Assessment of Metabolic Disturbances and Their Effects on Epilepsy Outcome In Patients with Juvenile Myoclonic Epilepsy

Abstract

Background: Juvenile myoclonic epilepsy (JME) is a common epilepsy syndrome that is classified as one of the idiopathic generalized epilepsies. The relationship between obesity and epilepsy is a rich and interesting area for research. There are potential reasons to consider that patients with epilepsy have a higher risk of developing obesity than the general population.
Objectives: To assess the possible causes of metabolic disturbances in patients with JME and the relationship between these disturbances and epilepsy outcome.
Methods: A case control study was conducted on 50 patients with JME divided into 2 groups: obese and non-obese. All patients were subjected to detailed medical and neurological history taking, complete general and neurological examinations, anthropometric measurements, laboratory investigations including serum insulin and adiponectin levels and Magnetic resonance spectroscopy (MRS) for the liver.
Results*:* Median serum insulin and HOMA IR were higher among obese cases than non-obese cases. serum Adiponectin levels were found to be relatively low in both groups. There was a statistically significant difference of Steatosis according to lipid peak between obese and non-obese groups with higher score detected among obese cases.
Conclusion: Obesity and related metabolic disturbances in children with JME are a particularly concerning topic which emphasises the importance of early diagnosis of obesity and individualized tailored treatment plan for every patient with JME

Key words: Juvenile myoclonic epilepsy, insulin, adiponectin, magnetic resonance spectroscopy.

Introduction

Obesity in epilepsy is a particularly concerning topic. There are potential reasons to consider that patients with epilepsy have a higher risk of developing obesity than the general population. Epilepsy itself may cause progressive weight gain through central nervous system (CNS) pathways. The regulation of food intake is a complex process involving interactions between brain regions responsible for behavioural control; a dysfunction in these centers may result in increased appetite and weight gain ***(Ladino et al., 2014)***. Bodyweight gain is a common and frequent undesirable effect associated with the use of anticonvulsant drugs. This has been observed for many years with valproic acid (sodium valproate) and carbamazepine, and also, more recently, with some of the newer anticonvulsants such as vigabatrin and gabapentin ***(Jallon & Picard, 2001)***. Valproic acid enhances GABA transmission within the hypothalamic axis, causing appetite stimulation, hyperinsulinaemia and hyperleptinaemia, and decreased concentrations of ghrelin and adiponectin. All these phenomena can be prompted by insulin and leptin resistance and by becoming overweight. Carbamazepine can cause overeating, fat deposition, water retention, and oedema which also can result in overweight. Finally, some studies have found that patients with epilepsy participate less frequently in physical activities than the general population. This restriction has been explained, partly due to fears of either injury during seizures or the possibility of exercise-induced seizures ***(Ladino et al., 2014)***.

On the other hand, Obesity has serious effects on the brain. Metabolic dysfunction may exacerbate the outcomes of seizures and brain injuries. Insulin resistance, hepatic steatosis, and macrophage infiltration in adipose tissue contribute to neuro-inflammation and exacerbate neuronal death ***(Kong et al., 2015)***. While many metabolic changes may occur as a consequence of epilepsy or AEDs usage, a pediatric study detected obesity as a common comorbidity in children with newly-diagnosed untreated epilepsy, suggesting that obesity may prime the CNS for seizures ***(Daniels et al., 2009)***.

Subjects and methods

This cross-sectional study was conducted in the period from June 2018 to May 2021 on fifty patients with Juvenile Myoclonic Epilepsy (JME) fulfilling the International League Against Epilepsy (ILAE) criteria ***(Scheffer et al., 2017).*** Patients were selected from the Outpatient's Epilepsy Clinic of the Neurology Department of Mansoura University Hospitals. They were divided into 2 groups:

Group A: Including non-obese JME patients.

Group B: Including obese JME patients who have body mass index (BMI) greater than 95th percentile for age and gender according to the National Egyptian Growth Curves of Children and Adolescents.

The two groups were compared as regard their metabolic disturbances and their relation to genetic susceptibility.

Ten age and sex matched healthy subjects with no family history of epilepsy or any relation to the patients were used as a control group.

Inclusion criteria
Patients already diagnosed as having Juvenile myoclonic epilepsy and proved by sleep deprived EEG and free MRI brain with age less than 18 years old.

Exclusion criteria
Patients with liver diseases, patients taking medications other than antiepileptic drugs which have metabolic side effects, patients with abnormal MRI brain and patients aged 18 years old or older.

All patients were subjected to:
1- *Detailed medical and neurological history taking including:*
- Seizure history (duration of epilepsy, risk factors for seizures and frequency of seizures/month).
- Details of medications given for treatment of epilepsy.
- Past medical and surgical history.
- Family history of epilepsy, obesity and diabetes mellitus.
- Assessment of epilepsy outcome by detection of time to control in controlled patients and number of seizures per month in patients with active seizures and incidence of breakthrough seizures

2- Complete general and neurological examinations.
3- Anthropometric measurements:
Including height, height, BMI, waist circumference, hip circumference, waist-to-hip ratio and blood pressure
For all subjects, body weight and height were measured using a scale and a wall-mounted stadiometer to the nearest 0.5 kg and 0.5 cm respectively. BMI was computed as weight (in kilograms) divided by height (in meters) squared. Waist circumference (cm) was measured in the middle between the 12th rib and the iliac crest, and hip circumference (cm) was measured around the buttocks, at the level of the maximum extension. The waist-to-hip ratio was then calculated. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured on the right arm, after a 15min sphygmomanometer.
4- Laboratory investigations:
Including fasting blood sugar, fasting insulin level, homeostasis model assessment (HOMA), serum Adiponectin level, lipid profile and liver function tests. Venous blood samples were collected after an overnight fast, and plasma, and serum samples were either used immediately for analysis or stored frozen at −80°C.
Commercial enzymatic test kits were used for determining high density lipoprotein cholesterol (HDLC), triglyceride (TG) concentrations and total cholesterol (T cholesterol), low density lipoprotein cholesterol (LDLC) were calculated by the formula of Friedewald (LDLC = T cholesterol − HDLC − TG/5 mg/dL).
Insulin level was determined by enzyme linked immunosorbent assay. The degree of insulin sensitivity/resistance was calculated according to the homeostasis model assessment (HOMA) which is a good index for assessing insulin sensitivity/resistance. IR was calculated as follows: IR = FI × g/22.5; where FI = fasting insulin (μu/mL) and g = fasting glucose (mmol/L).

Adiponectin was assayed with enzyme linked immunosorbent assay method. The fasting glucose concentration wasmeasured by glucose oxidase peroxidase (GODPOD) method.

5- Magnetic resonance spectroscopy (MRS) for the liver:

Localization for 1H-MRS was achieved by acquiring three orthogonal planes (sagittal, transverse, and coronal). Automatic shimming of the system was applied for homogeneity of the magnetic field before recording the spectrum. When automatic shimming proved difficult due to significant susceptibility differences, manual shimming with a line width of 12-14 Hz was performed. A single voxel 1H-MRS was performed on liver. A 20 X 20 X 20-mm spectroscopic volume of interest (VOI) was used for 1H- MRS. The position of VOI was localised within the solid part of the liver at axial, sagittal and coronal plane. Water suppression was achieved through chemical shift selective suppression. Spectral suppression of lipid signals was performed using frequency selective pulses, with a width of 1.55 ppm. The acquisition parameters were as follows: TR/TE, 1500/135 ms; spectral bandwidth, 1250 Hz; and averages, 256.

Statistical analysis and data interpretation

Data were fed to the computer and analyzed using IBM SPSS Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non-parametric data and mean, standard deviation for parametric data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the (0.05) level.

Results

In the present study, the mean age in Group A was 13.86 years old, versus 14.33 years old in Group B patients. Among Group A, 55.2% were males and 71.4% of Group B were males. There was no statistically significant difference between obese and non-obese patients regarding their age and sex.

Regarding seizure history, there was statistically significant difference between Goup A and B regarding time since last seizure which was longer in Group B (obese patients).

Regarding the used AEDs, Lamotrigine use was significantly higher in group A (non-obese patients), and Valproate was the most used drug in both groups.

There was no statistically significant difference between the 2 groups regarding incidence of breakthrough seizures which was 43.8 % in Group A versus 14.3 % in Group B.

Regarding family history, there was no statistically significant difference between the 2 groups. There was positive family history of consanguinity in 41.4% of group A and 23.8% of group B.

There was statistically significant higher mean weight, body mass index, waist and hip circumference among obese than non-obese cases with higher mean systolic and diastolic blood pressure. There was statistically significant lower mean HDL among obese cases than non-obese ones (49.32 versus 41.49, respectively, p=0.02).

Median serum insulin and HOMA IR and were higher among obese cases than non-obese cases (8.75 mIU/L & 1.82) versus (7.01 mIU/L & 1.39), respectively.

Serum Adiponectin levels were found to be relatively low in both groups with no statistically significant difference between the two groups.

Table (1): MRS Liver parameters distribution among studied groups.

MRS liver	Non-obese N=29	Obese N=21	test of significance
Steatosis according to lipid peak			
0	15(51.7)	0(0.0)	MC
1	11(37.9)	4(19.0)	P<0.001*
2	3(10.3)	11(52.4)	
3	0(0.0)	6(28.6)	
FA (first observer)	0.317±0.081	0.422±0.094	t=4.22 p<0.001*
FA (second observer)	0.319±0.08	0.429±0.097	t=4.42 p<0.001*
ADC (first observer)	1.273±0.145	1.255±0.28	t=0.296 p=0.769
ADC (second observer)	1.272±0.16	1.275±0.296	t=0.044 p=0.965
FF% (first observer)	3.17±1.77	9.33±4.66	Z=6.52 P<0.001*
FF% (second observer)	3.069±1.71	9.95±5.05	Z=6.84 P<0.001*

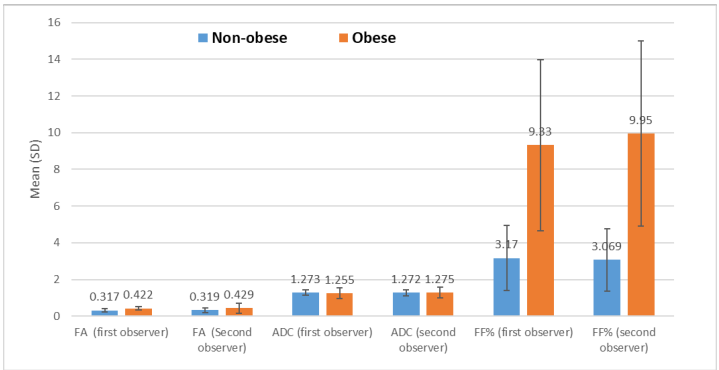

Figure (1): radiological findings of the studied groups

Table (1) and figure (1) show a statistically significant difference of Steatosis according to lipid peak between obese and non-obese groups with higher score detected among obese cases. Mean FA was significantly higher among obese cases than non-obese groups for first and second observers . Mean FF% have statistically significant higher mean among obese cases than non-obese cases (9.33 versus 3.17 for first observer and 9.95 versus 3.07 among second observer).

Table (2):

Validity of MRI parametrs in differentiating Obese from non- obese cases.

	AUC (95%CI)	P value	Cut off point	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Fa (first observer)	0.840 (0.680-0.939)	<0.001	≤0.395	82.8	71.4	80.0	75.0	78.0
Fa (second observer)	0.815 (0.690-0.940)	<0.001	≤0.415	89.7	66.7	78.7	82.4	80.0
FF% (first observer)	0.938 (0.874-1.0)	<0.001	≤4.5	86.2	90.5	92.6	82.6	88.0

FF% (second observer)	0.936 (0.872-1.0)	<0.001	≤5.5	89.7	76.2	83.9	84.2	84.0
ADC (first observer)	0.612 (0.422-0.803)	0.178	≥1.175	72.4	61.9	72.4	61.9	68.0
ADC (second observer)	0.596 (0.404-0.788)	0.250	≥1.145	75.9	57.1	71.0	63.2	68.0

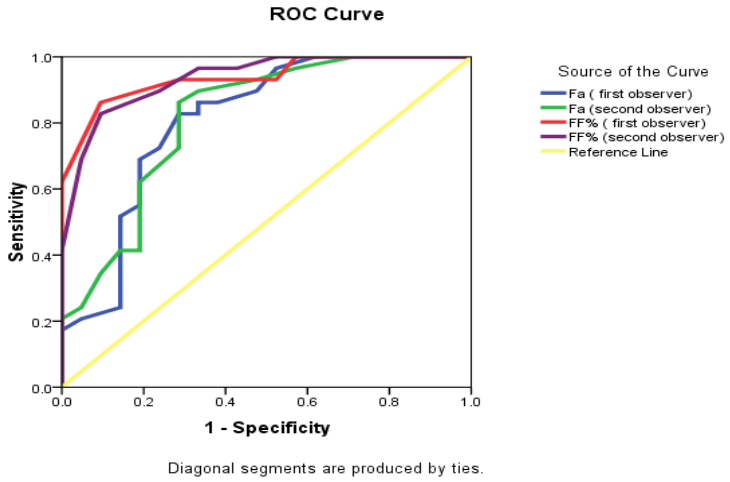

Figure (2): Receiver Operating characteristics curve for FA & FF in differentiating obese from non-obese cases.

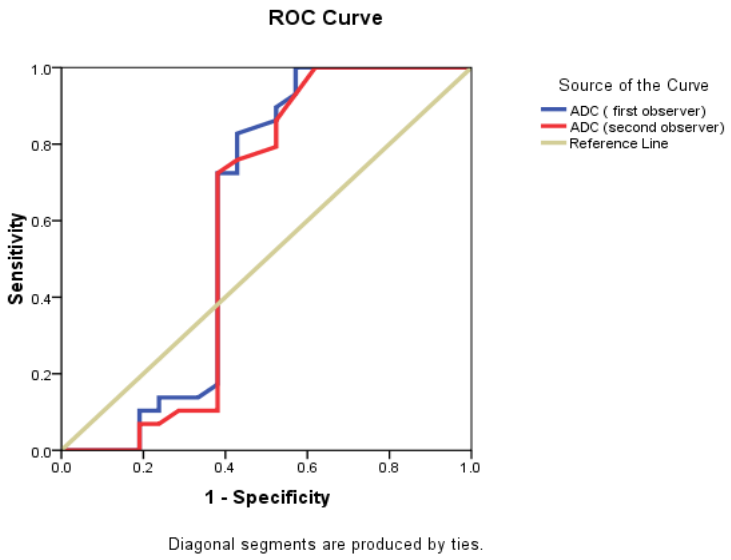

Figure (3): Receiver Operating characteristics curve for ADC in differentiating obese from non-obese cases.

Table (2) and figures (2,3) illustrate that area under curve for FA & FF was excellent for first and second observers in differentiating obese cases from non- obese cases. However ; area under curve for ADC was poor and non-statistically significant. The best detected cut off point for FA ≤0.395 & ≤0.415 for 1st and 2nd observers yielding accuracy of 78% & 80%, respectively. The best detected cut off point for FF ≤4.5& ≤5.5 for 1st and 2nd observers yielding accuracy of 88% & 84%, respectively.

Table (3): Correlation between steatosis degree and other variants

	steatosis according to lipid peak				
	0	1	2	3	test of significance
Insulin	9.18(4.18-39.13)	6.6 (4.14-13.69)	8.31(5.33-15.08)	9.18(4.75-47.18)	KW P=0.123
Homa IR	1.68 (0.8-10.53)	1.39(0.82-3.08)	1.72 (0.93-3.8)	1.86 (0.94-9.09)	KW P=0.338
Serum adiponectin	2.25 (1.38-20.32)	2.68(1.22-5.46)	2.84(1.11-8.71)	5.51(1.85-33.1)	KW P=0.274
Last seizure occur since/months median (min-max)	1(0.03-7)	5(0.25-30)	24(0.13-60)	12(0.25-48.0)	KW P=0.004*

CONTROL SINCE	6(3-60)	6(3-18)	12(1-36)	6.5(1.0-12.0)	KW P=0.695
Seizures control	7(46.7)	8(53.3)	11(78.6)	4(66.7)	χ^2=3.51 p=0.319
incidence breakthrough seizures	6(85.7)	1(12.5)	2(18.2)	0	MC P=0.003*
Weight /Kg	48.1±11.50	65.0±14.32	80.71±19.52	95.5±18.75	F=17.26 P<0.001*
BMI (Kg/m^2)	18.13±2.05	25.0±4.70	31.15±6.16	35.50±3.29	F=31.09 P<0.001*
Waist circumference	78.93±6.30	83.13±9.99	97.14±14.13	105.33±13.69	F=12.71 P<0.001*
Hip circumference	90±15.03	96.2±23.15	116.93±13.22	126.83±5.85	F=10.89 P<0.001*
Waist/hip ratio	0.90±0.17	0.920±0.27	0.828±0.04	0.829±0.083	F=0.838 P=0.480

	steatosis according to lipid peak				
	0	1	2	3	test of significance
Systolic blood pressure	110±10.69	115.33±6.39	121.43±8.64	123.33±5.16	F=5.95 P=0.002*
Diastolic blood pressure	70±10.69	76±7.37	82.85±9.14	83.33±5.16	F=6.30 P=0.001*
HDL mean±SD	51.73±7.61	45.89±15.91	44.26±10.53	36.28±5.23	F=2.85 P=0.048*
LDL	77.49±30.15	82.02±30.75	81.66±31.37	77.81±7.32	F=0.09 P=0.967
SGPT	18.74±6.58	19.04±6.39	16.03±3.07	39.0±22.31	F=9.75 P<0.001*
SGOT	23.36±5.88	21.79±4.95	23.53±3.81	29.17±10.68	F=2.27 P=0.09
AST/ALT	1.3±0.26	1.21±0.32	1.50±0.26	0.906±0.378	F=6.15 P=0.001*
Serum cholesterol	146±30.44	148.27±33.99	140.62±27.56	128.83±7.55	F=0.716 P=0.548
serum TGS	81.80±23.85	103.03±43.78	77.29±27.31	77±37.97	F=1.83 P=0.155
FA	0.289±0.084	0.314±0.067	0.441±0.07	0.468±0.024	F=17.98 P<0.001*
ADC	1.32±0.15	1.30±0.12	1.27±0.32	1.03±0.02	F=3.18 P=0.032*
FF%	2.33±1.05	3.67±1.17	7.86±3.32	14.67±2.34	F=58.09 P<0.001*

A statistically significant positive correlation is detected between steatosis degree and duration since last seizure, weight , body mass index, waist circumference , hip circumference , systolic and diastolic blood pressure , SGPT, FA and FF% . Inverse correlation is detected between degree of steatosis and the following ; incidence of breakthrough seizures , HDL , AST/ALT and ADC

Table (4): Prediction of obesity among studied cases

Regression analysis for TT vs all					
predictors	β	P-value	odds ratio	95.0% C.I. for OR Lower Upper	predictors
DBP	1.942	.999	6.969	.000	.
SBP	-1.845	.999	.158	.000	.
FBS	-.013	.790	.987	.900	1.084
Cholesterol	.134	.411	1.143	.831	1.572
S.TG	-.006	.872	.994	.926	1.068
HDL	-.025	.885	.976	.699	1.361
LDL	-.100	.541	.905	.658	1.246
SGPT	.050	.529	1.051	.900	1.229
SGOT	-.243	.051	.784	.615	1.001
Constant	57.561	.999	9.967E24		

Multivariate analysis was carried out to predict obesity among studied cases and detected that none of the studied variables is significant predictor of obesity among studied cases.

Discussion

In the present study there was statistically significant difference between Goup A and B regarding time since last seizure which was longer in Group B (obese patients). This may reflect that obese patients were on the same medications for a longer period of time than non-obese patients, as when the seizures are controlled, there is no need to change medications, and the longer the duration of treatment with a given medication, the more likely side effects will appear.

Lamotrigine use was significantly higher in group A (non-obese patients), and Valproate was the most used drug in both groups. In a study done in USA in 2001 to compare between Lamotrigine

and valproate associated weight gain, it was found that Valproate monotherapy was associated with significantly greater weight gain than lamotrigine monotherapy. Weight gain associated with valproate was significant within 10 weeks after initiating therapy and continued throughout the study, on the other hand, Lamotrigine tended to be more tolerated by the patients included in that study ***(Biton et al., 2001)***.

There was statistically significant higher mean weight, body mass index, waist and hip circumference among obese than non-obese cases with higher mean systolic and diastolic blood pressure. There was statistically significant lower mean HDL among obese cases than non-obese ones (49.32 versus 41.49, respectively, p=0.02). This refers to the known complications of obesity in children and the increased risks for developing hypertension among other diseases in obese children. It is clear that childhood obesity is associated with a wide spectrum of adverse outcomes, including many outcomes that are similar to those seen in adults. Obesity in childhood affects virtually every organ system in an adverse manner ***(Daniels, 2009)***.

Median serum insulin and HOMA IR and were higher among obese cases than non-obese cases (8.75 mIU/L & 1.82) versus (7.01 mIU/L & 1.39), respectively. Higher serum insulin and HOMA IR means higher risk for insulin resistance. Insulin resistance is a condition of gluco-metabolic sufferance that may result in the further development of type 2 diabetes and cardiovascular disease. The development of insulin resistance is mostly associated with the accumulation of excessive fat in the body. The epidemic impact of obesity in the youngest promoted an increase of the prevalence of insulin resistance also in children and adolescents. Increased fat accumulation in the peri-visceral area of the abdomen, occurring preferably at and after puberty, and in the liver, as non-alcoholic fatty liver disease, plays a role in the process ***(Maffeis and Morandi, 2018)***.

Serum Adiponectin levels were found to be relatively low in both groups with no statistically significant difference between the two groups. The expression of adiponectin decreases with increase in the adiposity. Adiponectin mediates insulin-sensitizing effect. Weight loss significantly elevates plasma adiponectin levels. Reduction of adiponectin has been associated with insulin resistance, dyslipidemia, and atherosclerosis in humans ***(Yadav et al., 2013)***. Hypoadiponectinemia is caused by interactions of genetic factors such as SNPs in the Adiponectin gene and environmental factors causing obesity ***(Kadowaki et al., 2006)***. Being relatively low in both obese and non-obese patients in our study, poses a question whether this may be related to the disease itself (JME).

There was a statistically significant difference of Steatosis according to lipid peak between obese and non-obese groups with higher score detected among obese cases. Mean FA was significantly higher among obese cases than non-obese groups for first and second observers. Mean FF% had statistically significant higher mean among obese cases than non-obese cases (9.33 versus 3.17 for first observer and 9.95 versus 3.07 among second observer). Non-alcoholic fatty liver disease is associated with obesity, diabetes, insulin resistance (IR), and hypertriglyceridemia. Although much remains to be learned about pediatric NAFLD, it is already evident that children with this disease risk progressive liver damage, including cirrhosis ***(Mathur et al., 2007)***.

A statistically significant positive correlation was detected between steatosis degree and duration since last seizure, weight, body mass index, waist circumference, hip circumference, systolic and diastolic blood pressure, SGPT, FA and FF% . Area under curve for FA & FF was excellent for first and second observers in differentiating obese cases from non-obese cases. However; area under curve for ADC was poor and non-statistically significant. The best detected cut off point for FA was ≤0.395 & ≤0.415 for 1^{st} and 2^{nd} observers yielding accuracy of 78% & 80%, respectively. The best detected cut off point for FF was ≤4.5 & ≤5.5 for 1^{st} and $2^{n\ d}$ observers yielding accuracy of 88% & 84%, respectively, which refers to the important role and high accuracy of MRS liver in diagnosing non-alcoholic fatty liver disease ***(Taouli et al., 2009)***. Inverse correlation was detected between degree of steatosis and the following: incidence of breakthrough seizures, HDL, AST/ALT and ADC.

In conclusion, Obesity and related metabolic disturbances in children with JME are a particularly concerning topic which emphasises the importance of early diagnosis of obesity and individualized tailored treatment plan for every patient with JME to avoid further complications which may lead to non-compliance to medications and worse disease outcome.

DISCLAIMER

The materials used for this research are commonly and predominantly use materials in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the materials because we do not intend to use these materials as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing companies rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

This clinical study was conducted on patients with primary JME selected from the Outpatient's Epilepsy Clinic of the Neurology Department of Mansoura University Hospitals. Written consents were taken from the patients' parents indicating their acceptance to participate in a research in order to find out the possible causes of metabolic disturbances in patients with JME and the relationship between these disturbances and epilepsy outcome. Approval was obtained from Faculty of Medicine , Mansoura university

AVAILABILITY OF DATA AND MATERIAL

The datasets generated and/or analyzed during the current study are not publicly available due to current Mansoura University regulations & Egyptian legislation but are available from the corresponding author on reasonable request and after institutional approval.

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