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Relapse numbers and earlier intervention by disease modifying drugs are related with progression of less brain atrophy in patients with multiple sclerosis

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ABSTRACT

Long term effect between disease-modifying drugs (DMDs) treatment duration and brain atrophy rate has not been fully investigated in patients with relapsing-remitting MS (RRMS). The aim of this study was to investigate whether DMDs could slow down the progression of brain atrophy in patients with RRMS by comparing DMDs-treated group with non-treated group during a certain period of time.

This was a retrospective investigation. Forty-nine RRMS patients underwent two brain MRI scans more than one year apart. Between scans, patients were treated with fingolimod (n = 16), interferon-beta (n = 23) or not treated with DMD (n = 10). Correlations between clinical characteristics and brain volume were calculated by statistical parametric mapping-12.

In all 49 patients, the total attack number before 1st MRI scan and the annualized rate of total lesion volume change between the two scans showed a positive correlation with annualized atrophy rate of grey matter volume (GMV) plus white matter volume (WMV). In patients with DMDs (n = 39), the period from drug initiation to 1st MRI scan was negatively correlated with the annualized atrophy rate of GMV + WMV and number of attacks between scans.

The number of total previous attacks could be a predictor of subsequent MS progression. Early intervention by DMDs could prevent brain atrophy in patients with MS.

1. Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system and dissemination of demyelination over time and space is its main feature elucidated by magnetic resonance imaging (MRI) [1]. Brain atrophy is of great concern as it can cause cognitive impairment, which been observed in 43%–63% of patients with MS [2]. Cognitive impairment was reported to be related to focal T2 hyperintense lesions, diffuse white matter damage and cortical and deep grey matter atrophy [3]. It deteriorates quality of life and often leads to unemployment [4]. In addition, thalamic atrophy was reported even in patients with the radiologically isolated syndrome, which is considered as a preclinical stage of MS [5]. Therefore, preventing brain atrophy of patients with MS warrants urgent attention.

Recently, disease-modifying drugs (DMD) including interferon-beta and fingolimod have been reported to slow down brain atrophy in patients with MS [6–9]. Whole-brain and white matter volume changes in the first year treatment of interferon-beta were also reported to be predictive of subsequent clinical evolution in patients with MS [10]. Although a number of previous studies reported the patterns of brain atrophy in patients with MS, the consensus about the pattern had not been obtained [11]. Meanwhile, significant linear atrophy of the brain parenchymal volume has been observed in patients with MS over a 10 year period [12]. Therefore, early treatment with DMDs may slow down brain atrophy in patients with MS. However, the effect of treatment duration on brain atrophy rate over long periods has not been fully investigated in patients with MS.

Therefore, the objective of this study was to investigate the correlations of brain atrophy rate in patients with MS and to clarify the relationship between DMD treatment duration and brain atrophy.

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2. Materials and methods

2.1. Standard protocol approvals and patient consent

The study procedure was approved by the ethics committee of the Chiba University School of Medicine (No. 2555). All the patients provided written, informed consent.

2.2. Study design and patient populations

Clinical records of 221 patients with MS at the Chiba University Hospital were reviewed retrospectively. Relapsing-remitting MS (RRMS) patients who received 1.5 T brain MRI scan twice and continued the same treatment between 1st and 2nd MRI scan during the observational period were included. The period of 1st and 2nd MRI scan was more than a year. The brain MRI were performed to all RRMS patients at least once a year and if more than one brain MRI scan was performed under the same treatment, the 2nd MRI was chosen as the time between 1st and 2nd MRI became longer as much as possible. All RRMS patients fulfilled the 2010 McDonald's diagnostic criteria [1]. Exclusion criteria were steroid pulse therapy for MS attacks 60 days prior to brain MRI scans, as steroids could affect brain volume by causing steroid-related pseudoatrophy [6,13], and presence of anti-aquaporin-4 antibodies confirmed by a cell-based assay.

Demographic characteristics (sex, age at disease onset, age at MRI scan) and clinical features (disease duration to MRI scan, number of attacks before MRI scan, number of attacks during one or two years before MRI scan, number of attacks between 1st and 2nd MRI scan, annualized relapse rate (ARR) before 1st MRI scan, ARR between 1st and 2nd MRI scan, Kurtzke Expanded Disability Status Scale (EDSS) at MRI scan, years from DMD initiation to MRI scan, days from last attack before 1st MRI scan to 1st MRI scan) were reviewed. Patients were divided into three groups based on specific treatment at MRI scan into interferon-beta (IFN) group, fingolimod (FIN) group or non-treatment (None) group. There were no brain MRI scan frequency differences among the groups.

2.3. Brain MRI scan

The brain MRI scan protocol included a conventional brain MRI, T1-weighted three-dimensional images and fluid-attenuated inversion recovery (FLAIR). Three different MR scanners were used in this study: 1.5-Tesla Signa HDxT (GE Healthcare, Milwaukee, Wisconsin, USA), 1.5-Tesla Achieva (Philips, Amsterdam, NL) and 1.5-Tesla Achieva dStream (Philips, Amsterdam, NL). The first MRI scans were done with Signa HDxT (n = 43) and Achieva (n = 6). The second MRI scans were done with Signa HDxT (n = 38), Achieva (n = 1) and Achieva dStream scanners (n = 10). Thirty-three patients had both pre and post MRI scans done with the same Signa HDxT scanner. Details of MRI systems are shown in Supplementary Table 1.

2.4. Brain volume measurements

Brain volume in patients with MS were calculated using statistical parametric mapping 12 (SPM12), implemented on MATLAB (Version R2016b; The MathWorks, Inc., Natick, Massachusetts, USA). Intracranial volume (ICV) was calculated by the sum of whole brain grey matter volume (GMV) plus white matter volume (WMV) and cerebrospinal fluid volumes and was subsequently treated to normalize for brain and lesion volume. Lesions were segmented by the lesion growth algorithm as implemented in the Lesion Segmentation Tool (LST) toolbox version 2.0.15 (www.statisticalmodelling.de/lst.html) for SPM [14]. We used an initial threshold (κ) value of 0.30 in accordance with author recommendation [14]. Lesion volume filled by LST was expressed as total lesion volume (TLV). GMV/ICV, WMV/ICV, (GMV + WMV)/ICV and TLV/ICV were defined as normalized grey matter volume (NGV), normalized white matter volume (NWV), normalized brain volume (NBV) and normalized lesion volume (NLV), respectively. Annualized atrophy rate was calculated as below after lesion filling was performed.

Annualized atrophy rate of X is defined as follows;

$$\frac{(\text{X at } 1^{st}\text{MRI scan} - \text{X at } 2^{nd}\text{MRI scan}) \times 12}{(\text{X at } 1^{st}\text{MRI scan}) \times (\#\text{of months between MRI scans})}$$

X = NGV, NWV or NBV.

2.5. Statistical analysis

Statistical tests were conducted using SPSS version 25.0 (IBM Corporation, Armonk, NY, USA). Continuous data were compared between the treatment and non-treatment groups using the Mann–Whitney U test. Categorical outcomes were evaluated using Fisher's Exact Test. Spearman's rank correlation test was performed to analyse correlations. Wilcoxon signed rank test was performed to compare the volumes between ICV at 1st MRI scan and ICV at 2nd MRI scan. Analysis of covariance (ANCOVA) was used when the brain volume was different at 1st MRI scan by using significant different items as covariates. A P value of < 0.05 was considered statistically significant. In addition, to consider the multiple testing problem, we applied Bonferroni correction on the computed P-values to reduce type I errors.

3. Results

3.1. Patient demographics and clinical characteristics at 1st MRI scan

Table 1 summarizes the demographics and clinical characteristics during the 1st MRI scan. Forty-nine MS patients were included in this study. Median age of disease onset was 27 and age at 1st MRI scan was 40 [interquartile range (IQR) and range were 12 and 13–54, and 12 and 17–68, respectively]. Median disease duration at 1st MRI scan was 9.0 years (IQR; 13, range; 0–35). Total number of attacks prior to the 1st MRI scan was median; 4.0, IQR; 5.5, and range; 1–34. Median number of attacks between 1st and 2nd MRI scan was 0.0 (IQR; 1.0, range; 0–4). ARR before 1st MRI scan was median; 0.45, IQR; 0.67, range 0.11–4.25 and between 1st and 2nd MRI scan was median; 0.0, IQR; 0.30, and range; 0.0–1.5. Two patients were excluded in the ARR

Table 1
Demographic and clinical characteristics at 1st MRI scan in patients with MS.

	MS (n = 49)	Range
Female	40 (82%)	NA
Age at disease onset (years)	27 [12]	13–54
Age at 1st MRI scan	40 [12]	17–68
Disease duration at 1st MRI scan (years)	9.0 [13]	0–35
Total attack number before 1st MRI scan	4.0 [5.5]	1–34
Attack number during one year before 1st MRI scan	0.0 [1.0]	0–6
Attack number during two years before 1st MRI scan	0.0 [1.0]	0–13
Attack number between 1st and 2nd MRI	0.0 [1.0]	0–4
ARR before 1st MRI scan	0.45 [0.67] n = 47	0.11–4.25
ARR between 1st and 2nd MRI scan	0.0 [0.30]	0.0–1.5
EDSS at 1st MRI scan	2.0 [3.0]	0–7.5
Years from DMD initiation to 1st MRI scan	1.0 [3.0]	0–14
Days from last attack to 1st MRI scan	811 [1563]	20–5081

ARR: annualized relapse rate; DMD: disease-modifying drugs; EDSS: Kurtzke's Expanded Disability Status Scale; FIN: fingolimod; IFN: interferon-beta; MS: multiple sclerosis; NA: not applicable.
Data are presented as number (percentage) or median [interquartile range].
In ARR before 1st MRI scan, two patients were excluded because their disease duration was less than a year.

Table 2
Demographic and clinical characteristics based on treatment at 1st MRI scan in patients with MS.

	DMD (n = 39)		None	P value		
	FIN	IFN		FIN vs IFN	FIN vs None	IFN vs None
Number	16	23	10			
Female	12 (75%)	19 [83%]	9 (90%)	0.69	0.62	1
Age at disease onset (years)	23 [9.0]	28 [21]	32 [5.8]	0.17	0.003[a]	0.37
Age at 1st MRI scan	35 [9.5]	43 [14]	41 [9.5]	0.083	0.034	0.83
Disease duration at 1st MRI scan (years)	10 [15.4]	9.0 [12]	11 [12]	0.98	0.69	0.68
Total attack number before 1st MRI scan	6.0 [8.3]	4.0 [3.0]	3.0 [6.3]	0.010[a]	0.047	0.71
Attack number						
During 1 year before 1st MRI scan	0.0 [2.5]	0.0 [1.0]	0.0 [0.25]	0.27	0.45	1
During 2 years before 1st MRI scan	0.50 [3.3]	0.0 [1.0]	0.0 [1.0]	0.46	0.37	0.71
Attack number between 1st and 2nd MRI	0.0 [1.0]	0.0 [1.0]	0.0 [1.0]	0.78	1	0.8
ARR before 1st MRI scan	0.9 [0.9]	0.3 [0.7]	0.3 [0.5]	0.008[a]	0.024	0.66
(number)	(15)	(23)	(9)			
ARR between 1st and 2nd MRI scan	0.0 [0.3]	0.0 [0.6]	0.0 [0.4]	0.88	1	0.87
EDSS at MRI scan	4.0 [4.0]	1.5 [3.0]	1.0 [3.1]	0.045	0.014[a]	0.18
Years from DMD initiation to 1st MRI scan	0.0 [2.0]	2.0 [5.0]	NA	0.015[a]	NA	NA
Years from last attack to 1st MRI scan	1.5 [2.2]	3.1 [4.6]	4.5 [10.2]	0.09	0.041	0.31

ARR, annualized relapse rate; DMD: disease-modifying drugs; EDSS: Kurtzke's Expanded Disability Status Scale; FIN: fingolimod; IFN: interferon-beta; MS: multiple sclerosis; NA: not applicable.
None shows no-treatment.
Data are presented as number (percentage) or median [interquartile range].
[a] Statistically significant after correction for multiple comparisons.

Table 3
Brain volumes at 1st and 2nd MRI scan and the annualized atrophy rate between 1st and 2nd MRI scan in each treatment group in MS patients.

	DMD (n = 39)		None	P value		
	FIN	IFN		FIN vs IFN	FIN vs none	IFN vs none
At 1st MRI scan						
ICV	1.4 [0.14]	1.4 [0.12]	1.4 [0.066]	0.99	0.86	0.66
NLV	8.5 [9.0]	3.5 [6.5]	2.7 [10.5]	0.053	0.077	0.52
NGV	0.43 [0.052]	0.45 [0.061]	0.47 [0.056]	0.45	0.18	0.36
NWV	0.29 [0.041]	0.30 [0.035]	0.31 [0.032]	0.42	0.005[a]	0.031
NBV	0.73 [0.061]	0.74 [0.069]	0.77 [0.080]	0.22	0.017	0.11
At 2nd MRI scan						
ICV	1.4 [0.16]	1.4 [0.12]	1.4 [0.061]	0.92	0.78	0.5
NLV	10 [8.1]	3.1 [7.2]	3.3 [13]	0.032	0.11	0.8
NGV	0.42 [0.047]	0.44 [0.062]	0.45 [0.061]	0.34	0.11	0.5
NWV	0.29 [0.037]	0.30 [0.023]	0.31 [0.033]	0.37	0.06	0.18
NBV	0.71 [0.077]	0.75 [0.091]	0.75 [0.10]	0.14	0.047	0.18
Time from 1st to 2nd MRI scan						
(months)	25 [26]	29 [20]	32 [28]	0.88	1	0.77
Annualized atrophy rate (%)						
NGV	0.88 [1.8]	0.47 [0.82]	0.32 [1.8]	0.22	0.39	1
NWV	0.55 [2.5]	0.60 [1.8]	0.57 [2.3]	0.56	0.98	0.8
NBV	0.68 [1.5]	0.47 [1.1]	0.51 [1.0]	0.14	0.62	0.45

ICV: intracranial volume; DMD: disease-modifying drugs; FIN: fingolimod; IFN: interferon-beta; MS: multiple sclerosis; NBV: normalized brain volume; NGV: normalized grey matter volume; NLV: normalized lesion volume; NWV: normalized white matter volume.
None shows no-treatment.
Annualized atrophy rate of X is defined as follows.
$$\frac{(\text{X at 1st MRI scan} - \text{X at 2nd MRI scan}) \times 12}{(\text{X at 1st MRI scan}) \times (\text{Months between 1st and 2nd MRI scans})}.$$
X = NGV, NWV or NBV.
Data are presented as median [interquartile range].
[a] Statistically significant after correction for multiple comparisons.

analysis prior to 1st MRI scan due to short disease duration (< 1 year). Time (years) from DMD initiation to 1st MRI scan was: median; 1.0, IQR; 3.0, range; 0–14. Median days from last attack to 1st MRI scan was 811 (IQR; 1563, range; 20–5081).

3.2. Demographic and clinical characteristics based on treatment at 1st MRI scan

Demographic and clinical characteristics based on treatment at 1st MRI scan are summarized in Table 2. The number of patients in the FIN, IFN and None groups was 16, 23 and 10, respectively. Age at disease onset was significantly younger in the FIN group compared to the None group (median; 23 versus 32, IQR; 9.0 versus 5.8, range; 13–37 versus 22–40, respectively, P = .003). Total attack number and ARR before 1st MRI scan was higher in the FIN group than in the IFN group (median; 6.0 versus 4.0 and 0.9 versus 0.3, IQR; 8.3 versus 3.0 and 0.9 versus 0.7, range; 1–34 versus 1–14 and 0.24–2.42 versus 0.00–1.26, and P = .010 and 0.008, respectively). The FIN group had higher EDSS score compared with None group (median; 4.0 versus 1.0, IQR; 4.0 versus 3.1, range; 1–7 versus 0–7.5, respectively, P = .014). Years from DMD

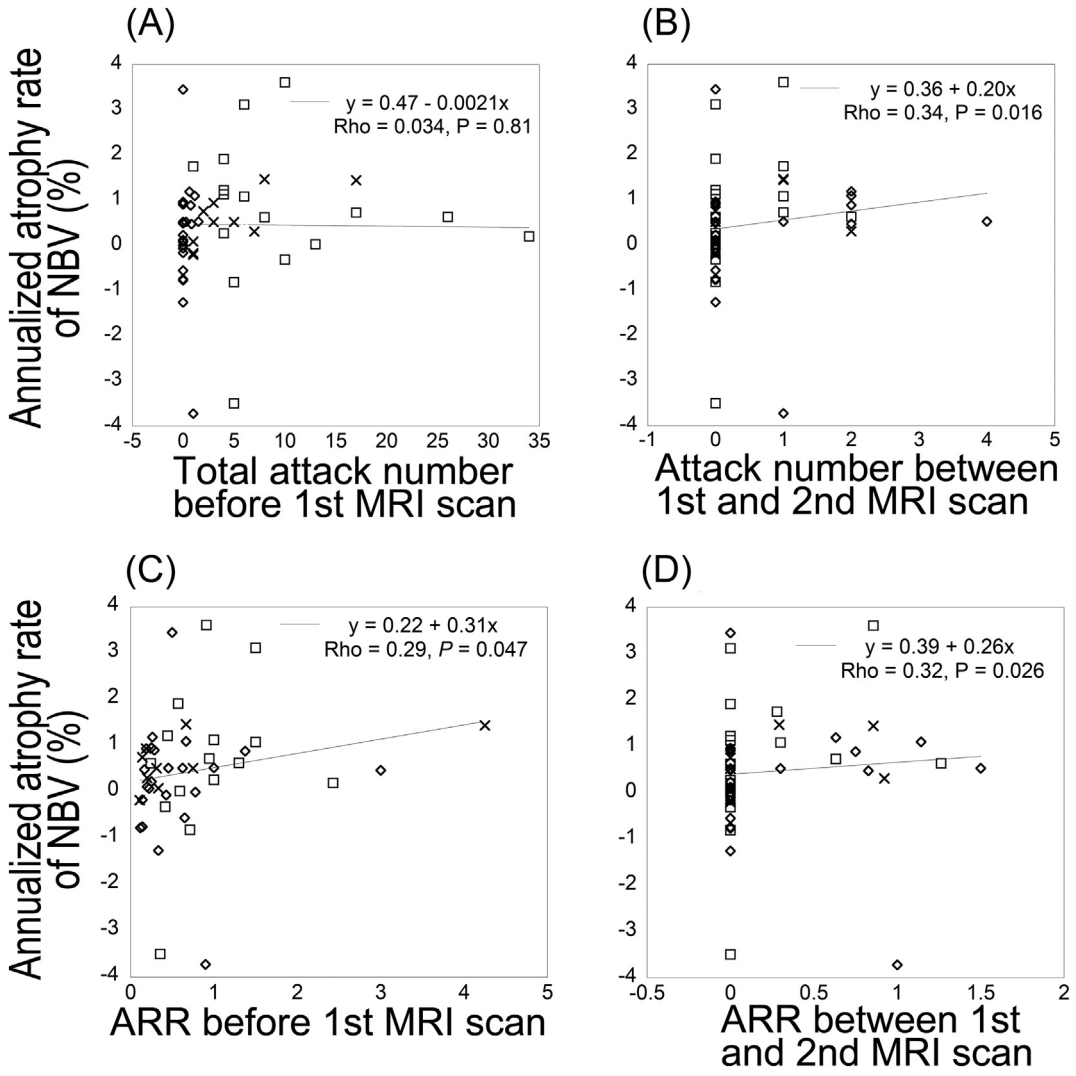

Fig. 1. The association between annualized atrophy rate of brain volume and other clinical parameters in all MS patients. (A) Correlation with attack number before 1st MRI scan. (B) Correlation with number of attacks between 1st and 2nd MRI scans. (C) Correlation with ARR before 1st MRI scan. (D) Correlation with ARR between 1st and 2nd MRI scans. Square, diamond and cross mark shows FIN, IFN and None, respectively. ARR; annualized atrophy rate, FIN; patients with MS treated with fingolimod between scans, IFN; patients with MS treated with interferon-beta between scans, None; patients with MS without treatment between scans, NVB; normalized brain volume.

initiation to 1st MRI scan were longer in the IFN group than in the FIN group (median; 0.0 versus 2.0, IQR; 2.0 versus 5.0, range; 0–3 versus 1–14, respectively, $P = .015$). No differences were found in the disease duration at 1st MRI scan, Age at 1st MRI scan, disease duration at 1st MRI scan, attack number during 1 year and 2 years before 1st MRI scan, attack number between 1st and 2nd MRI, ARR between 1st and 2nd MRI scan, and years from last attack to 1st MRI scan.

3.3. Brain volumes at 1st and 2nd MRI scans and the annualized atrophy rate between 1st and 2nd MRI scans

The result showed the significant difference between ICV at 1st MRI scan and 2nd MRI scan in all MS patients ($P = .015$). Table 3 shows brain volumes at 1st and 2nd MRI scans and the annualized atrophy rate between 1st and 2nd MRI scans in each treatment group in patients with MS. No differences were found in ICV, NLV, NGV, or NBV at 1st MRI scan, nor NLV, NGV, NWV, NBV at 2nd MRI scan, among FIN, IFN and None groups. NWV at 1st MRI scan in FIN group was lower than the None group ($P = .005$). However, there was no difference in NWV at 1st MRI scan between FIN and None groups after ANCOVA using age and EDSS as covariates after correction of multiple comparisons ($P = .029$). Age and EDSS was used as covariates because they showed the significant difference in FIN group after correction of multiple comparisons. The time from 1st to 2nd MRI scan was not different among FIN, IFN and None groups (median; 25, 29 and 32 months, range: 12–61, 12–49, and 12–48 months, respectively). No differences were found in the annualized atrophy rate of NGV, NWV and NBV among any groups.

3.4. Association between annualized atrophy rate of brain volume and other clinical parameters

Fig. 1 shows the association between the annualized atrophy rate of brain volume, and other clinical parameters, in all MS patients. Although annualized atrophy rate of NBV showed no correlation with total attack number before 1st MRI scan (Spearman's rho = 0.034, $P = .81$) (Fig. 1A), a significant correlation was found between annualized atrophy rate of NBV and attack number between 1st and 2nd MRI scan in all MS patients (Spearman's rho = 0.34, $P = .016$, Fig. 1B). This difference was not observed in subgroups including FIN (square), IFN (diamond), or None (cross mark) groups ($P = .17$, 0.32 and 0.25, respectively), likely due to the small sample size. Annualized atrophy

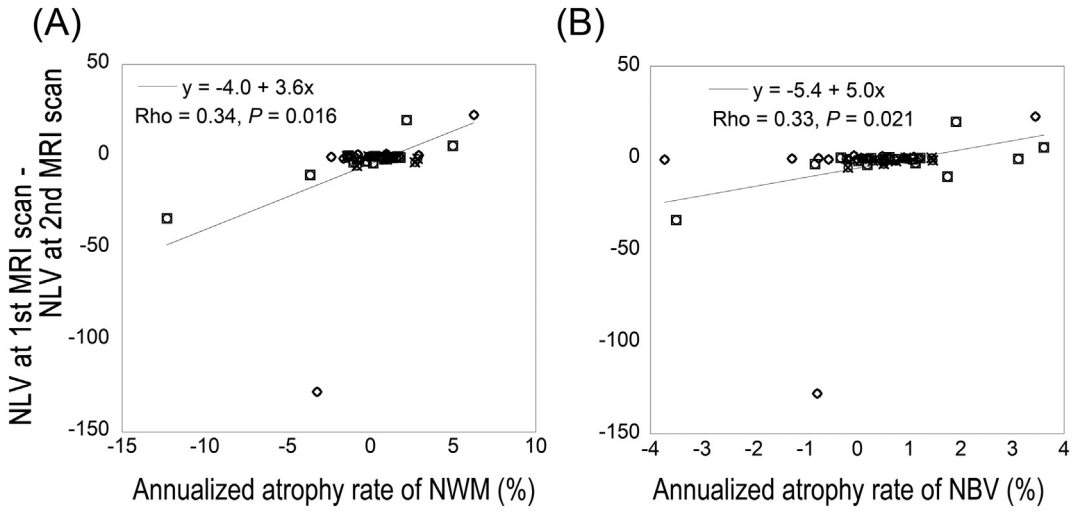

Fig. 2. (A) Correlation between annualized atrophy rate of NWM and NLV at 1st MRI scan-NLV at 2nd MRI scan in all patients with MS. (B) Correlation between annualized atrophy rate of NBV and NLV at 1st MRI scan-NLV at 2nd MRI scan in all patients with MS. Square, diamond and cross mark shows FIN, IFN and None, respectively. FIN; patients with MS treated with fingolimod between scans, IFN; patients with MS treated with interferon-beta between scans, None; patients with MS without treatment between scans. NBV; normalized brain volume, NLV; normalized lesion volume, NWV; normalized white matter volume.

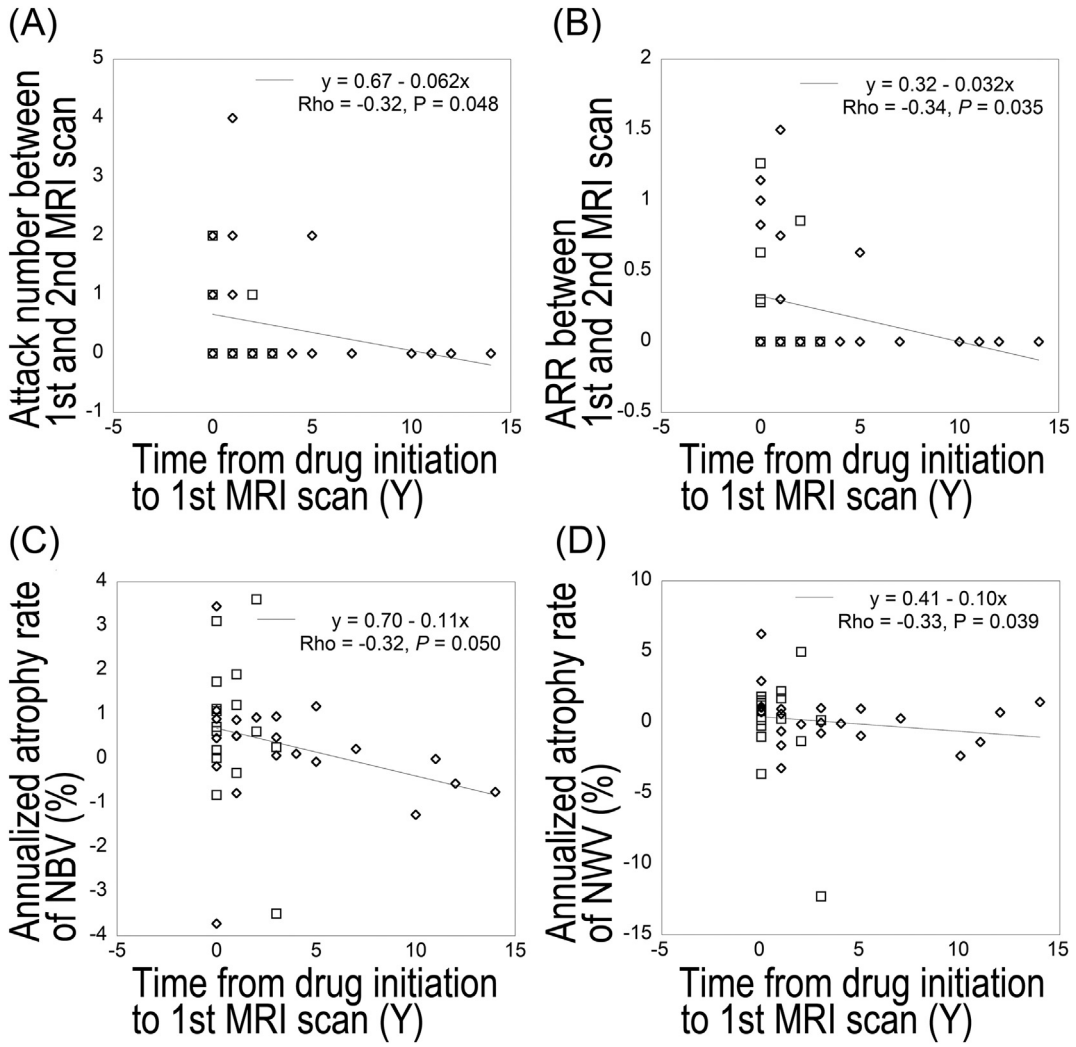

Fig. 3. The association between time from drug initiation to 1st MRI scan and other clinical parameters in FIN and IFN groups. (A) Correlation with attack number between 1st and 2nd MRI scans. (B) Correlation with ARR between 1st and 2nd MRI scans. (C) Correlation with annualized atrophy rate of NBV. (D) Correlation with annualized atrophy rate of NWV. Square and diamond shows FIN and IFN, respectively. ARR; annualized atrophy rate, FIN; patients with MS treated with fingolimod between scans, IFN; patients with MS treated with interferon-beta between scans, NBV; normalized brain volume, NWV; normalized white matter volume.

rate of NBV also indicated a positive correlation with ARR before 1st MRI scan and ARR between 1st and 2nd MRI scan (Spearman's rho = 0.29 and 0.32, $P = .047$ and 0.026, respectively, Fig. 1C and D). On the other hand, annualized atrophy rate of NBV indicated no correlation with NLV at 1st MRI scan (Spearman's rho = 0.16, $P = .28$) and with NLV at 2nd MRI scan (Spearman's rho = −0.17, $P = .26$). Total attack number before 1st MRI scan was positively correlated with attack number between 1st and 2nd MRI scan (Spearman's rho = 0.35, $P = .013$). Meanwhile, NLV at 1st MRI scan -NLV at 2nd MRI scan was positively correlated with annualized atrophy rate of NWM and NBV (Spearman's rho = 0.34 and 0.33, $P = .016$ and $P = .021$, respectively, Fig. 2), but not with the annualized atrophy rate of NGV (Spearman's rho = 0.11, $P = .46$).

3.5. Association between time from drug initiation to 1st MRI scan and other parameters

In DMD group (FIN and IFN groups combined), time from drug initiation to 1st MRI scan was negatively correlated with attack number between 1st and 2nd MRI scans (Spearman's rho = −0.32, $P = .048$) (Fig. 3A), ARR between 1st and 2nd MRI scans (Spearman's rho = −0.34, $P = .035$) (Fig. 3B), annualized atrophy rate of NBV (Spearman's rho = −0.32, $P = .050$) (Fig. 3C), and annualized atrophy rate of NWV (Spearman's rho = −0.33, $P = .039$) (Fig. 3D), but not with the annualized atrophy rate of NGV (Spearman's rho = −0.036, $P = .83$).

3.6. Difference in annualized atrophy rate with or without attack in patients with MS being treated with DMDs between 1st and 2nd MRI scans

The difference in annualized atrophy rate with or without attack between 1st and 2nd MRI scans was investigated in the DMD group (FIN and IFN groups combined). The percentage of annualized atrophy rate of NBV tended to be higher in the DMD group with attack than in the group without attack (median; 0.81 versus 0.20, IQR; 0.64 versus 1.3, range; −3.7–3.6 versus −3.5–3.4, respectively, $P = .052$). No differences were found in annualized atrophy rate of NBV in DMD group with or without attack ($P = .73$ and 0.17, respectively).

4. Discussion

In this study, we investigated the correlations between DMD treatment duration and brain atrophy. This study showed two main findings. First, the duration from drug initiation to 1st MRI scan showed a negative correlation with the annualized atrophy rate of NBV between 1st and 2nd MRI scans in DMD group (FIN and IFN groups combined). Second, the total attack number before 1st MRI scan positively correlated with subsequent annualized atrophy rate of NBV in all MS patients.

A previous report showed MS patients with three or more relapses showed significantly greater brain atrophy progression compared with those with no relapse [15]. The results of the current study are consistent with the study; NLV at 1st MRI scan-NLV at 2nd MRI scan showed a positive correlation with the annualized atrophy rate of NWV and NBV in all MS patients. This result indicates that total lesion volume change is correlated with the annualized atrophy rate of NWV and NBV. Moreover, our findings demonstrated that the total attack number before 1st MRI scan showed a positive correlation with annualized atrophy rate of NBV, which means the more the relapse number increases, the more the brain atrophy progresses in patients with MS.

Our study also indicated that duration from drug initiation to 1st MRI scan was negatively correlated with the annualized atrophy rate of NBV between 1st and 2nd MRI scans in both DMD groups. In addition, we observed a negative correlation between attack number between 1st and 2nd MRI scan and the time from first DMD initiation to 1st MRI scan. Our study also demonstrated that patients with a greater number of attacks tended to show higher annualized atrophy rate of NBV compared with fellow DMD patients who did not experience attacks. These results suggest that early intervention by DMD could lead to decrease the attack number and the progression of brain atrophy.

A previous study showed that fingolimod improved brain atrophy more so than IFN-beta 1b [16]. In our study, there was no difference in the annualized atrophy rate among FIN, IFN and None groups in our study, although the exact comparison was not performed in our study because of the background differences in each group. It is possible that we are statistically underpowered to determine this finding. Recently, the significant reduction of the brain volume loss was reported in RRMS patients treated with Teriflunomide [17]. Therefore future studies should target specific DMD interventions to determine the optimal drug to improve brain atrophy.

There are some limitations in to study. First, three MRI scanners were used in this study, and there are intrinsic differences in signal and noise between scanners. This leads to our second limitation in that some patients were imaged with a different scanner at 1st and 2nd MRI scans. However, 67% of our patients had their pre and post scans using the 1.5-Tesla Signa HDxT scanner. Therefore, MRI scanner difference was considered to show little effect on the results. Also, in this retrospective study, patients who received the same treatment for more than one year were included, which means patients could take various treatments before the period. However, in None group, only two patients took some DMDs before; a patient had used IFN for four months five years before the period, and another patient continued DMDs for three years two years before the period, which may affect the result. However, the period and the number of patients taking another DMDs are low, the effect is considered to be little. Our result may also be affected by DMD-associated pseudoatrophy. Accelerated, non-tissue related brain volume atrophy called pseudoatrophy can be caused by anti-inflammatory therapies like DMDs [18]. So, IFN and FIN groups may tend to show DMD-related pseudoatrophy, which may affect the results. Selection bias may also be involved in our study, as highly active patients with MS could have been excluded from our study due to changes in DMD treatment within the year. Also FIN group had much higher EDSS at 1st MRI scan compared to the other groups, which may affect the results. Another selection bias is that we included the patients who received the brain MRI scan including T1-weighted three-dimensional images. However it depended on each neurologist's decision whether T1-weighted three-dimensional images were performed. Therefore, T1-weighted three-dimensional images may have tended to be excluded from the protocol for the non-active MS patients because they were considered to have tendency to show less brain atrophy compared with the active MS patients.

In conclusion, the number of total attacks and change in lesion volume are associated with brain atrophy in patients with MS. Early and effective commencement of DMD may reduce clinical attacks and reduce brain atrophy in patients with MS.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.06.011.

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