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Volumetric Assessment of Extratemporal Structures in Patients With Temporal Lobe Epilepsy

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Abstract

Background: We assessed the presence of brain volume loss in the extratemporal structures in patients with temporal lobe epilepsy (TLE). The associations between brain volume loss in these structures and epilepsy duration, magnetic resonance imaging (MRI) findings, and occurrence of focal to bilateral tonic-clonic seizures (TCS) were assessed.

Methods: In this cross-sectional study, all adult patients with drug-resistant TLE, who were admitted to the epilepsy monitoring unit at Loghman-Hakim Hospital, Tehran, Iran, during 2016-2020, were included. For all the participants, brain MRI was performed and patients with TLE were divided into two subgroups of those with hippocampal sclerosis (TLE-HS) and patients with normal-appearing brain MRI findings (TLE-no). Independent sample *t* test was applied to compare quantitative variables in the study groups. Pearson correlation test examined the correlation between the clinical and volumetric features.

Results: 203 participants (81 patients with TLE and 122 healthy controls) were studied. Compared with healthy controls, patients with TLE showed a decrease in their midbrain ($P=0.02$) and thalamus ($P=0.01$) volume. The degree of thalamic atrophy was more significant in TLE-HS ($P=0.03$). Moreover, the degree of midbrain volume loss was more significant ($P=0.07$) in patients who had TCS in the past two years (N=31) compared with those who did not (N=50). The volume of the thalamus (r: -0.252, $P=0.02$) and pallidum (r: -0.255, $P=0.02$) had inverse correlations with the epilepsy duration.

Conclusion: Patients with TLE have lower midbrain and thalamus volume compared with the healthy controls, which may be attributed to the seizure-induced injury. Midbrain atrophy may theoretically increase the risk of sudden unexpected death in epilepsy (SUDEP) because of the enhanced autonomic dysfunction.

Keywords: Midbrain; Thalamus; Seizure; Temporal lobe epilepsy; Atrophy

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Introduction

Temporal lobe epilepsy (TLE) is the most common form of focal epilepsies. Hippocampal sclerosis (HS), also known as mesial temporal sclerosis (MTS), is the most common pathological substrate of TLE and about 70% of patients with drug-resistant TLE show signs of HS on their brain magnetic resonance imaging (MRI).[1-4] Some studies in patients with TLE have revealed structural abnormalities in regions beyond the region of the temporal lobes, with thalamic atrophy reported as the most common extratemporal abnormality.[5-9] Moreover, cerebellar and brainstem atrophy has been associated with TLE, according to some studies.[5-7,10] Previous studies have suggested that epilepsy duration, occurrence of focal to bilateral tonic-clonic seizures (TCS), and MRI findings (HS *vs.* non-lesional TLE) were associated with the atrophy of these structures in patients with TLE.[6,7,11]

Abnormalities of some of the infratentorial structures may contribute to critically impaired autonomic function, predisposing the patients to a life-threatening breakdown of autonomic control during a seizure, which may result in sudden unexpected death in epilepsy (SUDEP).[5,12] Defining the involvement and the roles of extratemporal brain structures in patients with TLE may lead to the discovery of novel targets to treat or prevent the deleterious effects of seizures in TLE.[12]

In this study, we assessed the presence of atrophy in the basal ganglia, thalamus and infratentorial structures, including cerebellum and brainstem (medulla oblongata, midbrain, and pons) in patients with TLE. We hypothesized that these structures have atrophy compared with that in matched healthy controls. Furthermore, the associations between brain volume loss in these structures and epilepsy duration, MRI findings (HS *vs.* non-lesional TLE), and the occurrence of TCS were assessed.

Methods and Materials

Patients

In this cross-sectional analytic study all consecutive adult patients with drug-resistant TLE, who were admitted to the epilepsy monitoring unit at Loghman-Hakim Hospital, Tehran, Iran, during 2016-2020, were included. The epilepsy type was determined by the epileptologists, who clinically assessed the patients and reviewed their video-EEG monitoring (V-EEG) recordings. The inclusion criteria were age of 18-55 years and a definite diagnosis of TLE (with HS or a normal brain MRI). Patients with dual pathology, other neurological conditions, significant psychiatric comorbidities (receiving treatment for major depression, schizophrenia, obsessive-compulsive disorder, panic attacks), significant cognitive impairment (evident in routine neurological examination), or comorbid functional (psychogenic) seizures (confirmed by V-EEG monitoring) were excluded from the study. The patients' demographic data (i.e., sex, age) and clinical characteristics (i.e., epilepsy duration and type, and the presence of TCS within the past two years) were collected.

Controls

The control group consisted of healthy people randomly selected from our reference biometric imaging pool, which has gradually been developed from healthy volunteers during the past five years. They were healthy subjects without a diagnosis of epilepsy or other neurological diseases and had no pathological findings in their brain MRI after thorough inspection by an expert neuroradiologist. A ratio of 3 to 2 (controls to patients) was considered and the two groups were matched for their sex and age.

MRI Acquisitions and Volumetric MRI Analyses

For all patients and healthy controls brain MRI with epilepsy protocol was performed and reviewed by an expert neuroradiologist. Brain MRI was performed on a 1.5 T Siemens Avanto scanner (Magnetom Syngo MR B17) with an unenhanced 3D T1-weighted gradient-echo sequence (MPRAGE) with 176 axial slices (voxel size of 1 mm × 1 mm × 1 mm; TR: 2300 ms; TE: 3.26 ms; Flip angle 9, matrix 256 × 256 mm^2). Atlas-based volumetry, a fully automated and objective method for volumetric brain analysis of individual subjects, using algorithms of the Statistical Parametric Mapping 12 software (SPM12; Welcome Trust Centre for Neuroimaging, London, UK) was applied to the MPRAGE sequences of patients and controls to determine the volumes of basal ganglia, thalamus and infratentorial structures (i.e., cerebellum, brainstem, midbrain, pons and medulla oblongata). The method has been successfully used in a variety of cross-sectional and longitudinal studies,[13, 14] and the intrascanner variability of volumetric results was shown to be less than 1% for most structures investigated[15]. The individual brain of each subject in this study was segmented into grey matter, white matter, and cerebrospinal fluid compartments, and the resulting tissue component images were mapped into a template space using high-dimensional elastic registration. Then, in the same space, predefined regions of interest derived from the LONI Probabilistic Brain Atlas (LPBA40)[16] were used to extract regional brain volumes. For midbrain, pons, and medulla oblongata, the LPBA40 brainstem mask was further divided by two cutting planes, the first one passing through the superior pontine notch and the inferior edge of the quadrigeminal plate; the second one, parallel to the first plane and through the inferior pontine notch [10]. All resulting volumes were corrected for individual intracranial volume (ICV) as determined by the "tissue volumes" utility of SPM12[17] and normalized to an average ICV of 1400 mL (Figure 1). Als, all volume results are given in in milliliter (mL), the areas of midsagittal planes are expressed in mm^2.

Statistical Analysis

First, we compared the whole patient group with the

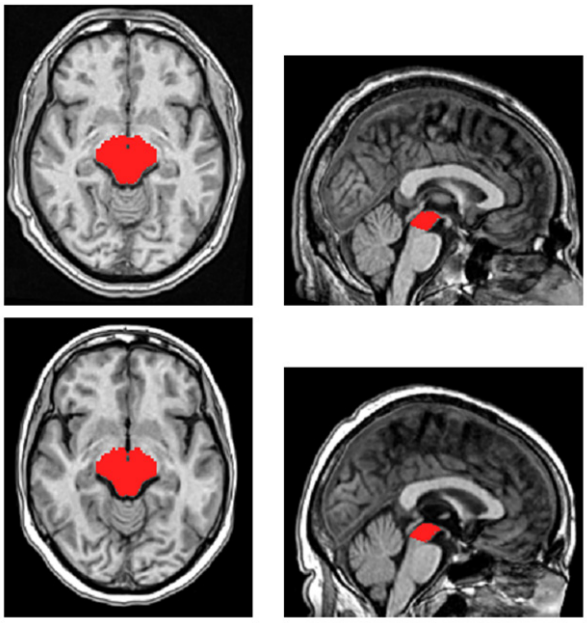

Figure 1. Showing Exemplarily the Segmentation Results in MNI Space for Midbrain (Left Column) and Midsagittal Midbrain Tegmentum Plane (Right Column) in a 33-Year-Old Healthy Control (Upper Row) and a 50-Year-Old TLE Patient (Lower Row).

healthy controls for means of the volumetric assessments of their infratentorial and basal ganglia structures (i.e., cerebellum, brainstem, pons, midbrain, medulla, caudate, putamen, pallidum, accumbence, and thalamus). Then, in the patient group, we compared those with HS in their brain MRI with patients who had normal MRIs (by visual assessment) with regards to the means of the volumetric assessments structures. Finally, we investigated the association between the presence of TCS and also epilepsy duration with the means of the volumetric assessments of the infratentorial structures in the patient group. To test the normality of distribution of the continuous variables, Kolmogorov–Smirnov test was used. For sex and age comparisons, chi-square and student *t* tests were used. Group differences between patients and healthy controls and subgroup analyses of MRI findings for volumetric assessments were performed using *t* test. Pearson correlation test was used to examine the correlation between epilepsy duration and volumetric assessments. The volumetric results were presented as mean ± standard deviation (SD). A $P<0.05$ was considered as significant.

Results

This study included 203 participants (81 patients with TLE and 122 healthy controls). The two study groups were well-matched with respect to age and sex (Table 1). Table 2 shows the mean volumetric assessments of the brain structures in patients and healthy controls. Compared to the healthy controls, patients with TLE showed a decrease in the volume of their midbrain (10.36 ± 0.67 in TLE *vs.* 10.57 ± 0.62 in healthy controls; 2% volume difference; $P=0.02$). Moreover, patients with TLE displayed a significant reduction in the volume of their thalamus compared to the healthy controls. To assess the possible effect of the side of ictal-onset zone on the volume of ipsilateral and contralateral thalamus, we measured the association between these two variables. We found that the thalamic volume loss was not significantly associated with the side of seizure-onset zone neither in the right (5.76 ± 0.64 for ipsilateral vs. 6.02 ± 0.64 for contralateral, $P=0.073$) nor in the left (6.19 ± 0.68 for ipsilateral vs. 6.14 ± 0.51 for contralateral, $P=0.75$). There were no other significant differences between the patients and the controls in the volumetric assessments of other infratentorial and basal ganglia structures.

Comparing patients with TLE with hippocampal sclerosis (n = 46) with normal-appearing brain MRIs (n = 35), the former group showed a significant decrease in the volume of their right and left thalamus ($P=0.03$; $P=0.04$), as well as the right accumbens ($P=0.001$). No other significant differences were found in the volumetric assessments of the infratentorial structures and basal ganglia between the two TLE groups (HS and normal MRIs, Table 3). Moreover, there were no significant associations between the volume of the studied brain regions and the side of seizure-onset zone.

Comparing patients who had TCS within in the past 2 years (n = 31) with those with no TCSs (n = 50), the volume of midbrain was lower in the former group (10.19 ± 0.72 *vs.* 10.47 ± 0.62; $P=0.07$). Other infratentorial structures, basal ganglia, and thalamus did not show any significant differences in this comparison ($P>0.1$).

Finally, Pearson correlation showed that the volume of

Table 1. Demographic and Clinical Data of the Study Groups

Variables	Temporal Lobe Epilepsy (n = 81)	Heathy Subjects (n = 122)	*P* Value
Gender			
Male	39 (48%)	56 (46%)	0.7
Female	42 (52%)	66 (54%)	
Age	34 ± 9	33 ± 8	0.4
Disease duration (years)	17.7 ± 11.7		
Seizure frequency (per month)	9.22 ± 9.74		
The side of seizure-onset zone			
Right_	36 (44.4%)		
Left	45(55.6%)		
TCS within the past 2 years			
Yes	31 (38%)		
No	50 (62%)		
MRI findings			
Normal	35 (43%)		
Hippocampal sclerosis	46 (57%)		

Table 2. Mean ± Standard Deviation of Brain Volumetric Assessments in the Study Groups

Variables	Temporal Lobe Epilepsy (n = 81)	Heathy Controls (n = 122)	*P* Value
Cerebellum	118.87 ± 8.82	120.35 ± 8.48	0.23
Right	60.44 ± 4.49	61.12 ± 4.26	0.28
Left	58.43 ± 4.44	59.23 ± 4.28	0.20
Brainstem	29.41 ± 2.11	29.75 ± 1.90	0.24
Right	15.61 ± 1.14	15.79 ± 1.01	0.23
Left	13.80 ± 0.97	13.95 ± 0.90	0.24
Midbrain	10.36 ± 0.67	10.57 ± 0.62	0.02*
Pons	15.00 ± 1.30	15.12 ± 1.17	0.50
Medulla	4.10 ± 0.34	4.12 ± 0.29	0.69
Caudate	4.74 ± 0.54	4.76 ± 0.44	0.7
Right	2.31 ± 0.28	2.32 ± 0.22	0.7
Left	2.42 ± 0.27	2.43 ± 0.22	0.8
Putamen	6.80 ± 0.81	6.76 ± 0.73	0.7
Right	3.39 ± 0.45	3.37 ± 0.35	0.7
Left	3.41 ± 0.4	3.39 ± 0.37	0.7
Pallidum	3.84 ± 0.24	3.89 ± 0.24	0.1
Right	1.93 ± 0.14	1.96 ± 0.12	0.1
Left	1.90 ± 0.13	1.93 ± 0.12	0.07
Nucleus accumbens	1.08 ± 0.09	1.08 ± 0.09	0.9
Right	0.5 ± 0.06	0.5 ± 0.05	0.7
Left	0.57 ± 0.05	0.57 ± 0.07	0.8
Thalamus	12.07 ± 1.16	12.44 ± 0.80	0.01*
Right	5.91 ± 0.65	6.09 ± 0.41	0.02*
Left	6.17 ± 0.61	6.35 ± 0.45	0.02*

*$P<0.05$.

thalamus (r: -0.252 and $P=0.02$; Figure 2) and pallidum (r: -0.255 and $P=0.02$; Figure 3) had inverse correlations with epilepsy duration. No significant correlation was found between the seizure frequency and the volume of studied brain region.

Discussion

In this large well-matched cross-sectional analytic study, we showed that compared to the healthy controls, patients with TLE had lower midbrain and thalamus volume. With advance in quantitative imaging techniques, it became apparent that epilepsy is a widespread network disease. It encompasses remote but anatomically relevant regions, most importantly the central autonomic nervous system.[18-20]

The midbrain, also known as the mesencephalon, is a component of the brainstem. Its functions extend to various parts of the central nervous systems, from motor to sensory and autonomic functions.[21] In a previous voxel-based morphometric study of 43 patients with unilateral drug-resistant mesial-TLE, the authors observed that patients had grey matter atrophy in subcortical nuclei such as the thalamus and caudate, in the cerebellum, and in the midbrain.[22] This corroborates our observation. There is a temporopontine or temporoparietopontine tract occupying the lateral quarter of the basis pedunculi in the midbrain,[23] that may explain the relation between TLE and midbrain atrophy, at least to some extent. Our observation of midbrain atrophy could hypothetically be explained by seizure-induced injury to midbrain structures due to TLE. One of the major proposed mechanism of SUDEP is the breakdown of the autonomic system because of the disturbance of the respiratory function followed by cardiac failure.[24] This theory suggested the potential role of brainstem structures controlling autonomic function in SUDEP,[25] which is also supported by findings in animal models.[26] The role of brainstem dysfunction in SUDEP was further supported by a MRI study demonstrating brainstem volume loss that was most prominent at the level of the dorsal mesencephalon in patients suffering from drug resistant TLE.[5] A recent study demonstrated a correlation between volume loss in the mesencephalon and autonomic nuclei in the medulla oblongata and reduced heart rate variability.[10] Reduced heart rate variability has been shown to be associated with increased risk of cardiac death.[27] Although, the central autonomic system has also a cortical representation and these regions can be affected in TLE, as well.[5] In another study based on resting-state functional magnetic resonance imaging

Table 3. Subgroups Analysis of MRI Findings in TLE Patients

	Hippocampal Sclerosis (n=46)	Normal (n=35)	*P* Value
Cerebellum	118.31±9.87	119.62±7.29	0.5
Right	60.1±5.02	60.78±3.72	0.4
Left	58.21±4.99	58.64±3.63	0.6
Brainstem	29.47±2.04	29.34±2.22	0.79
Right	15.63±1.12	15.55±1.17	0.7
Left	13.83±0.9	13.73±1.02	0.6
Midbrain	10.32±0.69	10.41±0.64	0.53
Pons	15.12±1.27	14.84±1.35	0.35
Medulla	4.09±0.32	4.12±0.37	0.67
Caudate	4.66±0.6	4.83±0.44	0.1
Right	2.28±0.31	2.36±0.23	0.1
Left	2.39±0.3	2.47±0.22	0.1
Putamen	6.67±0.76	6.97±0.84	0.1
Right	3.33±0.46	3.46±0.42	0.1
Left	3.34±0.37	3.50±0.42	0.08
Pallidum	3.83±0.27	3.85±0.21	0.6
Right	1.93±0.17	1.94±0.10	0.7
Left	1.88±0.14	1.91±0.10	0.4
Accumbens	1.06±0.1	1.10±0.08	0.1
Right	0.48±0.06	0.53±0.04	0.001*
Left	0.56±0.05	0.58±0.05	0.09
Thalamus	11.83±1.28	12.38±0.92	0.03*
Right	5.79±0.75	6.07±0.45	0.04*
Left	6.05±0.67	6.32±0.47	0.04*

*$P<0.05$.

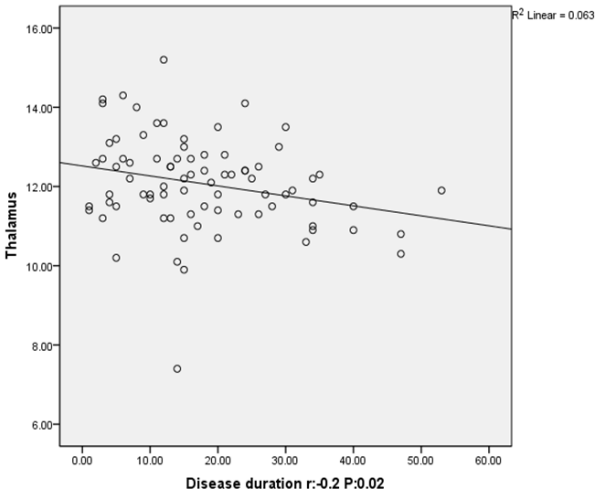

Figure 2. The Volume of the Thalamus Had Inverse Correlation With the Epilepsy Duration.

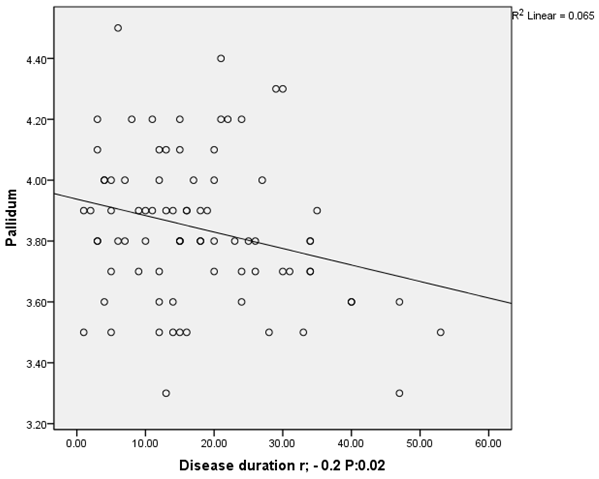

Figure 3. The Volume of the Pallidum Had Inverse Correlation With the Epilepsy Duration.

(rs-fMRI), patients with TLE, who were at high risk of SUDEP, displayed widespread functional connectivity differences between the key autonomic regulatory brain regions compared to those at low risk of SUDEP.

We had a trivial observation of the relationship between the recent TCSs and the degree of midbrain atrophy. This observation may imply that the disease severity affects the midbrain and corroborates our hypothesis of seizure-induced injury. Conversely, a previous study demonstrated that there is a progression of diffuse extrahippocampal gray matter atrophy in seizure-free patients with TLE.[28] This finding proposed an underlying pathological mechanism which result in progressive brain volume loss in patients with TLE even in seizure-free periods.[28] The association between the degree of midbrain volume loss and the occurrence of TCS could also be explained by the previously described "two-hit" mechanism. The two-hit mechanism assumes that, excitotoxicity effects of spreading seizure activity could result in mesencephalic abnormalities that represent the "first hit." Dorsal mesencephalic structures not only play an important role in cardio-respiratory autonomic control but also in seizure termination and arousal.[29-35] As a result, structural abnormalities in mesencephalic regions could render the patient prone to longer and more severe seizures that are more likely to be generalized.[36-38]

Another structural change beyond the borders of the temporal lobes in our study, was thalamic atrophy. Involvement of thalamus is a documented finding in the previous literatures[9,39-41] with altered structural and functional thalamo-hippocampal connectivity.[9,40,42-44] Animal models of mesial TLE (MTLE) have shown the role of thalamus as a central contributor of seizure initiation, a synchronizer, and even regulator of secondary generalization to neocortical areas.[45] Furthermore, ictal SPECT and diffusion tractography studies in MTLE patients, demonstrated the role of medial thalamus in MTLE network and its potential involvement in seizure initiation.[46,47] In our study, the degree of thalamic atrophy was inversely correlated with the epilepsy duration and was more prominent in TLE-HS group than patients with normal MRI. The association between the degree of thalamic atrophy and the epilepsy duration could be explained by the notion of more prolonged epilepsy duration could render more injury to susceptible brain structures.[48] Moreover, hippocampal neuronal loss in TLE-HS could result in decreased efferent synaptic activities to the thalamus, causing decreased neuronal activity in this structure with consequent thalamic atrophy.[48] We found no association between the sides of thalamic atrophy with the side of the seizure-onset zone. This may imply that, the seizure-induced injury may involve widespread brain areas rather than involvement of neighborhood regions.

There were no significant differences in the volumetric assessments of cerebellum, medulla oblongata, and pons, between TLE group and the healthy controls in our study. Reduction in the volume of cerebellar gray matter has been reported in patients with TLE in previous studies,[6,7,49] which is inconsistent with our findings. The difference in our results could be explained by the landmarks of the measured brain areas, the scanner resolution, and intra- or inter-rater reliability. A previous volumetric study in patients succumbed to SUDEP, showed atrophy of lower brainstem structures.[10] Atrophy of the lower brainstem structures and medulla may only be observed in severe epilepsy cases, endanger of SUDEP.

Our study had some limitations. First, we did not include drug-responsive patients with TLE. Recruiting such patients at a referral epilepsy center, such as ours, is difficult. Moreover, we only assessed subcortical structures, including thalamus, basal ganglia and infratentorial structures. In addition, all of our patients were taking antiseizure medications that may potentially enhance brain atrophy.

In conclusion, we found that patients with TLE had significant midbrain and thalamus volume loss compared to healthy controls. The amount of midbrain atrophy was greater in patients with history of TCSs. We assumed that midbrain volume loss may potentially alter autonomic nervous system function and put patients at risk of SUDEP. Future research is recommended on the possible association between the degree of brainstem atrophy and assessment of SUDEP risk.

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Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

Ethics Statement

The study has been approved by the ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (ethics committee number: IR.SBMU.RETECH.REC.1399.450).

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