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Frontier of Psychiatry

Pineal volume reduction in patients with mild cognitive impairment transitioning to Alzheimer's disease.

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Psychiatria et Neurologia Japonica 123: 461-467, 2021

Abstract

[Purpose] Decreased pineal parenchymal volume (PPV) is observed in Alzheimer's disease (AD). Therefore, PPV may be used as a predictor of progression from mild cognitive impairment (MCI) to AD in a clinical setting. In this study, we investigated whether PPV is related to progression to AD in patients with MCI. [Methods] A total of 237 MCI patients who had undergone MRI were included. A two-sample t-test was used to compare PPV at the baseline between patients who transitioned from MCI to AD (MCI-C) and those who did not transition (MCI-NC). Logistic regression analysis (forced entry method) was used to examine predictors of the transition from MCI to AD, using the baseline PPV, age, sex, years of education, APOE-ε4 alleles, MMSE scores, and intracranial volume as variables. Two-way repeated-measures ANOVA was performed to compare PPV at the baseline and last measurement in the MCI-C and MCI-NC groups. [Results] Baseline PPV in the MCI-C group was significantly lower than that in the MCI-NC group. Logistic regression analysis identified MMSE and PPV at the baseline as predictors of the transition from MCI to AD, and two-way repeated-measures ANOVA showed significant group effects but no effect of time. [Conclusions] Pineal volume is a predictor of the transition from MCI to AD, and pineal volume reduction in AD has already begun at the time of MCI. Therefore, pineal volume reduction may be a useful predictor of the transition from MCI to AD in a clinical setting.

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Keywords: Alzheimer's disease, mild cognitive impairment, pineal gland, MRI, ADNI

Introduction

Most studies of Alzheimer's disease (AD) have been based on the amyloid hypothesis, and it is well-known that neuropathological changes in AD occur even before the onset of clinical symptoms 4). Specifically, in AD, a decrease in amyloid-β (Aβ)1-42 in cerebrospinal fluid (CSF) occurs first, followed by Aβ accumulation in the brain, an increase in tau protein in CSF, brain atrophy, decreased brain glucose metabolism, and cognitive dysfunction 4). Therefore, concepts such as preclinical AD 26) and MCI due to AD 2) have been proposed. In preclinical AD, AD pathology is recognized but does not meet the clinical diagnostic criteria for mild cognitive impairment (MCI) or dementia 26). Because MCI has various pathological backgrounds 22), MCI due to AD has been proposed as a precursor stage of AD 2). Preclinical AD, MCI due to AD, and AD are considered to be continuous 5).

Early measurement of Aβ is possible by CSF testing, amyloid PET, and plasma Aβ biomarker measurement 16)23)31), but these tests are not yet routinely used in clinical practice. Therefore, it is important to identify factors that can be used to predict cognitive decline in clinical practice. Neuroimaging studies have revealed brain regions associated with the transition from MCI to AD. Using head MRI, the temporal lobe 3)31), medial temporal lobe 8)21)31), hippocampus 7)19)28)31)33), and parahippocampal gyrus 15) have been identified as predictors of the transition, while using functional imaging, the precuneus 3)19), frontal lobe 3), and temporoparietal lobe 33) have been identified as predictors.

Recently, melatonin has been implicated in AD pathology. Melatonin has been found to attenuate tau protein phosphorylation, and has anti-amyloid, anti-apoptotic, antioxidant, and anti-inflammatory effects 27)29)30). Melatonin has also been found to regulate circadian rhythms and sleep 27), and its decrease causes sleep disturbances. The glymphatic pathway plays an important role in the excretion of Aβ in the brain, and sleep disturbance causes a disruption of the glymphatic pathway, resulting in the accumulation of Aβ in the brain 12) 32). Therefore, AD pathology progresses due to sleep disturbance caused by melatonin depletion 12)32). In fact, melatonin

levels in CSF have already decreased in the precognitive stage, and decreased melatonin levels in CSF may be one of the early signs of AD 27). Thus, melatonin may be involved in the progression of AD and also play an important role in the prevention of AD progression.

Melatonin is secreted from the pineal gland, and the pineal volume is known to be decreased in AD 11). Melatonin is secreted at night, and its secretion is low during the daytime, making it difficult to employ melatonin measurements clinically. However, measurement of the pineal volume using MRI may be applicable as a predictive factor for progression to AD in clinical practice. Therefore, the purpose of this study was to investigate whether the pineal volume can be used as a predictor of progression to AD by measuring it longitudinally and cross-sectionally in patients with MCI.

I. Methods and Results

1. Methods

1) Subjects

In this study, we used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database 1) and included 237 patients who had undergone cranial MRI (3 Tesla, T1-weighted images, MP-RAGE), had been followed for at least 12 months, met the diagnostic criteria for MCI, had no history of psychiatric or neurological disorders, and were undergoing the Mini Mental State Examination (MMSE). In the ADNI study, a diagnosis of MCI was made when a person had an MMSE score of 24 ~ 30, a complaint of memory impairment, objective memory impairment according to scores adjusted for years of education on the Wechsler Memory Scale Logical Memory II, a Clinical Dementia Rating (CDR) of 0.5, no obvious impairment in cognitive domains other than memory, and no dementia. AD was defined as an MMSE score of 20 ~ 26, a CDR score of 0.5 ~ 1, and meeting the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association diagnostic criteria for probable AD 14). Subjects were evaluated every 6 to 12 months. Patients with MCI who had progressed to AD were included in the MCI-C group, and those with MCI who had not progressed to AD at the last evaluation were included in the MCI-NC group. The ADNI study was approved following ethical review at all participating centers, and signed consent was obtained from all subjects at the start of the study.

2) Assessment

Head MRI data from ADNI-1, ADNI-GO, and ADNI-2 were used. Head MRI was performed using machines from

Siemens, Philips, or GE Medical Systems. In 98% of the subjects, baseline and final imaging were performed using the same machine. The pineal parenchymal volume (PPV) was measured in the same way as in our previous study 11). The pineal gland was identified in multiple sections (horizontal, sagittal, and coronal sections), and the pineal volume and pineal cysts volume were measured manually using MRIcro 13). PPV was defined as the pineal volume minus the pineal cysts volume. Intracranial volume (gray matter + white matter + CSF) was measured using SPM12, and Aβ1-42 and phosphorylated tau (p-tau181) at the baseline were used as biomarkers in CSF.

3) Statistical analysis

The t-test and $\chi 2$ test were used for comparison between the two groups at the baseline. Analysis of covariance was performed using the intracranial volume as a covariate to correct for the effect of the intracranial volume when comparing PPV between the two groups.

To identify predictors of the transition from MCI to AD, logistic regression analysis (forced entry method) was performed using baseline PPV, age, sex, years of education, APOE-ε4 alleles, MMSE scores, and intracranial volume as variables. The same logistic regression analysis (forced entry method) was performed for patients with CSF data by adding CSF Aβ1-42 and CSF p-tau181 at the baseline as variables.

In the previous study 11), a cut-off value of 66.56 mm for PPV, which had the highest Youden index (sensitivity + specificity -1) for differentiating AD patients from healthy subjects, was used to examine the differentiation ability between MCI-C and MCI-NC groups. This cut-off value was applied to PPV at the baseline, and subjects were divided into high- and low-PPV groups.

Because the observation period differed between subjects, Kaplan-Meier survival analysis (log-rank test) was used to compare the time to AD onset in the high- and low-PPV groups. To estimate the hazard ratios for AD onset, Cox proportional hazards analysis (forced entry method) was performed using PPV at the baseline (high- or low-PPV group), age, sex, years of education, APOE-ε4 alleles, MMSE scores, and intracranial volume as variables. Hazard ratios for PPV were examined for the low-PPV group compared with the high-PPV group. The same Cox proportional hazards analysis (forced entry method) was performed for patients with CSF data, adding CSF Aβ1-42 and CSF p-tau181 at the baseline as variables.

Two-way repeated-measures analysis of variance (ANOVA) was performed to examine the differences in the change in

PPV over time between the MCI-C and MCI-NC groups. Two-way repeated ANOVA was performed to compare PPV at the baseline and at the final measurement between MCI-C and MCI-NC groups (Group x Time).

2. Results

1) Comparison of MCI-C and MCI-NC groups at the baseline

Of the 237 MCI patients, 68 patients progressed to AD, with a mean time to AD of 20.8±15.2 months, and significant differences between the two groups in APOE-ε4 alleles, MMSE scores, PPV, CSF Aβ1-42, and CSF p-tau181 (Table 1). Analysis of covariance also showed a significant difference in PPV between the two groups.

2) Logistic regression analysis

In 237 MCI patients, MMSE scores and PPV were identified as predictors of progression to AD (Table 2), and in 195 MCI patients with CSF data, MMSE scores (odds ratio: 0.718, 95% confidence interval: 0.574-0.898, P = 0.004), CSF Aβ1-42 (odds ratio: 0.984, 95% confidence interval: 0.975-0.992, P<0.001), and PPV (odds ratio: 0.985, 95% confidence interval: 0.974-0.997, P=0.014) were identified as predictors of progression to AD.

3) Diagnostic utility of the pineal volume to differentiate between MCI-C and MCI-NC groups

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 24, 89, 46, 74, and 70%, respectively, when the cutoff value of PPV was 66.56 mm3. Only sex was significantly different between the low- and high-PPV groups (Table 3). CSF Aβ1-42 tended to be lower and CSF p-tau181 higher in the low-PPV group (Table 3).

4) Kaplan-Meier survival analysis, Cox proportional hazards analysis

Kaplan-Meier survival analysis of 237 MCI patients showed a significant difference between the low- and high-PPV groups (Figure 1). In the Cox proportional hazards analysis, the hazard ratio of developing AD was 2.258 (95% confidence interval: 1.258-4.055, P=0.006) in the low- compared with high-PPV group, and the hazard ratio of MMSE scores was 0.719 (95% confidence interval: 0.630-0.820, P<0.001).

Kaplan-Meier survival analysis of 195 MCI patients with CSF data generated similar results: Cox proportional hazards analysis showed a hazard ratio of 2.046 (95% confidence interval: 1.033-4.053, P=0.040) for developing AD in the low- compared with high-PPV group. The hazard ratio of the MMSE score was 0.746 (95% confidence interval: 0.638-0.873, P<0.001), and that of CSF Aβ1-42 was 0.989 (95% confidence interval: 0.983-0.995, P<0.001).

5) Two-way repeated-measures ANOVA

The mean time from the baseline MRI to final MRI was 30.4±14.8 months. Two-way repeated-measures ANOVA showed a significant between-group effect (MCI-C and MCI-NC groups), but no significant time (baseline and final imaging) effect or interaction between groups and time (Figure 2).

II. Discussion

Pineal volume may be a predictor of the transition from MCI to AD, as PPV at the baseline was significantly lower in the MCI-C than MCI-NC group. Furthermore, the pineal volume did not change during the observation period. These results suggest that the decrease in pineal volume observed in AD has already begun at the stage of MCI.

In this study, 29% of patients with MCI developed AD during a mean observation period of 41 months. In addition to the pineal volume, cognitive function and CSF Aβ1-42 were predictors of the transition from MCI to AD. In a previous study, 23-68% of MCI patients transitioned to AD during an observation period of 13-60 months 3)7)15)19)28)31)33). However, there are various pathologies as causes of MCI 22), and not all MCI patients transition to dementia 22). Although the background pathology of MCI varies, a decrease in the pineal volume may be a phenomenon observed in MCI patients transitioning to AD.

PPV, MMSE scores, and CSF Aβ1-42 were identified as predictors of the transition from MCI to AD, but not APOE-ε4 alleles, a risk factor for AD, or CSF p-tau181, a biomarker of AD. The odds ratio of PPV was similar to that of CSF Aβ1-42 2)5)23)26), a biomarker of AD. These results suggest that PPV could be used as a predictor of AD in clinical practice.

Patients with a decreased pineal volume tended to have decreased CSF Aβ1-42 and increased CSF p-tau181 compared with patients without a decreased volume. Melatonin secreted from the pineal gland has anti-amyloid and attenuating effects on tau phosphorylation 27)29)30). Therefore, decreased melatonin secretion may influence the progression of AD pathology. Melatonin is synthesized in the skin, lens, ciliary body, intestine, and glial cells in addition to the pineal gland, but only melatonin derived from the pineal gland has circadian rhythm-regulating effects 29). Therefore, a decrease in pineal-derived melatonin may lead to sleep disturbances and cause AD pathology by impairing glymphatic pathways related to amyloid excretion 12)32).

Decreased melatonin in CSF has been observed in the preclinical stage of AD 27). In the older people, the higher the melatonin secretion, the lower the frequency of cognitive dysfunction18),

and the melatonin secretory capacity has been suggested to be directly proportional to PPV 6)10)17). Therefore, a decrease in melatonin secretion may be caused by a reduction in the pineal volume, which, in turn, may lead to the progression of AD pathology. Considering Jack, C.R.'s suggestion 5) that there may be a common cause of amyloid and tau accumulation, pineal dysfunction may be the cause.

The relationship between the pineal gland and AD is still unknown. In the present study, the pineal volume did not change significantly over an average period of approximately 2 to 3 years of observation. The results also indicate that the pineal volume reduction observed in AD has already occurred at the time of MCI, and it is significant that the pineal volume reduction may be observed even before the progression from MCI to AD. It is also significant that a relatively large number of MCI patients were included in the study using ADNI data, and that data on CSF and APOE-ε4 alleles were also used in the analysis.

Conclusion

Future work is needed to verify whether PPV is decreased in dementia other than AD, and whether PPV can be used as a biomarker of AD in clinical situations.

In this study, PPV was evaluated only from the MCI stage, and PPV in the preclinical stage of AD was not evaluated, so it is not clear when the pineal volume decrease occurs. Although the cause of pineal volume reduction is still unknown, it is not caused by AD pathology based on the results of this study and previous studies. For example, typical AD pathologies such as neurofibrillary tangles have not been observed in pineal cells 20)24). The degree of calcification of the pineal gland in AD has been reported to be significantly more severe than in other forms of dementia, depression, and healthy controls 9). Since the non-calcified pineal tissue area is positively correlated with melatonin secretion 10), calcification of the pineal gland may be one of the causes of decreased melatonin secretion 25). Although the mechanism of pineal calcification is not fully understood, chronic vascular inflammation, brain tissue hypoxia, intracranial pressure, and sunlight exposure have been suggested as possible causes 25)29). It is necessary to elucidate the mechanism of pineal volume reduction in AD by observing older people with a normal cognitive function and subjects in the preclinical stage of AD over time to determine at what stage the pineal volume reduction occurs. Elucidating the mechanism of pineal volume reduction in AD may lead

to the development of new treatments for AD.

This paper is a translation of a recent research article 13) published in PCN, rewritten in Japanese by one of the authors at the request of the editorial board, with additional information on the significance and prospects of the paper.

There are no conflicts of interest to disclose in connection with this article.

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表 1　ベースライン時の対象者の背景

	MCI-C 群 (n＝68)	MCI-NC 群 (n＝169)	*P* 値
性別（男性/女性）	38/30	99/70	0.704
年齢（歳）	74.1±7.3	72.5±7.5	0.140
教育年数（年）	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（点）	26.7±1.9	28.1±1.7	<0.001
頭蓋内体積（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
フォローアップ期間（月）	41.4±21.1	41.8±20.4	0.882
（範囲）	(12～108)	(12～96)	
AD への移行までの期間（月）	20.8±15.2		
（範囲）	(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

AD：Alzheimer's disease（アルツハイマー型認知症），CSF：cerebrospinal fluid（脳脊髄液），MCI：mild cognitive impairment（軽度認知障害），MMSE：Mini Mental State Examination，PPV：pineal parenchymal volume（松果体実質体積），p-tau_{181}：phosphorylated-tau_{181}（リン酸化タウ）
性別と APOE-ε4 alleles を除いて，データは平均±標準偏差で示している．
（文献 13 より和訳して引用）

Table 1 Background of subjects at baseline

	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
Years of 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 (points)	26.7±1.9	28.1±1.7	<0.001
Intracranial volume (cm3)	1467.4±164.8	1491.5±144.4	0.265
PPV (mm3)	93.3±33.0	110.7±41.4	0.002
Follow-up period (months) (range)	41.4±21.1(12-108)	41.8±20.4(12-96)	0.882
Time to transition to AD (months) (range)	20.8±15.2 (6-96)		
CSF Aβ1-42 (pg/mL)	164.2±47.2(n=52)	242.6±79.8(n=146)	<0.001
CSF p-tau181 (pg/mL)	35.1±12.5(n=52)	23.9±11.7(n=146)	<0.001

AD: Alzheimer's disease, CSF: cerebrospinal fluid, MCI: mild cognitive impairment, MMSE: Mini Mental State Examination, PPV: pineal parenchymal volume, p-

tau181: phosphorylated-tau181

Data are presented as mean ± standard deviation except for sex and APOE-ε4 alleles.

(Cited in Japanese from Reference 13)

表 2　全対象者（n＝237）におけるロジスティック回帰解析（強制投入法）の結果

	オッズ比	95%信頼区間	*P* 値
PPV（mm^3）	0.986	0.976～0.995	0.004
年齢（歳）	1.016	0.973～1.061	0.466
女性	0.967	0.419～2.233	0.938
教育年数（年）	1.040	0.929～1.164	0.494
APOE-ε4 alleles（0/1/2）	1.266	0.817～1.961	0.291
MMSE（点）	0.656	0.548～0.786	<0.001
頭蓋内体積（cm^3）	0.998	0.995～1.000	0.100

MMSE：Mini Mental State Examination，PPV：pineal parenchymal volume（松果体実質体積）

（文献 13 より和訳して引用）

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

Odds ratio 95% confidence interval P-value

PPV (mm3) 0.986 0.976 to 0.995 0.004

Age (years) 1.016 0.973 to 1.061 0.466

Female 0.967 0.419~2.233 0.938

Years of education (years) 1.040 0.929 to 1.164 0.494

APOE-ε4 alleles (0/1/2) 1.266 0.817 to 1.961 0.291

MMSE (points) 0.656 0.548~0.786 <0.001

Intracranial volume (cm3) 0.998 0.995~1.000 0.100

MMSE: Mini Mental State Examination, PPV: pineal parenchymal volume

(Cited in Japanese from Reference 13)

表 3　low-PPV 群と high-PPV 群の背景

	low-PPV 群 (n＝35)	high-PPV 群 (n＝202)	*P* 値
性別（男性/女性）	26/9	111/91	0.032
年齢（歳）	74.7±6.7	72.7±7.6	0.146
教育年数（年）	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（点）	27.5±1.9	27.7±1.9	0.466
頭蓋内体積（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
フォローアップ期間（月）	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

CSF：cerebrospinal fluid（脳脊髄液），MMSE：Mini Mental State Examination，PPV：pineal parenchymal volume（松果体実質体積），p-tau$_{181}$：phosphorylated-tau$_{181}$（リン酸化タウ）
性別と APOE-ε4 alleles を除いて，データは平均±標準偏差で示している．
（文献 13 より和訳して引用）

Table 3 Background of low- and high-PPV groups

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

Years of 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 (points) 27.5±1.9 27.7±1.9 0.466

Intracranial volume (cm3) 1527.5±188.5 1477.2±142.3 0.068

PPV (mm3) 55.0±8.8 114.5±36.2 <0.001

Follow-up period (months) 30.2±23.9 36.8±20.7 0.091

CSF Aß1-42 (pg/mL) 197.6±71.3(n=28) 226.0±81.3(n=170) 0.083

CSF p-tau181 (pg/mL) 30.6±15.7(n=28) 26.2±12.3(n=170) 0.092

CSF: cerebrospinal fluid; MMSE: Mini Mental State Examination; PPV: pineal parenchymal volume; p-tau181: phosphorylated-tau181

Data are presented as mean ± standard deviation except for sex and APOE-ε4 alleles.

(Cited in Japanese from Reference 13)

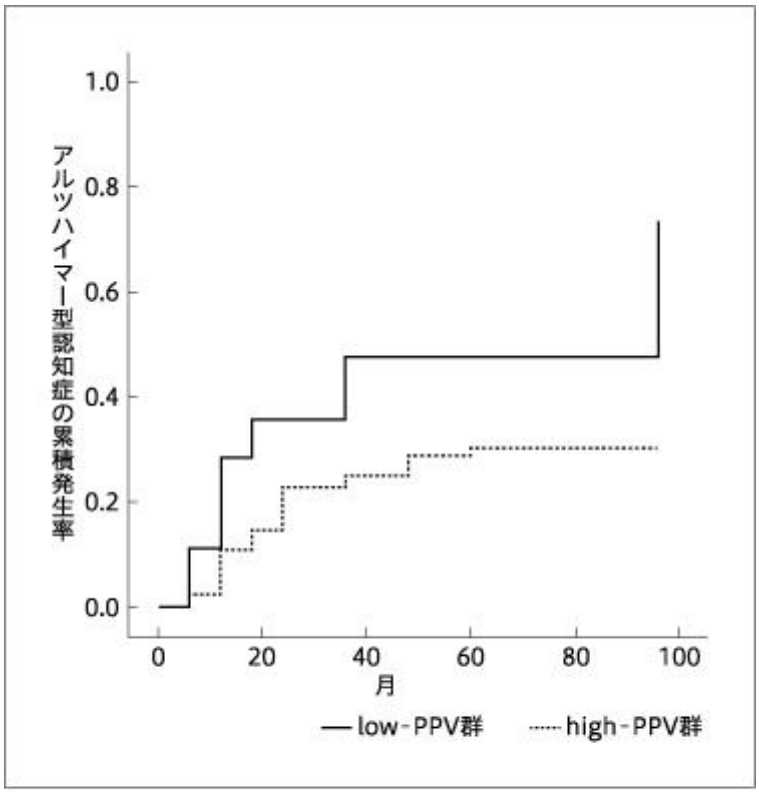

図1　全対象者（n＝237）におけるカプラン-マイヤー生存分析の結果

Low-PPV 群と high-PPV 群との間に有意差を認めていた（*P* ＝0.007）.

（文献 13 より和訳して引用）

Figure 1 Results of Kaplan-Meier survival analysis in all subjects (n=237)

There was a significant difference between the low- and high-PPV groups (P=0.007).

(Cited in Japanese from Reference 13)

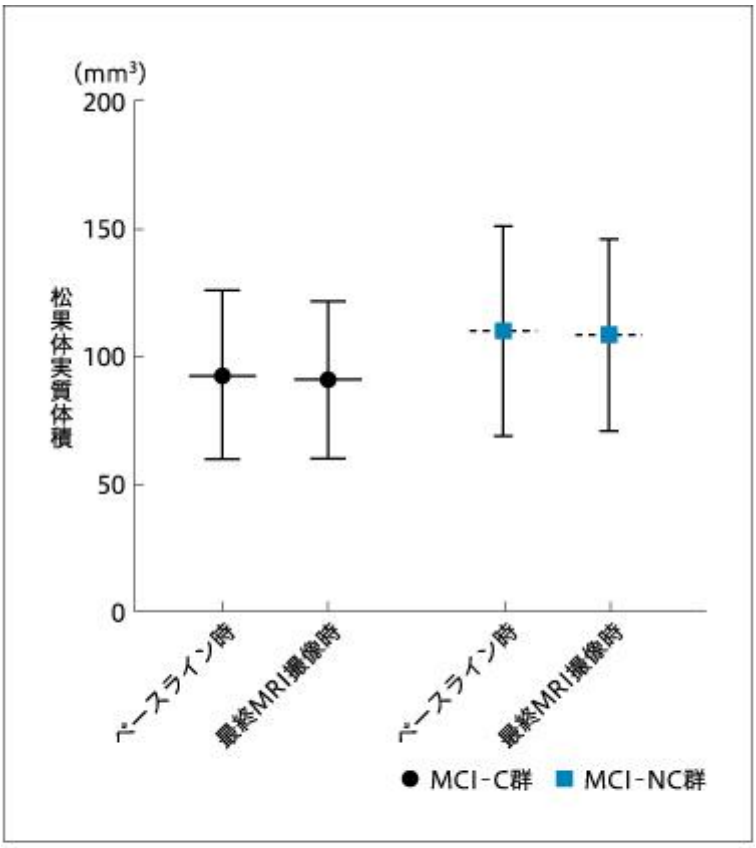

図 2　Two-way repeated measures ANOVA の結果
群間の効果は有意（$P=0.001$）であったが，時間（$P=0.114$）と群間 x 時間の交互作用（$P=0.909$）の効果は有意ではなかった．エラーバーは標準偏差を示している．
（文献 13 より和訳して引用）

Figure 2 Two-way repeated measures ANOVA results

The effect between groups was significant (P=0.001), but the effect of time (P=0.114) and the interaction of group x time (P=0.909) were not significant. Error bars indicate standard deviation.
(Cited in Japanese from Reference 13)