The role of Thalamus in A sample of Egyptian Idiopathic Generalized Epilepsy: Clinical and Advanced Radiological Study

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Abstract: The determination of the role of thalamus in a sample of Egyptian IGE patient using advanced neuroradiological technique. We assess the structural integrity, volume and functions of the thalamus in patients with Idiopathic generalized epilepsy and their relation to seizure frequency and duration of epilepsy. **Methods:** forty IGE patients (10 with JAE, 20 with JME and 10 with GTCs), and 20 healthy matched controls were submitted manual tracing volumrtic study to bilateral thalamus in 3D MIP work station on FSPGR software for evaluation structure integrity of thalamus and to a single voxel MRS of bilateral thalamus measuring N-acetyl aspartate (NAA) and NAA/creatine (Cr).-acetyl aspartate (NAA) and NAA/creatine (Cr). And assess severity with liverpol severity scale. **Results:** Patients with IGE were found to reduction than controls in volumetric in bilateral thalami and individual subgroup. JAE, JME, GTCs than control group P value < 0.001 with non- significant difference in volumetry of right and left thalamus in between the IGE subgroup JAE versus JME (P value 0.153 & 0.115), JAE versus GTCS (P value 0.210 & 0.238) and JME group versus GTCS group (P value 0.989 & 0.821 no significant difference in between the IGE subgroup with negative correlation to disease duration and generalized attack per disease duration to all group and severity scale of liverpol to JME and JAE. A significant reduction of bilateral thalami NAA and NAA/Cr ratio was observed in patients with IGE P value < 0.001 with subgroup compare JME & JAE patients had statistically highly significant lower mean values of NAA ratio than GTCS. A significant correlation between the change in neurometabolites of the patient's age and the seizure duration. JME patients show significant reduction of NAA/Cr ratio in correlate with severity scale. **Conclusion**: IGE was associated with reduction of bilateral thalami volume implying reduced overall neuronal numbers or neuronal dysfunction supporting the hypothesis of abnormal thalamocortical circuitry as a substrate of seizure generation. Also, we speculate that greater thalamic atrophy could be consequence of duration and cumulative of seizure and that thalamic volume may have a potential role as biomarker for disease progression. NAA and NAA/Cr reduction in IGE patient with seem worsened with increasing age, duration of epilepsy and the frequent of generalized seizures. Are consistent with epilepsy related ecotoxicity as underlying mechanism. Different result in IGE sub syndrome may be due extend different specific modifying gene.

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1. Introduction:

Epilepsy is a disease of the brain and a common cause of chronic neurological disorder. Epilepsy is defined by any of the following conditions: At least two unprovoked seizures occurring >24 h apart, one unprovoked seizure and a probability of further seizures if a lesion has generated an enduring predisposition similar to the general recurrence risk at least 60% after two unprovoked seizures occurring over the next 10 years and diagnosis of an epilepsy syndrome. Unprovoked implies absence of a temporary or reversible factor lowering the threshold and producing a seizure at that point in time (Robert S et al., 2014). An epileptic seizure is a transient symptom of excessive or synchronous neuronal activity in the brain consequence by neurobiological, cognitive, psychological, and social changes. It can manifest as an alteration in mental state, tonic or clonic movements, convulsions, and various other psychic symptoms. The clinical signs or symptoms of seizures depend on the location of the epileptic discharges in the cortex and pattern of the propagation of the epileptic discharge in the brain (Shneker and Fountain, 2003; Robert S et al., 2014).

Incidence rates of 35 to 94 per 100,000 and, despite differences in definitions, prevalence rates of 3 to 11 per 1,000, depending on children's ages (Hauser and Banerjee, 2008). Epilepsy is slightly lower in

females compared to males 46.2 vs.50.7 per 100,000. This difference constituted by the higher preponderance in males to develop partial epilepsies due to higher prevalence of lesional epilepsy in men and partial epilepsies most common various type of epilepsies. In an Egyptian study conducted by Mekky et al. (1981) on El-Gabal El-Asfar population, the prevalence rate for epileptic seizures was 4.1 per 1000 population, with highest prevalence rate in the age group 10-19 years where it reached 7.4 per 1000. El-Afify and Mostafa (1981) detected a higher prevalence rate which was 9.87 per 1000. However, the higher prevalence rates in developing countries could be related to the younger age of the population, different etiological profiles, and the effect of socioeconomic factors (Raafat, 1991).

The ILAE embarked on an ambitious effort to classify and catalog the various types of epileptic seizures and to classify the different disorders that lead to such seizures. The efforts were published in 1981 for seizures Chief among these classifications are the distinctions of focal versus generalized and idiopathic versus symptomatic. These distinctions continue to be the focus of epilepsy care and epilepsy research (Berg et al. 2010). Idiopathic generalized epilepsies constitute approximately 15–20% of all epilepsies. They affect all races equally and may have a slight predilection for women. Seizures usually, but not always, have an onset early in life, from childhood to early adulthood (Behrouz and Benbadis, 2008). idiopathic generalized epilepsy (IGE) constitutes a heterogenous group of epilepsy syndromes with a non-focal mechanism of seizure onset and no identifiable cause other than a genetic predisposition. Childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with generalized tonic–clonic seizures only (GTCS) are the well-recognized subsyndromes of IGE, according to predominant seizure semiology and age of seizure onset. Typical interictal EEG features of IGE consist of 3–5 Hz generalized spike-wave discharges (GSW) on a normal background with dominant frontocentral accentuation. Based on genetic traits, similar seizure semiology, and EEG features, these IGE subsyndromes are considered to share a common pathogenetic mechanism (Kim JH et al.,2013).

Pathophysiology of Generalized Epilepsies: Generalized epilepsy is thought to be initiated by 3 different mechanisms: (1) abnormal response of hyper excitable cortex to initially normal thalamic input, (2) primary subcortical trigger, and (3) abnormal cortical innervation from subcortical structures (Clark and Wilson, 1999). Physiologically, a seizure results from a paroxysmal high-voltage electrical discharge of susceptible neurons within an epileptogenic focus. These neurons are known to be hyper excitable and, for unknown reasons, remain in a state of partial depolarization. The neurons surrounding the epileptogenic focus are GABA-ergic and hyperpolarized, and they inhibit the epileptogenic neurons. At times, when the epileptogenic neurons overcome the surrounding inhibitory influence, the seizure discharge spreads to neighboring cortical structures and then to subcortical and brainstem.

The best-understood example of the pathophysiologic mechanisms of generalized seizures is the thalamocortical interaction that may underlie typical absence seizures. The thalamocortical circuit has normal oscillatory rhythms, with periods of relatively increased excitation and periods of relatively increased inhibition. The circuitry includes the pyramidal neurons of the neocortex, the thalamic relay neurons, and the neurons in the nucleus reticularis of the thalamus (NRT). Altered thalamocortical rhythms may result in primarily generalized-onset seizures. The thalamic relay neurons receive ascending inputs from spinal cord and project to the neocortical pyramidal neurons. Cholinergic pathways from the forebrain and the ascending serotonergic, noradrenergic, and cholinergic brainstem pathways regulate circuitry (McCormick, 1992).

The thalamic relay neurons can have oscillations in the resting membrane potential, which increases the probability of synchronous activation of the neocortical pyramidal neuron during depolarization and which significantly lowers the probability of neocortical activation during relative hyperpolarization. The key to these oscillations is the transient low-threshold calcium channel, also known as T-calcium current. In animal studies, inhibitory inputs from the NRT control the activity of thalamic relay neurons. NRT neurons are inhibitory and contain GABA as their main neurotransmitter. They regulate the activation of the T-calcium channels in thalamic relay neurons because those channels must be de-inactivated to open transitorily (Blumenfeld, 2003).

T-calcium channels have 3 functional states: open, closed, and inactivated. Calcium enters the cells when the T-calcium channels are open. Immediately after closing, the channel cannot open again until it reaches a state of inactivation. The thalamic relay neurons have GABA-B receptors in the cell body and receive tonic activation by GABA release from the NRT projection to the thalamic relay neuron. The result is a hyperpolarization that switches the T-calcium channels away from the inactive state, permitting the synchronous opening of a large population of the T-calcium channels every 100 milliseconds (Khosravani and Zamponi, 2006). The fundamental pathogenesis that underlies IGE is not fully elucidated; however, cumulative evidence has

suggested a critical role of abnormal thalamocortical circuit in the generation of GSW (Blumenfeld H.,2005)

In the present study, we combined two methods of structural MRI analysis (i.e., manual tracing volumetry, with spectroscopy in order to assess thalamic volume changes and metabolic changes to identify changes in IGE patients as compared to control subjects. In addition, we correlated thalamic volume and metabolic changes with clinical variables including age of onset, disease duration, and seizure frequency and severity of disease.

2. Patient and Methods:

This was a cross-sectional study conducted on 60 Egyptian subjects, including 40 patients with idiopathic generalized epilepsy with age range from 20 to 40 years with a mean of 28.95 ±5.89 years, they were 25 females (62.5 %) and 15 males (37.5 %), and 20 healthy persons who are age, sex matched with patients. The patients were collected from Epilepsy outpatient clinic, Neurology department Maadi Military Hospital. Patients were diagnosed on clinical and EEG basis, according to the International classification of epileptic seizures (Commission on classification and terminology of International League Agnist Epilepsy (ILAE), 1989, 2005).

This study was approved by the ethical committee of the faculty of medicine, Al-Azhar University at January 2015. Objectives of the study were briefly and clearly described to participants. The written consent to participate in the study was done.

The Patient groups were divided into three groups:

Group 1: 10 patients with juvenile absence epilepsy .

Group 2: 20 patients with juvenile myoclonic epilepsy.

Group 3: 10 patients with generalize tonic clonic epilepsy seizures .

Inclusion criteria:

Age 18 to 40 years (which meets the age of occurrence of non-symptomatic generalized epilepsy and range of age in military hospital, Unequivocal seizure semiology of IGE; typical absence seizures, myoclonic seizures and or GTCS (ILAE, 1989, 2005). All patients must have at least one EEG examination demonstrating typical generalized spike, poly spike /sharp and slow wave with normal background, Patients were not taking any medications except anti-epileptic drugs at the time of study inclusion. Control group: Healthy volunteers matched for age and sex 20cases recruited and underwent detailed interview as well as full neurological examination to ensure that they had: No history of neurological, psychiatric, or systemic disorders that affect epilepsy. No neurological abnormality and global cognitive impairment (MMSE scores not less than 26/30 no family history of epilepsy. With normal conventional MR images.

Exclusion criteria:

Evidence of developmental abnormalities, Global cognitive impairment on Mini-Mental State Examination (MMSE scores not less than 26/30, Abnormal findings on conventional MR images and Patients with co-morbid neurological illness, neurosurgical procedures, psychiatric diseases and chronic systemic disorders those affect epilepsy.

Methods:

All subjects were subjected to the following assessment:

Clinical history based on interview with patients and their relatives with special emphasis on family history, the age at onset of symptoms, semiology of attacks and their associated symptoms, their frequency, the presence of other seizure types and the treatment plane. The history, Clinical examination and neurological examination was carried out in all patients according to the clinical neurological sheet of epilepsy clinic Neurology Department, Maadi Military Hospital.

Mini Mental state examination Scoring and Liverpool Seizure Severity Scale Items with Interpretation represent seizure activity Major seizures (Grade 4) to Minor seizures (grade 1) depend on seizure sever problem or not to patient.

Laboratory evaluations were carried out in the Chemical Pathology Unit of Maadi Military Hospital: Complete Blood Picture (CBC), Liver Function Tests, Kidney Function Tests Fasting and Post –Prandial Blood Sugar.

Neurophysiological tests: All patients had their conventional inter-ictal electroencephalographic assessment carried out at the neurophysiology unit of Maadi Military Hospital, using Nihon Kohden 14-channels EEG machine. EEG electrodes were placed to the patient's head according to the international 10-20 system, using referential and bi-polar montages. All EEGs were carried out under normal standard conditions i.e., with the patient awake, lying supine, completely relaxed in a quiet room. Hyperventilation for 3 minutes together with intermittent photic stimulation (IPS) was used to provoke any existing abnormality. The EEGs were reviewed for clinical correlation. The International League Against Epilepsy (ILAE; 1989, 2005) diagnostic criteria were used for the diagnosis of epileptic syndromes. When the interictal EEG was normal, another recording was repeated later after 6 months with add provocative sleep deprivation and long-term record for 2hour to detect ictal or interictal discharges to fit the diagnosis of the IGEs syndrome.

MRI acquisition

Non-enhanced MRI of the brain was performed for all patients and controlled included in this study in the MRI unit of radio diagnosis department of Maadi Military Hospital using a 3Tesla (Philips Medical Systems). The patient was placed in a supine position. A head coil was used to image the brain. MRI studies were performed to all patients and control subjects using the epilepsy protocol of radio diagnosis: -Axial planes (T1, T2, FLAIR-weighted images) & Coronal planes (T2, FLAIR-weighted images) & Sagittal planes (T1-weighted images) .

T1 weighted spin echo images (TR: 415-1000 msec and TE: 17-20msec) and T2 weighted dual spin echo (TR: 1800-3000 msec and TE: 20 -90msec).

Volumetric evaluation of the thalamus

Using high resolution brain MRI using manual tracing technique to thalamus. The anatomical landmarks were determined according to the description by (Kretschmann and Weinrich, 1992). The anterior tip; is directed toward the interventricular foramen. The anterior margin; was defined as the level of the anterior end of the interventricular foramen. The medial margin; was defined as the wall of the third ventricle and the interthalamic adhesion, which connects both thalami. The inferior margin; Was defining as the superior border of midbrain structure. The lateral margin; was defined as the medial border of the posterior limb of the internal capsule. The superior margin; was defined as the inferior margin of the central part of the lateral ventricle and the caudate nucleus laterally. The lateral and medial geniculate nuclei were not included in measurements.

Manual Tracing Volumetry Of the Thalamus

Scan 3D sequence (FSPGR). Open this sequence on 3D MI. Scroll to first slice showing the thalamus, in the left side of the screen click on segment. Then click on (paint on slices) and press shift button and draw on the borders of thalamus with scroll more slices and press shift button and draw again. Then scroll again and draw until thalamus finish. Presses apply on the left side of screen and on same view part clicks on the red sentence up showing the name of sequence and select volume rendering. Then go to display on the left, select the 3D ROI and click on thalamus that we drawed it will give the volume (figure 4) .

MR spectroscopy (MRS):

The proton MR spectroscopy (1H-MRS) was performed with a single voxel technique using a 3 Tesla whole-body system (Philips Medical Systems) in the interictal period to all patients and control subjects.

Preparation:

Axial T2-weighted images, Coronal T2-weighted images, Sagittal T2-weighted images were used to place the volume of interest (VOI) in 3 planes with an average volume of 8 ml (20×20×20mm). The VOI were placed over both thalami. The thalamus VOI covered all thalamic nuclei.

Imaging:

MRI spectroscopy (we use PRESS; point resolved spectroscopy); as it give better signal to noise ratio because the stimulated echo is formed from only half the available equilibrium magnetization and there is complete recovery of signal. Pulse sequence was used with the following parameters: TR= 2000msec, 2048 data points, measurement of 128. Before recording the homogeneity of the magnetic field over the ROIs was optimized (shimming) automatically, water suppression was achieved using chemical shift selective (CHESS) radiofrequency pulses before PRESS excitation. A long echo time (272 mes) were used to study peak of NAA and NAA/Cr ratio. Peak areas of metabolites were quantified and then the position (the place as parts per million (ppm), width (the width of metabolite as part per minute (ppm) at half spike length and amplitude (as maximum intensity) of the metabolites were held. The volume of interest (ROI) of the single-voxel MRS included the thalamus. (Figure4)

Statistical Package for Social Science (SPSS) version 16 are used and Parametric data was expressed as mean ± SD, and non-parametric data was expressed as: Qualitative data were expressed as frequency and percentage. For quantitative data comparison between two groups was done using independent t-test. Comparisons between more than two groups were done using ANOVA test. Correlation between variables was tested using Pearson's correlation coefficient (r) test.

3. Results

Demographic and clinical characteristics

The age of IGE patients ranged from 20 – 40years with a **mean** of 28.95 ± 5.89 years and the age of control subjects ranged from 22 – 39years with a mean of 28.75 ± 5.12years and 15 of IGE patients (37.5%) were males and 25(62.5%) were females, while in the control group 12 (60%) were males and 8(40%) were females with no statistically significant difference in age and gender between IGE patients and control. disease duration and GTCS attack showed in figure (1);

Antiepileptic drugs taken monotherapy; valporic acid 9 (22.5%), levetiracetam 18(45%) lamotrigen 2(5%). Polytherapy; valporic acid and levetiracetam 1 (2.5%), valporic acid and lamotrigen 5 (12.5%) and levetiracetam and lamotrigen 5 (12.5%). Distributed as table (1):

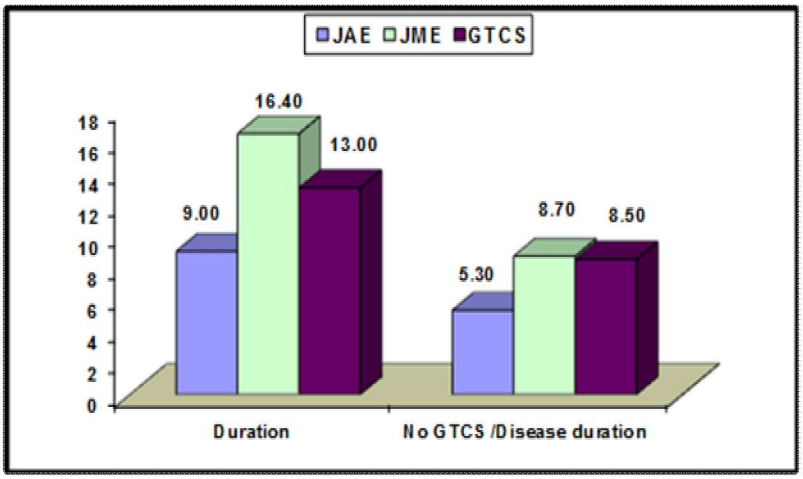
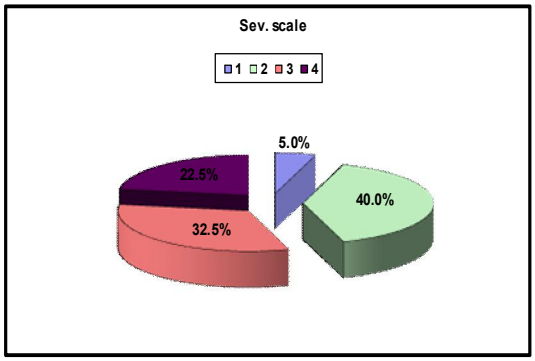


Figure (1); Disease duration and number of generalized attack per disease duration.

Table (1): The distribution of patient's groups according to AEDs

		Patient	JAE	JME	GTCS
		No. = 40	No. = 10	No. = 20	No. = 10
Drug	1-valporic acid	9 (22.5%)	3 (30.0%)	3 (15.0%)	3 (30.0%)
	2-levetiracetam	18 (45.0%)	7 (70.0%)	8 (40.0%)	3 (30.0%)
	3-valporic acid and levetiracetam	1 (2.5%)	0 (0.0%)	1 (5.0%)	0 (0.0%)
	4-valporic acid and lamotrigen	5 (12.5%)	0 (0.0%)	4 (20.0%)	1 (10.0%)
	5-levetiracetam and lamotrigen	5 (12.5%)	0 (0.0%)	4 (20.0%)	1 (10.0%)
	6-lamotrigen	2 (5.0%)	0 (0.0%)	0 (0.0%)	2 (20.0%)



Distribution of patient's groups according to Liverpool Seizure Severity Scale Liverpool Seizure Severity Scale

1: grade (1): mild 2: grade (2): moderate 3: grade (3) severe 4: grade (4) very severe

Liverpool Seizure Severity Scale grade 1 two (5%), grade 2 sixteen (40%), grade 3 thirteen (32.5%) and grade 4 nine (22.5%). •JAE grade1 two (20%), grade 2 four (40%) and grade 3 four (40%). •JME grade 2 six (30%), grade 3 six (30%) and grade 4 eight (40%). •GTC grade 2 six (60%), grade 3 three (30%) and grade 4 one (10%).

Neurophysiological Results: Interictal EEG was abnormal in 33(82.5%) patients; the abnormality was in the form of generalized spike-wave or polyspike-wave complexes, while it was normal in 7 (17.5%) JME patients. The frequency of generalized discharges in GTC patients was 3-4 cycles/sec and in JAE patients was 2.5-4 cycles/sec. Ictal EEG Seven patients with JME having normal interictal recording developed myoclonic jerks during another EEG recording and it showed generalized polyspikes and wave complexes of 4-6 cycles/sec. table (2);

Table (2); The distribution of interictal and ictal discharges in patient's groups.

Patients groups	Abnormal Interictal EEG		Abnormal Ictal EEG	
	No	%	No	%
JME (n=20)	13	65	7	35
GTC (n=10)	10	100	*	*
JAE (n=10)	10	100	*	*

Magnetic Resonance Imaging Volumetric of Thalamus

Compare of the two group IGE and control and sub group individual with control and to each other There was statistically highly significant decrease in the volume of both thalamus in the patients than control group P value < 0.001, There was statistically significant decrease in the volume of both thalamus in the patients JAE, JME, GTCs than control group P value < 0.001 as in (table 3) and There was non-significant difference in volumetry of right and left thalamus JAE versus JME (P value 0.153 & 0.115), JAE versus GTCS (P value 0.210 & 0.238) and JME group versus GTCS group (P value 0.989 & 0.821).

Table 3; Comparison between IGE subgroups and control as regard volumetric of thalamus

		JAE	JME	GTCS	Control group	P1	P2	P3
		No. = 10	No. = 20	No. = 10	No. = 20			
RT	Mean ± SD	6289.81 ± 179.23	6187.84 ± 157.96	6186.88 ± 221.89	7827.97 ± 250.86	0.001	0.001	0.001
	Range	5892.4 – 6528.5	5824.2 – 6372.1	5842.2 – 6528.4	7500.2 – 8214.9			
LT	Mean ± SD	6360.16 ± 186.89	6252.38 ± 136.93	6267.58 ± 218.93	7912.68 ± 267.57	0.001	0.001	0.001
	Range	5974.2 – 6593.7	5916.4 – 6408.4	5916.8 – 6587.6	7584.9 – 8331.4			

P1: control group vs JAE group P2: control group vs JME group P3: control group vs GTCS group

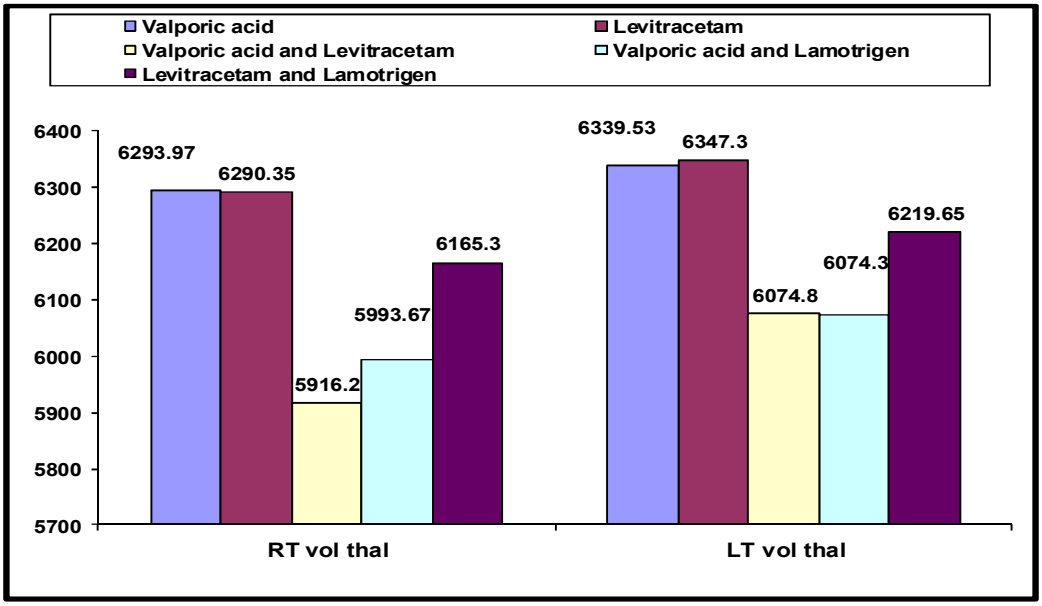


Figure (3) Correlation between volumetry of both thalamus of JME patient and their drug history

There was statistically highly significant negative correlation between the age of JAE & JME patients and volume of right and left thalamus (JAE P value 0.001 & 0.002), (JME P value 0.001) these mean increase age of absence and myoclonic patient associate with decrease thalamic volume but no statistically significant correlation in GTCS patients (GTCs P value 0.726 & 0.960) there was statistically significant negative correlation between the duration of disease and volume of right and left thalamus in all patients groups (P value in all patient groups 0.001). No GTS /Disease Duration statistically significant negative correlation between the number of generalized attacks in JAE & JME patients and volume of right and left thalamus (JAE P value 0.001 & 0.018), (JME P value 0.001) these mean increase No generalized attack /Disease Duration of absence and myoclonic patient associate with decrease thalamic volume but no statistically significant correlation in GTCS patients (GTCs P value 0.171 & 0.859). Frequency per month no statistically significant correlation between the frequency per month and volume of right and left thalamus in all patients groups (JAE P value 0.124), (JME P value 0.104 & 0.191) and (GTCs P value 0.721 & 0.325) and Last attack per day no statistically significant correlation between the Last attack per day and volume of right and left thalamus in JAE & GTCS patients groups (JAE P value 0.102), (GTCs P value 0.546 & 0.800). But there is statistically significant positive correlation in JME (JME P value 0.016 & 0.022) these mean that last attack are associate with

increase thalamic volume.

AED statistically highly significant correlation in JME patient (P value 0.001). we found more decrease in volume in patient on Valporic acid & Levitracetam and Valporic acid & Lamotrigen. these mean that polypharmacy in JME associate with more decrease in volume of thalami and no significant decrease to volume to valporic acid and no statistically significant correlation between drug history and volumetry of both thalamus in JAE & GTCS (figure 3).

liverpol severity scale and volumetry of thalamus we found statistically significant correlation between severity scale and volumetry of right thalamus and highly significant left thalamus in JAE & JME patient (JAE P value 0.022 & 0.005) and (JME P value0.009 & 0.010) but there is no statistically significant correlation in GTCs patient (P value 0.264 & 0. 254. we found more decrease in volume in JAE patient with sever scale and in JME with more sever scale. These mean that increase severity in JAE & JME associate with more decrease in volume of thalamus.

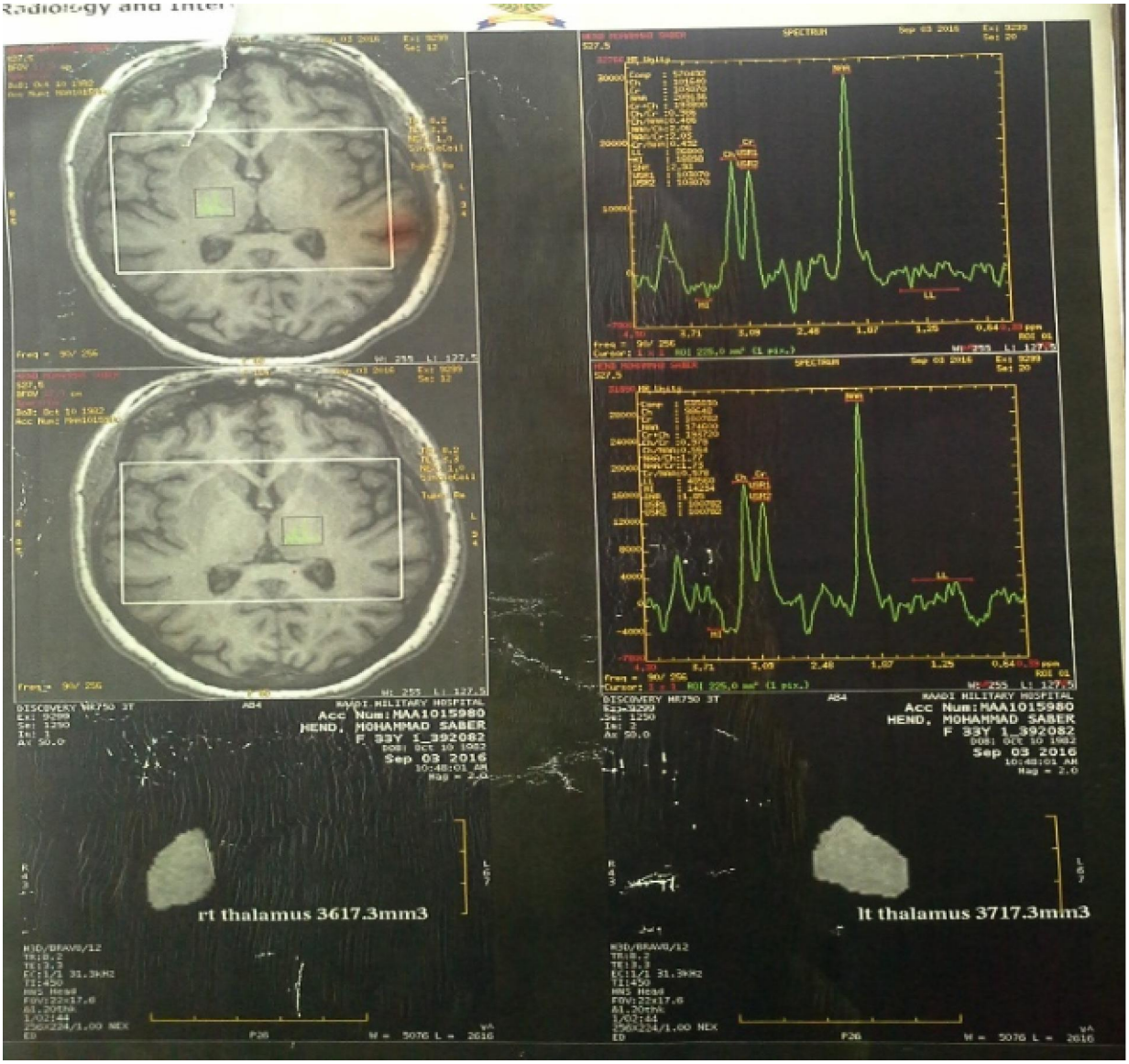


Figure 4; Volumetric and spectroscopy of female 28y with JME

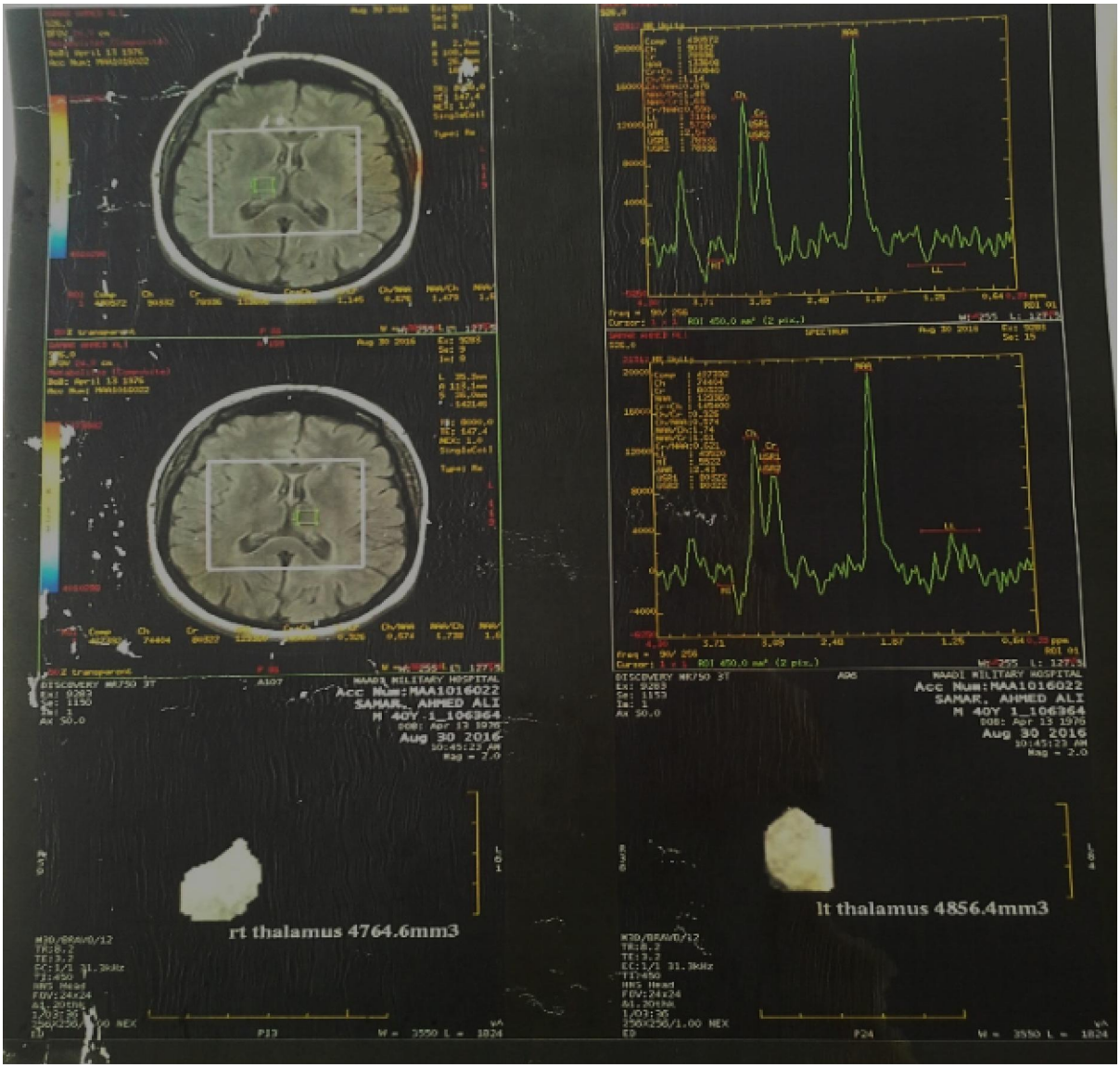


Figure 4; Volumetric and spectroscopy of female 21 with JAE

In the other axis Magnetic Resonance Imaging Spectroscopy of bilateral thalami Compare of the two group IGE and control and sub group individual with control and to each other revealed that IGE patients had statistically highly significant lower mean values of NAA and NAA/Cr ratio at TE (272) in both thalamus than control P-value< 0.001and MRS metabolites between IGE subgroup and controls. It revealed that JAE & JME patients had statistically highly significant lower mean values of NAA and NAA/Cr ratio at TE (272) in both thalamus and in GTCs patient had statistically highly significant lower mean values NAA/Cr ratio and significant lower RT NAA but no significant difference in LT NAA as showed in (table 4). And IGE subgroup revealed that JME & JAE patients had statistically highly significant lower mean values of NAA ratio at TE (272) in both thalamus than GTCs patient as showed in (figure 5).

Table (4) Comparison between IGE patients sub group and control subjects MRS metabolites of both thalamus.

		JAE	JME	GTCS	Control group	P1	P2	P3
		No. = 10	No. = 20	No. = 10	No. = 20			
RT NAA	Mean ± SD	14.26 ± 1.68	14.87 ± 1.37	18.90 ± 3.04	20.79 ± 3.08	0.001	0.001	0.047
	Range	12.22 – 17.32	12.32 – 17.56	14.32 – 23.37	15.32 – 24.48			
RT NAA/cr	Mean ± SD	1.68 ± 0.17	1.74 ± 0.16	1.71 ± 0.16	2.49 ± 0.26	0.001	0.001	0.001
	Range	1.5 – 2	1.48 – 2.11	1.52 – 2.01	1.83 – 2.76			
LT NAA	Mean ± SD	14.81 ± 1.84	15.34 ± 1.42	19.45 ± 3.06	21.18 ± 2.97	0.001	0.001	0.067
	Range	12.52 – 18.22	12.52 – 17.88	14.85 – 24.22	15.92 – 24.66			
LT NAA/cr	Mean ± SD	1.73 ± 0.19	1.81 ± 0.19	1.77 ± 0.20	2.55 ± 0.22	0.001	0.001	0.001
	Range	1.53 – 2.11	1.52 – 2.32	1.54 – 2.22	2.01 – 2.82			

P1: control group vs JAE group P2: control group vs JME group P3: control group vs GTCS group

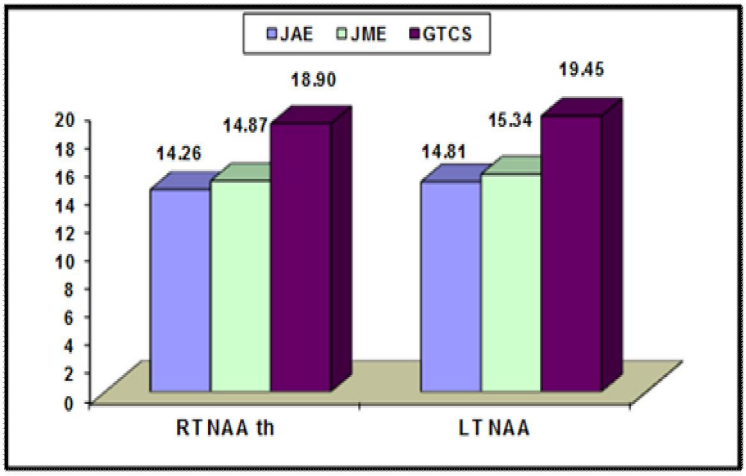


Figure (5): Comparison between IGE subgroup patients as regard MRS metabolites NAA of both thalami

JAE had significant negative correlation between the age patients, disease duration and number of GTC attack P-value< 0.001 and MRS metabolites both thalamus NAA ratio & NAA/Cr with no significant with frequency per month right thalamus p value 0.066 and left thalamus 0.068 last attack right thalamus.

p value 0.057and left thalamus 0.070. AED no statistically significant correlation and spectroscopy of both thalamus in JAE right thalamus p value P-value0.837 and left P-value 0.914 and liverpol severity scale significant correlation between spectroscopy of both thalamus in JAE P-value< 0.001.

JME had significant negative correlation between the age patients, disease duration and number of GTC attack right P-value< 0.001 and left P-value< 0.003 and MRS metabolites both thalamus NAA ratio & NAA/Cr with no significant with frequency per month right thalamus p value 0.166 and left thalamus 0.112 but last attack had positive correlation right thalamus p value 0.048 and left thalamus 0.034. AED statistically significant lower mean values of NAA ratio & NAA/Cr in both thalamus more with (Valporic acid & Levitracetam) and (Valporic acid & Lamotrigen) and no statistically significant with valporic and levitracetam. liverpol severity scale significant correlation between spectroscopy of both thalamus in JME. P-value< 0.001.

GTCs had non-significant correlation between the age patients, frequency per month, number of GTC attack and last attack but disease duration had significant negative correlation P-value< 0.001 and MRS metabolites both thalamus NAA ratio & NAA/Cr. AED and liverpol severity scale no statistically difference in mean values of NAA ratio & NAA/Cr in both thalamus in GTCs p value >0.05.

4. Discussion

The thalamus is of central interest in many disorders of the nervous system. The functioning of the thalamus is crucial to many sensory, motor and cognitive systems, and therefore has also been subject to a great deal of investigation in neurosciences (Basso., et al. 2005). It is in these capacities that analysis of thalamic structure and function is a continually researched, particularly using magnetic resonance imaging (Keller., et al.2012).

Idiopathic generalized epilepsy (IGE) occurs in the absence of any macroscopic brain abnormalities

(Prassouli., et al. 2007). These provide over the last decade important to analysis of volume using MRI techniques automated method free surfer, SPM and manual inspite the later are the gold standard method. Volumetric study to thalamus provides important information with respect to the involvement of the thalamus in generalized epilepsy (Seeck M., et al 2005; Huang W., et al 2011; Kim JH., et al 2013., Saini J., et al 2013; Swartz BE., et al2016; Correa DG., et al 2017).

1H-MRS has contributed toward understanding the changes in brain metabolism associated with IGE. Nevertheless, there is relative inhomogeneity in studied IGE groups, and thus the results have been highly variable (Bernasconi et al., 2003; Mory et al., 2003;; Savic et al., 2004; Haki et al., 2007; Lin et al., 2009; Dolken et al.,2010; Kabay et al.,2010; Lin et al., 2016).

The aim of this study was to verify structural thalamic impairment in IGE patients, and to quantify the neurometabolites in the thalamus, in a trial to find a possible link between thalamic neuronal dysfunction, evidenced by change in neurometabolites and structural abnormality in IGE patients, which may provide an objective basis to correlate the change in deep grey matter thalamus among epileptics and also may reveal hidden dimensions in the pathophysiologic process in IGE. We also aimed to correlate the findings with a number of epilepsy-related variables; as age, seizure frequency and duration of epilepsy.

Several issues were considered in this study regarding the patients' criteria. The age of studied patients met the age occurrence of idiopathic generalized epilepsy sub syndromes; and also age provide normalize ratio of brain volume and no different in brain metabolite. We excluded patients with a co morbid condition, in order to reach no underling cause to epilepsy and no effect on brain metabolite. In this study, all IGE patients showed that there was statistically significant decrease in the volume of right and left thalamus in the patients JAE, JME, GTCs than control group with mean of right thalamus volume of IGEpatient (6213.09mm3 ± 181.50) and control (7827.97 mm3 ± 250.86). mean of left thalamus volume of IGE patient (6283.13 mm3± 174.14) and control (7912.68 mm3 ± 267.57) with (P value < 0.001).

In agreement with our findings (Kim et al., 2007) who reported reduction in thalamic grey matter concentration in patient JME when he assay morphometric change of thalamus in JME, (Huang W et al.,2011) reported reduction in bilateral thalamic grey matter volume in patient GTCS. (O'muircheartaigh J et al., 2012) report decreases in the anterior medial thalamic volume and changes in surface shape thalamus in JME. (Saini J., et al 2013) they observed structural changes in the thalamus using multiple methods volumetry and shape analysis. a large areas of focal shape differences and volume reduction were seen in the anteromedial as well as lateral aspect of the thalamus. The involved thalamus suggests an essential role of the thalamocortical network in GTCS patients.

The present study found volume reductions in the bilateral thalami, thus supporting a central pathophysiological role of the thalamocortical network in GTCS (Blumenfeld H et al.,2003). In addition, not only is the thalamus important, but it is also the most impaired structure in GTCS. Both animal and clinical studies have shown that the thalamocortical circuitry is involved in seizure generalization and maintenance of the GSW discharge (Meeren H et al.,2005; Brevard ME et al.,2006). Thalamo–cortical network substrate is capable of generating the faster polyspike generalized spike and wave of juvenile myoclonic epilepsy as well as the slower generalized spike and wave of other idiopathic generalized epilepsies, this may be due to differential modulatory influences of the subcortical and cortical structures involved (Marten F et al.,2009; Rodrigues S et al., 2009).

(Simon SK et al., 2012) assessment of thalamic volume in JME using automated free surfer technique and manual stereology and report both techniques were equally sensitive in detecting bilateral thalamic volume atrophy in patients with JME relative to controls Using stereology, mean (SD) left and right thalamic volume was (6843.2 mm3±746.6) and (6763.3 mm3± 824.0) in patients with JME, and (7507.8 mm3±805.6) and (7482.6 mm3±767.2) in controls, respectively. Volume reduction in patients was found to be statistically significant for the left and right (p00.01) thalamus compared to controls. These in agreement with our findings using manual tracing techniques. Using Free Surfer, thalamic volumes were similarly smaller in patients relative to controls in the left (p00.03) and right (p00.008) hemispheres. Validate automated volumes and manual of the left and right thalamus. Based on the congruence between the data obtained from Free Surfer and manual stereology but the latter of which is considered to represent the 'gold standard.

(Kim JH et al.,2013; kim JB et al.,2014) found that bilateral thalamic volumes are reduced in IGE patients compared to controls by using shape analysis and automated volumetry technique, and that thalamic atrophy is mainly localized to the anterior-medial and posterior-dorsal aspects. The atrophied regions within the thalamus are not consistent across the studies: ventro-medial atrophy in JME and GTCS (Helmes J et al.,2006) and medio-dorsal and pulvinar atrophy in GTCS (wang Z et al.,2012). The reported patterns of thalamic atrophy in JME are also variable and include

ventro-lateral (Kim JH etal.,2013), medio-dorsal (Lin k et al.,2009) and antero-inferior thalamus (Mory SB et al.,2011).

In our study assess global volume reduction of both thalamus to avoid these divergences and all its nuclei are sharing in pathology of IGE. (Bin G et al., 2017) report different finding in IGE sub syndrome grey matter volume, in IGE significant GMV decrease in bilateral pulvinar. And JME, significant GMV decrease was found in right pulvinar. So this divergence of atrophy patterns might be attributed not only to the different IGE sub syndromes included, but also to the differences in MR scanner and methodology used in each study.

In disagree with our study result some author find no difference in thalamic volume of IGE patient and control (Seeck M et al., 2005) studies of 11 JME/AE/GTCS patients and (Betting LE et al.,2006) studies 15 GTCS patients and reported that the volumes of the thalamus did not differ between the patient and control groups. This finding is in agreement with an earlier volumetric study of patients with IGE (Natsume J et al., 2003). In against the present study result some author find large thalamic volume of IGE patient than control subject (Betting LE et al., 2006; Bin G et al., 2017) reported increase anterior thalamic volume in IGE with absence. (Swartz BE et al., 2016) studies MR volumetry of 17 JME patient and report that the thalamus of the JME subjects was larger than controls, a larger thalamus may due to greater white matter in the manual tracing volumetric analysis, and a higher signal in the pulvinar nucleus using VBM.

The difference in volumetry of thalamus in IGE sub syndrome which reduce in our study and (Kim JH et al., 2013; kim JB et al., 2014) and no difference in (McGill ML et al., 2014) in IGE and (Correa DJ et al., 2016) in AE and in against finding large thalamic (Bin G et al., 2016) in AE and (Swartz BE et al., 2016) in JME.

These findings support the hypothesis of different mechanisms for generalized seizures. Thalamic anatomy may be modulated by other factors as well. Seizure frequency, antiepileptic drugs, and genetic profile may also influence the final arrangement of the thalamus (Mory SB et al., 2011). JME have been five mendelian genes, three SNP alleles and three micro deletions associated with the 'JME phenotype' (Delgado-Escueta AV et al., 2013) The pleomorphism of JME is obvious clinically, physiologically. The need of deep phenotyping in studies of JME to highlight that neuroimaging difference related to the genotype of the individual subjects with JME (Greenburge DA et al., 2011; Swartz BE et al., 2016).

Our study showed statistically highly significant negative correlation between the patient age and duration of disease of JAE & JME patients and volume of right and left thalamus (JAE P value 0.001 & 0.002), (JME P value 0.001) but GTCS have significant negative correlation with duration of disease only. Our study in agree with (Huang W et al., 2011) result demonstrated a negative correlation between duration of epilepsy and GM volume in the thalamus in GTCs, indicating that epilepsy can directly impair these brain regions. On other hand (Bernasconi A et al.,2003) speculated that the abnormalities observed in patients of JME are related to disease duration and they increase with passage of time. also (Kim JH et al., 2007; O'muircheartaigh J et al., 2012 and Saini J et al., 2013) consistent findings decreased GMV in the bilateral thalamus in JME. And appear to worsen with longer duration of epilepsy.

Kim et al. (2013) observed negative effects of disease duration on the whole thalamic volumes as well as regional atrophy of anterior-medial and posterior dorsal thalamus. It is of note that the regions of thalamic atrophy found in between group comparison correspond to the regions that were negatively correlated with disease duration, strongly suggesting that anterior- medial and posterior-dorsal aspects of thalamus are preferentially affected in IGE.

In disagree with our study Pulsipher et al. (2009) report significant volumetric abnormalities in patients of JME who were analyzed relatively early in the course of the disease. They hypothesized that structural abnormalities are present even before the onset of first seizure and they are possibly developmental in origin. the lack of correlation between seizure duration and volumetry of thalamus supported in their study.

Our study showed statistically highly significant negative correlation between the number of generalized attacks in JAE & JME patients and volume of right and left thalamus (JAE P value 0.001 & 0.018), (JME P value 0.001) but no statistically significant correlation in GTCS patients (GTCs P value 0.171 & 0.859). these confirm the hypothesis GM volume reduction in the bilateral thalami suggesting that progressive GM volume changes may be due to seizures frequency. These in agree with (Saini J et al., 2013) consistent findings decreased GMV in the bilateral thalamus appear to worsen with more frequent seizures. (Chahboune H et al., 2009) report that the changes were not present in the rat model before onset of SWD, suggesting changes are secondary to chronic seizures.

In disagree with current study demographic data correlations (swartz BE et al.,2016) report There was no correlation between regional volumes and age, age of onset, duration of epilepsy, incidence of (GTCs) or seizure free duration. JME patients with positive family history were more have structural abnormalities

than those without.

Interestingly, in this work report statistically significant lower volume of males in comparison to females in JME patient (P value 0.031 & 0.032) but no statistically significant correlation between gender and volumetry of both thalamus in JAE & GTCS. inspite (McGill ML et al.,2014) no difference structural volumetry in correlation to gender. this correlation may have explained by long disease duration in male than female in JME patient.

In the present study report no statistically, significant correlation between drug history and volumetry of both thalamus in JAE & GTCS patient but there is statistically highly significant correlation in JME patient (P value 0.001). we found more decrease in volume in patient on Valporic acid & Levitracetam and Valporic acid & Lamotrigen. JME patients 3 (15%) on valporic acid, 8 (40%) on levetiracetam, 1 (5%) on valporic acid and levetiracetam, 4 (20%) valporic acid and lamotrigen and 4 (20%) on levetiracetam and lamotrigen. AED used in the IGE patient population could be reflected in brain volume (Marsh ED et al., 1999) Furthermore, valproate may be associated with reversible cerebral atrophy in neuroimaging studies, with an acute or insidious clinical course (Beeting LE et al., 2006). VPA has been identified to cause brain pseudoatrophy (Seeck et al., 2005; Papazian et al.,1995) However, the prevalence of asymptomatic cerebral atrophy in patients chronically using valproate is unknown (Chahboune H et al., 2009; Correa et al., 2016). Our findings do not seem to be associated with drug exposure but to nature of disease itself.

Regarding liverpol severity scale and volumetry of thalamus we found statistically significant correlation between severity scale and volumetry of right thalamus and highly significant left thalamus in JAE & JME patient (JAE P value 0.022 & 0.005) and (JME P value0.009 & 0.010) but there is no statistically significant correlation in GTCs patient (P value 0.264 & 0.254). in agree with (O'muircheartaigh J et al., 2012) found decreases in the thalamic volume and changes in surface shape in JME apparently worsen with severity of disease.

The other axis in this study was the assessment of some brain neurometabolites; we measured NAA, NAA/Cr ratio, using single voxel proton MRS technique, in the right and left thalamus The choice of these locations, rather than other brain regions, is based on an analogous study in IGE patients which did not report any abnormal concentration of NAA/Cr in the insular cortex, posterior temporal lobe white matter, splenium of the corpus callosum, or cerebellum, compared to healthy control (Bernasconi et al., 2003). Since NAA/Cr ratio showed a symmetrical distribution in both right and left thalami among patients and healthy controls as reported by (Fojtikova et al., 2006), meanwhile more involvement of thalamus in IGE, we selected the thalamus than rather regions, to perform our study on. The scanning of thalamus alone was more time saving as patients spent shorter period on the MRS device which made them more cooperative.

Bernasconi et al. (2003); Simister et al. (2003) and Savic et al. (2004) reported that NAA is found exclusively in neurons and neuronal processes and is considered an indicator of neuronal function, whereas Cr is relatively homogeneously distributed throughout the brain. Bernasconi et al. (2003) and Simister et al. (2003) mentioned that because metabolites are measured in voxels, their increase or reduction could be related to a large variety of confounding factors, such as neuronal shrinkage or increase/decrease in water content; so to avoid pitfall in measuring neurometabolites, with subsequent misinterpretation of our results, we performed an analysis of the NAA & NAA/Cr ratio to provide a more reliable data.

Our analysis of spectroscopic images acquired revealed a significant reduction of mean NAA and NAA/Cr ratio in the both thalamus of IGE patients compared to controls, this goes in agreement with Bernasconi et al. (2003) and Savic et al. (2004) who reported reduction of mean thalamic NAA/Cr in a heterogeneous group of patients with IGE in comparison to normal controls, Lin et al. (2009) reported that in IGE, irrespective of whether cell density is normal or elevated there is reduced concentration of NAA, which implies neuronal metabolic dysfunction in addition to neuronal loss.

On comparing individual groups of patients with JAE, JME and GTC we found a significant reduction of thalamic NAA and NAA/Cr ratio compared to controls except left thalamic NAA in GTCs had no significant reduction, and there was no significant inter difference among the three patients groups in the mean thalamic NAA or NAA/Cr ratio except bilateral mean NAA in JME & JAE significant lower than GTCs Patient.

Fojtikova et al. (2006) reduction of NAA as a reflection of neuronal loss also considering that neither increase in tissue water content nor decrease in other metabolites were found. Alternatively, it could reflect neuronal dysfunction associated with an impaired NAA (precursor pool) a specific mitochondrial dysfunction, or a neuronal lesion leading to release of NAA aminohydrolase resulting in degradation of NAA.

Mory (2003); Haki et al. (2007); and Lin et al. (2009) reported that single voxel MRS study showed abnormally low NAA/Cr levels in JME patients. In addition, progressive thalamic atrophy was reported in present study, Kim et al. (2007) and Pulsipher et al.

(2009). In another single voxel study, significant thalamic reduction of NAA was observed in patients with pure primarily generalized tonic clonic epilepsy in comparison to controls (Savic, 2004). Reflecting thalamic dysfunction in these patients. Fojtikova et al. (2006) demonstrated a significantly lower thalamic NAA/Cr ratio in patients with typical absence epilepsy when compared to healthy controls. MRS studies have shown neuronal loss in the form of decreased NAA/Cr in the thalamus (Tae et al., 2008).

Kabay et al. (2010) reported that single voxel MRS study showed abnormally low NAA and NAA/Cr levels in JAE patients in early stage of disease it may reflect excitotoxic effect of epilepsy on thalamus this reflect neuronal dysfunction secondary to epilepsy. In multivoxel study, significant thalamic reduction of NAA was observed in GTCS patient (Dolken et al., 2010). Lin et al. (2016) meta-analysis reported significant thalamic reduction of NAA in JME patient.

This study showed significant negative correlation between thalamic NAA, NAA/Cr ratio and age, disease duration and generalized attack per disease duration in JAE and JME patients, whereas, a statistically significant negative correlation existed between NAA, NAA/Cr ratio and the disease duration only in GTC patients. Regarding the last attack showed significant positive correlation between thalamic NAA, NAA/Cr ratio in JME patient it may reflect lack of a significant impact of attack activity on thalamus but more on duration. Bernasconi et al. (2003) found a negative correlation between thalamic NAA/Cr and the duration of epilepsy in IGE patients. On other hand there was a negative correlation between duration of epilepsy and more frequent GTCS and lower thalamic NAA concentrations (Savic et al., 2004).

Lin et al. (2009; 2016) observed lower thalamic NAA/Cr in JME patients which correlated negatively with advancing age and duration of epilepsy. In JAE patients, there was no statistically significant correlation between thalamic NAA/Cr ratio neither with the duration of epilepsy nor with the seizure frequency which was also reported by Fojtikova et al. (2006). These agree with Kabay et al. (2010) observation lower thalamic NAA/Cr in JAE can occur in early stage of disease. Either of these controversial results is not supported by other studies, which focused only on quantifying neurometabolites without correlating them to epilepsy associated variables (Mory et al., 2003; Haki et al., 2007).

Regarding impact of gender on neurometabolic changes, we found that there was no significant difference in mean values of NAA ratio & NAA/Cr in both thalami of males in comparison to females in JAE and GTCs, however significant correlation more reduction in male than female in JME. On the other hand, Komoroski et al. (1999) performed MRS in a number of brain regions of neuropsychiatric interest in male and female control subjects to determine if gender and region affect the measured metabolite ratios. They reported that no significant differences were seen in any region for any metabolite ratio between males and females; however, the female to male ratio in our study is about 3:1 which may not serve for a fair comparison in this respect.

Our results showed regarding the type of AED used that there was no significant difference in mean values of NAA ratio & NAA/Cr in both thalami in JAE and GTCs, with statistically significant lower mean thalamic NAA in patients receiving polytherapy in comparison to those receiving monotherapy was found in JME patient. This is in agreement with Lin et al. (2009) who demonstrated that poorly controlled seizures may be associated with more altered brain metabolites in patients with JME. On the contrary, no effect of AED regarding the type or the use of monotherapy or polytherapy on NAA or NAA/Cr ratio was found in most other studies. the lack of difference of NAA/Cr between JME patients with adequate seizure control and those with persistent seizures Haki et al., 2007). Again, the small number of patients on polytherapy (11/40) relative to those on monotherapy can offer a possible explanation for such discrepancy. Overall, our results denoted severity scale and spectroscopy of thalamus there is statistically significant correlation more increase in severity scale associate with significant lower mean values of NAA ratio & NAA/Cr in both thalami in JAE and JME. This is in agreement with Lin et al. (2016) they speculate that thalamic network dysfunction progress continuously. These data inferred differences in the neurobiological substrate of IGE sub syndromes.

This study was motivated by observations that structural and neurometabolic changes in patients with IGE are found in the thalamus: reduction in thalamic NAA in MRS and reduced thalamic volume might point to a permanent thalamic neuronal dysfunction. Moeller et al. (2011) support the hypothesis that pathologic thalamocortical interactions are not restricted to disease activity but also in free period from GSWDs.

5. Conclusion

Idiopathic generalized epilepsy patients may exhibit no underlying etiology. although thalamus is the key in initiation and propagation of activity in IGE patient and this can attributed by structural and neuronal dysfunction secondary to epileptic activity itself in the absence of any macroscopic lesions in the brain. Volumetric study and proton magnetic resonance spectroscopy is useful in the assessment of

idiopathic generalized epilepsy because they can assess subtle structural lesion and demonstrate subtle neurochemical changes in subjects when conventional MRI results are negative. IGE was associated with reduction of bilateral thalami volume implying reduced overall neuronal numbers or neuronal dysfunction supporting the hypothesis of abnormal thalamo-cortical circuitry as a substrate of seizure generation in this form of epilepsy. Also we speculate that greater thalamic atrophy could be consequence of duration and cumulative of seizure and that thalamic volume may have apotential role as biomarker for disease progression. NAA and NAA/Cr reduction in IGE patient with seem worsened with increasing age, duration of epilepsy and the frequent of generalized seizures. are consistent with epilepsy related excitoxicity as underlying mechanism. JME patient report positive correlation to last attack may support not only dysfunction of thalamic network but it multifocal generate activity rather than truly generalized syndrome and the different in IGE sub syndrome may be due extend different specific modifying gene.

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