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Different metabolic and clinical profiles between patients with pure Alzheimer dementia and epileptic Alzheimer dementia: a metabolic study

Saf Alzheimer Demansı ile Epileptik Alzheimer Demansı Hastaları Arasındaki Faklı Metabolik ve Klinik Profiller: Metabolik bir çalışma

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ABSTRACT

Aim: To investigate the clinical characteristics and cerebral FDG PET metabolisms of dementia patients who were also diagnosed with epilepsy and compare the differences with pure Alzheimer dementia patients.
Methods: In this case-control study, a total of 14 patients, 7 patients with pure Alzheimer disease as a control group and 7 age and gender-matched patients with Alzheimer disease and concomitant epilepsy as a study group, were included. Detailed neurocognitive battery and brain fludeoxyglucose positron emission tomography (FDG PET-CT) were performed for all subjects.
Results: In comparison of neurocognitive test scores, there was no significant difference between the study and control groups. However, geriatric depression scale scores were significantly lower in study group than the controls (p= 0.026). In cerebral FDG-PET CT profiles of subjects we detected significantly lower metabolism in left and right cerebellum, left lentiform nucleus, right thalamus and vermis in the study group (p=0.008, p=0.023, p=0.003, p=0.002, p=0.002, respectively). In the right parietotemporal cortex and right and left associative visual cortex, we found higher metabolism in the study group than controls (p=0.023, p=0.012, p=0.003, respectively).
Conclusion: Epileptic patients with Alzheimer's dementia may have distinct clinical and metabolic profiles, than pure Alzheimer's disease patients. Even if there is no difference in the neurocognitive clinical scores of the patients, depression and related functional abnormalities may be a biomarker of epileptic AD.

Key words: Alzheimer disease, epilepsy, FDG-PET CT, metabolism, depression

ÖZ

Amaç: Epileptik Alzheimer hastalarının klinik özelliklerini ve serebral FDG PET metabolizmalarını araştırmak ve saf Alzheimer demansı hastaları ile arasındaki farkları karşılaştırmaktır.
Yöntemler: Bu vaka-kontrol çalışmasına Alzheimer hastalığı olan 7 hastadan oluşan control grubu ve Alzheimer hastalığına eşlik eden epilepsisi olan 7 hastadan oluşan çalışma grubu olmak üzere toplam 14 hasta dahil edildi. Tüm katılımcılara ayrıntılı nörobilişsel bateri ve beyin florodeoksiglukoz pozitron emisyon tomografisi (FDG PET-CT) uygulandı.
Bulgular: Nörobilişsel test puanları karşılaştırıldığında, çalışma ve kontrol grupları arasında anlamlı bir fark yoktu. Ancak geriatrik depresyon ölçeği puanları çalışma grubunda kontrollere göre anlamlı derecede düşüktü (p= 0.026). Çalışma grubundaki olguların serebral FDG-PET BT profillerinde sol ve sağ serebellum, sol lentiform nükleus, sağ talamus ve vermiste anlamlı düzeyde daha düşük metabolizma saptadık (p=0,008, p=0,023, p=0,003, p=0,002, p =0,002, sırasıyla). Sağ parietotemporal korteks ve sağ ve sol birleştirici görsel kortekste, çalışma grubunda kontrollere göre daha yüksek metabolizma bulduk (sırasıyla p=0.023, p=0.012, p=0.003).
Sonuç: Alzheimer demansı olan epileptik hastalar, saf Alzheimer hastalarından farklı klinik ve metabolik profile sahip olabilir. Hastaların nörokognitif klinik skorlarında fark olmasa bile depresyon ve ilişkili fonksiyonel anormallikler epileptik AD hastaları için bir biyobelirteç olabilir.

Anahtar Kelimeler: Alzheimer hastalığı, epilepsi, FDG-PET BT, metabolizma, depresyon

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INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by extensive brain network alterations, implicated in several other neurological disorders. Epilepsy and depression are two of these conditions that may also be accompanied by a degree of cognitive impairment [1].

Some research suggests that elderly epilepsy patients are more likely to acquire cognitive impairment and eventually dementia [2,3]. This raises the issue of whether dementia causes seizures, or if both are caused by the same pathophysiological processes. This could be related to the fact that the neuropathological underpinning of seizures in Alzheimer's disease is a disproportional neuronal degeneration in distinct brain regions involving several changes at the cellular and molecular level, such as toxic accumulation of proteins, synaptic degeneration, circuit remodelling, and abnormal synchronization. This bidirectional relationship between epilepsy and dementia has been suggested by the observation that dementia patients appear to be at a higher risk of experiencing seizures [4].

Depression or major depressive disorder (MDD), the most common neuropsychiatric condition in AD, is also a risk factor for the development of AD, through the neurodegeneration in the brain [5-7]. It is likely that depression influences the risk of AD by diminishing the neuroprotective capability of the brain, hence accelerating the course of the disease. Nonetheless, it is also plausible that depression is an early sign of AD (8). However, compared to either AD or MDD alone, hospitalization rates are much greater when AD and MDD coexist. The exact process that causes depression in people with dementia is still not well understood.

Despite this, fundamental molecular abnormalities, such as an increase in plasma brain amyloid beta protein and neurofibrillary tangles of MDD patients have been observed [9-13]. In addition, an overactivation of the HPA axis, as well as neuroinflammation could be responsible for the occurrence of both disorders [14].

In spite of these encouraging findings, it has been found that there are no case reports or longitudinal studies that indicate a common pathophysiology between epilepsy, depression and dementia. In this study, our objective was to evaluate and contrast the clinical characteristics, cerebral FDG PET metabolism and clinical features of dementia patients, who also presented with epilepsy. To the best of our knowledge, no previous research has investigated the role of functional features, as well as the neurobehavioral outcomes associated with those pathologies, in dementia patients who have also been diagnosed with epilepsy and depression.

MATERIAL AND METHODS

Patient Selection: For this case-control study, a total of fourteen patients were included: seven patients with pure Alzheimer's disease and seven patients with Alzheimer's disease and concomitant epilepsy. Detailed neurocognitive batteries and brain fludeoxyglucose positron emission computerized tomographies (FDG PET-CT) were performed for all participants.

The study was approved by the Local Ethics Committee of Istanbul Medipol University (with the number E-10840098-772.02-2712, date 05.05.22) and followed the Helsinki Declaration principles. The participants were informed about the study and written consent was provided from all participants. The potential participants with a history of cranial trauma, intracranial operation, tumor or any lesion that may affect the metabolism of the central nervous system, those with drug or alcohol use, younger than fifty and older than eighty, were all excluded from the study.

Cognitive evaluation: Neuropsychological assessment of the participants was consisted of mainly attention and executive functions, memory, visuospatial functions, language and mood. Digit span and Stroop Test for attention and executive functions assessment, Verbal Memory Processes Test (VMPT) for memory assessment, Verbal Fluency and Boston Naming Test (BNT) for language assessment, Benton Face Recognition Test (BFRT) for evaluation of visuospatial functions, as well as the Geriatric Depression Scale for mood assessment and Mini Mental State Evaluation (MMSE) for global assessment, were applied to all participants.

Neuroimaging: Brain fludeoxyglucose positron emission tomography computerized tomography (FDG PET-CT) images were taken using a Philips Gemini TF PET/CT equipped with 16 slice computerized tomography. Patients with a glucose level lower than 160 mg/dl, and 18F FDG were administered intravenously at a dose of 0.1 mCi (3.7 MBq) / kg. After the injection, the patient had a rest quietly in a dimly lit room for minimum 30 minutes during the uptake phase. At 60 minutes after the injection, data was acquired and PET images were reconstructed with CT data for PET attenuation correction. The raw FDG-PET data was processed by the NeuroQ software (Version 3,5. Syntermed Inc., Atlanta, USA). Brain 18F-FDG PET images in axial, coronal, and sagittal slices and the quantitative results of NeuroQ analysis were visually evaluated by two blinded nuclear medicine physicians. The NeuroQ programme calculated the average pixel values in standardized regions of interest (ROI) and compared these counts with the control database. Finally, hypometabolic brain regions were significantly defined as a decrease of more than two standard degrees of regional brain metabolism.

Statistical Analyses: Behaviours of quantitative variables were expressed with centralization and measures of variance: Mean ± standard deviation (SD). The Fisher Exact Test was used to determine the differences in ratios or relationships between categorical variables. To show the behavioral differences of the group averages, the Mann-Whitney U-Test method was used where they did not meet the assumptions of normality and homogeneity. Statistical significance was determined as p = 0.05 for all cases. Statistical analyses were provided with the IBM SPSS (Statistics Package for Social Sciences for Windows, Version 21.0, Armonk, NY, IBM Corp.) package programme.

RESULTS

In this study, we evaluated the data of fourteen subjects consisting of seven (2 male/5 female) patients with Alzheimer Disease and Epilepsy as a study group and seven (5 male/ 2 female) patients with pure Alzheimer Disease as a control group. The mean age of the study group was 67.14 ± 9.08 years and similarly, the mean age of the control group was 61.71 ± 5.65 years; there was no statistically significant difference between the groups in terms of age and gender (p > 0.05, Table 1).

Table 1. Demographic Features of Subjects

Subjects		Study Group (AD + E)	Controls (AD)	p
Sex n (%)	F	5 (71.4%)	5 (71.4%)	1
	M	2 (28.6%)	2 (28.6%)	
Age		67.14 ± 9.08	61.71 ± 5.65	0.336
(Mean ± SD, Median Min–Max)		73 (54 - 75)	62 (53 - 72)	

p> 0.05 is significance

In comparison of neurocognitive test scores including MMSE, Digit Span, Stroop test, VMPT, Verbal Fluency, BFRT, BNT there was no significant difference between the study and control groups. However, geriatric depression scale scores were significantly lower in the study group than in the controls (p= 0.026, shown in Table 2).

Table 2. Comparison of Cognitive Test Scores Between Two Groups

Neurocognitive Battery	Study Group	Controls	P
Benton Facial Recognition Test	37.86 ± 5.15	43.4 ± 7.5	0.085(m)
	40 (30 - 44)	47 (30 - 47)	
Boston Naming Test	16.86 ± 3.08	18.14 ± 7.49	0.367(m)
	18 (12 - 20)	19 (7 - 27)	
Digit Span	5.0 ± 2.52	5.57 ± 2.7	0.795(m)
	5 (2 - 8)	5 (2 - 10)	
Geriatric Depression Scale	12.14 ± 4.15	5.33 ± 4.37	0.026(m)
	12.5 (7 - 18)	4 (0 - 12)	
MMSE	20.25 ± 1.5	15.0 ± 5.39	0.105(m)
	20 (19 - 22)	15 (7 - 23)	
Stroop Interference	106.5 ± 31.82	172.5 ± 95.08	0.8(m)
	106.5 (84 - 129)	160.5 (83 - 286)	
Verbal Fluence	8.29 ± 5.02	12.57 ± 11.39	0.949(m)
	9 (0 - 17)	7 (0 - 28)	
Verbal Memory Task Learning	43.43 ± 25.84	39.29 ± 20.34	0.902(m)
	33 (6 - 84)	42 (2 - 61)	
Verbal Memory Task Total Recall	9.57 ± 4.08	6.71 ± 5.53	0.326(m)
	10 (2 - 13)	6 (0 - 13)	

Stats: Mean ± SD/Median (Min–Max), (m) Mann Whitney U Test

In cerebral FDG-PET CT profiles of subjects, we detected significantly lower metabolism in left and right cerebellum, left lentiform nucleus, right thalamus and vermis in the study group

Table 3. Comparison of FDG-PET Profiles of Groups

Localisation	Study Group	Controls	P
Left Associative Visual Cortex	-0.25 ± 2.17	-5.55 ± 3.62	0.003(m)
	0.27 (-4.21 - 2.3)	-5.62 (-11.74 - 0.11)	
Left Caudate Nucleus	-0.17 ± 0.62	0.9 ± 1.52	0.252(m)
	-0.24 (-0.91 - 0.82)	0.49 (-1.02 - 3.16)	
Left Cerebellum	1.76 ± 1.23	3.93 ± 1.19	0.008(m)
	1.8 (0.04 - 3.56)	3.85 (2.34 - 5.99)	
Left Inferofrontal Cortex	-1.93 ± 1.58	-0.65 ± 1.61	0.142(m)
	-1.61 (-4.09 - -0.34)	-0.43 (-3.98 - 1.17)	
Left Inferolateroposterior Temporal cortex	-1.6 ± 1.53	-3.27 ± 1.88	0.091(m)
	-1.02 (-3.99 - -0.11)	-3.29 (-6.24 - -0.77)	
Left Inferior Parietal Cortex	-1.31 ± 2.05	-0.31 ± 2.72	0.47(m)
	-1.09 (-4.79 - 1.93)	-0.44 (-4 - 4.83)	
Left Lentiform Nucleus	0.04 ± 0.74	1.71 ± 0.96	0.003(m)
	-0.41 (-0.49 - 1.49)	1.76 (0.37 - 2.96)	
Left Medial Frontal Cortex	-0.59 ± 1.76	-1.86 ± 1.72	0.114(m)
	-0.2 (-4.34 - 0.69)	-1.45 (-4.8 - 0.7)	
Left Parietotemporal Cortex	-3.23 ± 2.07	-5.64 ± 2.21	0.071(m)
	-2.69 (-6.46 - -1.16)	-4.97 (-8.86 - -3.08)	
Right Associative Visual Cortex	0.83 ± 1.59	-3.87 ± 3.63	0.012(m)
	1.2 (-1.34 - 3.54)	-4.71 (-7.75 - 2.63)	
Right Cerebellum	1.4 ± 0.98	2.72 ± 1.14	0.023(m)
	1.81 (-0.01 - 2.49)	2.61 (1.13 - 4.67)	
Right Inferofrontal Cortex	-0.53 ± 2.57	0.69 ± 1.58	0.252(m)
	-1.91 (-2.74 - 4.2)	0.66 (-1.92 - 2.82)	
Right Inferoparietal Cortex	-0.2 ± 1.63	-1.46 ± 3.72	0.408(m)
	-0.21 (-2.42 - 1.96)	-1.46 (-6.65 - 3.94)	
Right Parietotemporal Cortex	-0.47 ± 1.75	-3.73 ± 2.95	0.023(m)
	-0.05 (-3.71 - 1.4)	-4.71 (-6.63 - 2.32)	
Right Posterior Cingulate Cortex	-2.34 ± 1.86	-3.62 ± 1.42	0.114(m)
	-2.07 (-5.87 - -0.45)	-3.8 (-6.42 - -1.87)	
Right Thalamus	0.44 ± 0.54	1.85 ± 0.82	0.002(m)
	0.49 (-0.27 - 1.38)	1.84 (0.62 - 2.89)	
Vermis	0.72 ± 1.83	3.21 ± 0.52	0.002(m)
	-0.12 (-1.6 - 3.23)	3.32 (2.53 - 4.09)	

Stats: Mean ± SD/Median (Min–Max), (m) Mann Whitney U Test

(p=0.008, p=0.023, p=0.003, p=0.002, p=0.002, respectively). In the right parietotemporal cortex and right and left associative visual cortex, we found higher metabolism in the study group than controls (p=0.023, p=0.012, p=0.003, respectively) (Table 3).

DISCUSSION

According to our findings, AD patients with epilepsy and high depressive scores showed relatively

increased metabolism in the parieto-temporal cortex, and right associative visual cortex, but a decreased metabolism in the cerebellum, vermis, left lentiform nucleus and right thalamus. Our findings contradict previous human data that indicated a significant overlap in areas associated with Alzheimer's disease and temporal lobe epilepsy pathophysiology, characterized by critical hippocampal metabolic and structural changes that are also connected to memory loss or dementia symptoms, even in the absence of seizures [15]. However, while histological diagnosis in humans is challenging and can only be done post-mortem,

detecting dynamic brain alterations in AD patients with concurrent epilepsy problems is conceivable [3]. Based on this, the clinical, neuropsychometric assessment and neuroimaging techniques, have astounding importance and continue to be exciting ways to determine whether shared and unshared alterations among these disorders are related to clinical presentation and prognosis.

Various functional and structural abnormalities might also play a part in depression in the AD. For instance, data from magnetic resonance imaging (MRI) has demonstrated that older people who suffer from depression symptoms have degeneration in both the frontocortical and limbic circuits, which are similar networks that are compromised when AD starts in its earliest stages [16-19]. It is possible that the high incidence of major depressive disorder in Alzheimer's disease can be explained by the role of corticolimbic dysfunction in the development of affective disorders [20]. Notable is the discovery that a disturbance of corticolimbic networks is essential for fundamental facets of cognitive and emotional functions. Despite this, there is not yet sufficient evidence to demonstrate a causal association between atrophy in these brain regions and the co-occurrence of these two disorders [21]. Our research found that Alzheimer's patients with epilepsy showed specific regions linked to depression and epilepsy pathogenesis, in addition to an Alzheimer's disease-specific metabolic pattern consistent with the literature [22]. Common regions included crucial areas (the left parietotemporal, left Broca, left post cingulate, left post temporal, left sup lateral and right temporal right sensorimotor cortical regions), all of which have been attributed to Alzheimer's disease. Our findings of overlapping regions in AD and AD+Epilepsy groups are consistent with recent clinical data showing reduced resting-state activity and functional connectivity within the default mode network in patients with epilepsy or Alzheimer's disease [23]. Within this framework, we found substantial parallel changes in both groups that are pertinent to the research on Alzheimer's disease. For example, Alzheimer's disease patients who also had epilepsy, were discovered to exhibit patterns of lower cortical and crucial regional hypometabolism, which are not common in pure Alzheimer's disease patients but observed more commonly in patients with epilepsy and depression. In accordance with this, the prevalence of geriatric depression in the AD and epilepsy groups was significantly higher than in the pure AD group. Hence, decreased metabolism in the left lentiform nucleus and increased metabolism in the post temporal regions, may indicate a common cortico-limbic axis impairment in MDD, and the existence of some hypermetabolic areas, which are uncommon in Alzheimer's disease, may be a signal of epilepsy-associated elevated brain metabolism. In a comparable manner, significant hypometabolism in the cerebellum, as well as increased activity in the visual association and parietotemporal cortices, are consistent with prior research on epilepsy, AD and depression [24].

To the best of our knowledge, AD patients who present with both seizures and depression are extremely rare, and no previous research has employed FDG PET to detect shared and unshared regions across these comorbid illnesses.

Limitations: Our study had offered valuable metabolic and clinic information for alternative treatment options in AD and epilepsy [25]. Nevertheless, the sample size was quite limited. The inability to pinpoint the precise epileptic origin of patients may be seen as another limitation of our work.

CONCLUSION

Our findings show that AD and epilepsy patients have a more distinct clinical and metabolic profile than pure AD patients, and that depression and associated functional abnormalities may be a biomarker of AD patients with concomitant epilepsy.

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