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Role of Volumetric Magnetic Resonance Imaging of the Brain in Children with Non-Lesional Epilepsy

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Abstract

Background: **Epilepsy in children carries high risks of comorbidity and mortality, and non-lesional epilepsy (NLE), where MRI appears normal, is particularly difficult to diagnose and treat. Volumetric MRI (vMRI) improves the detection of subtle cortical abnormalities and provides quantitative brain volume analysis. It is essential for enhancing diagnosis and guiding surgical decisions in pediatric NLE.** ***Aim:*** **To evaluate the role of volumetric MRI in diagnosing children with non-lesional epilepsy.** ***Subjects and Methods:*** **Fifty-nine children with NLE and 59 controls under 18 years underwent comprehensive clinical evaluation, electroencephalography, and standardized 1.5T MRI using an epilepsy protocol. vMRI using volBrain 1.0 for whole-brain segmentation and HIPS 1.0 for hippocampal subfield segmentation. Quantitative measures assessed gray matter (GM), white matter (WM), subcortical structures, and hippocampal subfields, with asymmetry indices and age- and sex-adjusted norms applied to identify subtle abnormalities.** ***Results:*** **Children with NLE showed reduced volume of WM and subcortical structures, with no significant GM differences from controls. The amygdala was the most significantly affected structure, followed by bilateral reductions in hippocampal subfields (CA1, CA2–CA3, CA4–DG, SR-SL-SM), thalamus, putamen, and globus pallidus. No significant differences were detected in the caudate nucleus or subiculum. Receiver Operating Characteristic (ROC) analysis revealed that amygdala volume was the strongest diagnostic marker (AUC 0.963, sensitivity 94.9%, specificity 100%). Hippocampal volume showed moderate diagnostic accuracy (AUC 0.705, sensitivity 67.8%, specificity 64.4%).** ***Conclusion:*** **Volumetric MRI is a valuable tool for detecting subtle brain changes in childhood non-lesional epilepsy. Early validation in pediatric patients is recommended to improve prognosis and guide therapy.**

Keywords: Children, Non-lesional epilepsy, Volumetric MRI

Introduction:

Epilepsy is a neurological illness defined by recurrent and spontaneous seizures. It is a varied condition that includes various seizure types and syndromes, different underlying causes, and varying prognoses. Currently, the global incidence of epilepsy is approximately 1–2% [(1)]. The frequency is especially elevated in pediatric patients, and the syndrome frequently correlates with substantial comorbidities and heightened mortality rates [(2)]. Epilepsy is divided into focal, generalized, combined focal, generalized, and undetermined types [(3)]. A combination of imaging procedures, electrophysiological testing, and clinical evaluations is required to diagnose epilepsy. Traditional imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), do not reveal any lesions in non-lesional epilepsy (NLE). As a result, diagnosing the underlying cause of NLE can be pretty challenging [(4)]. Studies indicate that the overall prevalence of NLE in surgical cases is approximately 26% [(5)]. MRI is considered the gold standard for imaging

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in epilepsy research because it offers detailed anatomical information about the brain structures that may be involved [6, 7]. Neuroimaging is essential in epilepsy as it aids in detecting the seizure onset zone, minimizing surgical risks, and identifying epileptogenic foci [8, 9].

Children's non-lesional (MRI-negative) epilepsy is difficult to diagnose and treat. Even in experienced facilities implementing optimized epilepsy protocols, a significant fraction of drug-resistant pediatric cases have no detectable lesion on conventional MRI and have poorer postoperative seizure freedom rates. This gap has driven the systematic use of advanced structural post-processing and quantitative methods to detect minor anatomical defects that may be missed visually [9]. Volumetric Magnetic Resonance Imaging (vMRI) is a novel T1-weighted sequence in standard epilepsy treatment protocols. It enhances the visualization of the grey matter (GM) and white matter (WM) interface, which facilitates the accurate detection and characterization of minor cortical abnormalities, mainly Focal cortical dysplasia (FCD). vMRI also allows for automatic computation of volumes in various brain areas [10]. Consequently, assessing the role of volumetric MRI in pediatric patients with non-lesional epilepsy is crucial to ascertain its diagnostic efficacy in identifying subtle abnormalities and determining its effectiveness in informing surgical candidacy.

Aim of the work

This study aims to evaluate the role of volumetric MRI in the diagnosis of children with non-lesional epilepsy.

Subjects and Methods:

This case–control study enrolled 118 participants (59 cases and 59 controls) referred from the Pediatric Neurology clinic to the MRI Unit, Radiology Department, Suez Canal University Hospital. Eligible patients satisfied the following criteria: either sex, age under 18 years, clinical and electroencephalographic (EEG) data indicative of epilepsy, absence of structural abnormalities on conventional MRI, and a seizure-free interval of at least 72 hours prior to the MRI. Patients were excluded if they were in a postoperative state, had a history of head trauma, experienced febrile seizures, presented with a structural lesion on MRI that could elucidate the seizures, had contraindications to anesthesia necessary for MRI, or were not good candidates for an MRI, like children with hearing implants; none of our patients were given any contrast material.

All eligible participants underwent evaluation as follows: baseline demographic and clinical data were documented, encompassing age, sex, prenatal, perinatal, postnatal history, familial, and other relevant medical history. A comprehensive seizure history, including type, semiology, onset, and progression, was recorded, and all patients underwent standard scalp EEG as part of the evaluation.

The research ethics committee of the Faculty of Medicine at Suez Canal University approved the study. After an explanation of the MRI process and its expected advantages, informed written consent was obtained from all participants.

Imaging procedure

MRI scan

Patient preparation:

Children received sedation prior to the imaging, and the procedure was fully explained to their parents. Imaging was conducted using a Philips Ingenia 1.5 T MRI system equipped with a 16-channel head coil (Philips Medical Systems). The scan duration was approximately 25 minutes.

The imaging followed the routine epilepsy MRI protocol of Suez Canal University, utilizing standard pulse sequences.

The procedure encompassed the subsequent pulse sequences: T1-weighted imaging (T1WI) 3D: sT1W_3D_TFE, field of view (FOV): including entire brain (230 mm), voxel dimensions 1 × 1 × 1 mm isotropic, signal-to-noise ratio (SNR) = 1. Echo pulse sequence: gradient, flip angle 30°, Echo Time (TE)3.4 ms, (Repetition Time)TR 7.3 ms; T2-weighted imaging (T2WI) _3D_DRIVE: Field of View: including the entire brain (230 mm), isotropic voxel dimensions of 1 × 1 × 1 mm, Signal-to-Noise Ratio = 1, Echo Time 245 ms, Repetition Time 1500 ms, Signal-to-Noise Ratio = 1; 3D (Fluid-Attenuated Inversion Recovery) FLAIR: Field of View 230, voxel dimensions 1.16 1.44 5 mm, repetition time 11,000 ms, echo time 140 ms, signal-to-noise ratio = 1.

Imaging analysis:

An initial report was generated using a standard evaluation utilizing Philips ISP (Intellispace Portal v. 9).

Volumetric and segmentation reporting:

The online MRI-brain volumetric system, www.volbrain.com, received a compressed T1WI file in NIFTI (Neuroimaging Informatics Technology Initiative) format. Upon completing the automated process, a PDF report was generated with volumetric data for the following: GM, WM, cerebrospinal fluid (CSF), subcortical GM, and hippocampal segmentation. Using the ITK-SNAP Version 3.4.0 software, we obtained NIFTI files in every case. The VolBrain methodology, which involved using volBrain version 1.0 for whole brain segmentation and HIPS version 1.0 for hippocampus segmentation, was described in detail by Manjon and Coupé[11].

We could access all of the volumetry data produced by the segmentations after receiving an email notification that the process was finished. The following is the methodology for measuring volumes in each report: volBrain report: CSF, GM, and WM volumes were analyzed together with brain macrostructure and subcortical structure. Automated subcortical structure segmentation and asymmetrical indices were also provided, in addition to volume data for numerous macroscopic regions like the thalamus, cerebellum, brainstem, and brain hemispheres. Brain lesion report: types, sizes, and locations of lesions. Subfield volumes of the hippocampus CA1, CA2-3, CA4-DG, Stratum radiatum-Stratum lacunosum-Stratum moleculare (SR-SL-SM), and subiculum are reported in the hippocampus report. A number of quality control snapshots of the various labelling outcomes are also included in the report. All volumes were provided in cubic centimeters (cm^3) and relative values proportionately to the intracranial volume (ICV).

The asymmetry index is calculated by taking the percentage difference between the left and right volumes and dividing it by their respective means. The values inside the brackets are the expected limits (95%) of normalized volume for each metric when considering sex and age. The predicted boundaries are indicated by green values, while red values indicate that the volume is outside of them.

Statistical Analysis:

The data were input and analyzed using the IBM SPSS software package, version 20.0 (Armonk, NY: IBM Corp.). We used percentages and numerical values to display the qualitative data. To determine if the distribution was normal, the Kolmogorov-Smirnov test was used. To describe the quantitative data, the following measures were used: range

(minimum and maximum values), mean, standard deviation, and median. A significant level of 5% was determined for the findings. The categorical variables were compared using the Chi-square test, and the quantitative variables, which were not normally distributed, were compared using the Mann-Whitney test. Also, to assess how well the characteristics under study performed diagnostically, we used receiver operating characteristic (ROC) curve analysis. After calculating the area under the curve (AUC), the optimal cutoff values were chosen by considering the sensitivity and specificity.

Results:

There were 59 controls and 59 cases in this investigation of non-lesional epilepsy. The average age of patients was 6.12 years (± 4.09), and their ages varied from 0.5 to 17 years. The control group had participants aged 1–16, averaging 6.39 years (± 3.06). In the control group, there were 36 females (61.0%) and 23 males (39.0%), but in the patient group, there were 34 females (57.6%) and 25 males (42.4%). Regarding gender and age, no statistically significant difference was found between the two data sets (Table 1).

Table (1): Demographic data among the studied groups.

Demographic data	Cases (n = 59)	Control (n = 59)	Test of Sig.	p
Sex				
Male	25 (42.4%)	23 (39.0%)	χ^2= 0.140	0.708
Female	34 (57.6%)	36 (61.0%)		
Age (years)				
Mean ± SD.	6.12 ± 4.09	6.39 ± 3.06	U= 1611.50	0.485
Median (Min. – Max.)	6.0 (0.50 – 17.0)	7.0 (1.0 – 16.0)		

SD: Standard deviation , U: Mann-Whitney test , c^2: Chi-square test
p: p-value for comparing the two studied groups

The patient group is evenly divided between focal seizures (52.5%) and generalized seizures (47.5%). Temporal lobe focal seizures are the most common (27.1%), followed closely by frontal lobe seizures (25.4%). Among the generalized types, generalized tonic-clonic seizures (GTC) account for 25.4%, while tonic seizures comprise 18.6%; myoclonic seizures are rare (3.4%) (Table 2).

Table (2): Distribution of seizures in patients (n=59)

Seizures	No. (%)
Focal frontal lobe	15 (25.4%)
Focal temporal lobe	16 (27.1%)
Generalized tonic	11 (18.6%)
Generalized tonic clonic	15 (25.4%)
Generalized myoclonic	2 (3.4%)

The total gray matter (GM) volume did not differ significantly between groups (cases: 52.35 ± 15.11 vs. controls: 52.45 ± 10.36, p = 0.421), but white matter (WM) volume was significantly reduced in the epilepsy group (36.05 ± 13.92 vs. 38.29 ± 88.12, p = 0.014). At the cerebral level, the total WM was lower in patients (32.30 ± 11.79 vs. 33.88 ± 6.60, p = 0.030), whereas total GM was nearly identical between groups. Both right and left cerebral WM volumes were significantly reduced in cases compared to

controls, while GM volumes in these hemispheres showed no significant differences. Bilateral thalamic volumes were substantially smaller in the epilepsy group (right: 0.43 ± 0.03 vs. 0.77 ± 2.82, p = 0.037; left: 0.46 ± 0.04 vs. 0.61 ± 1.42, p = 0.008). The amygdala showed strikingly lower volumes in epilepsy patients (total: 0.06 ± 0.04 vs. 0.12 ± 0.02, p < 0.001), with both right and left sides significantly smaller. Volumes of the globus pallidus were significantly reduced bilaterally in cases (right: 0.08 ± 0.02 vs. 0.09 ± 0.01 c, p = 0.004; left: 0.08 ± 0.02 vs. 0.09 ± 0.01, p = 0.003). There was also a significant asymmetry difference (p = 0.024). No significant volumetric differences between groups were observed in caudate volumes (total: 0.58 ± 0.11 in cases vs. 0.57 ± 0.12 in controls, p = 0.701). The putamen was significantly smaller in the epilepsy group (total: 0.56 ± 0.12 vs. 0.61 ± 0.08, p = 0.010), with both right and left sides reduced (p < 0.001 and p = 0.014, respectively) (Table 3).

Children with non-lesional epilepsy demonstrated significantly smaller hippocampal volumes than controls (0.25 ± 0.06 cm^3 vs. 0.28 ± 0.02 cm^3, *p* < 0.001). This reduction was evident bilaterally. The CA1 subfield was significantly reduced in cases compared to controls (0.09 ± 0.02 vs. 0.10 ± 0.01, *p* = 0.007). Marked reductions were observed in CA2–CA3 volumes among cases (total: 0.02 ± 0.01vs. 0.02 ± 0.0, *p* = 0.001). The CA4–DG subfield was significantly smaller in patients (0.06 ± 0.02 vs. 0.07 ± 0.01, *p* = 0.002). The SR-SL-SM showed the most pronounced reduction, with patients having 0.04 ± 0.01 compared to 0.05 ± 0.01 in controls (*p* < 0.001). Both hemispheres demonstrated highly significant differences (*p* < 0.001). In contrast, the subiculum volumes were not significantly different between groups (0.03 ± 0.01 in both groups, *p* = 0.133). Regarding asymmetry, there are generally no differences between the groups, except in the CA2-CA3 region, which shows significantly higher asymmetry in patients (30.51 ± 38.17 vs. 14.46 ± 25.08, *p* = 0.025) (Table 4).

In ROC analysis, the total percentage of the amygdala was the most effective discriminator, achieving an area under the curve (AUC) of 0.963, with a sensitivity of 94.9% and a specificity of 100%. The accuracy at the cutoff of ≤0.08% was 97.5%. In comparison, other markers demonstrated only fair to moderate performance. The total percentage of the hippocampus had an AUC of 0.705, with a sensitivity of 67.8% and a specificity of 64.4%. The CA1/CA2–CA3/CA4–DG regions produced AUC values between 0.645 and 0.671, with accuracies around 62-65%. Among these, the CA4–DG region provided the highest specificity at 72.9%. The putamen percentage had an AUC of 0.637 and an accuracy of 67.0%. All AUCs were statistically significant (p ≤ 0.01) (Table 5).
Cases with non-lesional epilepsy are shown in figures 1, 2, 3

Table (3): Volumetric measures of different brain regions among the studied groups.				
Volume (cm^3/%)	Cases (n = 59) Mean ± SD.	Control (n = 59) Mean ± SD.	U	p
Whole brain tissue volume				
White matter (WM)	36.05 ± 13.92	38.29 ± 8.12	1283.0*	0.014*
Gray matter (GM)	52.35 ± 15.11	52.45 ± 10.36	1591.0	0.421
Cerebrum volume				
Total GM	45.58 ± 13.40	45.26 ± 9.14	1573.0*	0.367
Total WM	32.30 ± 11.79	33.88 ± 6.60	1337.0*	0.030*
Right GM	22.48 ± 6.61	22.67 ± 4.55	1657.0	0.653
Right WM	16.81 ± 7.05	17.18 ± 3.31	1360.0*	0.040*
Left GM	22.94 ± 6.08	22.58 ± 4.59	1494.0	0.184
Left WM	15.97 ± 5.83	16.72 ± 3.83	1342.0*	0.032*
Asymmetry	0.32 ± 5.76	0.41 ± 1.59	1711.500	0.876
Thalamus volume				
Right	0.43 ± 0.03	0.77 ± 2.82	1355.500*	0.037*
Left	0.46 ± 0.04	0.61 ± 1.42	1252.0*	0.008*
Asymmetry	-4.47 ± 9.69	-5.46 ± 13.79	1690.0	0.786
Amygdala volume				
Total	0.06 ± 0.04	0.12 ± 0.02	129.0*	<0.001*
Right	0.03 ± 0.01	0.10 ± 0.14	13.500*	<0.001*
Left	0.03 ± 0.01	0.08 ± 0.10	9.500*	<0.001*
Asymmetry	10.66 ± 50.58	16.24 ± 49.26	1601.0	0.450
Globus pallidus volume				
Total	0.17 ± 0.08	0.18 ± 0.02	1246.500*	0.007*
Right	0.08 ± 0.02	0.09 ± 0.01	1221.500*	0.004*
Left	0.08 ± 0.02	0.09 ± 0.01	1202.500*	0.003*
Asymmetry	-4.09 ± 10.97	-1.28 ± 9.04	1324.0*	0.024*
Caudate volume				
Total	0.58 ± 0.11	0.57 ± 0.12	1669.500	0.701
Right	0.30 ± 0.03	0.30 ± 0.04	1713.500	0.883
Left	0.29 ± 0.03	0.29 ± 0.04	1629.0	0.537
Asymmetry	2.97 ± 5.14	4.29 ± 3.80	1589.0	0.412
Putamen volume				
Total	0.56 ± 0.12	0.61 ± 0.08	1263.0*	0.010*
Right	0.29 ± 0.06	0.32 ± 0.03	1079.0*	<0.001*
Left	0.28 ± 0.06	0.30 ± 0.05	1289.500*	0.014*
Asymmetry	1.32 ± 7.92	-0.35 ± 5.63	1443.0	0.107

SD: Standard deviation, U: Mann-Whitney test
p: p-value for comparing the two studied groups ***: Statistically significant at p ≤ 0.05***

Table (4): Volumetric measures of the hippocampus among the studied groups				
Volume (cm^3/%)	Cases (n = 59) Mean ± SD.	Control (n = 59) Mean ± SD.	U	p
Hippocampus volume				
Total	0.25 ± 0.06	0.28 ± 0.02	1028.0*	<0.001*
Right	0.13 ± 0.04	0.14 ± 0.01	1259.0*	0.009*
Left	0.12 ± 0.03	0.14 ± 0.02	1115.0*	0.001*
Asymmetry	3.69 ± 26.82	2.92 ± 11.59	1623.0	0.526
CA1 volume				
Total	0.09 ± 0.02	0.10 ± 0.01	1237.0*	0.007*
Right	0.05 ± 0.01	0.05 ± 0.01	1359.0*	0.040*
Left	0.05 ± 0.01	0.05 ± 0.01	1185.0*	0.003*
Asymmetry	4.43 ± 32.08	2.13 ± 14.70	1506.0	0.206
CA2-CA3 volume				
Total	0.02 ± 0.01	0.02 ± 0.0	1145.0*	0.001*
Right	0.01 ± 0.0	0.01 ± 0.0	1377.0*	0.049*
Left	0.01 ± 0.0	0.01 ± 0.0	1012.0*	<0.001*
Asymmetry	30.51 ± 38.17	14.46 ± 25.08	1324.0*	0.025*
CA4-DG volume				
Total	0.06 ± 0.02	0.07 ± 0.01	1179.0*	0.002*
Right	0.03 ± 0.01	0.04 ± 0.01	1143.0*	0.001*
Left	0.03 ± 0.01	0.04 ± 0.01	1210.0*	0.004*
Asymmetry	8.77 ± 25.21	7.01 ± 16.51	1638.0	0.581
SR-SL-SM volume				
Total	0.04 ± 0.01	0.05 ± 0.01	943.0*	<0.001*
Right	0.02 ± 0.01	0.03 ± 0.0	1023.0*	<0.001*
Left	0.02 ± 0.01	0.03 ± 0.0	1035.0*	<0.001*
Asymmetry	5.95 ± 37.37	3.53 ± 13.75	1687.0	0.773
Subiculum volume				
Total	0.03 ± 0.01	0.03 ± 0.01	1462.0	0.133
Right	0.02 ± 0.01	0.02 ± 0.0	1482.0	0.163
Left	0.02 ± 0.01	0.02 ± 0.0	1589.0	0.414
Asymmetry	-16.30 ± 37.69	-11.03 ± 23.92	1594.0	0.430

SD: Standard deviation, U: Mann-Whitney test
*p: p-value for comparing the two studied groups *****: Statistically significant at p ≤ 0.05*

Table (5): Receiver operating curves (ROC curves) for volumetric changes among the non-lesional epilepsy patients								
Volume (cm^3/%)	Sensitivity	Specificity	PPV	NPV	Accuracy	Cutoff value	AUC	p value
Total hippocampus	67.80%	64.41%	65.6%	66.7%	66.11%	≤0.2701	0.705	<0.001*
Total CA1	59.32%	64.41%	62.5%	61.3%	61.87%	≤0.1028	0.645	0.007*
Total CA2-CA3	61.02%	62.71%	62.1%	61.7%	61.87%	≤0.0189	0.671	0.001*
Total CA4-DG	57.63%	72.88%	68.0%	63.2%	65.26%	≤0.0692	0.661	0.003*
Total amygdala	94.92%	100.0%	100.0%	95.2%	97.46%	≤0.08	0.963	<0.001*
Total putamen	66.10%	67.80%	67.2%	66.7%	66.95%	≤0.59	0.637	0.010*

AUC: Area Under a Curve *p value: Probability value* *CI: Confidence Intervals*
NPV: Negative predictive value *PPV: Positive predictive value*
******: Statistically significant at p ≤ 0.05* *# The cutoff was chosen according to the Youden index*

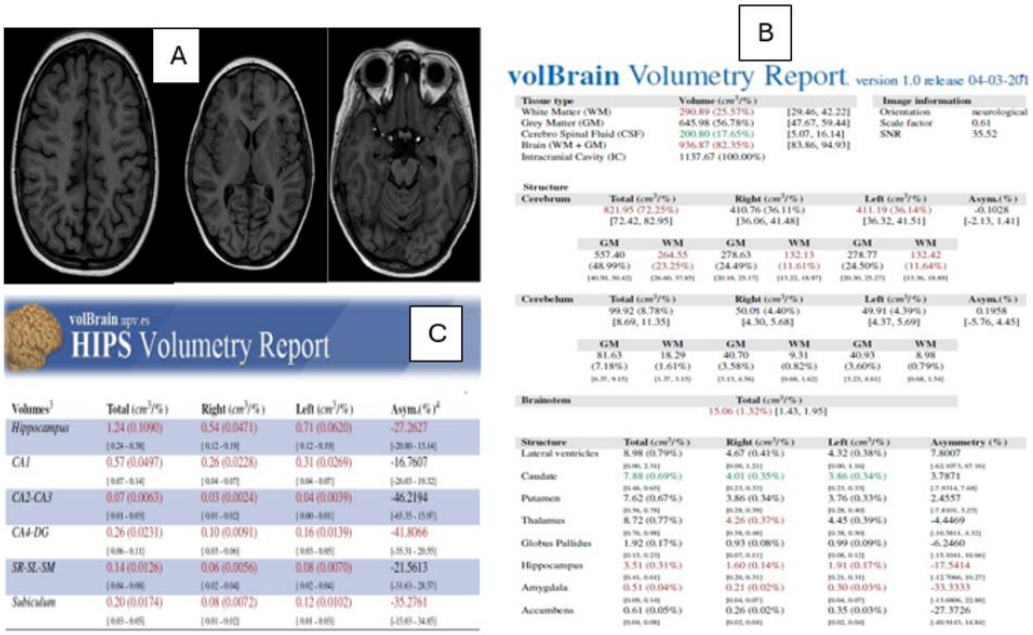
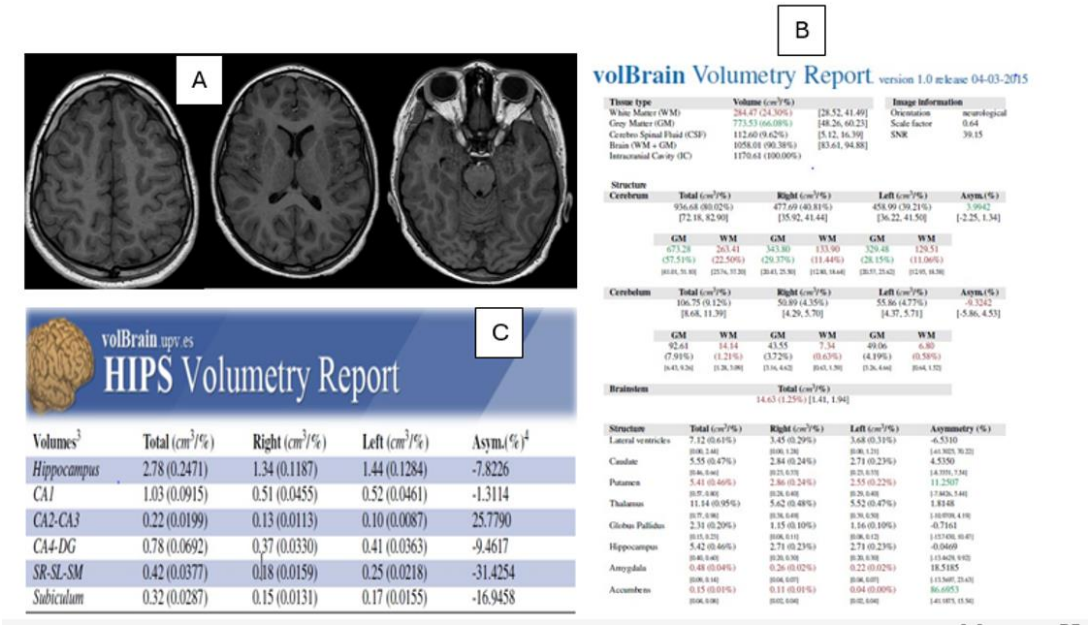


Figure 1: A 7-year-old male patient presented with temporal lobe epilepsy. A. The 3D axial MRI of the brain shows no structural abnormalities or abnormal signals. B. MRI volumetry reveals reduced volumes in the white matter, thalamus, hippocampus, and amygdala, as well as asymmetry between the right and left hippocampus and amygdala. In contrast, the volume of the caudate nucleus is increased. C. MRI volumetry indicates a decrease in the overall volume of the hippocampus and its segments.



Volumes[3]	Total (cm^3/%)	Right (cm^3/%)	Left (cm^3/%)	Asym.(%)[4]
Hippocampus	2.78 (0.2471)	1.34 (0.1187)	1.44 (0.1284)	-7.8226
CA1	1.03 (0.0915)	0.51 (0.0455)	0.52 (0.0461)	-1.3114
CA2-CA3	0.22 (0.0199)	0.13 (0.0113)	0.10 (0.0087)	25.7790
CA4-DG	0.78 (0.0692)	0.37 (0.0330)	0.41 (0.0363)	-9.4617
SR-SL-SM	0.42 (0.0377)	0.18 (0.0159)	0.25 (0.0218)	-31.4254
Subiculum	0.32 (0.0287)	0.15 (0.0131)	0.17 (0.0155)	-16.9458

Figure 2: A 9-year-old male patient with generalized tonic-clonic seizures. A. The 3D axial MRI of the brain shows no structural abnormalities or abnormal signals. B. MRI volumetry indicates an increase in the volume of grey matter, while showing a reduction of white matter, putamen, amygdala, and accumbens volumes. There is also asymmetry between the right and left putamen and accumbens. C. The MRI volumetry shows normal volume for the hippocampus and its segments

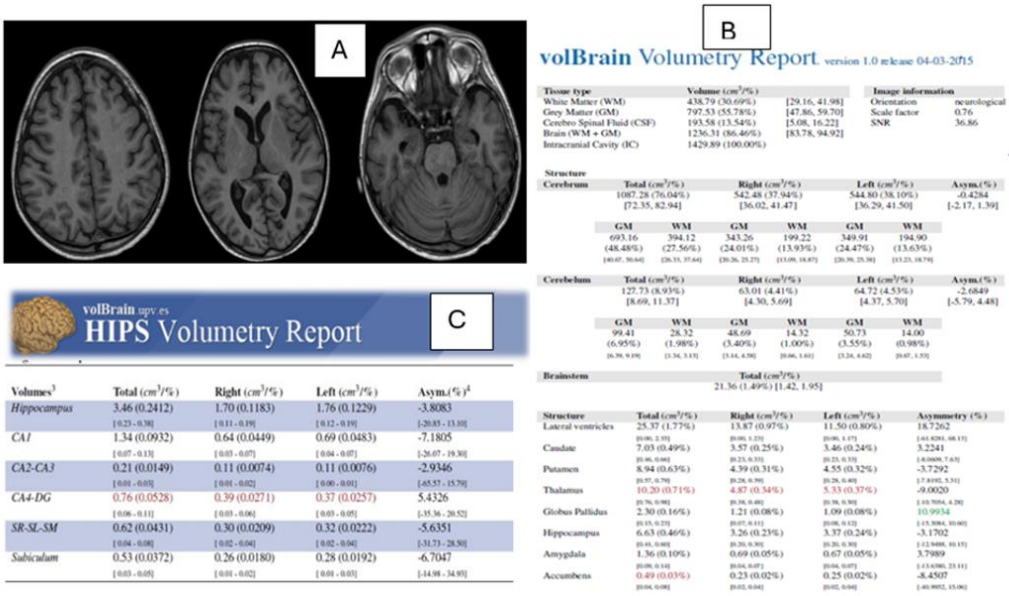


Figure 3: A 12-year-old male patient with generalized tonic-clonic seizures. A. The 3D axial MRI of the brain shows no structural abnormalities or abnormal signals. B. MRI volumetry indicates a decrease in the volume of the right and left thalamus and the right accumbens volumes. C. MRI volumetry indicates a decrease in the volume of right and left CA4-DG segments.

Discussion:

The application of modern MRI techniques in researching individuals with non-lesional epilepsy has been limited, especially concerning regional brain segmentation and volumetric evaluation. In our work, we performed a thorough assessment of various cerebral regions in children with non-lesional epilepsy compared to normal controls.

This study used volBrain version 1.0 for whole brain segmentation and HIPS version 1.0 for hippocampus segmentation, an online MRI-brain volumetric system. The automated technique was employed for volumetric and segmentation reporting. The system can be found at www.volbrain.com. After the automated process, a PDF report with volumetric data was generated. Because cortical malformations and the hippocampus are the primary pathologic features linked to the most prevalent epilepsy in children, they have received considerable attention ever since MR imaging was first used in the treatment of epilepsy.

Our study found a general decrease in WM while GM remained stable. This agrees with what Abdelgawad et al. [12] found: decreased WM and relatively preserved or even increased GM in the abnormal volumetry subgroup of children with non-lesional epilepsy. Another considerable multi-centre research demonstrates widespread compromise of WM in epilepsy, alongside effects in cortical and subcortical regions [13].

In a study by Lee et al. [14], newly diagnosed pediatric epilepsy patients were evaluated for cognitive dysfunctions, regional WM, and GM volumes. Reduced volumes in the frontal areas bilaterally, mainly the left inferior and right middle frontal gyri, were the most noticeable structural abnormalities in these patients. Additionally, Beheshti et al. [15]. found that

those with HS who also suffer from temporal lobe epilepsy (TLE) had significantly lower volumes of WM and GM. A slight enlargement of the GM and amygdala was also noted in patients with right TLE who did not have HS.

Our study found bilateral amygdala reduction, which aligns with recent research on the amygdala in epilepsy, which has noted decreased axon and dendrite density. This finding is consistent with microstructural reorganization [16, 17]. On the other hand, other studies have described amygdala enlargement in specific subgroups, such as those prone to tonic-clonic seizures, TLE, or with a higher risk of sudden unexpected death in epilepsy (SUDEP) [18-20].

Our research identified bilateral decreases in thalamic volume, corroborating the results of Perani et al. [21], who noted that the thalamus was the sole structure exhibiting reduced GM volume in anti-epileptic drug (AED) naive individuals with new-onset genetic idiopathic generalized epilepsy (IGE) compared to healthy controls. Additionally, Leek et al. [22] provided preliminary evidence suggesting that atrophy in the temporal and subcortical regions, particularly in the thalamus, is present during diagnosis. Another study indicates that atrophy of the thalamus is associated with generating and maintaining focal seizures [23]. Our research identified that in the basal ganglia, particularly the putamen and pallidum, there is a decrease in volume for both structures. This is in line with reports on focal epilepsy that highlight striatal atrophy within thalamo-striatal circuits [22]. However, recent studies have noted increases in pallidal volume and surface dilations in the putamen in cases of genetic IGE [24]. The caudate region shows a null difference, consistent with recent volumetric and shape studies indicating that the caudate can be variably affected or spared compared to the thalamus, putamen, and pallidum [23].

Therefore, our results provide more evidence that volumetric MRI might be a helpful tool in the search for hidden pathology. They also imply that non-lesional epilepsy in children might be linked to small but quantifiable structural alterations.

Our study revealed that Patients with NLE exhibited a smaller total volume of the hippocampus and reductions in both hemispheres across several fields, notably in CA1, CA2–CA3, CA4–DG, and the molecular layers (SR–SL—SM). However, there was no significant difference in the volumes of the subiculum. The hemisphere asymmetry indices were similar between the two groups, except for a greater asymmetry observed in the CA2–CA3 region among the epilepsy cases.

Coan et al.[25] found that hippocampus quantification by 3T MRI could assist in identifying patients with hippocampal sclerosis that may escape ocular assessment. These patients may benefit from surgical interventions to manage drug-resistant seizures. The comprehensive usefulness of employing hippocampus quantification measurements in 3T MRI for the presurgical evaluation of patients with drug-resistant mesial temporal lobe epilepsy can be evaluated through follow-up data and surgical outcomes. Bernasconi et al. [26] described a decrease in the volume of the right and left CA4–DG segments and the hippocampal head, body, and entorhinal regions. Seidenberg et al.[27] reported that patients with chronic unilateral TLE have volumetric abnormalities that go beyond just the affected side of the hippocampus and temporal lobe. While it was expected that these patients would show a reduction in

the volume of the ipsilateral hippocampus, they also demonstrated a significant decrease in cerebral white matter on both the side of seizure onset and the opposite side, compared to healthy controls. Additionally, A study by Princich et al.[28] revealed that different hippocampus subfields in the right (non-lesional) hemisphere of patients with left hippocampal sclerosis exhibited considerably greater sizes than those in healthy controls.

Therefore, our results emphasize the significance of subfield volumetric analysis, which offers a more detailed perspective than total hippocampal volume alone, and suggests potential anatomical biomarkers of epileptogenic susceptibility in children with non-lesional epilepsy.

Our study revealed that the amygdala (total %) achieved 94.9% sensitivity and 100% specificity. The hippocampus (total %) showed 67.8% sensitivity and 64.4% specificity. Among hippocampal subfields, CA4–DG had the highest specificity at 72.9%. Consistent with the utility of volumetric MRI in measuring hippocampus volume in epilepsy, Abdelgawad et al.[12] found that the sensitivity of right hippocampus subiculum volume and CA4-DG was 100%, white matter volume had a sensitivity of 85%, and the thalamus had a sensitivity of 55%.

Giorgio and De Stefano's [29] study proved that volumetric MRI is functional for evaluating the epileptogenic locus in TLE before surgery. It showed an asymmetry in the hippocampus volume on the side opposite the seizure focus, and the sensitivity was 95%. Farid et al. [30]found that hippocampus asymmetry as measured by quantitative MR imaging could reliably differentiate between control participants and patients with temporal lobe epilepsy, with a sensitivity of 86.7-89.5% and a specificity of 92.2-94.1%.

Our research showed that volumetry plays a significant role in the diagnosis of epileptic patients when traditional MRI fails to indicate any abnormality, as we could detect selective decreased volume of total hippocampus and its subfields and subcortical structures, specifically the thalamus, amygdala, pallidum, and putamen, as well as white matter. In contrast, cortical gray matter and caudate remain spared. More research is required to determine the clinical relevance of these volumetric alterations and how they may help in developing individualized treatment plans for people with non-lesional epilepsy.

Conclusion

Volumetric magnetic resonance imaging is a promising technique for assessing childhood non-lesional epilepsy, potentially altering prognosis and therapeutic approaches. To identify any volumetric changes, it is advisable to validate the MRI volumetry technique in pediatric epilepsy patients at the earliest opportunity.

Limitations

The study's small sample size and single-center methodology may restrict generalizability. Compared to 3T imaging, a 1.5T MRI scanner may be less sensitive to minor cortical abnormalities. Cross-sectional studies also hinder longitudinal volumetric changes and clinical correlations. The results should be further validated and expanded upon by future multi-center research using bigger populations, more sophisticated imaging procedures, and follow-up data.

List of abbreviations:

CA1: Cornu ammonis segment 1
CA4-DG: Cornu ammonis-Dentate gyrus
SR-SL-SM: Stratum radiatum-Stratum lacunosum-Stratum moleculare
FCD: Focal cortical dysplasia
MTS: Mesial temporal sclerosis
NLE: Non-lesional epilepsy
vMRI: Volumetric Magnetic Resonance Imaging
CT: Computed tomography
MRI: Magnetic resonance imaging
EEG: Electroencephalographic
T1WI: T1-weighted imaging
T2WI: T2-weighted imaging
FLAIR: Fluid-attenuated inversion recovery
TE: echo time
TR: repetition time
SNR: Signal-to-noise ratio.
FOV: Field of view
NIFTI: Neuroimaging Informatics Technology Initiative
GM: grey matter
WM: white matter
CSF: cerebrospinal fluid
cm^3: cubic centimeters

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