The Relationship of White Matter Hyperintensities with Depressive Symptoms and Daily Living Activities in Early-Stage Alzheimer's Disease Patients

Erken Evre Alzheimer Hastalığında İzlenen Ak Madde Hiperintensitelerinin Depresif Semptomlar ve Günlük Yaşam Aktiviteleri ile İlişkisi

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ABSTRACT

Introduction: Cerebral white matter hyperintensities (WMHs) detected on magnetic resonance imaging scans are frequently seen in both Alzheimer's disease (AD) and depression patients and believed to play an important role in cognition and mood. Depressive symptoms and depression may accompany AD in all stages of the disease. The aim of the study was to evaluate the relationship of regional WMHs with depressive symptoms, cognitive status, medial temporal lobe atrophy, and daily living activities in early-stage AD patients.

Method: Forty-five patients with very mild or mild AD were examined. All subjects underwent MRI and were assessed by the Geriatric Depression Scale (GDS) and the Addenbrooke's Cognitive Examination-Revised (ACE-R) for the evaluation of depressive symptom severity and cognitive status, respectively. The patients were divided into two groups based on the selected cut-off point in the GDS. CDR sum of the boxes (CDR-sb) scores were calculated as a measure of activities of daily living (ADLs). MRI T2-FLAIR slices were used to rate the white-matter lesions according to the Age-Related White Matter Changes Rating Scale, assessing the WMHs in frontal, parietooccipital, temporal, infratentorial and basal ganglia areas individually. Medial temporal lobe atrophy was assessed with high-resolution T1 images using visual rating scale.

Results: In the depressive group, frontal WMH scores were found to be higher than in the non-depressive group ($p=0.006$). ACE-r, CDR-sb and medial temporal lobe atrophy scores did not differ among the groups. CDR-sb scores showed a significant correlation with frontal WMH scores (left frontal WMH $r=0.439$, $p=0.003$, right frontal WMH $r=0.459$, $p=0.001$). Linear regression models revealed the effect of WMHs on depressive symptoms among the other factors including age, functionality and atrophy in the medial temporal areas.

Discussion: Our findings underscore the potential role of regional, particularly frontal AMHs in depressive symptoms and functionality of the early AD patients. (*Archives of Neuropsychiatry* 2013; 50: 360-363)

Key words: White-matter, Alzheimer's disease, depressive symptoms

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ÖZET

Giriş: Serebral ak madde hiperintensiteleri (AMH), Alzheimer hastalığı (AH) ve depresyon hastalarında sık olarak izlenen manyetik rezonans görüntüleme (MRG) bulgularındandır ve selim lezyonlar olmadıkları gibi kognisyon ve duygudurum ile de ilişkili oldukları anlaşılmıştır. AH'de en sık izlenen mood bozukluğu olan depresyon ve depresif semptomlar, AH seyrinin tüm evrelerinde izlenebilmektedir. Bu çalışmanın amacı erken evre AH (Klinik Demans Evreleme [CDR] skoru 0.5 ve 1 olanlar) hastalarında izlenen AMH'lerin depresif semptomlar, kognitif durum, medyal temporal atrofi ve günlük yaşam aktiviteleriyle bağlantısının araştırılmasıdır.

Yöntem: Çok erken ve erken evrede olan 45 AH hastası çalışmaya dahil edilmiştir. Tüm hastalara ak madde değerlendirmesi yapmak ve medyal temporal atrofiyi incelemek için beyin MRG incelemesi yapılmış, depresif semptomları değerlendirmek için Geriatrik Depresyon Ölçeği (GDS), kognitif durumu belirlemek için Addenbrooke Kognitif Değerlendirme ölçeğinin revize edilmiş formu (ACE-r) uygulanmıştır. Hastalar GDS'de 11 puanı sınır değer alınarak dikotomize edilip gruplandırılmıştır. Günlük yaşam aktivitelerini değerlendirmek için ise CDR ölçeği kutu toplamaları skorları (CDR-kts) hesaplanmıştır. Ak madde hiperintensitelerini değerlendirmek için MRG T2-FLAIR görüntüleri incelenmiş ve ak maddeyi bölgesel olarak (frontal, parietookspital, temporal, infratentorial ve bazal ganglia) değerlendiren Yaşla İltisli Ak Madde Değişiklikleri Değerlendirme Ölçeği kullanılarak skorlanmıştır. Medyal temporal lob atrofi ise yüksek çözünürlüklü T1 kesitler incelenerek görsel değerlendirme ölçeği aracılığı ile skorlanmıştır.

Bulgular: GDS skorları yüksek olan grupta frontal AMH skorları anlamlı olarak yüksek bulunurken ($p=0.006$) diğer bölgelerde bu anlamlılık saptanmamıştır. Gruplar arasında ACE-r, CDR-kts ve medyal temporal lob atrofi skorları açısından farklılık saptanmamıştır. Tüm hastalar birlikte ele alındığında CDR-kts skorları ile frontal AMH skorları anlamlı korelasyon göstermiştir (sol frontal AMH $r=0.439$, $p=0.003$, sağ frontal AMH $r=0.459$, $p=0.001$). Lineer regresyon analiz modelleri de depresif semptomlar üzerine yaş, işlevsellik kaybı ve medyal temporal atrofi arasında sadece frontal AMH'lerin etkiye bulunduğunu göstermiştir.

Sonuç: Bulgularımız özellikle frontal yerleşimli AMH'lerin depresif semptomların şiddeti ve işlevsellik ile ilişkili olabileceğini göstermektedir. (*Nöropsikiyatri Arşivi* 2013; 50: 360-363)

Anahtar kelimeler: Ak-madde, Alzheimer hastalığı, depresif semptomlar

Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

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Introduction

Alzheimer's disease (AD) is the most common type of degenerative dementia in which aging is the most important and unchangeable risk factor. Another condition which increases in frequency is vascular risk factors. Therefore, it is not surprising that vascular mechanisms and neurodegenerative factors are intertwined for AD. Atherosclerosis which is the most important cardiovascular problem has been found to be strongly related with neuritic plaques observed in Alzheimer's disease (1). In addition, vascular changes in AD occur before the clinical findings similar to amyloid plaques and neurofibrillary tangles which are the pathological indicators of the disease (2,3). Another finding which is observed more frequently in the elderly is hyperintense lesions observed in the white matter (HWM) in the sequences which are sensitive to the white matter including the T2, Fluid Attenuated Inversion Recovery (FLAIR) weighted images and on brain magnetic resonance imaging. Many studies suggest that these lesions are nonspecific markers of axonal damage which develop lifelong and display exaggeration with cerebrovascular and neurodegenerative diseases (4,5). Although these MRI lesions were conceptualized as more benign lesions, it has been shown that they are directly related with cognitive disorder and vascular diseases (6,7,8,9). Presence of HWM leads to progressive cognitive disorder independent of neurodegenerative diseases in normal elderly individuals (9). Another condition which HWMs are related with is depression. Not only geriatric depression, but also depression observed for a life time shows relation with white matter lesions (10). A state of intertwining similar to Alzheimer's disease and vascular findings is also true for depression and AD. For example, depression is both a risk factor for AD and one of the frequently observed behavioral findings in the course of the disease. The clinical picture is more severe in Alzheimer's patients in whom depression accompanies, the burden of the caregiver is markedly increased and the patients are hospitalized in hospitals or nursing homes with a higher rate. In terms of depression, vascular risk factors are a risk factor for geriatric depression and patients with vascular risk factors may be more resistant.

Our hypothesis in this study is that HWMs observed in the frontal white matter in early stage AD patients in whom frontal cortical involvement is not expected lead to depressive symptoms relatively independent of medial temporal lobe (MTL) atrophy by interrupting fronto-subcortical circuits and this leads to additional impact in patients whose activities of daily living are already affected.

Method

Patient Selection

Fortyfive early stage Alzheimer's patients were included in this study. These patients were selected from the patients for whom MRI, cognitive and behavioral evaluations were performed in a study which was initiated previously and is still continuing. Local ethics committee approval was obtained both for the main study and for this retrospective study before collecting data and all patients were informed about the study before the study and informed consent forms were filled in. Among the 140 patients in this study, 45 patients whose imaging, cognitive and behavioral

assessments were present and whose CDR scores were between 0.5 and 1 were included in our study. In all patients, cranial MR examinations were performed and T2-FLAIR (FOV, 24cm; 256x160; 21sections; TE, 147 millisecond; TR, 8800 millisecond, section thickness 5.0mm, gap 2.5mm) sequences in the axial plane and 3-dimension high resolution T1 sequences (TR/TE=8.6/4.0 second, flip angle=8°, FOV=240 mm, acquired voxel size=1.25/1.25/1,2 mm (reconstructed=0.94/0.94/1,2 mm), 150 coronal section) were also present. Addenbrook Cognitive Examination Revised (ACE-r) and Geriatric Depression Scale (GDS) were used to assess cognitive status and depressive symptoms. Both scales are widely used to screen symptoms. Clinical Dementia Rating scale (CDR) was applied to grade dementia and to measure activities of daily living in the patients and the score of the scale was used to grade dementia and sum of the boxes score was used as a measure of activities of daily living. Only early stage AD patients who scored between 0.5 and 1 according to the CDR scale were included in the study.

Evaluation of MRG Results

For cranial MRI examinations of the patients high resolution T1-weighted images and T2-weighted and FLAIR sections in the axial plane were taken using 1.5 Tesla MR device (Philips Achieva, Holland). In terms of shooting standardization, all shooting were done using the same device by the same technician in the same time interval (10.00-12.00 in the morning). FLAIR sequence images in the transverse plane were used to evaluate the white matter. White matter hyperintensities were classified using Age-Related White Matter Changes Rating scale (11). This scale is a scale which classifies HWMs regionally as frontal, parietooccipital, temporal, infratentorial and basal ganglia hyperintensities. According to the frequency and extension of HWMs in the specified region, a score ranging between 0 and 3 is given to the lesions. As the score increases, the frequency and extension of the lesion increases. In Picture 1, MR samples scored between 1 and 3 are shown in order. Atrophy in the medial temporal lobes was scored using the scale developed by Scheltens et al. after high resolution T1 images were examined (12).

Statistics

Descriptive statistics were performed to evaluate the whole of the group. The patients were dichotomized by taking a limit value

Figure 1. Sample MR images of the patients who obtained a score between 1 and 3 according to the Age-Related White Matter Changes Rating scale. Since focal flushings were observed in the frontal white matter in the axial section on the far left, a score of 1 was given according to the scale (A). In the middle section, a score of 2 was given, since flushings which showed confluence were present in the parietooccipital white matter, though they did not involve the whole area (B). In the third section, extensive white matter flushing showing confluence were observed in both frontal and parietooccipital white matter involving the whole area and also U fibers and this appearance was equivalent to a score of 3 which was the highest score in the scale (C).

of GDS of 11 and the two groups were compared by the models established considering age factor (ANCOVA) and Bonferoni confirmation was done for the values obtained. To examine the relation of HWM and activities of daily living Spearman correlation coefficients (r) were calculated by correlation analyses. Regression models were established to analyse the effect of white matter hyperintensities and MTL atrophy on GDS. All statistics were done using XLstat program (Addinsoft, Paris, France) and a p value of <0.05 was considered significant.

Results

The descriptive data belonging to all patients are shown in Table 1. Only 6 of the patients were very early stage (CDR score: 0.5) AD patients and the remaining 39 patients were in a relatively later stage compared to these 6 patients, though they were still considered early stage (CDR score: 1). Fourteen of the patients obtained 11 points and above in the GDS which suggested clinical depression. However, most of the patients had lower scores in terms of depressive symptomatology.

When the patients who were dichotomized according to GDS scores were compared as two groups considering age factor, no significant difference was observed in terms of the scores of ACE-r which measures cognitive status and the scores of CDR-SOB which measures activities of daily living. MTL atrophy scores were also considerably close to each other and no difference was observed. When the white matter scores were examined, the total score and regional parietooccipital, temporal, infratentorial and basal ganglia white matter scores did not show significant difference. In contrast, frontal white matter scores were observed to be significantly high in the depressive group (Table 2). This significance was found for both the right ($p=0.006$) and left frontal ($p=0.007$) white matter separately in addition to the total frontal white matter. These differences did not lose their significance after Bonferoni correction was made. Although CDR-SOB scores did not show significant difference between the two groups, marked positive correlation was observed between both the right ($r=0.439$ $p=0.003$) and the left ($r=0.459$ $p=0.001$) frontal HWM scores and CDR-SOB scores.

Table 1. Clinical and imaging findings of the patients

n	45
Age (years)	70.0±8.08 (54-86)
Female=Male	25=20
CDR 0.5= CDR 1	6=39
ACE-r	50.78±16.42 (13-75)
GDS	7.86±4.43 (2-21)
CDR-SOB	6.03±1.05 (4.5-8)
MTL total atrophy score	3.71±1.57 (0-6)
HWM total score	6.11±6.24 (0-28)
The data are expressed as mean ± standard deviation (range)	
CDR: Clinical Dementia Rating Scale, ACE-r: Addenbrook Cognitive Examination Revised, CDR-SOB: Clinical dementia Rating Scale Sum of Boxes score, MTL: Medial temporal lobe, HWM: Cerebral white matter hyperintensities	

When GDS scores were taken as dependent variable and CDR-SOB, age and MTL atrophy scores were used as independent variables in the regression analysis to examine the relation of aging, limbic system involvement and loss of autonomia with depressive symptoms, the model was not found to be significant, while significance was observed only in the frontal HWMs when the total frontal HWM scores were added to these (Table 3).

Discussion

It is known that presence of behavioral symptoms affects the prognosis of AD negatively. Recognition of these symptoms which response better compared to the others and initiation of appropriate treatment at the appropriate time carry considerable importance in terms of the prognosis of the disease, the burden of the caretaker and socioeconomic burden. The relation between frontal HWMs and depressive mood which was found in this study by MRI was also shown in a recent study performed by Mueller et al. In this study, white matter lesions were examined in the lobes by automated analysis methods and right-left hemisphere differentiation was not made (13). In contrast, this relation was not observed in a series involving patients with frontotemporal dementia and vascular dementia other than Alzheimer's disease (14). Frontal white matter lesions may lead to depressive mood

Table 2. Cognitive state, activities of daily living and regional HWM scores in depressive and non-depressive patients

	GDS<10 (n=29)	GDS≥11 (n=16)	p*
ACE-r	48.67±17.24 (13-75)	53.92±14.68 (22-74)	0.681
CDR-SOB	6.00±0.94 (5-8)	6.10±1.06 (4.5-8)	0.394
MTL total atrophy score	3.78±1.67 (0-6)	3.53±1.25 (1-6)	0.925
Total HWM score Frontal	5.78±6.68 (0-28)	6.41±4.48 (0-18)	0.242
HWM score	2.17±1.69 (0-6)	3.21±1.62 (0-6)	0.006**
Parietooccipital HWM	2.03±2.38 (0-6)	2.00±2.06 (0-6)	0.474
Temporal HWM score	0.42±1.20 (0-6)	0.46±0.71 (0-2)	0.687
Infratentorial HWM score	0.39±1.26 (0-6)	0.13±0.49 (0-2)	0.729
Basal ganglia HWM score	0.75±1.50 (0-6)	0.13±0.49 (0-2)	0.514

The data are expressed as mean ± standard deviation (range)

ACE-r: Addenbrook Cognitive Examination Revised, CDR-SOB: Clinical dementia Rating Scale Sum of Boxes score, MTL: Medial temporal lobe, HWM: Cerebral white matter hyperintensities

* ANCOVA model p value

Table 3. Regression models examining the effect of medial temporal atrophy, activities of daily living and age on depressive symptoms

Model terms	Model 1		Model 2	
	β	p	β	p
MTL atrophy	0.155	0.72	-0.37	0.393
CDR-SOB	0.44	0.51	-0.39	0.558
Age	1.29	0.88	-4.73	0.567
Frontal HWM	NA	NA	1.30	0.005

While the independent variables in Model 1 included MTL atrophy scores, age and CDR-SOB scores, total frontal HWM scores were added to these independent variables in the second model

MTL: Medial temporal lobe, CDR-SOB: Clinical Dementia Rating Scale Sum of Boxes, HWM: cerebral white matter hyperintensities

by interrupting the connections between the frontal (BA9, 10, 11, 24) region and subcortical areas (14,15). Although the relation between depression and hypoactivity of the left hemisphere has been known for a long time (16), it is observed that there is no right-left differentiation when white matter involvements are in question and bilateral involvement of the circuits may lead to depressive symptoms in patients with dementia.

HWMs observed in elderly patients without dementia affect the response to antidepressant treatment negatively (17). In studies conducted with patients with dementia, the treatment response to serotonin reuptake inhibitors were found to be more limited compared to elderly individuals without dementia (18). Observation of HWMs more frequently in AD patients compared to normal elderly individuals (19) may be the underlying cause of this reduced response.

The fact that HWMs do not show a relation with ACE-r which is a general cognitive screening tool, though they are related with depressive mood may be related with lack of use of a detailed neuropsychological assessment battery as a limitation of our study. Similar to our study, there are other studies in which HWMs were found to be related only with depressive mood, but not with cognitive state (13). An explanation of lack of a relation may be the fact that the patients included in the study were early stage patients with cognitive findings and HWMs do not lead to an additional cognitive disorder in this stage. Clinical symptoms in early stage AD patients occur with involvement of the limbic structures and parietotemporal structures. In such a case, it can be speculated that frontal HWMs may lead to behavioral symptoms without leading to cognitive disorder, but it should be kept in mind that neuropsychological tests including Wisconsin Card sorting, Stroop, London tower etc. which assess the frontal symptoms in detail were not used in our study. Conduction of a study with a similar methodology with a larger neuropsychological inventory will elucidate the answer to this question.

According to the results of our study, presence of HWM in early stage AD patients carries the potential to affect the prognosis of the disease. As the frontal HWM burden increases, affection of activities of daily living also increases. Thus, the burden of caretakers increase indirectly and the socioeconomical dimension of the disease becomes more dramatic. White matter disruption may have an impact on the activities of daily living by way of non-cognitive findings including walking difficulty and incontinence which are observed in vascular dementia due to small vessel disease or by leading to apathy other than depression. The fact that quantitative evaluation of motor findings and apathy was not performed was one of the limitations of our study and prevents answering the question discussed above definitely.

In linear regression analyses performed with multiple variables, it was observed that age, hippocampal atrophy and activities of daily living had no impact on depressive symptoms. Inability to show this relation in early stage dementia patients suggests that the risk factors for depressive symptoms in the course of dementia may be different. The observation that only frontal white matter flushings among other variables were a serious risk factor for depressive symptoms with addition of frontal white matter HWM scores suggested that white matter involvement in the early stage might be the underlying cause of depression.

Conclusively, white matter flushings detected by MRI appear to be related with depressive symptoms in patients with dementia and

this relation provides clues in understanding the neural substrates of mood disorders. Considering the relation of HWMs with vascular risk factors, decreasing the prevalence of depression by controlling these risk factors and decreasing the suffering of dementia patients and their relatives would be possible.

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