performed with the same instrument in 233/237 subjects (98%). The pineal parenchymal volume (PPV) was measured as in our previous study.[22] The pineal gland was identified using multiplanar images. The pineal gland and pineal cysts were outlined manually using MRIcro (Chris Rorden, Columbia, SC, USA; http://people.cas.sc.edu/rorden/mricro/index.html). The PPV was defined as the pineal gland volume minus the total cyst volume (Fig. 1).

One rater (T.M., a psychiatrist with 14 years of experience in diagnostic imaging for cognitive impairment) was blinded to the clinical data and measured the PPV in all subjects. As our previous study calculated the sample size for the intraclass correlation coefficient (ICC),[22] 14 randomly selected subjects were reassessed after at least 4 months by the same rater. The other rater (N.O., a psychiatrist with 4 years of experience in diagnostic imaging for cognitive impairment) was blinded to the clinical data and independently measured the PPV in these 14 subjects. The inter- and intra-rater reliability were examined by calculation of the ICC.

Total intracranial volume (gray matter + white matter + CSF) was calculated in SPM 12 (Wellcome Department of Cognitive Neurology, University College, London, UK) in MATLAB R2012b (MathWorks, Sherborn, MA, USA).

CSF Measurement

Baseline CSF samples were collected at ADNI clinical centers, frozen at −80°C, and shipped to the ADNI Biomarker Core Laboratory at the University of Pennsylvania.[6] Baseline levels of CSF $A\beta_{1\text{-}42}$ and phosphorylated-tau_{181} (p-tau_{181}) were measured using a microbead-based multiplex immunoassay (Research Use Only INNO-BIA AlzBio3 immunoassay; Fujirebio, Ghent, Belgium) on the Luminex platform (Luminex Corp., Austin, TX, USA).

Statistical Analysis

Comparison between the two groups at baseline was performed using independent group *t*-tests and χ^2-tests. Analysis of covariance (ANCOVA) using total intracranial volume as a covariate was also performed to compare PPV between the groups, with adjustment for the effect of intracranial volume.

Logistic regression analysis with forced entry was used to identify predictors of AD, with variables of PPV, age, sex, education, APOE-ε4 alleles, MMSE score, and total intracranial volume at baseline. Variables with a possible impact on conversion were selected.[2,3,5,24–26] Logistic regression was also performed for subjects with CSF data, with variables of PPV, age, sex, education, APOE-ε4 alleles, MMSE score, total intracranial volume, CSF $A\beta_{1\text{-}42}$, and CSF p-tau_{181} at baseline. Goodness of fit was determined by Hosmer–Lemeshow test.

A PPV cut-off of 66.56 mm,[3] which had the highest Youden index (sensitivity + specificity − 1) for discriminating between AD and healthy subjects in our previous study,[22] was used to examine the diagnostic performance of pineal volume for discriminating between MCI-C and MCI-NC. The PPV cut-off was applied to the PPV at baseline, and the subjects were divided into low- and high-PPV groups. Sensitivity was calculated as the proportion of subjects with low PPV in MCI-C, specificity as the proportion of subjects with high PPV in MCI-NC, positive predictive value as the proportion of MCI-C subjects in the low-PPV group, negative predictive value as the proportion of MCI-NC subjects in the high-PPV group, and accuracy as the proportion of subjects with low PPV and MCI-C and with high PPV and MCI-NC among all subjects.

As the duration of follow-up varied among subjects, Kaplan–Meier survival analysis with a log–rank test was performed to compare the time to onset of AD between the low- and high-PPV groups. An event was defined as conversion to AD. Time was defined as the duration of conversion to AD in the MCI-C group, and as the duration of follow-up in the MCI-NC group. Cox proportional hazard regression with forced entry was also conducted to estimate the hazard ratio (HR). The independent variables included group, age, sex, education, APOE-ε4 alleles, MMSE score, and total intracranial volume at baseline. Variables with a possible impact on conversion were selected. The HR for the low-PPV group was estimated compared to the high-PPV group. Similar Kaplan–Meier survival analysis and Cox proportional hazard regression were performed in subjects with CSF data, with CSF $A\beta_{1\text{-}42}$ and CSF p-tau_{181} added to the variables in the Cox proportional hazard model.

Two-way repeated-measures analysis of variance (ANOVA) was conducted to examine the difference in longitudinal change of PPV between the MCI-C and MCI-NC groups. PPV at baseline and at the last examination was compared between the MCI-C and MCI-NC groups (Group × Time) using two-way repeated ANOVA.

All calculations were performed using SPSS 22 (IBM, Armonk, NY, USA), with $P < 0.05$ considered to be significant.

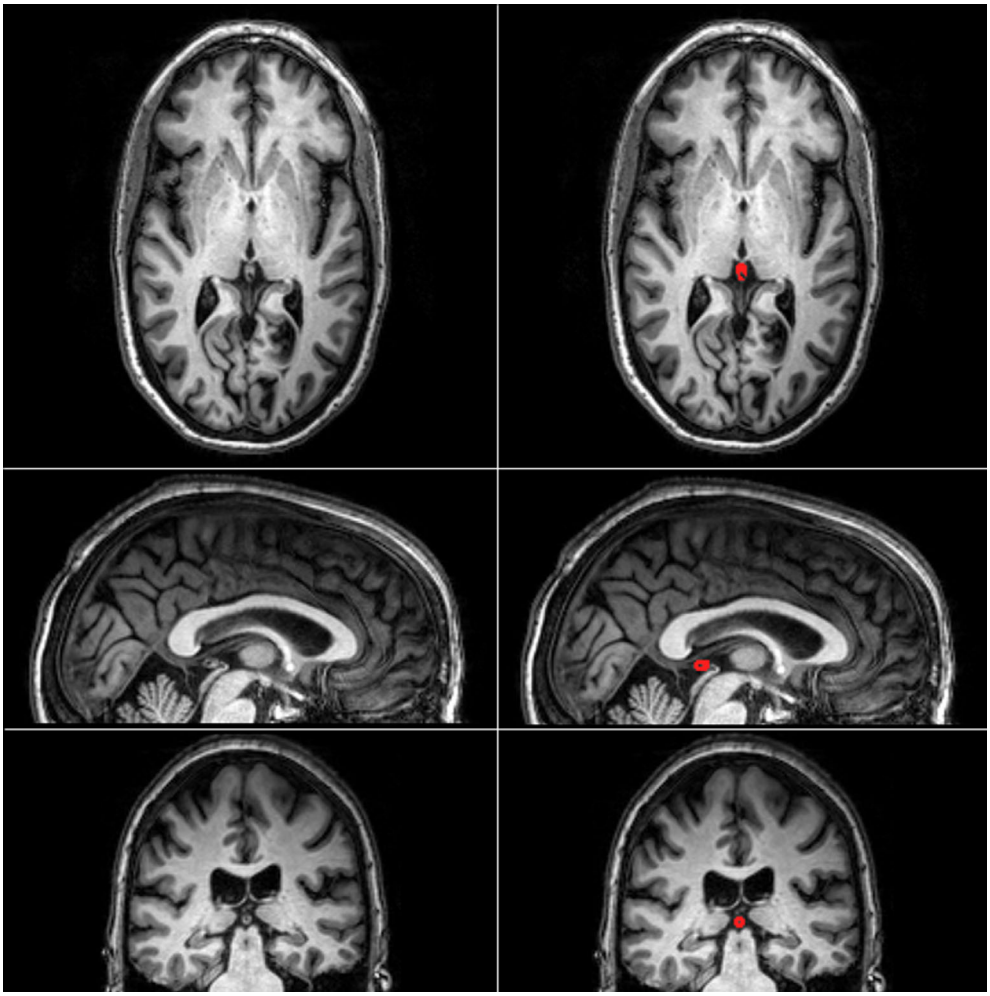

Fig.1 Examples of measurements of pineal parenchymal volume.

Results

Inter-rater and Intra-rater Reliability of PPV Measurements

The inter- and intra-rater ICC for the PPV were 0.833 (95% confidence interval [CI]: 0.480–0.946, $P = 0.001$) and 0.966 (95%CI: 0.899–0.989, $P < 0.001$), respectively.

Comparison of Patients with MCI-C and MCI-NC at Baseline

The characteristics of the patients with MCI are shown in Table 1. Sixty-eight patients with MCI converted to AD. The mean time to conversion was 20.8 ± 15.2 months. There were significant differences in APOE-ε4 alleles, MMSE score, PPV, CSF $A\beta_{1\text{-}42}$, and CSF p-tau_{181} between the MCI-C and MCI-NC groups. ANCOVA also showed a significant difference in PPV between the two groups ($P = 0.001$).

Logistic Regression Analysis

In logistic regression analysis with forced entry in all 237 subjects, two independent predictors of AD were identified: MMSE score and PPV (Table 2). A Hosmer–Lemeshow test showed goodness of fit for the prediction model ($P = 0.740$; a high P-value indicates a better fit). In logistic regression analysis in 195 subjects with CSF data, MMSE score (odds ratio [OR]: 0.718, 95%CI: 0.574–0.898, $P = 0.004$), CSF $A\beta_{1\text{-}42}$ (OR: 0.984, 95%CI: 0.975–0.992, $P < 0.001$), and PPV (OR: 0.985, 95%CI: 0.974–0.997, $P = 0.014$) were identified as predictors of conversion. A Hosmer–Lemeshow test showed goodness of fit for the prediction model ($P = 0.789$).

Diagnostic Performance of Pineal Volume for Discriminating MCI-C from MCI-NC

Analysis of diagnostic performance for discriminating between MCI-C and MCI-NC using a PPV cut-off of 66.56 mm^3 gave a sensitivity of 24% (16/68), specificity of 89% (150/169), positive predictive value of 46% (16/35), negative predictive value of 74% (150/202), and accuracy of 70% (166/237). The characteristics of the low- and high-PPV groups are shown in Table 3. Only sex differed significantly between the groups. CSF Aβ1-42 levels tended to be lower and CSF p-tau181 tended to be higher in the low-PPV group.

Kaplan–Meier Survival Analysis and Cox Proportional Hazard Regression

Kaplan–Meier survival analysis in all 237 subjects showed a significant difference between the low- and high-PPV groups ($P = 0.007$ by log–rank test; Fig. 2). In Cox proportional hazard regression with forced entry, low PPV (HR: 2.258, 95%CI: 1.258–4.055, $P = 0.006$) and MMSE score (HR: 0.719, 95%CI: 0.630–0.820, $P < 0.001$) were significant independent variables.

In the 195 subjects with CSF data, Kaplan–Meier survival analysis showed a significant difference between the low- and high-PPV groups ($P = 0.002$ by log–rank test). In the same subjects, low PPV (HR: 2.046, 95%CI: 1.033–4.053, $P = 0.040$), MMSE score (HR: 0.746, 95%CI: 0.638–0.873, $P < 0.001$), and CSF $A\beta_{1\text{-}42}$ (HR: 0.989, 95%CI: 0.983–0.995, $P < 0.001$) were significant independent variables in Cox regression analysis.

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Table 1 Clinical characteristics of subjects at baseline

Characteristic	MCI-C group (n = 68)	MCI-NC group (n = 169)	P-value
Sex, male/female	38/30	99/70	0.704
Age, years	74.1 ± 7.3	72.5 ± 7.5	0.140
Education, years	15.7 ± 3.0	16.1 ± 2.7	0.412
APOE-ε4 alleles, 0/1/2	27/28/13	96/54/19	0.046
MMSE score	26.7 ± 1.9	28.1 ± 1.7	<0.001
Total intracranial volume, cm^3	1467.4 ± 164.8	1491.5 ± 144.4	0.265
PPV, mm^3	93.3 ± 33.0	110.7 ± 41.4	0.002
Duration of follow-up, months (range, months)	41.4 ± 21.1 (12–108)	41.8 ± 20.4 (12–96)	0.882
Duration of conversion to AD, months (range, months)	20.8 ± 15.2 (6–96)		
CSF $A\beta_{1\text{-}42}$, pg/mL	164.2 ± 47.2 (n = 52)	242.6 ± 79.8 (n = 146)	<0.001
CSF p-tau_{181}, pg/mL	35.1 ± 12.5 (n = 52)	23.9 ± 11.7 (n = 146)	<0.001

Data are shown as the mean ± SD, except for sex and APOE-ε4 alleles.
AD, Alzheimer's disease; CSF, cerebrospinal fluid; MCI-C, mild cognitive impairment patients who converted to AD; MCI-NC, mild cognitive impairment patients who did not convert to AD; MMSE, Mini Mental State Examination; PPV, pineal parenchymal volume; p-tau_{181}, phosphorylated-tau_{181}.

Two-way Repeated-measures ANOVA

The mean duration between the baseline and last brain MRI examination was 30.4 ± 14.8 months. The mean PPV in the MCI-C and MCI-NC groups at the last examination were 91.7 ± 33.0 and 109.2 ± 37.5 mm^3, respectively. Two-way repeated-measures ANOVA revealed a significant group effect (F = 11.038, P = 0.001), but no significant time effect (F = 2.510, P = 0.114) or Group × Time interaction (F = 0.013, P = 0.909; Fig. 3).

Discussion

PPV was substantially reduced in MCI patients who converted to AD, compared with those who did not, which indicates that the pineal volume is a predictor of conversion. Moreover, pineal volumes were similar throughout the follow-up period. These results indicate that pineal volume reduction in AD starts early, when patients are still at the MCI stage.

In the current study, 68 patients (29%) with MCI developed AD during a follow-up period of about 41 months. In addition to pineal volume, cognitive function and CSF $A\beta_{1\text{-}42}$ were significant predictors of AD conversion. The conversion rate from MCI to AD ranges from 23% to 68% for follow-up periods from 13 to 60 months.[7,9,12–16] Dementia incidence in people over age 50 years with MCI is much higher than that in psychiatric outpatients of a similar age (249 vs 31 cases per 1000 person-years).[26] However, MCI has various pathologies, and not all MCI patients progress to dementia. The neuropathology of MCI includes Alzheimer change, argyrophilic grain change, neurofibrillary tangle predominant change, Lewy body disease change, vascular change, and trauma.[4] Despite such a heterogeneous background pathology of MCI, pineal atrophy may be a constant phenomenon across all subjects who progress to AD.

Table 2 Results of logistic regression analysis with forced entry in all subjects (n = 237)

Variable	Odds ratio	95% confidence interval	P value
Pineal parenchymal volume	0.986	0.976–0.995	0.004
Age	1.016	0.973–1.061	0.466
Female sex	0.967	0.419–2.233	0.938
Education	1.040	0.929–1.164	0.494
APOE-ε4 alleles	1.266	0.817–1.961	0.291
Mini Mental State Examination score	0.656	0.548–0.786	<0.001
Total intracranial volume	0.998	0.995–1.000	0.100

Only PPV, MMSE score, and CSF $A\beta_{1\text{-}42}$ were identified as significant predictors of AD conversion. APOE-ε4 alleles and CSF p-tau181 did not show this relation. The OR for PPV in the logistic analysis was close to 1, but this is similar to the OR for CSF $A\beta_{1\text{-}42}$, which is a biomarker for AD.[2,3,5,6] The HR for low PPV was higher than those of MMSE score and CSF $A\beta_{1\text{-}42}$. Furthermore, the specificity of diagnostic performance of PPV for discriminating between MCI-C and MCI-NC was relatively high, although the sensitivity was low. These results indicate the possibility of use of PPV as a predictor of AD in clinical settings. Further studies are needed to examine whether reduction of PPV occurs in other types of dementia, and to validate the usefulness of PPV as a biomarker for AD in clinical settings.

Patients with reduced pineal volume tended to have a relatively low level of CSF $A\beta_{1\text{-}42}$ and a high level of CSF p-tau_{181} compared with those without pineal volume loss. Melatonin has anti-amyloid and anti-tau protein hyperphosphorylation effects.[17–19] Thus, lack of sufficient melatonin secretion might influence development of an AD pathology. It has been recently shown that melatonin is synthesized in the skin, lens, ciliary body, gut, astrocytes, glia cells, and neurons, as well as in the pineal gland.[18] However, extra-pineal melatonin does not have a circadian rhythm, and only pineal melatonin is important as a chemical signal of darkness.[18] Reduction of pineal-derived melatonin also causes sleep disturbance, and might cause an AD pathology via a dysfunctional glymphatic pathway.[20,21]

A reduction in CSF melatonin is seen in preclinical stages.[17] Higher production of melatonin in elderly people results in a lower prevalence of cognitive impairment,[27] and the melatonin secretory capacity is proportional to the PPV.[28–30] Based on these findings, a reduced pineal volume will result in reduced melatonin secretion, which might accelerate an AD pathology. Pineal gland dysfunction may be a common upstream pathologic process that is responsible for both amyloid and tau deposition, as proposed by Jack *et al*.[5]

Table 3 Clinical characteristics of the low- and high-PPV groups

Characteristic	Low-PPV group (n = 35)	High-PPV group (n = 202)	P-value
Sex, male/female	26/9	111/91	0.032
Age, years	74.7 ± 6.7	72.7 ± 7.6	0.146
Education, years	15.3 ± 3.3	16.1 ± 2.7	0.117
APOE-ε4 alleles, 0/1/2	17/14/4	106/68/28	0.754
MMSE score	27.5 ± 1.9	27.7 ± 1.9	0.466
Total intracranial volume, cm^3	1527.5 ± 188.5	1477.2 ± 142.3	0.068
PPV, mm^3	55.0 ± 8.8	114.5 ± 36.2	<0.001
Duration of follow-up, months	30.2 ± 23.9	36.8 ± 20.7	0.091
CSF $A\beta_{1\text{-}42}$, pg./mL	197.6 ± 71.3 (n = 28)	226.0 ± 81.3 (n = 170)	0.083
CSF p-tau_{181}, pg./mL	30.6 ± 15.7 (n = 28)	26.2 ± 12.3 (n = 170)	0.092

Data are shown as the mean ± SD, except for sex.
CSF, cerebrospinal fluid; MMSE, Mini Mental State Examination; PPV, pineal parenchymal volume; p-tau_{181}, phosphorylated-tau_{181}.

Since PPV in the preclinical stage of AD was not assessed in the current study, it is unclear when the pineal volume reduction occurred. The true causes of pineal atrophy are still unclear, but there is some evidence suggesting that this is not a consequence of AD pathology. For instance, typical AD changes, such as neurofibrillary tangles, are not evident in pinealocytes.[31,32] Pineal calcification might be one cause of reduced melatonin,[33] since the degree of pineal calcification in AD is significantly higher than that in other types of dementia, depression, and controls.[34] Uncalcified pineal tissue is also positively correlated with the degree of melatonin excretion.[29] Little is known about the mechanisms of pineal calcification, but chronic vascular inflammation, brain tissue hypoxia, intracranial pressure, and sunlight exposure have been suggested as causes.[18,33] Further studies in cognitively normal subjects and subjects in the preclinical stage of AD are needed to unravel the mechanism of pineal volume reduction in AD.

There are some limitations in the current study. First, the serum concentration of melatonin was not available in this cohort. Therefore, the relation between PPV and melatonin was unclear. Second, the true causes of pineal volume reduction in AD could not be investigated due to lack of autopsy data. Third, assessment of calcifications of the pineal gland was not possible because the volume of calcifications cannot be assessed using MRI. Fourth, the MRI parameters differed slightly among institutions. MRI was performed with instruments from Siemens in 178 subjects (about 75%), Philips Medical Systems in 54 subjects, and GE Medical Systems in five subjects. There was no significant difference in the total intracranial volume (P = 0.079), but there were significant differences in PPV between each instrument

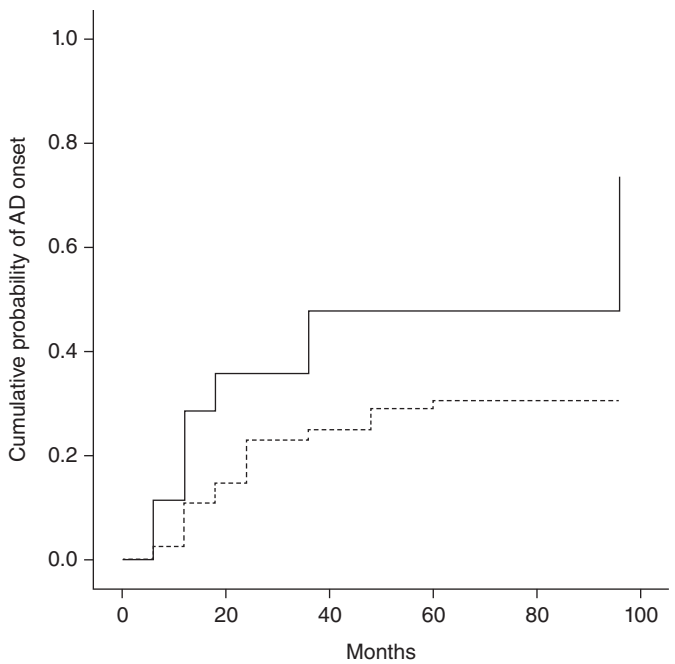

Fig.2 Results of Kaplan–Meier survival analysis in all subjects (n = 237). There was a significant difference between the (——) low- and (·····) high-pineal parenchymal volume groups (P = 0.007 by log–rank test). AD, Alzheimer's disease.

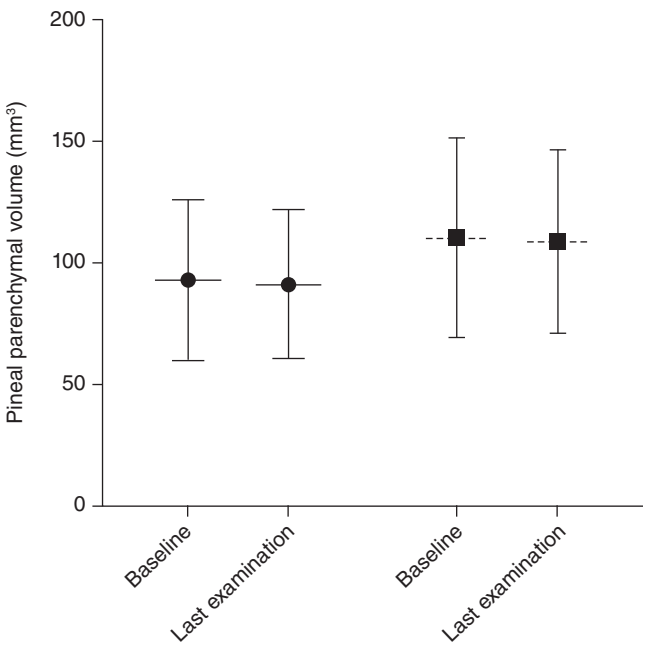

Fig.3 Results of two-way repeated-measures ANOVA. There was a significant group effect (P = 0.001), but no significant time effect (P = 0.114) or Group × Time interaction (P = 0.909). The error bars denote the SD. (—●—) Mild cognitive imapairment patients who converted to Alzheimer's disease. (·-■-·) Mild cognitive imapairment patients who did not convert to Alzheimer's disease.

(104.5 ± 38.9 Siemens vs 105.9 ± 39.0 Philips vs 149.0 ± 60.0 GE, $P = 0.046$). Fifth, the causal relation between pineal volume reduction and CSF $A\beta_{1\text{-}42}$ and p-tau_{181} was not fully evaluated in this study. Sixth, it might be difficult to measure the pineal volume accurately using conventional MRI because the pineal gland is a small tissue. The 95%CI of inter-rater ICC for the PPV was somewhat wide, which reflects the limitations of manual volume measurement.

In conclusion, pineal volume reduction might be useful as a predictor of developing AD in clinical settings. Biochemical, physiological, and neuropathological studies are needed to examine the cause of pineal volume reduction. An improved understanding of the mechanism of pineal volume reduction in the AD continuum may lead to development of a new treatment for AD.

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Disclosure statement

The authors declare no conflicts of interest.

Author contributions

T.M. designed the study, analyzed the data, and wrote the paper. N.O. assisted with analyzing the data and writing the article. H.Y., K.A., K.Y., and J.N. assisted with designing the study and writing the article. All authors have approved the final version of the manuscript.

References

1. Jack CR Jr, Knopman DS, Jagust WJ *et al*. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol.* 2010; **9**: 119–128.
2. Sperling RA, Aisen PS, Beckett LA *et al*. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011; **7**: 280–292.
3. Albert MS, DeKosky ST, Dickson D *et al*. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011; **7**: 270–279.
4. Saito Y, Murayama S. Neuropathology of mild cognitive impairment. *Neuropathology* 2007; **27**: 578–584.
5. Jack CR Jr, Bennett DA, Blennow K *et al*. NIA-AA research framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* 2018; **14**: 535–562.
6. Shaw LM, Vanderstichele H, Knapik-Czajka M *et al*. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Ann. Neurol.* 2009; **65**: 403–413.
7. Trzepacz PT, Yu P, Sun J *et al*. Comparison of neuroimaging modalities for the prediction of conversion from mild cognitive impairment to Alzheimer's dementia. *Neurobiol. Aging* 2014; **35**: 143–151.
8. Nakamura A, Kaneko N, Villemagne VL *et al*. High performance plasma amyloid-beta biomarkers for Alzheimer's disease. *Nature* 2018; **554**: 249–254.
9. Hojjati SH, Ebrahimzadeh A, Khazaee A, Babajani-Feremi A, Alzheimer's Disease Neuroimaging Initiative. Predicting conversion from MCI to AD by integrating rs-fMRI and structural MRI. *Comput. Biol. Med.* 2018; **102**: 30–39.
10. Ma X, Li Z, Jing B *et al*. Identify the atrophy of Alzheimer's disease, mild cognitive impairment and normal aging using morphometric MRI analysis. *Front. Aging Neurosci.* 2016; **8**: 243.
11. Reas ET, Hagler DJ Jr, White NS *et al*. Microstructural brain changes track cognitive decline in mild cognitive impairment. *Neuroimage Clin.* 2018; **20**: 883–891.
12. Luk CC, Ishaque A, Khan M *et al*. Alzheimer's disease: 3-dimensional MRI texture for prediction of conversion from mild cognitive impairment. *Alzheimers Dement.* 2018; **10**: 755–763.
13. Tabatabaei-Jafari H, Walsh E, Shaw ME, Cherbuin N, Alzheimer's Disease Neuroimaging Initiative. A simple and clinically relevant combination of neuroimaging and functional indexes for the identification of those at highest risk of Alzheimer's disease. *Neurobiol. Aging* 2018; **69**: 102–110.
14. Ottoy J, Niemantsverdriet E, Verhaeghe J *et al*. Association of short-term cognitive decline and MCI-to-AD dementia conversion with CSF, MRI, amyloid- and (18)F-FDG-PET imaging. *Neuroimage Clin.* 2019; **22**: 101771.
15. Zhou H, Jiang J, Lu J *et al*. Dual-model radiomic biomarkers predict development of mild cognitive impairment progression to Alzheimer's disease. *Front. Neurosci.* 2018; **12**: 1045.
16. Mitolo M, Stanzani-Maserati M, Capellari S *et al*. Predicting conversion from mild cognitive impairment to Alzheimer's disease using brain (1)H-MRS and volumetric changes: A two- year retrospective follow-up study. *Neuroimage Clin.* 2019; **23**: 101843.
17. Srinivasan V, Kaur C, Pandi-Perumal S, Brown GM, Cardinali DP. Melatonin and its agonist ramelteon in Alzheimer's disease: Possible therapeutic value. *Int. J. Alzheimers Dis.* 2010; **2011**: 741974.
18. Tan DX, Xu B, Zhou X, Reiter RJ. Pineal calcification, melatonin production, aging, associated health consequences and rejuvenation of the pineal gland. *Molecules* 2018; **23**: 301.
19. Tobore TO. On the central role of mitochondria dysfunction and oxidative stress in Alzheimer's disease. *Neurol. Sci.* 2019; **40**: 1527–1540.
20. Yulug B, Hanoglu L, Kilic E. Does sleep disturbance affect the amyloid clearance mechanisms in Alzheimer's disease? *Psychiatry Clin. Neurosci.* 2017; **71**: 673–677.
21. Matsuoka T, Imai A, Fujimoto H *et al*. Neural correlates of sleep disturbance in Alzheimer's disease: Role of the Precuneus in sleep disturbance. *J. Alzheimers Dis.* 2018; **63**: 957–964.
22. Matsuoka T, Imai A, Fujimoto H *et al*. Reduced pineal volume in Alzheimer disease: A retrospective cross-sectional MR imaging study. *Radiology* 2018; **286**: 239–248.
23. 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**: 939–944.
24. Wolf H, Julin P, Gertz HJ, Winblad B, Wahlund LO. Intracranial volume in mild cognitive impairment, Alzheimer's disease and vascular dementia: Evidence for brain reserve? *Int. J. Geriatr. Psychiatry* 2004; **19**: 995–1007.
25. Podcasy JL, Epperson CN. Considering sex and gender in Alzheimer disease and other dementias. *Dialogues Clin. Neurosci.* 2016; **18**: 437–446.
26. Matsuoka T, Ismail Z, Narumoto J. Prevalence of mild behavioral impairment and risk of dementia in a psychiatric outpatient clinic. *J. Alzheimers Dis.* 2019; **70**: 505–513.
27. Obayashi K, Saeki K, Iwamoto J *et al*. Physiological levels of melatonin relate to cognitive function and depressive symptoms: The

HEIJO-KYO cohort. *J. Clin. Endocrinol. Metab.* 2015; **100**: 3090–3096.
28. Kunz D, Schmitz S, Mahlberg R *et al*. A new concept for melatonin deficit: On pineal calcification and melatonin excretion. *Neuropsychopharmacology* 1999; **21**: 765–772.
29. Mahlberg R, Kienast T, Hadel S, Heidenreich JO, Schmitz S, Kunz D. Degree of pineal calcification (DOC) is associated with polysomnographic sleep measures in primary insomnia patients. *Sleep Med.* 2009; **10**: 439–445.
30. Nolte I, Lutkhoff AT, Stuck BA *et al*. Pineal volume and circadian melatonin profile in healthy volunteers: An interdisciplinary approach. *J. Magn. Reson. Imaging* 2009; **30**: 499–505.
31. Pardo CA, Martin LJ, Troncoso JC, Price DL. The human pineal gland in aging and Alzheimer's disease: Patterns of cytoskeletal antigen immunoreactivity. *Acta Neuropathol.* 1990; **80**: 535–540.
32. Skene DJ, Swaab DF. Melatonin rhythmicity: Effect of age and Alzheimer's disease. *Exp. Gerontol.* 2003; **38**: 199–206.
33. Song J. Pineal gland dysfunction in Alzheimer's disease: Relationship with the immune-pineal axis, sleep disturbance, and neurogenesis. *Mol. Neurodegener.* 2019; **14**: 28.
34. Mahlberg R, Walther S, Kalus P *et al*. Pineal calcification in Alzheimer's disease: An in vivo study using computed tomography. *Neurobiol. Aging* 2008; **29**: 203–209.