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Clinical Profile and Comorbidity of Epilepsy in El Minia, Egypt: A Hospital-Based Study

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ABSTRACT

Background: Classifying epileptic cases based on in-depth study and analyzing groups of different ages and gender can enhance the accuracy of diagnosing epileptic patients.

Objective: This research aimed to identify the different clinical profiles of epilepsy and its comorbid disorders.

Methods: A one-year hospital-based cross-sectional study conducted on hundreds of epileptic patients including a detailed history, clinical examination, electroencephalography (EEG), neuroimaging (MRI), and psychometric assessment.

Results: There were two groups including 56.0% males and 44 % females. 83.5% of patients were rural residents. Generalized onset seizures were 73.5%, focal-onset seizures reported 20.5% and 6.0% unknown type. Abnormal EEG occurred in 77.5% and 22.5% of patients showed abnormal neuroimaging findings. Structural causes of epilepsy were recorded in only 20.5%. Monotherapy was applied to 80.5% and 19.0% received polytherapy. The treatment gap was reported at 17% with a significant statistical difference between age groups. Attention-deficit hyperactivity disorder (ADHD) was recorded in 15.0%, migraine was reported in 12.0%, cerebral palsy (CP) was recorded in 7.5%, and intellectual disability was reported in 3.0%. A significant negative correlation between the IQ level and both duration of epilepsy and seizure frequency/month was reported. Furthermore, a significant positive correlation was reported between the duration of epilepsy and seizure frequency/month.

Conclusion: Epilepsy is characteristic in our patients and shows age and sex differences in terms of many features. Most of the patients were receiving monotherapy. There were patients with a positive treatment gap, ADHD, and intellectual disability (ID). Structural causes of epilepsy were recorded among more than a fifth of patients.

Keywords: Epilepsy, Treatment regimens, Etiology, Seizure semiology, Comorbidity.

INTRODUCTION

Epilepsy is one of the most common chronic brain diseases characterized by a persistent predisposition to generate seizures, unprovoked by any immediate insult to the central nervous system [(1)].

It is a global problem that affects the entire population and causes a significant burden on the patient and society [(2)]. Epilepsy affects up to 50-70 million people worldwide, without age, racial, social, national, or geographic boundaries, and accounts for 0.75% of the global burden of disease. Although previous studies were carried out on the prevalence and comorbidity of epilepsy, little data are available in our studied area. Scattered countries have been estimated as in Iran, the active prevalence was 0.95% [(3)].

A study in Algeria, Egypt, and Palestine demonstrated that the prevalence of epilepsy is higher than that previously reported by 3 times in the same region. In Egypt, in the Al Kharga and Al Quseir regions (desert areas of Upper Egypt), the lifespan spreading of epilepsy in teenagers and children less than eighteen years old was 0.97% [(4)]. Additionally, in Gharbia Governorate, the spreading of idiopathic epilepsy among young adults was 7.2/1000 [(5).]

Data regards the epidemiology of epilepsy varies from country to country. Furthermore, epilepsy impacts hundreds of million people, 80% of them live in developing countries [(6)]. Epidemiology is the most common research method for evaluating epilepsy and its relative disorders as it can provide a better understanding of the etiology, frequency, and natural history of the disorder. Moreover, it forms the basis of undertaking to hinder epileptogenesis as the main prophylaxis of epilepsy [(7)].

The etiology of epilepsy varies according to the sociodemographic characteristics of the affected population, the extent of diagnostic work-up, and the documented cause is still lacking in about 50% of cases [(1)]. Upper Egypt, most notably in the rural areas, suffers from a compound developmental gap in health and other sectors, which are less available, of poor quality, and an imbalance in the distribution of primary health care and other basic services. Like many other areas in Upper Egypt, the studied area is far away from our university, suffers from a scarcity of neurologists, poor health services, and is less equipped with modern centers of neurological diagnoses [(4)]. To our knowledge, there are multiple studies about the epidemiology of epilepsy in Egypt, but studies are few in our governorate clinical data. Therefore, our study was conducted to evaluate the clinical profile and comorbidities of epilepsy in our governorate.

Methodology: This study was a hospital-based cross-sectional analytical study that was conducted at EL-Edwa Central Hospital in EL Minia Governorate, South Egypt, in the outpatient clinic. The study was carried out on a sample size of 200 epileptic patients.

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Inclusion criteria

- Patients aged 6-30 years old of males and females.
- the epileptic patient is defined based on the International League Against Epilepsy (ILAE) in 2014 as "having > 2 seizures taking place within > 24 hours apart, one unprovoked seizure and a probability of recurrent seizure risk higher than 60%, and a probability of further seizures like the general recurrence risk after two unprovoked seizures, occurring over the next 10 years, and diagnosis of an epilepsy syndrome.
- Seizure types and the etiology of epilepsy were identified based on the definition of the ILAE.
- Patients with epilepsy were considered to have active epilepsy if they had their most recent seizure within the previous 5 years or who are currently being treated for epilepsy.

Exclusion criteria

- The patients who declined to participate in our research.
- Patients out of the age scope of this research.

Treatment gap means the number of patients with active epilepsy, not on treatment, or inadequately treated.TG is expressed as a percentage of the total number of people with active epilepsy**.** The study was carried out in sequential steps as follows:

Sociodemographic data, questionnaire for epilepsy, and epileptic sheet:

All participants were subjected to fulfill sociodemographic data and an epilepsy questionnaire. All epileptic patients were evaluated using an epileptic sheet. A detailed clinical history was taken from all patients themselves and/or their parents or those who attended the seizure and from a close witness.

Neurophysiologic assessment Electroencephalogram: Standard EEG was done for all patients to diagnose epilepsy and its type. We used 21-channel monopolar and banana bipolar montage. Analyzing EEG activities included: Background activity, morphology and distribution of epileptiform discharge**.**

Psychometric assessment of:

Intelligence quotient (IQ):

We used a standardized and validated Arabic version of the Stanford–Binet test (version V) to perform the intelligence quotient (IQ) for all epileptic patients.

Detection of comorbid disorders (Psychiatric and Cognitive disorders): Like ADHD and ID. ADHD patients were diagnosed according to DSM-5 criteria and the Arabic version of the ADHD-rating scale (Translation into Arabic). Patients with ID were diagnosed according to DSM-5 criteria. This assessment scale was performed for patients under 18 years old. IQ, ADHD, and ID tests were administered through referral of cases to health insurance hospitals.

Assessment of other comorbid disorders (Medical and neurodevelopment)

As cerebral palsy (CP) and migraine were diagnosed according to ICHD-3, while patients with CP were diagnosed according to the history of (prenatal, natal, and postnatal), clinical examination, and MRI findings.

Radiological assessment (magnetic resonance imaging):

Brain imaging of epilepsy patients was performed using a high-resolution MRI at 1.5 T. Standardized MRI protocol consisted of (a) T1-weighted axial images, (b) T2- weighted coronal images, and (c) T2/Flair coronal images.

Ethical Approval:

The study was approved by the Ethics Board of the Faculty of Medicine for girls, Al-Azhar University, and informed written consent was taken from every participant in the study. This work has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Design

The collected data were manually coded, processed, and analyzed using the Statistical Package for Social Science software Version 17 (SPSS, Inc., Chicago, IL. Qualitative data were represented by percentages and frequencies. Quantitative data were represented based on the mean and standard deviation (SD). Comparison between groups was done using Chi-square (x^2) test for qualitative (nominal) data variables and an Independent t-test for quantitative (numerical) data variables. Pearson correlation test was used to assess the association between variables. The level of significance was considered at a p-value ≤ 0.05. The confidence level was 95%, and the confidence interval was 5%.

RESULTS

In the current study, 200 individuals aged 6-30 years were recruited, males represented 56.0% and 44% females, with no significant difference between groups. The majority of cases (83.5%) lived in rural areas. Both groups reported nearly the same frequency of seizures/month, while the duration of epilepsy showed a significant difference ($p < 0.05$) between the group of children <18 years and the group of adults ≥ 18 years. Moreover, most cases reported a negative history of febrile convulsions, a family history of epilepsy, and a kinship history with no significant difference between age groups ($p > 0.05$) (Table 1).

Table (1): Demographic and clinical characteristics of the studied cases by age group

Items	Total	Age group		Sign .test and p-value
		< 18 years No. = 102	≥ 18 years No. = 98	
	No. (%)	No. (%)	No. (%)	
Sex				
Male	112 (56.0)	62 (60.8)	50 (51.0)	X^2 =1.9 p-value = 0.16
Female	88 (44.0)	40 (39.2)	48 (49.0)	
Residence				
Rural	167 (83.5)	90 (88.2)	77 (78.6)	X^2=3.3 p-value = 0.066
Urban	33 (16.5)	12 (11.8)	21 (21.4)	
IQ level (Mean ± SD)	81.6 ± 16.6	79.9 ± 19.1	83.3 ± 13.4	t-test= 1.4 p-value = 0.15
Seizure frequency/Month	3.39 ± 2.8	3.3 ± 3.2	3.5 ± 2.3	t-test= 0.55 p-value = 0.58
Duration of Epilepsy /years				
< 5 years	169 (84.5)	85 (83.3)	84 (85.7)	X^2=10.8 p-value = 0.013*
5- <10	14(7.0)	8 (7.8)	6 (6.1)	
10-<15	7 (3.5)	7 (6.9)	0 (0.0)	
≥ 15	10 (5.00	2 (2.0)	8 (8.2)	
History of febrile convulsions				
Negative	181 (90.5)	92 (90.2)	89 (90.8)	X^2 = 0.22 p-value = 0.88
Positive	19 (9.5)	10 (9.8)	9 (9.2)	
Family history of epilepsy				
Negative	186 (93.0)	95 (93.1)	91 (92.9)	X^2 = 0.006 p-value = 0.93
Positive	14 (7.0)	7 (6.9)	7(7.10	
History of Consanguinity				
Negative	174 (87.0)	87 (85.3)	87 (88.8)	X^2 = 0.53 p-value = 0.46
Positive	26 (13.0)	15 (14.7)	11 (11.2)	

*Significant p-value X^2 =Chi-Square test

The majority of cases (76.5%) showed unknown etiologies versus one-fifth (20%) having a structural etiology with no significant difference between age groups. The most common clinical type of seizure was the generalized tonic-clonic seizure (58.0%) among the whole group, with a slightly higher percentage among children than adults (63.7% vs 53.1%, respectively). Whereas, the focal tonic-clonic was higher among children than adults (13.7% vs 5.1%, respectively).

On the other hand, the focal tonic-clonic with impaired awareness and atonic seizures was higher among adults than children (12.2% vs 2.9% and 14.3% vs 2.9% respectively). This variation in values showed a significant difference between the age groups.

Regarding associated comorbidities, ADHD patients showed the highest percentage followed by migraine in the whole sample (15% and 12%, respectively), ADHD was higher among the children group < 18 years, migraine was higher among the adult group, CP was reported among both groups and ID was reported among children < 18 years group only. This variation showed a significant difference between the age groups ($p < 0.05$) Table **2**.

Table (2): Etiology of epilepsy, clinical types of epileptic seizures, and associated comorbidities among the studied epileptic patients by age group

Items	Total No. = 200	Age group		Sign .test and p-value
		< 18 years No. = 102	≥ 18 years No. = 98	
	No (%)	No. (%)	No. (%)	
Etiology				
Unknown	153 (76.5)	78 (76.5)	75 (76.5)	Chi-Square (X^2) = 6.5 p-value =0.15
Structural	41 (20.5)	23 (22.5)	18 (18.4)	
Others (metabolic, infectious and substance abuse)	6 (3.0)	1 (1.0)	5 (5.1)	
Clinical Types of seizures				
Generalized seizures	147(73.5)	77(75.5)	70(71.5)	Chi-Square (X^2) = 26.3 p-value =0.000*
GTCs	117 (58.5)	65 (63.7)	52 (53.1)	
Atonic seizures	17 (8.5)	3 (2.9)	14 (14.3)	
Absence seizure	7 (3.5)	7 (6.9)	0 (0.0)	
Myoclonic seizure	6 (3.0)	2 (2.0%)	4 (4.1)	
Focal seizure	41(20.5)	20(19.5)	21(21.4)	
Focal tonic clonic	19 (9.5)	14 (13.7)	5 (5.1)	
Focal tonic clonic with impaired awareness	15 (7.5)	3 (2.9)	12 (12.2)	
Focal with bilateral tonic clonic	7 (3.5)	3 (2.9)	4 (4.1)	
Unknown	12 (6.0)	5 (4.9)	7 (7.1)	
Associated comorbidities				
No comorbidity	125 (62.5)	51 (50.0)	74 (75.5)	Chi-Square (X^2) = 46.77 p-value <0.001*
Migraine	24 (12.0)	6 (5.9)	18 (18.4)	
ADHD	30 (15.0)	30 (29.4)	0 (0.0)	
Cerebral palsy (CP)	15 (7.5)	9 (8.8)	6 (6.1)	
Intellectual disability	6 (3.0)	6 (5.9)	0 (0.0)	

ADHD: Attention-deficit hyperactivity disorder, **GTCs:** Generalized tonic-clonic seizures *Significant p-value

All patients were subjected to neurophysiologic, psychometric (IQ level), and radiological assessments. Abnormal EEG findings were found in 77.5% of patients 50.5% of patients with generalized sharp and slow waves, and 26.0% with focal EEG changes. Meanwhile, there was a statistically significant difference between patient groups. The generalized sharp and slow waves are more frequent in patients < 18 years. Conversely, normal EEG is more frequent in patients ≥18 years.

Pathological MRI data were reported in 22.5%, of which brain atrophy and encephalomalacia were 11.0%, cystic lesion, arachnoid or congenital cyst were 3.0%, inflammatory/infectious process was 2.0%, space-occupying lesion and hemorrhagic infarction were 1.5%, tuberous sclerosis, ischemic infarction, and mesial temporal sclerosis were 1.0%, and metabolic changes were 0.5%, with no significant difference between age groups.

Concerning IQ grades, it was found that 36.5% of patients with low average IQ, 28.0% with average level, 15.0% borderline impaired or delayed, and 7.5% mildly delayed and moderately delayed, with significant differences between children and adults in which increase the age of epileptic patients was associated with IQ grad decrease (Table **3**).

Table (3): Electrical diagnosis, findings of magnetic resonance image (MRI), and grades of IQ among the studied epileptic patients by age group

Items	Total No. = 200	Age group		Sign .test and p-value
		<18 years No. = 102	≥ 18 years No. = 98	
	No. (%)	No. (%)	No. (%)	
Conventional EEG changes				
Normal EEG	45 (22.5)	15 (14.7)	30 (30.6)	Chi-Square (X^2) = 9.36 p-value =0.025*
Generalized sharp and slow wave	101 (50.5)	61 (59.8)	40 (40.8)	
Focal EEG changes	52 (26.0)	25 (24.5)	27 (27.6)	
Generalized sharp and polyspikes wave	2 (1.0)	1 (1.0)	1 (1.0)	
MRI findings				
Normal	155 (77.5)	78 (76.5)	77 (78.6)	Chi-Square (X^2) = 14.5 p-value =0.1
Brain atrophy and encephalomalacia	22 (11.0)	14 (13.7)	8 (8.2)	
Cystic lesion, arachnoid, or congenital cyst	6 (3.0)	2 (2.0%)	4 (4.1)	
Inflammatory infectious process[(a)]	4 (2.0)	0 (0.0)	4 (4.1)	
SOL	3 (1.5)	0 (0.0)	3 (3.1)	
Hemorrhagic infarction	3 (1.5)	2 (2.0)	1 (1.0)	
Tuberous sclerosis	2 (1.0)	2 (2.0)	0 (0.0)	
Ischemic infarction	2 (1.0)	2 (2.0)	0 (0.0)	
Mesial temporal sclerosis (MTS)	2 (1.0)	1 (1.0)	1 (1.0)	
Metabolic changes	1 (0.5)	1(1.0)	0 (0.0)	
IQ Grade				
Superior (IQ 120-129)	4(2.0)	3 (2.9)	1 (1.0)	Chi-Square (X^2) = 19.626[a] p-value =0.003*
High average (IQ 110-119)	7 (3.5)	2(2.0)	5 (5.1)	
Average (IQ 90-109)	56 (28.0)	34 (33.3)	22 (22.4)	
Low average (IQ 80-89)	73 (36.5)	26 (25.5)	47 (48.0)	
Borderline impaired or delayed (IQ 70-79)	30 (15.0)	14 (13.7)	16 (16.3)	
Mildly delayed (IQ 55-69)	15 (7.5)	11 (10.8)	4 (4.1)	
Moderately delayed (IQ 40-54)	15 (7.5)	12 (11.8)	3 (3.1)	

[(a)] May be meningoencephalitis *Significant p-value < 0.05

Regarding the drug therapy and treatment gap, most cases (80.5%) were on monotherapy treatment (43.0% were on valproate, and 28.0% were on levetiracetam), while 19.5% were on polytherapy regimen (10.5% were on one traditional + new AEDS), with no significant difference between patients by age groups. As regards the treatment gap, there were 17.0% of cases with a positive treatment gap, with a statistically significant difference between patient groups, the treatment gap was more frequent in patients ≥ 18 years (Table 4).

Table (4): Drug regimens and treatment gap among the studied epileptic patients by age group

Items	Total No.= 200	Age group	
		<18 years No.= 102	≥ 18 years No.= 98
	No. (%)	No. (%)	No. (%)
Drug therapy			
Mono therapy	**161(80.5)**	**79 (77.5)**	**82 (83.7)**
Valproate	86 (43.0)	43 (42.2)	43 (43.9)
Levetiracetam	56 (28.0)	28 (27.5)	28 (28.6)
Carbamazepine	10 (5.0)	5 (4.9)	5 (5.1)
Oxcarbamazepine	9 (4.5)	3 (2.9)	6 (6.1)
Poly therapy	**39 (19.5)**	**23 (22.5)**	**16 (16.3)**
Two traditional AEDS **As (**Valproate and Carbamazepine**)**	2 (1.0)	2 (2)	0 (0.0)
One traditional + new AEDS **As (**valproate and levetiracetam) **or(**valproate and Lamotrigine**)**	21 (10.5)	12 (11.7)	9 (9.2)
One traditional + Two new AED **As** (valproate, Lamotrigine and levetiracetam)	9 (4.5)	6 (5.9)	3 (3.0)
Poly new AEDS **As** (levetiracetam and Zonisamide)	7 (3.5)	3 (2.9)	4 (4.1)
Treatment gap			
Negative	166 (83.0)	91 (89.2)	75 (76.5)
Positive	34 (17.0)	11 (10.8)	**23 (23.5)**
Sign .test and p-value	Chi-Square (X^2) = 5.7 p-value =0.017*		

*significant p-value

Many studied items differed among sexes, seizure semiology showed that GTCs and focal tonic-clonic seizures were more frequent in male than female patients. Furthermore, atonic and myoclonic seizures were significantly more in female than in male patients. In terms of comorbidity, migraine was more frequent in female than in male patients. In contrast, ADHD and ID were more frequent in male than in female patients. Moreover, CP was more frequent in male than in female patients. At the same time, the treatment gap came up with no significant changes between females and males (Table 5).

Table (5): Comparison between male and female epileptic patients as regards clinical types of epileptic seizures, associated comorbidities, and treatment gap among the studied epileptic patients

Items	Total No.= 200	Sex		Chi-square and p-value
		Male No. = 112	Female No. = 88	
	No. (%)	No. (%)	No. (%)	
Clinical types of seizures				
Generalized seizures	147(73.5)	84(75.1)	63(71.6)	Chi-Square (X^2) = 20.24 p-value = 0.005*
GTCs	117 (58.5)	75 (67.0)	42 (47.7)	
Atonic seizure	17 (8.5)	4 (3.6)	13 (14.8)	
Absence seizure	7 (3.5)	4 (3.6)	3 (3.4)	
Myoclonic seizure	6 (3.0)	1 (0.9)	5 (5.7)	
Focal seizure	41(20.5)	23(20.6)	18(20.5)	
Focal tonic-clonic	19 (9.5)	14 (12.5)	5 (5.7)	
Focal tonic-clonic with impaired awareness	15 (7.5)	7 (6.3)	8 (9.1)	
Focal with bilateral tonic-clonic	7 (3.5)	2 (1.8)	5 (5.7)	
Unknown	12 (6.0)	5 (4.5)	7 (8.0)	
Associated comorbidities				
No Comorbidity	125 (62.5)	64 (57.2)	61 (69.3)	Chi-Square (X^2) = 17.917[a] p-value =0.001*
Migraine	24 (12.0)	8 (7.1)	16 (18.2)	
ADHD	30 (15.0)	23 (20.5)	7 (8.0)	
Cerebral palsy (CP)	15 (7.5)	11 (9.8%)	4 (4.5)	
Intellectual disability	6 (3.0)	6 (5.4)	0 (0.0)	
Treatment gap				
Negative	166 (83.0)	95 (84.8)	71 (80.7)	Chi-Square (X^2) = 0.59 p-value = 0.439
Positive	34 (17.0)	17 (15.2)	17 (19.3)	

Regarding the distribution of antiepileptic drugs among patients with a positive treatment gap, ADHD, and ID. This study revealed that 70.6% of patients with a positive treatment gap were on valproate only, and 8.9% on valproate and lamotrigine. In epileptic patients with ADHD, 60.0% of them used valproate. While 50.0% of patients with ID were on valproate (Table **6**).

Table (6): Distribution of antiepileptic drugs among patients with positive treatment gap, ADHD, and ID

Drug therapy	Items	
	No.	%
	Patients with a Positive treatment gap	
	34	100.0%
Mono therapy	31	91.1
Valproate	24	70.6
Levetiracetam	7	20.5
Poly therapy (Valproate and lamotrigine)	3	8,9
	Patients with ADHD	
	30	100.0%
Mono therapy	22	73.3
Valproate	18	60.0
Levetiracetam	2	6.6
Carbamazepine	2	6.6
Poly therapy	8	26.7
One traditional + new AEDS **(**valproate and levetiracetam)	6	20.1
Two traditional AEDS **(**Valproate & Carbamazepine**)**	1	3.3
One traditional + new AEDS **(**Carbamazepine and levetiracetam**)**	1	3.3
	Patients with intellectual disability	
Monotherapy	6	100.0
Valproate	3	50.0
Levetiracetam	2	33.4
Carbamazepine	1	16.6

In this study, a significant negative correlation between the IQ level and both duration of epilepsy and seizure frequency/month was observed. As well as increases in both duration of epilepsy and seizure frequency/month. IQ level decreases were noted (Table **7**) and (Figures **1, 2**).

Table (7): Pearson correlation between the variables among the studied group

	Correlation coefficient (r)	**p-value**
Duration of epilepsy * IQ level	-0.503**	0.001**
Seizure frequency/Month * IQ level	-0.383**	0.001**

**Correlation is significant at the 0.01 level (2-tailed).

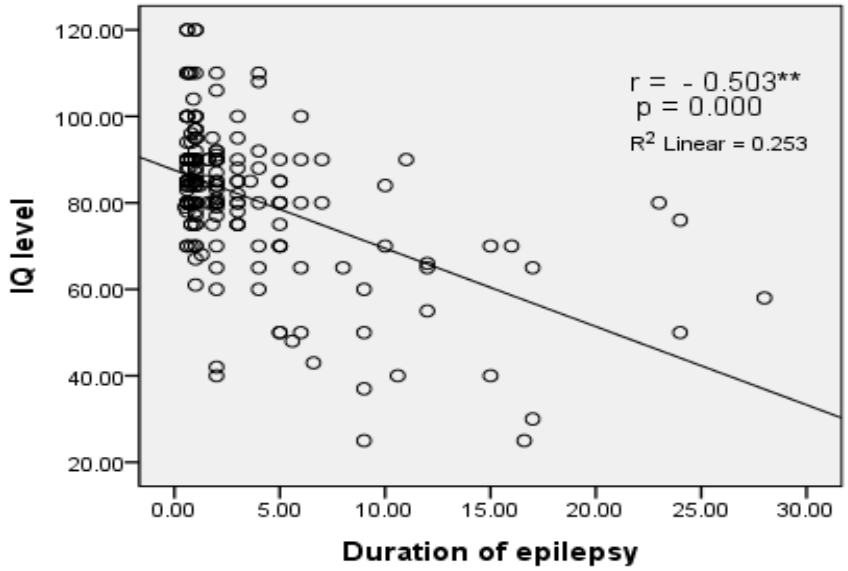

Figure (1): A scatter plot of a correlation test between the duration of epilepsy and IQ level

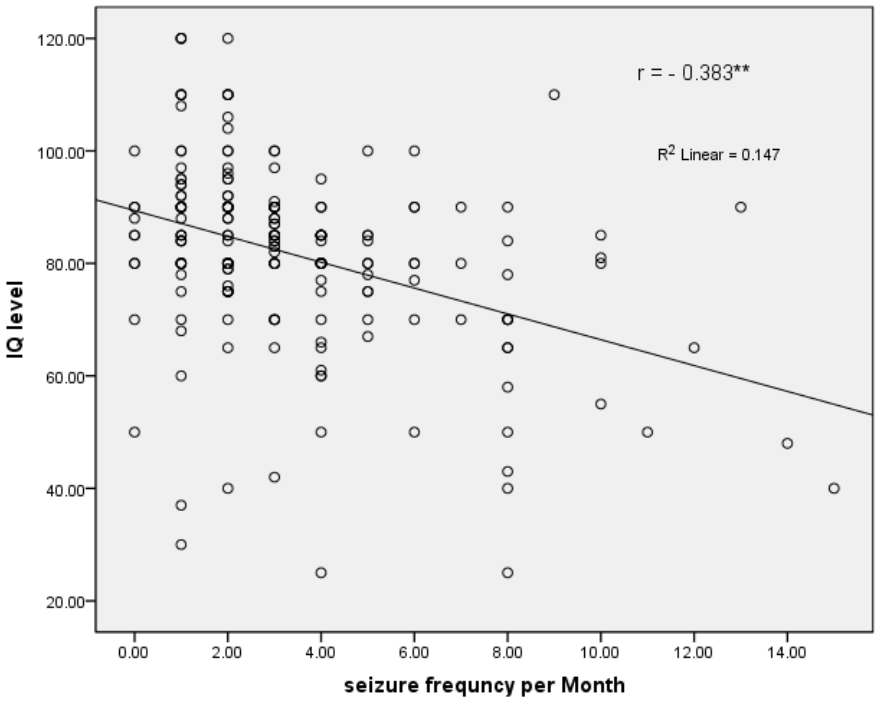

Figure (2): A scatter plot of a correlation test between the frequency of seizures and IQ level

DISCUSSION

Epilepsy is a widespread, socially significant disease that has been researched in medical literature and practice in recent decades**.** Although epilepsy affects both sexes, it is more common in males, as reported in many studies [6]. Meanwhile, this study revealed that 56.0% were males and 44.0% were females, with a non-significant difference detected. Moreover, a study in North-Western India revealed male-predominant epilepsy, with a female versus male ratio of 1:2.1. The low proportion of females among the studied sample might be ascribed to underdiagnosis due to cultural and social issues that gain the social isolation and diminish social support, preventing females from accessing healthcare facilities. Moreover, several reports have recommended reducing the rate of marriages among people with epilepsy. The social sign that companioned with the disease can significantly impede marital prospects immensely, especially among young women [8].

In this study, it was found that epileptic patients are higher in rural (83.5%) than in urban (16.5%) areas, which is similar to another study that was conducted in Assiut Governorate, Egypt [9]. The authors found that 78.0% of youngsters and children with epilepsy are countryside residents. Furthermore, a study in North-Western India showed a higher prevalence in the rural areas of 1.8 patients per 1,000 population than in urban areas of 0.4 patients per 1,000 population. These findings may indicate the relative influence of low socioeconomic status and lower approachability to specialized care in rural areas **[8].**

A history of febrile convulsions was represented among the studied epileptic patients (9.5%), which was less than that in a study conducted among school children in the Aseer Region, Saudi Arabia, where the history of positive febrile convulsion was 16.4% [10]. Additionally, another study done amongst school children in Erzincan, Turkey, reported that the positive febrile convulsion was 35.2% [6].

The presence of a family history of epilepsy was noted in 7.0% of epileptic patients, and the presented result was less than the study conducted in Aseer Region (28.2%) [10]. However, our results were more than the study conducted in Turkey [6], which reported that 3.3% had a family history of epilepsy in Erzincan. Our observations are roughly consistent with the finding in North-Western India, in which a family had a history of epilepsy in 18 patients. The familial aggregation of the disease may be explained by shared genes and exposure to similar environmental factors. Moreover, prospective studies could test for the cases of genetic epilepsies that have a history of epilepsy **[8].** On the other hand, the percentage of inbreeding among parents of epileptic patients in this study was 13.0%, which is more than that in a study conducted in Arar city, Northern Saudi Arabia [11]. The prevalence of consanguinity between parents was reported in 5.5% of the studied group of school children who had epilepsy. This result is attributed to the prevalent habit of inbreeding in the study area, especially in rural areas.

Regarding the etiology of epilepsy, 76.5% of the studied patients had unknown etiology. While structural causes of epilepsy were recorded among 20.5%. These results are almost similar to previous studies [12]. In that study, 76% of cases were idiopathic epilepsy. The current results regarding the structural cause of epilepsy are lower than those of a study presented in Punjab, Northwest India, in which epilepsies due to the structural causes were diagnosed in 41.3% [28]. The higher rate of diagnosed idiopathic epilepsy occurs more often in developing countries than in developed countries. This may be explained by the greater likelihood of sophisticated diagnostic tools, such as genetic testing and metabolic screening, to clarify possible etiologies, rather than any real geographic difference, with no significant difference between age groups.

The classification of seizures type is based on the operational classification of seizure types by the International League Against Epilepsy (ILAE). Accordingly, the generalized type was 73.5%, followed by the focal type at 20.5%, and 6.0% for the unknown type. Another study reported that 71.1% of the studied cases had generalized epilepsies **[12]**. Furthermore, in another study, it is reported that 78.8% of participants with generalized seizures and 21.7% with focal seizures. The high rate of generalized epilepsy could have a genetic explanation. Conversely, most prevalence studies from developed countries reported that focal epilepsy is more common in children than generalized epilepsy **[13]**. In Erzincan, Turkey, the focal-onset seizure type was detected in 54.8% of patients [6]. As for the semiology of seizures, the most common type of seizures among studied patients were generalized tonic-clonic seizures (58.5%), followed by simple focal seizures (9.5%). These results are consistent with a study in which generalized tonic-clonic seizures were detected in 51.8% of cases **[12]**. Moreover, in desert areas of Upper Egypt, GTC seizures were the most type presented among children (33%) [4].

In this study, there were significant differences between children and adults in seizure semiology; meanwhile, focal tonic-clonic was higher among children than adults (13.7% vs 5.1%, respectively). Additionally, it is reported that 78.4% of children up to 20 years had simple partial seizures **[8]**. However, in another study, it is concluded that focal seizures are the predominant type in children and adults [1]. The absence of seizures was reported in children, not adults (6.9% vs 0.0%, respectively). In addition, the absence of seizures was reported in 100.0% of < 10 years patients, as reported in [8]. On the other hand, focal tonic-clonic with impaired awareness and atonic seizures was higher among adults than in children (12.2% vs 2.9% and 14.3% vs 2.9% respectively). This disparity showed a significant difference between the age groups. Furthermore, one study found complex partial seizures in 10–20 years and 20–30 years groups, representing 66.66%), and myoclonic seizures were 50.0% in the 20–30 years

patients group [8]. These results are attributed to the different distribution of the underlying causes. Therefore, it is recommended to perform further research to investigate this issue, see.

In comparison between sexes in terms of seizures semiology, there were GTCs more frequent in males than females (67.0% vs 47.7%, respectively). Additionally, focal tonic-clonic seizures were (12.5% vs 5.7%, respectively). Conversely, atonic seizures were more common in females than in males (14.8% vs 3.6%, respectively), and myoclonic seizures were (5.7% vs 0.9%, respectively). Our results are similar to one study in which myoclonic epilepsy and idiopathic generalized epilepsy are more common in females [13]. On the other hand, the absence of epilepsy was more common in males. However, the numbers of subjects were limited. Therefore, it is suggested to interpret the obtained results with caution and further study.

Patients with ADHD were reported in 15.0%, which was higher among the children group <18 years. However, **Ghowinam1 and Seddeek** [14] reported ADHD disorders in 26.3% of children with epilepsy. In another study, ADHD was reported in 2.5% [28]. These findings are consistent with several possible explanations that can be made for the association between ADHD symptoms and epilepsy. These might be neurological abnormalities, seizure variables, medication effects, or psychosocial responses to epilepsy. Nevertheless, other clinical studies suggest the prevalence of ADHD among children with epilepsy ranges from 20% to 50% [15]. This difference might be due to sample variability.

In the present study, male patients with ADHD were more than females (20.5% vs 8.0%, respectively). Similarly, a study reported that the number of males with ADHD was approximately three times the number of females (2.3:1) [14]. Moreover, another study found that clinically diagnosed ADHD was more common in males as it reached 4.65%, while it was 1.88% in females [16]. This corresponds to a prevalence ratio of ~2.5:1. Nevertheless, gender ratios appear to be sample type-dependent, with higher male to female ratios in clinical versus population-based samples. The findings regarding gender differences in ADHD are variable and sometimes contradictory, partly due to differences in sample characteristics, a sex ratio ranging from 2:1 to 10:1 [16].

Migraine was reported as a common comorbid disorder that has been reported in 12.0% of epileptic patients. The current results are higher than a study in Punjab, Northwest India, which reported 5.8% of epileptic patients with migraines. In another study in Erzincan, Turkey, migraine was reported in 1.8% of patients [6].

This finding can be explained by the coincidence of migraine and seizures, headache as a symptom of epileptic activity, and the side effects of antiepileptic drugs. Moreover, an epileptic individual may have low self-confidence caused by a seizure-related sudden loss of self-control and feelings of insecurity, giving rise to more frequent headaches; this explains why migraine was high among the adult group. In addition, the prevalence of migraine became progressively higher with age between 25 and 30 years in a ratio of 1:2.6 [17].

In this study, there were sex differences concerning migraine, in which females were more frequent than males (66.6% vs 33.3%, respectively). Our results are consistent with normal male-female migraine distribution, in which the female-to-male ratio was 2.4:1 through the predicted prevalence of migraine in Assiut Governorate [17]. In contrast, another study reported a lower prevalence in girls than boys where the male-to-female ratio for migraine among adults varied from 1:2 to 1:3 [18].

In this study, another associated neuro-developmental disorder with epilepsy was CP, which was reported in 7.5% of patients. Additionally, CP in Qena Governorate in Upper Egypt was an etiology of symptomatic epilepsy in 12.5% of patients [12]. Earlier studies established that epilepsy may occur in up to 55.0% of CP cases [19].

However, by reviewing studies conducted in the last decade, it is estimated that between 17.0% and 35.0% of cases with CP suffer from an epileptic seizure disorder, with more evidence pointing to a rate of around 35.0%. This variability may be due to the lack of agreement in the definition of epilepsy between studies. The high rate of brain damage associated with CP as the main cause of epilepsy symptoms in children is attributed in part to consanguineous marriages, which are widespread in Arab societies [20].

Almost all studies on CP include both sexes, but specific data on possible gender differences have been reported only in a few of them. The review of the published studies suggests that CP occurs more frequently in male than in female participants. The higher incidence of CP in males is probably related to a greater biological vulnerability in terms of cerebral structure, hormone protective role, and genetic polymorphism [21]. This difference between children and adults is because some epileptic children have learning difficulties due to night-time seizures that can cause daytime drowsiness, which can affect learning and lead to poor scholastic performance, in addition to a coexisting condition, such as ADHD or autism spectrum disorder (ASD).

Patients with intellectual disabilities were more frequent in males than in females (5.9% vs 0.0%, respectively). Our results showed male predominance in this disorder, and these results are consistent with other studies [22].

EEG helps diagnose epilepsy, identify epileptic syndromes, and identify the localization of epileptic focus. However, detecting epileptiform activity on EEG does not always diagnose epilepsy because epileptiform discharges in EEG may occur in healthy individuals [6]. Abnormal EEG records were reported in 77.5% of epileptic patients. In a study in Erzincan, Turkey, amongst school children, pathological findings in EEG were detected in 48.2% [6]. Our study is nearly similar to other studies [23] where abnormal EEGs were recorded in

81.1% of epileptic patients. Generalized EEG changes showed a significant difference between children compared to adults (59.8% vs 40.8%, respectively). This could be explained by the generalized seizure type being more frequent in children and mainly associated with generalized EEG changes. On the other hand, normal EEG is more frequent in adults (≥18 years group), which may be attributed to normality in EEG due to good control of seizures with treatment, see (Table 3).

Regarding MRI finding, normal MRI was seen in 77.5%, and the abnormal finding was seen in 22.5% of patients (brain atrophy and encephalomalacia (11%), inflammatory infectious process (2%), benign cysts (3%), brain tumors (1.5%), hemorrhagic infarction (1.5%), tuberous sclerosis (1%), ischemic infarction (1%), mesial temporal sclerosis (1%), and metabolic changes (0.5%). Our results are consistent with a study [24], which reported about 23% of patients with MRI abnormalities. Lower numbers of cortical dysplasias and hippocampal sclerosis found in the study could be due to the restricted access to 3-Tesla Magnetic Resonance Imaging (MRI) and comprehensive epilepsy protocol imaging for the low funding and budget reasons, with no significant statistical difference between the age groups. The ILAE has suggested conducting diagnostic imaging for children when localization-related new-onset epilepsy is unknown and when epileptic syndrome with unlikely symptomatic etiology is present [25].

In our study, 36.5% of epileptic patients were with low average IQ, 28.0% average, 15.0% borderline delayed, and 15.0% mildly to moderately delayed according to DSM5 criteria. This means that the main bulk of patients had cognitive impairment, and these results are consistent with one study which reported that 28% of patients with epilepsy were mentally subnormal [9]. This study showed a significant difference between children and adults concerning low average IQ (25.5% vs 48.0%, respectively), as well as increasing the age of epileptics reduces patients' IQ. This could be explained that the cognitive status is affected by several clinical factors belonging to epilepsy, which include the duration of epilepsy, seizure type and severity, etiology, antiepileptic drugs, and other factors, considering epilepsy is a brain function disorder, not just a disorder that produces seizures [26].

In the current study, 80.5% of patients were receiving monotherapy antiepileptic drugs in the form of valproate (43.0%), levetiracetam (28.0%), carbamazepine (5.0%), and oxcarbazepine (4.5%). While (19.0%) on polytherapy regimen in the form of 10.0% as one traditional + new AEDS as valproate and levetiracetam or lamotrigine, 4.5% as one traditional + two new AED as valproate, lamotrigine and levetiracetam, 3.5% as poly new AEDS as levetiracetam and zonisamide, and 1.0% as two traditional AEDS as Valproate and carbamazepine. Our results differ from that of **Talaat *et al.*** [27]. in El-Manyal Island, Egypt, in which 62.8% of epileptic patients were prescribed carbamazepine (CBZ). A study in Erzincan, Turkey, amongst school children found that 58.9% of patients received one drug, 27.9% received two, 8.8% had three, 2.9% had four, and 0.7% received five antiepileptic drugs [6].

There is a treatment gap, that is, the number of people with active epilepsy who have not received vital biomedical services, are under treatment, or receiving insufficient treatment [28]. The treatment gap in our study was that 17.0% of patients with active epilepsy were not receiving regular AED treatment. Similarly, another study in Gharbia Governorate, Egypt, among children showed that 12.5% of patients with treatment gap [5]. Furthermore, a study in North-Western India reported that the primary treatment gap was documented in 18.8% of cases **[8]**. Contrary to our findings, other studies were conducted in Qena Governorate, Egypt, and Al-Manyal Island, Cairo Governorate, Egypt. They reported a higher treatment gap where the patients did not receive any treatment (59 and 66.7%, respectively) [12].

The differences in the reported rate of treatment gap between the studies could be explained by the differences in methodologies used, the age, and the population studied. Community-based studies that have used door-to-door surveys are better able to detect epileptic patients who may not seek medical advice, while hospital-based studies report only those who seek medical advice [29] Also, the higher treatment gap in Upper Egypt is mostly due to insufficient health care facilities, in addition to economic, cultural, and social factors [12]. Concerning the relations between the treatment gap and age of patients, about 67.6% of these patients were ≥ 18 years group, which can be explained by the fact that school children get their antiepileptic drugs free and regularly from the health insurance system.

Concerning the distribution of antiepileptic drugs among patients with a positive treatment gap, ADHD and ID, it was found that more than 70.0% of patients with a positive treatment gap on valproate. This result is attributed to most physicians prescribed valproate due to better seizure control and one of the broad-spectrum antiepileptic drugs. Valproate is still widely prescribed as a first-line treatment in patients with epilepsy. Moreover, the social stigma associated with the name of valproate in the market by the popular name of dopamine to the relative of patients who just knew about dopamine remembers side effects and advised not to use this drug for them or their children. Additionally, the reproductive system is affected by valproate in the form of decreased luteinizing hormone and follicle-stimulating hormones and a significant increase in prolactin [30]**.**

This may be the reason that more than 70.0% of patients who were treated with valproate in our study were with a positive treatment gap. In the current study, more than 70.0% of epileptic patients comorbid with ADHD were on traditional AEDS where valproate was the main AEDS, and occasionally carbamazepine. This finding is consistent with those who reported a

significant relationship between treatment with sodium valproate and the development of ADHD [14].

Numerous pieces of evidence show the capability of AEDs to contribute to symptoms of ADHD. In addition, valproic acid and carbamazepine can cause some issues with attention and hyperactivity. However, it is less extent than that provided with other AEDs as barbiturates [31]. Based on our results, most of the patients with ID received traditional AEDS (valproate 50.0% and carbamazepine 16.6%).

In the present study, a strong negative correlation between IQ level and both duration of epilepsy and seizure frequency/month was observed, and this study is in agreement with **Matricardi *et al.*** [32]. Also a study reported a negative correlation between duration of epilepsy cognitive function and increased frequency of seizures associated with cognitive impairment (CI) [33]. It was reported that the first seizure was significantly related to a child's impaired cognitive function. The younger the child had their first seizure, the higher the risk of developing CI. Similarly, in another study, approximately 20-30% of epilepsy patients had more than one seizure per month [6]. There was no difference between the two age groups in terms of seizure frequency**.** In this study, the mean duration of epilepsy was < 5 years in about 85.4% of patients. Our results may be attributed to long-lasting epilepsy and seizures that lead to changes in neurogenesis and synaptogenesis and alteration of excitatory/inhibitory balance, network connectivity, temporal coding, and MRI-detectable changes. These morphological and physiological changes are accompanied by parallel impairment in cognitive skills [26]. High and multiple seizure frequency caused an imbalance of the seizure-induced electrical damage to the immature brain, either generally or focally. This will delay the maturation of the child's central nervous system, such as the myelination process, mitotic cell activity, and neuronal development in the brain**.** Increasing the frequency of seizures can lead to a progressive mental decline in chronic and uncontrolled epilepsy [34].

CONCLUSION

The current study found that the most common type of epilepsy was a generalized type, and most of the patients were rural residents. Epilepsy showed a significant difference between children (< 18 years) and adult (≥18 years) patients in seizures semiology, conventional EEG changes, associated comorbid IQ grade, and treatment gap. Moreover, seizures semiology and associated comorbid highlighted the obvious difference between females and males, while the treatment gap showed no significant difference between males and females. Duration of epilepsy and seizure frequency/month negatively correlated with IQ level.

RECOMMENDATIONS

Health education for patients to increase treatment adoption among epileptic patients. Community awareness about epilepsy to decrease social stigma toward epilepsy. Continuous medical education for medical staff to update new treatment guidelines. The prescribed drugs should be updated and licensed. Physicians must put in consideration the age of patients, educational level, place of residence, and economic state with the prescription of drugs.

Abbreviations:

IQ: intelligence quotient; ADHD: Attention-deficit hyperactivity disorder; EEG: Electroencephalography; MRI: magnetic resonance imaging; ILAE: International League Against Epilepsy; MTS: Mesial Temporal Sclerosis; CP: Cerebral palsy; ASD: autism spectrum disorder; CI: cognitive impairment; GTCS: Generalized tonic-clonic seizures; AED: Antiepileptic Drugs; ID: intellectual disability; SPSS: Statistical Package for Social Science; SD: standard deviation.

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Authors' contributions

MAO and SAZ contributed to the research idea, data analysis, and interpretation. SAZ and MAO designed and conceptualized the study. SAZ contributed to data collection. SAZ and MAO contributed to data analysis, including statistical analysis. SAZ and MAO contributed to manuscript writing. OIA has contributed to the design and complete statistical and data analysis work. In addition, she has contributed all revising of the writing and the technical contents. EMS has contributed to planning the study and revising the work, including the manuscript and data analysis. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate All procedures performed in the study were under the ethical standards of The Research Ethics Committee of Faculty of Medicine for girls, Cairo, Al Azhar University (FMG-IRB), and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. We obtained approval from research ethics committee no. 201909147 on February 09, 2022. Verbal informed consent was obtained from each patient who participated in the study. This consent was approved by the research ethics committee of the Faculty of Medicine for girls, Cairo, Al Azhar University (FMG-IRB). All data

obtained from every patient were confidential and were not used outside the study.

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