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Original Research

Association Between Brain Atrophy with EDSS and Number of Lesion Sites in Indonesian Multiple Sclerosis Patients

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ABSTRACT

Introduction: Multiple sclerosis (MS) is a potentially disabling inflammatory demyelination of the central nervous system. The demyelination process will end up with the destruction of neurons that leads to the decrease of brain volume. Brain atrophy may cause more severe disability and affect the quality of life of MS patients, who are mostly at a young age.
Objective: Our study aims to assess the brain atrophy among Indonesian MS patients and the association between with the degree of disability.
Material and methods: A cross-sectional study included 28 MS patients. To determine the brain atrophy, we compared 11 healthy control group to the MS group. Head MRI was performed using 1.5T MRI and the brain volume was processed with Freesurfer type 6.0 automatic software.
Result: The white matter (WM) and gray matter (GM) volume of MS patients was significantly lower compared to normal control with 78.6% GM atrophy and 67.9% WM atrophy. EDSS score is significantly associated with WM atrophy but not with GM atrophy. Factors related to WM atrophy are age, age of onset, and subtype of MS. Several lesion sites were found greater in subjects with GM and WM atrophy.
Discussion: The mechanisms of brain atrophy in MS involve inflammatory processes and neurodegeneration. Various factors, including lesion volume impact atrophy rates. Brain atrophy had correlation with EDSS scores.
Conclusion: Brain atrophy was common in MS patients and significantly associated with the level of disability and number of lesion sites.

Keywords: multiple sclerosis; EDSS; atrophy

INTRODUCTION

Multiple sclerosis (MS) is a debilitating inflammation demyelinating disease of the central nervous system that mostly affected young age.[1] The global prevalence is 35.9 per 100,000 people in 2020, estimated 30% higher compared to 2013. The estimated Indonesia prevalence is 0.1 per 100.000 people, lower compared to the western country.[2] However, the number of reported cases is increasing in line with the increase of knowledge and awareness among health care.

The diagnosis of MS is confirmed

through clinical symptoms and imaging with magnetic resonance imaging (MRI) of the head and spine according to McDonald's 2010 criteria.[3] Demyelination process, axonal degeneration, astrogliosis which are pathological markers of MS produce plaque lesions on MRI images and cause clinical symptoms.[1] The pathological process continues and results in decreased brain volume. When clinical symptoms did not worsen, it turned out that atrophy continued, even in normal-appearing white matter (NAWM).[4]

The clinical symptoms get worse along with the increase in the volume of the lesion and the decrease in brain volume/atrophy.[1,5] Pathology that occurs continuously in the brain caused accelerating atrophy which also correlates with the degree of clinical disability as measured by the EDSS (Expanded Disability Severity Scale). EDSS worsening is in line with the rate of total atrophy.[6] Atrophy is a marker of ongoing damage to the brain, so it is believed to be correlated with EDSS. The worsening degree of disability triggers the decline in patients' quality of life.[7,8]

Many factors influence the rate of atrophy, such as age, age of onset, sex, occupation, level of education, duration of disease, frequency of relapse, lesions volume in T2 sequences, presence of acute lesions, and use of disease-modifying drugs (DMD). The highest correlation was in the volume of the lesions.[6,9] In terms of DMD, the availability of DMD is very limited with only 2 types of DMD from more than 18 that are licensed to be prescribed in Indonesia. The high price and not covered by public insurance make access to DMD for MS patients difficult. Many of them cannot afford DMD and have to use off-label immunosuppressants such as azathioprine or mycophenolate mofetil. Inadequate treatment might affect the rate of increased disability level which will end up in a decrease in productivity and quality of life. Knowing the brain volume status of our MS patients and the association with disability level is important as a basis evident to evaluate treatment effectiveness.

MATERIAL AND METHODS

Study design and subject criteria

This is a cross-sectional study involving 28 MS patients who visited the neurology outpatient clinic, Cipto Mangunkusumo Hospital, Jakarta. The study was conducted from Jul 2 to November 2018. Inclusion criteria for the MS group include (1) being diagnosed with MS according to McDonald 2010 criteria[3] at age 18-50 years old and (2) providing written consent to be recruited into the study. Exclusion criteria were (1) previous or current history of central nervous system diseases, (1) history of major depression, schizophrenia, and psychotropic drug use, and (3) having renal function impairment with eGFR <45 mL/min/1.73 m^2, and other conditions contraindicated for MRI or that might compromise the diagnostic testing result.

Inclusion criteria for the control group were (1) adults aged 18-50 years old, adjusted for age, gender, occupational status, and education level, and (2) providing written consent to be recruited into the study. Exclusion criteria were (1) previous or current history of central nervous system diseases, (2) history of major depression, schizophrenia, and psychotropic drug use, and other conditions contraindicated for MRI or conditions that might compromise the diagnostic testing results.

This study has been approved by the Health Research Ethics Committee of Faculty of Medicine, Universitas Indonesia (No: 0381/UN2.F1/ETIK/2018). All data and examination results were confidential.

Study measurement

History, physical examination, EDSS assessment, renal function test, and head MRI were taken from MS patients who visited the outpatient clinic and met the inclusion criteria. Head MRI scan was performed for 50 minutes using MRI GE Optima series 450 W 1.5 Tesla under 3D Brain Volume Imaging (BRAVO) acquisition protocol: matrix 1.5mm x 1.5mm x 1.5mm, TR 10.7 ms, TE 34.3 ms, TI 450 ms, FOV 256 x 192, thickness 1.5mm and gap 0. The obtained MRI images were stored in (dot)DCM format and transferred onto the computer to be further processed with Freesurfer type 6.0 automatic software with Linux OS.

Both white matter (WM) and grey matter (GM) volume calculations performed on 11 people of the normal

group were adjusted for age, gender, occupational status, and education level with the MS group. Every subject in the control group underwent a non-contrast head MRI scan with the volume of brain areas calculated using Freesurfer 6.0, which resulted in a GM mean volume of 578.95±33.04ml and a WM mean volume of 434.82±41.89ml for the control group.

The score for brain atrophy was acquired according to the literature, which was determined from the volumes of WM and GM with a z-score of less than -1.10 This method was utilized to calculate the WM and GM volumes of the MS cohort by calculating the z-score for this group using the following equation: subtraction of mean of subjects' volume of WM or GM with mean of control group volume divided with control group standard deviation. Z-score for each subject was obtained from this value and later divided into two categories, normal, if z-score ≥-1, and atrophy, if z-score <-1.

The WM volume is defined by the total volume of WM in the brain, whereas GM volume is the total volume of the cortical and deeper cortical area.

Statistical analysis

Data were analyzed using SPSS version 20.0 and Graph Pad Prism V5.02. A p-value of <0.05 was considered statistically significant. A normality test was conducted prior to analyzing numerical data using the Pearson test. Comparison of mean brain volume between MS group and control group were analyzed using T-test. Association between EDSS score and brain volume were calculated using the Mann Whitney U test. Categorical data were further analyzed using the Chi-square test. We are not performed multivariate analysis due to the small number of subjects.

RESULT

Thirty-one subjects with MS were recruited from June to November 2018. Three subjects were excluded (two people aged more than 50 years and one person had major depressive disorder). In the control group, eleven people were recruited. Most subjects were females (82.1%), with a median of age was 30 (range 20-50) years old. These subjects were also dominated by those obtaining higher

Table 1. Sociodemographic and clinical characteristics of the subjects

Variable	MS (n=28)	Control (n=11)	*p*
n(%)			
Gender			1
Male	5 (17.9)	2 (18.2)	
Female	23 (82.1)	9 (81.8)	
Subtype			
RRMS	20 (71.4)		
SPMS	8 (28.6)		
Occupational status			0.15
Unemployed	13(46.4)	2(18.2)	
Employed	15(53.6)	9(81.2)	
mean±SD			
Age	31.6±7.5	32.3±9	0.71
Age of initial onset	26.6±7.8		
median (range)			
Education (years)	16(12-22)	16 (12-18)	0.09
Relapse frequency (time/year)	4.5(1-13)		
Duration of disease	3.5(0.5-13)		
EDSS	3(0-7.5)		
Number of lesion sites	13(3-21)		

RRMS: Relapsing Remitting Multiple Sclerosis; SPMS: Secondary Progressive Multiple Sclerosis; EDSS: Extended Disability Severity Scale

education (64.3%) and those who were employed (53.6%). No significant difference was observed regarding gender, age, education level, and occupation between the MS patients and the control group (Table 1).

The RRMS subtype was the most dominant subtype among the subjects (71.4%). The mean age for initial onset was 26.9 ±7.9 years old with relapse frequency and duration of disease of 4.9± 3.3 times per year and 5±3.8 years, respectively. The mean EDSS was 3.6±2.3.

In the MS group, the mean WM and GM volumes were 356.1±67.8 ml and 520.8±46.8 ml, respectively. The WM and GM volumes of the MS group were considerably smaller compared to the control group with p values of p=0.001 for both (Figure 1). When the volume of the control group was converted into a z-score, 78.6% and 67.9% of the MS cohort were found to have atrophy of the GM and WM, respectively. Atrophy of both areas was found in 17 MS subjects, whereas WM atrophy was found only in two subjects, GM atrophy in five subjects and no presence of atrophy in four subjects.

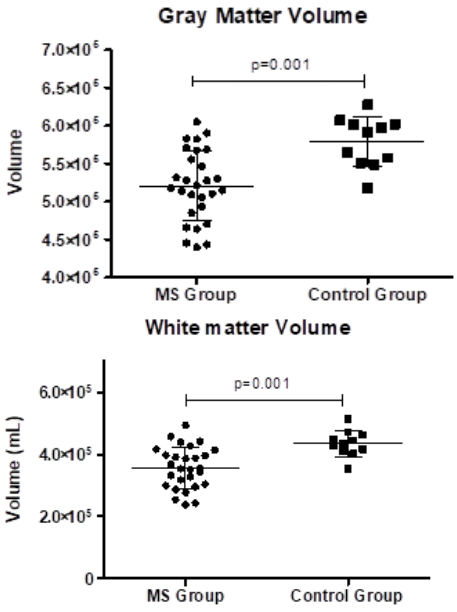
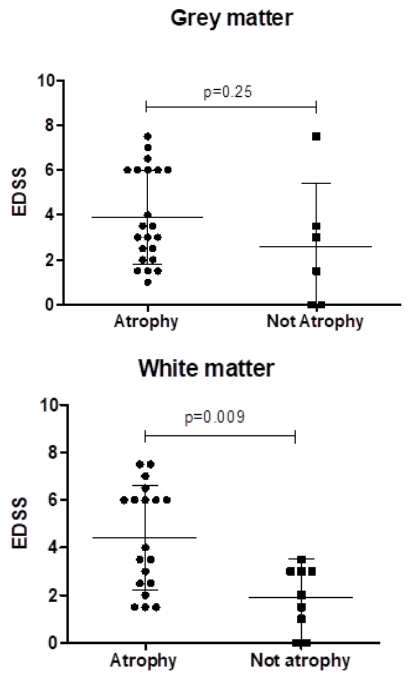


Figure 1. Grey and white matter volume in MS significantly lower than control group

Subjects with WM atrophy had higher EDSS value compared to those without atrophy (4.4±2.2 vs 1.9±1.3; p=0.009). Nevertheless, no difference in EDSS value was found among subjects with and without GM atrophy (3.9±2.1 vs 2.6±2.8; p=0.25) (Figure 2). Subjects with atrophy in both areas (GM and WM) had a significantly higher value of EDSS compared to non-atrophy and atrophy in one area only (4.4±2.0 vs 2.4±2.1; p=0.016).



Mann Whitney U Test

Figure 2. MS with white matter atrophy had worse EDSS score

From a total of 21 lesion sites predetermined by the authors as the most common predilection sites in MS, most lesions were found in cerebral lobes, especially in the right parietal (100%), left parietal (96.4%), left frontal, right temporal, and right occipital lobe (92.9%). The least common location was in the right and left internal capsules.

The median value on the number of lesion sites among the MS group was 13 (range 3-21). An unpaired t-test analysis revealed that the number of lesion sites was significantly greater in subjects with GM atrophy compared to those without (p=0.017). For white matter, the Mann-Whitney test showed that the number of lesion sites was significantly greater in patients with atrophy (p<0.001).

No significant age difference was found among subjects with and without GM atrophy (31.1±7.2 vs 31.5±9.7). In contrast, subjects with WM atrophy tend to be younger compared to those without WM atrophy (29.2±5.9 vs 35.6±9.3, p=0.04) (Table 2). No significant difference was found in terms of other demographic variables among both atrophic and non-atrophic group.

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No significant difference was found in terms of age of onset among subjects with and without GM atrophy (27.4±8.1 vs 25.3±7.7), however, subjects with WM atrophy had an earlier age of onset compared to the without WM atrophy (24.1±6.2 vs 33±8.2, p=0.003) (Table 3). All patients with a progressive type of MS had WM atrophy whereas only 55% of patients with RRMS had WM atrophy. No significant difference was found in terms of clinical presentations between patients with or without WM and GM atrophies.

Table 2. Association between Demographic Characteristics of MS Patients with brain Atrophy

Variable	Grey matter atrophy		p	White matter atrophy		p
	Yes (n=22)	No (n=6)		Yes (n=19)	No(n=9)	
Age	31.1±7.2	31.5±9.7	0.92[a]	29.2±5.9	35.6±9.3	**0.03[a]**
Education level	14.8±2.6	14.7±2.1	0.90[b]	14.4±2.8	15.4±1.3	0.21[b]
Gender			0.55[c]			0.14[c]
Women	17 (73.9%)	6 (26.1%)		14 (60.9%)	9 (39.1%)	
Men	5 (100%)	0 (0%)		5 (100%)	0 (0%)	
Occupational status			0.65[c]			0.11[c]
Employed	11 (73.3%)	4 (26.7%)		8 (53%)	7 (47%)	
Not employed	11 (84.6%)	2 (15.4%)		11 (85%)	2 (15%)	

[a]T-test, [b]Mann Whitney U Test, [c]Chi square

Table 3. Association Between Clinical Presentations in MS Patients with brain atrophy

Variable	Grey matter atrophy		p	White matter atrophy		p
	Yes (n=22)	No (n=6)		Yes (n=19)	No (n=9)	
Age of onset	27.4±8.1	25.3±7.7	0.59[a]	24,1±6,2	33±8,2	**0,003**[a]
Duration of disease	4.6±3.8	6.1±4.1	0.41[b]	5,0±3,9	4,8±3,96	0,89[b]
Relapse frequency	5,1±3,3	4,7±3,5	0,81[a]	5,6±3,6	3,7±1,8	0,07[a]
Type of MS			0,64[c]			**0,03[c]**
RRMS	15(75%)	5(25%)		11(55%)	9(45%)	
SPMS	7(87,5%)	1(12,5%)		8(100%)	0(0%)	

[a]T-tes, [b]Mann Whitney U Test, [c]Chi square;
RRMS: Relapsing Remitting Multiple Sclerosis; SPMS: Secondary Progressive Multiple Sclerosis

DISCUSSION

Our study showed evidence of brain atrophy in Indonesian MS patients. Both WM and GM were smaller compared to the control group. Comparing to other studies, the WM and GM volume in our MS patients was smaller than in other countries in Asia such as Japan, and in Europe such as Germany.[11,12] The underlying mechanisms of WM atrophy include inflammation, perpetual demyelination without subsequent remyelination hypothesis, axonal

degeneration, and damaged oligodendrocytes. Progressive and retrograde widespread destruction of WM towards the neuron body, cortical demyelination, and lymphocyte infiltration in the perivascular area in the cortex are hypothesized to be the mechanism of GM atrophy. These mechanisms are due to the process of oxidative injury which further alters gene expression and causes DNA damage, leading to changes in the glial cells and cortical regeneration process. Additionally, other hypotheses that explain the mechanism of atrophy in MS patients include neurodegenerative process, intraneuronal connectivity dysfunction, anterograde trans-synaptic degeneration, retrograde degeneration, Wallerian degeneration, and dendritic shrinkage.[13]

From the previous study, the development of total brain atrophy in MS patients varies, ranging from 0.5 to 1.3% per year, compared to normal adults (0.1-0.4% per year).[14,15] The rate of WM atrophy was 1.8% per year and 0.75-1.66% per year for GM atrophy in MS patients yet the atrophy rate in the control group was 0.23-0.51% per year.[5]

Our study revealed that widespread atrophy was more prevalent in GM than WM. This is not only due to the pathological process in WM but also due to increased degenerative processes compared to normal adults. MRI scans showed normal-appearing WM (NAWM), whereas diffuse tensor MRI images showed abnormal tissue integrity that may contribute to the normal appearance of the GM atrophy.[16]

The EDSS is an assessment scale evaluating the function of the CNS. It consists of assessment for the visual, brainstem, pyramidal, cerebellum, sensory, urination, defecation, cerebral/mental, and ambulation functions using a scale of 0-10. A score of zero means no neurological deficit and a score of ten means a severe disability that may be fatal in MS.

Analysis between WM and GM atrophy in the MS group demonstrated a significant association between WM atrophy group with EDSS score (p=0.009) and insignificant association in GM atrophy group (p=0.25). More lesions

can be found in WM than in GM, therefore clinical relapse occurs due to white matter pathology, and this is pathophysiologically correlated with white matter atrophy. There is no direct significant correlation between GM atrophy and clinical relapse, as it contributed as a secondary effect to the pathology in the WM. However, both pathologies cannot be neglected as both atrophies are related to future disability.[17] A cohort study by Gumberz et al. revealed that the GM atrophy rate has a better predictive value to EDSS compared to white matter atrophy in a longitudinal study. In such studies, cortical pathology plays a significant role in disability.[11] This may explain why in this study grey matter atrophy was not associated with EDSS, since this is a descriptive, cross-sectional study. Correlation between the rate of atrophy and EDSS could possibly be found only in consecutive longitudinal studies.

Our study found no significant association between GM atrophy with a number of lesion sites (p=0.017). In other hand, WM atrophy significantly related with age (p=0.035), age of onset (p=0.03), MS subtype (p=0.029), and a number of lesion sites (p<0.001).

Reduction of brain volume inevitably occurs to all individuals each year. The rate of brain atrophy in both normal and MS patients is affected by various factors. Current age and duration of disease are associated with WM and GM atrophy in MS patients.[12,18] In contrast, age of onset and gender have no association to both WM or GM atrophy, although men tend to have a higher rate of atrophy, longer duration of disease, and higher EDSS scores compared to women, resulting in more severe pathology.[12]

Age, sex, education level, chronic stress, history of past illness, history of alcohol and drug use such as cannabis are contributing factors for the higher rate of atrophy compared to the control group.[19,20] Although other studies found females have smaller brain volumes compared to men[21], in our MS patients we found no volume difference between males and females. This might be due to the small proportion of males in our subjects.

No study has ever discussed the relationship between brain atrophy in

MS patients with education level and occupational status, whereas, in the normal populations, education level correlates with WM and GM volume. Population with a higher level of education have a significantly higher volume of WM and GM, especially in temporoparietal and orbitofrontal lobes.[22] Occupations requiring higher intellectual ability (student, manager, employee) have a larger volume compared to workers that do not require much intellectual ability (farmer, gardener).[22] High stress works contribute to a faster rate of brain atrophy.

This study shows an insignificant association between GM and WM atrophy with gender, education level, and occupation status. That might be due to atrophy in MS occurs early and progress significantly since the early course of the disease, thus other factors become insignificant.

We found that all our SPMS subjects have WM and GM atrophy except one subject with only WM atrophy. This is due to more massive destruction in SPMS type compared to RRMS.[23] This finding is in accordance with previous studies which showed a significant negative correlation between the increased score of EDSS and MS type with WM and GM atrophy. We found no significant EDSS difference based on GM atrophy status. This could occur due to the nature of this study (cross-sectional), patients' duration of disease, and a limited number of samples, which were inadequate to portray the MS pathology towards disability.

This study found a significant difference in age of onset with brain atrophy. Younger subjects with younger age of onset show more atrophy compared to older patients. A larger proportion of younger subjects in this study may contribute to this result, thus showing that more WM atrophy is found in younger subjects.

This study also demonstrates a significant association between the number of lesion sites and either WM or GM atrophy. This is a novel finding, as prior studies never reported the correlation of several lesion sites and atrophy. Previous studies have reported that the accumulation of lesion volume in T2 MRI images reflects the amount of damage that contributes to WM or GM atrophy.[17] Our study analyzed the

number of lesion sites instead of lesion volume due to the limitation of available software.

In accordance with previous study reporting that atrophy still occurs even without any event of relapse[24], we also found no correlation between brain atrophy and relapse frequency.

CONCLUSION

In conclusion, brain atrophy is a common finding among Indonesia MS patients with 78.6% atrophy of GM and 67.9% WM. WM atrophy is significantly associated with EDSS score. Our finding might reflect the need for treatment improvement for MS in Indonesia. The availability of DMD which could slow the disease progression is very important as a point of care of MS treatment. Hopefully, our results can be used to encourage better access to DMD for Indonesian MS patients.

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