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Sex differences among epileptic patients: a comparison of epilepsy and its impacts on demographic features, clinical characteristics, and management patterns in a tertiary care hospital in Egypt

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Abstract

Background: Epilepsy is one of the most common neurological conditions. We aimed to identify sex differences in the demographic, clinical features, and treatment strategies in epileptic patients.

Objectives: To analyze and compare the differences in the impact of epilepsy on the socio-demographic characteristics of male and female patients along with gender differences in various types of epilepsies and treatment strategies.

Material and methods: A record-based study for 1000 individuals attending the epilepsy outpatient clinic. The medical records were reviewed through a predesigned questionnaire to obtain all relevant data.

Statistical analysis: Data was summarized using range, mean, standard deviation, and median interquartile range for quantitative variable or frequency and percentage for the qualitative ones. Comparison between groups was done using chi-square test.

Results: Females were more illiterate and unemployed compared to males. Tonic-clonic seizures were more frequent in males. Specific epileptic syndromes as juvenile myoclonic epilepsy (JME) were more frequent in females ($p = 0.01$). More males had an underlying secondary etiology ($p = 0.001$). The most common drug used was valproate (51.2%) which was more utilized by males.

Conclusions: Significant differences between both sexes were observed in certain social impacts in addition to seizure syndromes, etiology, and drug utilization.

Keywords: Epilepsy, Sex differences, Epilepsy impact, Tertiary hospital

Introduction

Epilepsy was defined in 2005 as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition [1]. Although the International League Against Epilepsy (ILAE) has developed a new practical (operational) definition of epilepsy [2], still the previous conceptual

definition stands, indicating the importance of the associated consequences in epilepsy disease.

Epidemiologic studies addressing gender differences in epilepsy are surprisingly scarce. Most studies reported that the incidence and prevalence of unprovoked seizures are higher in men than women [3], with some exceptions as juvenile myoclonic epilepsy [4] and absence epilepsy [5] are more common in women. Gender also has an important impact on the epileptic patient regarding health considerations, hormonal changes, and social function [6]. Almost all studies that examined sex

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differences in epilepsy focused on the seizure characteristics without much emphasis on the patients' characteristics.

Patients and methods

The aim of the current study was to investigate the differences in the demographic and social characteristics between epileptic male and female patients to compare its impact and define gender differences in various types of epilepsies and epileptic syndromes and treatment strategies.

This is a descriptive, record-based, retrospective study of 1000 patients with epilepsy who visited our epilepsy outpatient clinic in the period from January 2012 until January 2015.

The epilepsy clinic receives an average of 25 new epileptic cases and 350 follow-up cases per week.

Data were collected from the epilepsy outpatient clinic data sheets. Records with incomplete, non-conclusive clinical data or proved non-epileptic were excluded. We used Excel to generate a simple random sample of 500 male and 500 female patients. Each sheet provided detailed personal and clinical data, including results of relevant laboratory, neurophysiological and brain imaging, and history of antiepileptic drug (AED) use, responsiveness, and compliance. The sheets were not registered unless the patient him/herself was present with a reliable informant and both were interviewed by an experienced neurology staff member. A structured protocol was used to collect all relevant clinical information for each case.

The data included geographic distribution, gender, age, contact information, education, marital status, and occupation. Occupation was categorized as risky and non-risky according to the presence of a potential risk from the occupation that may expose the patient to danger [7].

We also recorded age at onset, family history, history of febrile convulsions, drug/substance abuse (as tramadol, cannabis, alcohol, clonazepam), and comorbidities. The comorbidities addressed in this study were those related to epilepsy either in terms of etiology or prediction of intractability.

We studied details related to seizure characteristics, underlying etiologies, prodromal symptoms, and precipitating factors, and we recorded neurophysiological and imaging results when available in addition to the types and numbers of antiepileptic drugs used.

Precipitating factors were defined as those circumstances that precede the onset of an epileptic attack and are considered by both the patient and the neurologist to provide a possible explanation as to why the seizure occurred [8], such as sleep deprivation, psychological/physical/mental stress, flickering lights, fever, use of epileptogenic drugs, and change of generic brand drugs.

Prodromal symptoms: prodromes were operationally defined as signs or symptoms, perceived by the patient and/or observer as premonitory, appearing up to 24 h preceding seizure onset, such as headache, pain, paresthesia, sleep/appetite disturbance, genitourinary/gastrointestinal symptoms, fatigue, speech disorders, and cognitive/behavioral or mood changes.

Epilepsy is considered as a condition characterized by recurrent (two or more) epileptic seizures occurring at least 24 h apart, unprovoked by any immediate identifiable cause [9]. Seizures are classified according to the guidelines of the International League Against Epilepsy (ILAE) [10]. Epilepsy is classified as idiopathic, symptomatic, or cryptogenic [11]. Family history is considered positive when epilepsy is present in a first-, second-, or third-degree relative.

Epilepsy syndrome: A complex of signs and symptoms that define a unique epilepsy condition with different etiologies [12]. The classification of epileptic seizures and syndromes were based on the clinical semiology and electroencephalographic (EEG) findings according to the International League Against Epilepsy's guidelines [13]. The electroencephalograph system used in our unit was a Neuro Galileo NT, PMS, USA machine, its model (Mizar.B8351037899.Version 3.61), unless the patient file stated that it was done elsewhere.

Statistical analysis

The data was transferred to the statistical package of the social science software program (SPSS Inc., Chicago, IL, USA version 16, 2007) to be statistically analyzed. Data was summarized using range, mean, standard deviation, and median interquartile range for quantitative variable or frequency and percentage for qualitative ones. Comparison between groups was done using chi-square test.

The study was assessed and approved by the Medical Ethical Committee of Cairo University.

Results

We analyzed, in depth, 1000 randomly selected data records of 500 male and 500 female patients with epilepsy who visited the epilepsy outpatient clinic, in the period from January 2012 until January 2015.

When comparing patients' demographic and social characteristics, a higher number of male patients were unmarried, had steady jobs, and reported a history of drug abuse (Table 1).

Generalized tonic-clonic seizures were seen more frequently in males while multiple seizure types were detected more in females. We explored the gender differences for patients who were diagnosed with specific epileptic syndromes and found that juvenile myoclonic epilepsy (JME), idiopathic generalized tonic-clonic (IGTC) epilepsy, and

temporal lobe epilepsy (TLE) were more frequent in females ($p = 0.01$, $p = 0.02$, $p = 0.02$) while juvenile absence epilepsy (JAE) was more common in males ($p = 0.02$) (Table 2).

More female patients reported prodromal and precipitating factors for seizure although diurnal seizures were more common in males ($p = 0.001$).

Seizure frequency was recorded in 662 patients: 302 (45.6%) showed good seizure control (< 1 seizure in 6 months) of these, and females showed significantly better seizure control and slightly better compliance than males ($p = 0.0001$) (Table 3).

A higher number of males suffered from symptomatic epilepsy ($p = 0.001$), with trauma and birth injuries being the leading causes while lesions due to immune disorders were more common in females (Table 4).

Diagnostic studies for epilepsy

Slightly higher than half of the patients who had available EEG report (53.1%) had abnormal EEGs, most of them (59.7%) had focal, rather than generalized (40.2%)

abnormal epileptiform activity. Only 35% of the patients with available neuroimaging studies had abnormal findings. Neither the EEG nor neuroimaging results revealed significant sex differences, as shown in Table 5.

Antiepileptic drugs (AED) utilization

Detailed drug history showed that a higher number of males were on monotherapy. Valproic acid (VPA) followed by carbamazepine (CBZ) was the most frequently prescribed AEDs in both groups, but higher number of males utilized VPA while more females utilized CBZ. Phenytoin was the third most common AED in the male group, while levetiracetam was the third in the female group and was significantly more prescribed to females than males. No significant difference was detected between both groups regarding the rest of the AEDs (Table 6).

Discussion

Sufficient knowledge of gender differences in epilepsy is still lacking, and the consequences of epilepsy on both

Table 1 Demographic data

Item	Total	Male	Female	p value
Age at presentation	26 ± 12.41	26.61 ± 12.750	26.20 ± 12.064	0.589
Age of fist seizure	18.17 ± 12.414	18.56 ± 13.218	17.78 ± 11.544	0.101
Age of seizure onset				
< 1 year	535 (54.9%)	262 (53.5%)	273 (56.4%)	0.630
18–60 years	432 (44.4%)	224 (45.7%)	208 (43.0%)	
> 60 years	7 (0.7%)	4 (0.8%)	3 (0.6%)	
Patient characteristics				
Family history	229 (22.9%)	114 (49.7%)	115 (50.2%)	0.76
Consanguinity	202 (20.2%)	96 (47.5%)	106 (52.4%)	0.2
Residency				
Lower Egypt	606 (97.3%)	300 (49.5%)	306 (50.4%)	0.51
Upper Egypt	44 (6.7%)	24 (54.5%)	20 (45.4%)	
Illiterate	186 of 637 (29.2%)	90 of 339 (26.5%)	96 of 298 (32.2%)	0.069
Married/previously married	452 (71.9%)	209 (46.2%)	243 (53.7%)	0.002*
Unmarried	176 (28.0%)	110 (62.5%)	66 (37.5%)	
Employed	243 (31.4%)	229 (94.2%)	14 (5.8%)	0.00*
Un Employed	531 (68.6%)	187 (35.2%)	344 (64.7%)	
Occupation risk	69 of 243 (28.3%)	69 (28.3%)	0	0.00*
Drug abuse	138 (13.7%)	134 (13.4%)	4 (0.04%)	0.00*
Tramadol	105 (76.08%)	101 (96.2%)	4 (3.8%)	
Cannabis	26 (18.8%)	26 (100%)	0	
Alcohol	2 (1.4%)	2 (100%)	0	
Clonazepam	5 (3.6%)	5 (100%)	0	
Comorbidities	720	358 (49.7%)	362 (50.2%)	0.83

* p value < 0.05 is considered statistically significant

Table 2 Clinical data

Type of seizure	Total	Male	Female	<i>p</i> value
Type of focal	472 (47.2%)	233 (49.3%)	239 (50.7%)	0.76
Simple focal	50 (11%)	26 (52%)	24 (48)	
Complex partial seizures	43 (9%)	19 (44.1%)	24 (55.9%)	0.37
Focal evolving to generalized:	379 (80%)			
▪ Simple focal onset	303 (64%)	151 (49.8%)	152 (50.2%)	0.94
▪ Complex partial onset	76 (16%)	37 (48.6%)	39 (51.4%)	1.00
Type of generalized	519 (51.9%)	265 (51%)	254 (49%)	
1. Typical absence	19 (3.7%)	12 (63.1%)	7 (36.9%)	0.2
2. Atypical absence	1 (0.17%)	1 (100%)	0	
3. GTCs	358 (19%)	207 (57.8%)	151 (42.1%)	0.04*
4. Tonic	17 (3.3%)	8 (47%)	9 (53%)	0.75
5. Atonic	6 (1.1%)	2 (33.3%)	4 (66.7%)	0.44
6. Myoclonic jerks	8 (1.5%)	3 (37.5%)	5 (62.5%)	0.49
Multi-seizure type	110 (21.1%)	32 (29%)	78 (71%)	0.004*
Unclassified	9 (0.09%)	2 (22.2%)	7 (77.8%)	0.45
Identified epilepsy syndromes				
JME	58	14 (24.1%)	44 (75.9%)	0.01*
JAE	8	7 (87.5%)	1 (12.5%)	0.02*
CAE	17	8 (47.5%)	9 (52.9%)	0.99
IGTC	23	1 (1.8%)	22 (95.6%)	0.02*
BECTS	8	4 (50%)	4 (50%)	1.0
FLE	5	2 (40%)	3 (60%)	0.99
TLE	44	17 (38.6%)	27 (61.4%)	0.02*

JME juvenile myoclonic epilepsy, JAE juvenile absence epilepsy, IGTC idiopathic generalized tonic-clonic epilepsy, CAE childhood absence epilepsy, BECT benign childhood epilepsy with centrotemporal spike, FLE frontal lobe epilepsy, TLE temporal lobe epilepsy

**p* value < 0.05 is considered statistically significant

sexes are not adequately approached. To our knowledge, this is the first report exploring sex differences in psychosocial issues, seizure types, etiological features, and utilization patterns of AEDs in people with chronic epilepsy in Cairo, Egypt.

Patients' demographic and social characteristics

The mean age of onset of epilepsy in our cohort was 26 ± 12.414; this was relatively higher than other studies [14] but may be explained by the presence of a specialized pediatric hospital in our vicinity.

Table 3 Gender differences in different seizure characteristics

Seizure characteristics	Total	Male	Female	<i>p</i> value
Precipitating factors	203	85(41.8%)	118(58.2%)	0.012*
Prodrome	75	11(14.6%)	64(85.2%)	0.00*
Cluster of seizures	107	53(49.5%)	54(49.4%)	1.0
Status epilepticus	70	32 (45.7%)	38 (54.3%)	0.536
History of Febrile seizure	54	27 (50%)	27 (50%)	1.0
Timing				
Both diurnal and nocturnal	623	301 (48.3%)	322 (51.7%)	0.19
Only diurnal	233	149 (64.9%)	84 (36/1%)	0.001*
Strictly nocturnal seizures	102	45 (44.1%)	57 (55.9%)	0.25
On awakening	18	5 (27.7%)	13 (72.3%)	0.09
Seizure control <i>n</i> = 662				
Controlled > 6 month fit free	302 (45.6%)	64 (21.2%)	238 (78.8%)	0.0001*
Uncontrolled	360 (54.3%)	177 (49.2%)	183 (50.8%)	
Compliance detected in 694	305 (43.9%)	130 (42.6%)	175 (57.4%)	0.09

**p* value < 0.05 is considered statistically significant

Table 4 Gender differences epilepsy etiologies

Etiology	Total	Males	Females	<i>p</i> value
Unknown	458	224 (48.9%)	234 (51.1%)	0.52
Idiopathic	203	82 (40.4%)	121 (59.6%)	0.01*
Secondary	339	194 (57.2%)	145 (42.8%)	0.00*
Trauma	51	41 (80.3%)	10 (19.7%)	0.0001*
Infection	45	17 (37.7%)	28 (62.3%)	0.105
Birth injury	28	21 (75%)	7 (25%)	0.027*
Vascular	21	15 (71.4%)	6 (28.6%)	0.119
SOL	16	10 (62.5%)	6 (37.5%)	0.45
TS	9	4 (44.4%)	5 (55.6%)	0.741
Immune disorder	9	0	9 (100%)	0.001*
MS	8	5 (62.5%)	3 (37.5%)	0.725

SOL space occupying lesion, TS tuberous sclerosis, MS mesial sclerosis

**p* value < 0.05 is considered statistically significant

Both illiteracy (29.2%) and unemployment (males 35.2%, females 64.71%) were higher in our cohort compared to the general population (illiteracy 20.9%; unemployment 9.4% in males and 24.2% in females) as reported by the Central Agency for Public Mobilization and Statistics (CAPMAS) of Egypt in 2015 [15]. When comparing both sexes, females were more illiterate and significantly higher numbers were unemployed.

Hazardous risks at workplaces were reported only by males (*p* < 0.00) and included handling sharp objects or heavy machines, long-hour drivers, builders, and exposure to fire as bakers.

Our study showed that less epileptic patients had ever been married (66.1% male and 80.4% females) in comparison to the general statistics (80% male and 90% females) [16], with more single epileptic males than females.

This significant psychosocial impact and the diverse effect of epilepsy on both sexes was also reported by others [17] and may be related, in general, to the epilepsy stigma, in addition to the males' higher social responsibilities [18] and the females' sociocultural restrictions.

The rate of drug abuse in our cohort (13.8%) was higher than that found in a recent cross-sectional, community-based survey on almost all Egyptian governments [19], which reported that about 6.7% of the Egyptians were dealing regularly with substance(s). In concordance with our results, they found significantly

Table 5 Gender differences in diagnostic studies

EEG recorded in 578	Total	Male	Female	<i>p</i> value
Normal EEG	307	146 (47.5%)	161 (52.4%)	0.94
Focal discharge	162	79 (48.7%)	83 (51.2%)	
Generalized discharge	109	51 (46.7%)	58 (53.2%)	
Brain imaging recorded in 377				
Abnormal findings	131	73 (55.7%)	58 (49.2%)	0.33

Table 6 Gender differences in AED utilization

AEDs	Total	Male	Female	<i>p</i> value
Monotherapy	593	329 (55.4%)	264 (44.6%)	0.00
Polytherapy	338	146 (43.1%)	192 (56.9%)	
Distribution of drug prescribed				
Valproate	514	285 (55.4%)	229 (44.6%)	0.0005*
Carbamazepine	395	187 (47.3%)	208 (52.7%)	0.001*
Levetiracetam	185	62 (33.5%)	123 (66.5%)	0.001*
Phenytoin	129	72 (55.8%)	57 (44.2%)	0.186
Lamotrigine	68	33 (48.5%)	35 (51.5%)	0.89
Clonazepam	21	11 (52.3%)	10 (47.6%)	1.00
Oxcarbazepine	13	8 (61.5%)	5 (38.4%)	0.57
Topiramate	11	3 (27.3%)	8 (72.7%)	0.22
Locosamide	6	4 (66.7%)	2 (33.3%)	0.68
Ethosuxamide	6	3 (50%)	3 (50%)	1.00

**p* value < 0.05 is considered statistically significant

higher numbers of male abusers (15.8% males versus 2.2% females). Similarly, Najafi and his colleagues [20], found drug abuse to be more frequent in epileptic patients compared to the general population, with the most frequent substance abused being tramadol.

Seizure types and epilepsy classification

The relative dominance of generalized epilepsies as seizure type is evident in several Egyptian [21], Arabian [22], and developing countries' studies [23]. However, some epidemiological Egyptian [24] [25] and developed countries' studies [26] reported the predominance of focal seizures. It is expected that in developing countries, in which more symptomatic epilepsy is found, a higher rate of focal seizures should be reported. However, in hospital-based studies, there is greater under-representation of focal epilepsy because of less frequent access for such patients to the hospital due to the less frightening aspect of these seizures, inferring a methodological rather than any real geographic difference.

Our results showed that more females complained of more than one seizure type and the same results were shown by Mullins and his colleagues [27]; however, they reported multi-seizure (> 2) type to be equal in both sexes, an observation that we recommend to be further studied. They also found that idiopathic generalized epilepsy (IGE) is more common in females; in our cohort, this was true for JME, IGTC, and TLE, but juvenile absence epilepsy (JAE) was more common in males (*p* = 0.02). However, due to the few numbers of subjects in this group, we suggest that our results would be interpreted with caution.

Seizures pattern and control

The overall reporting of precipitating factors was 20.3%; this is less than what was mentioned in previous studies

[8]. We relate such differences to methodological issues as most of those studies used predesigned, close-ended questionnaires while we recorded what was mentioned in the patients' files during their clinic interviews.

The higher reporting of precipitating factors by our female patients may be related to their having an additional factor related to hormonal changes during menstruation causing changes in seizure frequency in association with menstrual cycles [28]. It is also plausible that differences in both brain-derived and systemically derived estrogens between sexes may lead to differences in responses to the inciting event of the seizure [29].

Similarly, Maiwald and colleagues [30], also found that, out of 500 patients with epilepsy, 31 (6%) claimed to sense prodromal symptoms and most participants were females.

While differences in symptom reporting based upon sex are due to psychological, biological, or sociological factors remain unclear, the impact of one or all of these factors on epilepsy is points requiring further study [29].

Analysis of seizure timing revealed that males suffered from more diurnal seizures. In the context that males had a significantly higher number of GTCs, we find our results close to Fernández and his colleagues [31], who stated that evolution of GTCs peaks at 6–9 am; however, another study [32] found that tonic-clonic seizure distribution showed no difference between day and night. This disagreement can be related to methodological issues as we depended on self-reporting, while studies evaluating the relationship of sleep/awake and circadian patterns to seizures depended chiefly on EEG analysis [31, 32].

The control of seizures was much better in the female group; this may be attributed to better compliance to medication, idiopathic seizures, stability of social life, and lower rate of substance abuse compared to males. Similar results were reported by Obiako and his colleagues [33] when they investigated prognostic factors for epileptic seizure outcomes.

It is worth noting that the overall percentage of controlled patients (45.6%) was inferior to previous studies [34]. This may be related to being a hospital-based study carried out in the tertiary referral hospital, which is usually challenged with more cases of refractory epilepsy while easy-to-treat cases normally achieve good control after the first AED and do not require the assistance of an expert epileptologist; however, we do recommend further studies to investigate this issue.

Etiological causes of symptomatic epilepsy

A significantly higher number of females had idiopathic etiology, whereas more males had an underlying secondary etiology with trauma being the leading cause. Our results agree with previous reports indicating that head injuries [14] are the most common underlying etiological cause of chronic epilepsy, with males being at a greater

exposure risk. When comparing our results with another Egyptian study, led by Farghaly and his colleagues [35], they found that cerebrovascular stroke, rather than trauma, was the most common cause of symptomatic epilepsy among adults and the elderly while perinatal insults were the most common among children (< 18 years). This difference regarding adult epileptic patients may be related to the geographic characteristics as the mentioned study was carried out in Al-kharga District (New Valley), at the southern part of Egypt, where the majority live in rural areas with a density of 0.58/km², while the majority of our subjects came from Giza, the third-largest city in Egypt and the world's seventh largest suburb, with a density of 2.300/km², and the highest number of traffic accidents as reported by The Central Agency for Public Mobilization and Statistics [15].

It is noteworthy that the number of patients with unknown etiology (cryptogenic) is relatively high compared to previous studies [19, 33], in addition to low numbers of hippocampal sclerosis and cortical dysplasias detected in our study. This could be due to the limited access to 3Tesla Magnetic Resonance Imaging (MRI) and comprehensive epilepsy protocol imaging for economic reasons.

Diagnostic studies for epilepsy

Neither the EEG nor neuroimaging results showed gender differences between our cohorts. Although the percentage of patients who had undergone diagnostic tests is comparable to previous studies [14, 16, 17], it is still inadequate for such essential investigations. We attributed this deficiency to the lack of registration in the archived record and/or the reluctance in doing EEG studies either due to financial issues or good control of seizures with treatment.

AED utilization

Prescribers in our tertiary referral center generally followed treatment guidelines for epilepsy in terms of first-line drugs, with a tendency to shift towards the use of newer AEDs if indicated. Results showed that most patients were treated with first-generation AEDs, which are offered freely. Males were more likely to be prescribed VPA for generalized seizures, with a trend to shift to levetiracetam for females due to its better safety profile on females in the child-bearing period and in hepatic patients.

Since this study included patients attending a tertiary care hospital, it may bear certain selection biases. It did not include patients treated in other neurology clinics, at primary or secondary care centers, those treated privately, or undiagnosed patients. Also, being a retrospective study, some information was liable to recall bias and incompleteness as results of EEG or neuroimaging hindered the recognition of certain features and the diagnosis of epilepsy syndromes in some patients.

Conclusion

While epidemiological studies did not find persistent differences in the incidence of epilepsy in males and females, our study revealed significant differences in the psychosocial impact of epilepsy on both sexes in certain areas, such as education, marriage, and hazardous job exposure. Our results go with previous publications that reported that non-symptomatic epilepsy occurs more in women while symptomatic, localization-related epilepsy has a preponderance in men, with different treatment choices by epileptologists in relation to sex.

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Availability of data and materials

All datasets generated and analyzed during the current study are not publicly available but are available by reasonable request from the corresponding author.

Authors' contributions

All authors contributed to the research idea. NAK, NMS, and AAA contributed to the data collection. NAK and NMS analyzed the data and along with HSM and RMS, interpreted the data. Further, HSM and RMS completed the first draft of the article. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

Ethics approval and consent to participate

All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. The study was ethically approved by the research committee and reviewed by the faculty of medicine Cairo University board on 18 Nov. 2013. Written informed consent was obtained from all participants involved in this investigation prior to the conduct of any study-related activities.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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