International Journal of Clinical and Experimental Neurology, 2017, Vol. 5, No. 1, 18-27
Available online at http://pubs.sciepub.com/ijcen/5/1/5

DOI:10.12691/ijcen-5-1-5

Prevalence of Comorbidity of Migraine and Atopic Diseases among Patients with Idiopathic Epilepsy in Zagazig University Hospitals

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Abstract Comorbid conditions are common in people with epilepsy, and their presence has important implications for diagnosis, treatment, medical costs and quality of life. Migraines are most common in patients with epilepsy, with a reported prevalence of 20-40%, while epidemiologic studies on the association between allergic disease and epilepsy in adults and children have found conflicting results. **Objectives:** The study was designed to assess the prevalence of migraine and atopic diseases: bronchial asthma(BA) and atopic eczema in patients with idiopathic epilepsy. **Methods:** This study included 118 patients with idiopathic generalized epilepsy(IGE), 68 male and 50 female with ages ranged from 2-20 years (mean age 9.8±5.4 years). The patient will be considered :to have migraine according to criteria of ICHD 3 (2013), to have BA according to diagnostic criteria of National Asthma Education and Prevention Program (2007) and to have atopic eczema according to Williams criteria (1994). The patients were classified into two groups, group I epileptic patients without comorbidity and groupII epileptic patients with comorbidity which was further classified into 2 subgroups, groupII-A epileptic patients with one comorbidity, group II-B epileptic patients with multiple comorbidity. All patients were subjected to**:** clinical assessment via thorough history taking, complete general and neurological examination, EEG, MRI brain and routine laboratary investigations. The data were compared in both groups. **Results:** IGE was more common in male than female (55.9 % vs 44.1 %). Atopic eczema was the most frequent comorbid illness (32.2%) followed by migraine (24.6%) and BA (24.6%) while The prevalence of atopic eczema, migraine and BA and in the general population was 20%, 15% and 4%-20%, respectively. Epileptic patients with multiple comorbidities had a statistically significant older age of onset than epileptic patients one comorbidity and without comorbidities (P= 0.001). Also female sex was statistically significant higher in epileptics with comorbidities. Epileptics with migraine had female preponderence (69%). MA was more common (79.3%). Migraine onset followed epilepsy onset in 48.2%.Migraine attacks occurred mostly interictally. The bronchial asthma comorbidity in our patients was with a more prominent onset before epilepsy (76%). Mild asthma was more common in epileptics in our study and it was common postictally. Atopic eczema comorbidity in our patients was with an onset more commonly prior to that of epilepsy & it occurred in a mild form and usually interictally. **Conclusion:** Patients with IGE had comorbidity with atopic eczema (32.2%) migraine (24.6%) and BA (24.6%).Family history for epilepsy was more in patients with comorbidity and they need polytherapy of AEDs more than those without comorbidity.

Keywords: *ICHD 3: international classification of headache disorders, 3rd edition MA: migraine with aura AEDs:antiepileptc drugs.*

Cite This Article: Yosria Abd Al Hameed Altaweel, Amal Salah El-Din Mohamed El-Motayam, Khaled Aly El-Sharkawy, and Mohammed Hanafy Aly Ghonemy, "Prevalence of Comorbidity of Migraine and Atopic Diseases among Patients with Idiopathic Epilepsy in Zagazig University Hospitals." *International Journal of Clinical and Experimental Neurology*, vol. 5, no. 1 (2017): 18-27. doi: 10.12691/ijcen-5-1-5.

1. Introduction

Epilepsy is a major public health concern in terms of the burden of the disease, nature of illness and its impact on individuals and families [1].

Comorbid conditions are common in people with epilepsy, and their presence has important implications for diagnosis, treatment, medical costs and quality of life [2].

Comorbidity refers to the co-occurrence of two conditions with a greater frequency than found in the general population [3].

Understanding the comorbidity of epilepsy is important from several perspectives. First, understanding comorbidity can improve the diagnosis of epilepsy because of the substantial symptomatic overlap with several of the comorbid conditions**.** Second, some comorbidities may influence the prognosis of epilepsy, as has been shown for migraine [4]. Third, recognition of comorbidities can inform

therapeutic choices, either by creating opportunities to treat two conditions with a single drug (e.g., divalproex sodium or topiramate may treat both epilepsy and migraine) or by imposing therapeutic limitations (e.g., tricyclic antidepressants may lower seizure threshold). Finally, knowledge of comorbidities may provide insight into pathogenesis by revealing shared neurobiologic mechanisms underlying multiple disorders [5].

2. Patients and Methods

This study was conducted on patients attending the Neurology and the Pediatric Neurology Outpatient Clinics at Zagazig University Hospitals during the period from October 2014 to September 2017. The study included 118 patients with idiopathic generalized epilepsy, 68 male and 50 female with ages ranged from 2-20 years (mean age 9.8±5.4 years SD). Children and adolescent patients suffering from idiopathic generalized epilepsy with ages ranged from 2-20 years of both sexes were choosen consequetivly.

The diagnosis of idiopathic generalized epilepsy was confirmed clinically, neurophysiologically via EEG and neuroradilogically via MRI brain. Also routine laboratory investigations and ECG were done.

We excluded patients with idiopathic focal, secondary generalized epilepsy and symptomatic epilepsy were excluded from the study, as: congenital malformations of the brain, birth injury or trauma to the brain, developmental disabilities as cerebral palsy, CNS infections, brain tumors, cerebrovascular insults, neurocutanous syndromes, mesial temporal sclerosis, metabolic causes (e.g hypogycemia, hypocalcemia....) and autoimmune disorders. All patients were subjected to:

- Clinical assessment via thorough history taking, complete general and neurological examination, EEG, MRI brain and routine laboratary investigations.
- The patient will be considered to have migraine according to criteria of ICHD 3 (2013), considered to have bronchial asthma according to diagnostic criteria of National Asthma Education and Prevention Program, (2007) and considered to have atopic eczema according to Williams criteria (1994).

Statistical analysis was done using SPSS version 22 [6].

3. Results

IGE was more common in male than female (55.9% vs 44.1%). Atopic eczema was the most frequent comorbidity (32.2%) followed by migraine comorbidity (24.6%) and BA (24.6%) while the prevalence in the general population was as follow atopic eczema: 20%, migraine 15% and BA: 4%-20%.Female sex was statistically significantly higher in epileptics with comorbidity.

In comorbidity of atopic eczema with IGE: its onset started prior to that of epilepsy & it occurred in a mild form usually interictally.

Epileptics with migraine had female preponderence (69%). MA was more common, epilepsy started first in 48.2% and migraine attacks occurred mostly interictally.

Bronchial asthma started before epilepsy in 76% of IGE, the mild form of BA was more common & it usually occurred postictally.

Family history of epilepsy was more in epileptic patients with comorbidity than IGE patients without comorbidities, but the difference was not statistically significant.

IGE patients with multiple comorbidities were on polytherapy of AEDs more than those without or with one comorbid illnesses (p= 0.0012).

Table 1. Frequency of epilepsy comorbidities

Epileptic patients characteristics No = 118			No	%
Sex	Male		66	55.9
	Female		52	44.1
comorbidity	Without comorbidity		52	44.1
	With comorbidity	Total	66	55.9
		One comorbidity	41	34.7
		Multiple comorbidities	25	21.2
Type of comorbidity	Migraine		29	24.6
	Bronchial asthma		29	24.6
	Atopic eczema		38	32.2

Table 1 illustrated that male patients were more common than female and atopic eczema was the most frequent comorbidity (32.2%) followed by migraine comorbidity (24.6%) and bronchial asthma (24.6%).

Table 2 showed that the female sex and older age of patients were statistically significant in epileptic patients with comorbidity than epileptic patients without comorbidity (P = 0.003, P = 0.009 respectively). Family history of epilepsy was more in epileptic patients with comorbidity than epileptic patients without comorbidities, but the difference was not statistically significant.

Table 2. Demographic characteristics and family history of epilepsy of our epileptic patients with and without comorbidity

		Epilepsy with comorbidity		Epilepsy without comorbidity		X^2	P
		NO	**%**	**NO**	**%**		
		66	**55.9**	**52**	**44.1**		
Sex	Male	29	43.9	37	71.2	8.74	0.003*
	Female	37	56.1	15	28.2		
Age	Mean±SD	10.9±5.4		8.3±5.0		2.62	0.009*
	Range	(2-20)		(2-20)			
Family history of epilepsy	Positive	34	51.5	22	42.3	0.99	0.32
	Negative	32	48.5	30	57.7		

Table 3. Demographic characteristics of all epileptic patients in our study

		Epilepsy without comorbidity (n=52)		Epilepsy with one comorbidity (n=41)		Epilepsy with multiple comorbidities (n=25)		Significance	
		No	%	No	%	No	%	F	P
Age	Mean±SD	8.3±5.0		9.6±4.7		13.1±5.8*		7.29	0.001*
	Range	(2-20)		(2-20)		(2-20)			
Sex	Male	37	71.2*	18	43.9	11	44.0	x^2	*P*
	Female	15	28.8	23	56.1	14	56.0	*8.74*	*0.012**
Socioeconomic status	High	4	7.7	5	12.2	4	16.0	8.96	0.06
	Moderate	15	28.8	13	31.7	14	56.0		
	low	33	63.5	23	56.1	7	28.0		
Residence	Urban	37	71.2	34	82.9	16	64.0	3.19	0.2
	rural	15	28.8	7	17.7	9	36.0		
Onset of epilepsy	Mean±SD	6.4±4.1		7.4±3.9		7.9±3.6		F	P
	Range	(1-18)		(1-16)		(2-17)		1.52	0.22

Table 4. The prevalence of migraine and its characters in epileptic patients

		No		%	
Migraine	-ve	89		75.4	
	+ve	29		24.6	
Sex		(n= 29)			
	Male	9		31.0	
	female	20		69.0	
Age at migraine onset	Mean ±SD	9.9±2.5			
	Range	(5-15 years)			
Type of migraine		(N=29)			
	MA	23		79.3	
	MO	6		20.7	
Relation between epilepsy onset & migraine	onset	MA	MO	TOTAL	%
	before epilepsy	7	2	9	31.0%
	same year	5	1	6	20.8%
	after epilepsy	11	3	14	48.2%
Duration(years)	Mean ±SD	3.2±1.5			
	Range	(1-5)			
Frequency	1⁄month	1		3.4	
	2⁄month	8		27.6	
	3⁄month	6		20.7	
	Weekly	14		48.3	
Severity Partially	Unaffected	12		41.4	
	affected	12		41.4	
	Do nothing	5		17.2	
Temporal relationship between migraine & epilepsy	preictal	6		20.7	
	postictal	10		34.5	
	inter ictal	13		44.8	

MA=migraine with aura MO=migraine without aura.

Table 3 illustrated that epileptic patients with multiple comorbidities had a statistically significant older age of onset than epileptic patients one comorbidity and without comorbidities (P 0.001). Also female sex was statistically significant higher in epileptics with comorbidities.

Table 4 showed that migraine comorbidity was present in 24.6% of epileptics. Female preponderence was higher (69%). MA was more common (79.3%).48.2% of epileptics had migraine onset after epilepsy. Mostly migraine attacks occurred interictally.

Table 5 demonstrated that epileptic patients comorbid with migraine had a statistically significant higher female sex, mean age of epilepsy onset and positive family history of epilepsy than epileptic patients without migraine comorbidity (P = 0.0018, <0.001, 0.006 respectively). Also polytherapy was more commonly used in epileptics with migraine.

Table 5. A comparison between epileptic patients with and without migraine comorbidity

		Epileptic patients without migraine (n=89)		Epileptic patients with migraine (n=29)		t	p
Sex	Male	No	%	No	%	9.6	0.0018**
		57	64.0	9	31.0		
	Female	32	36.0	20	69.0*		
Age of epilepsy onset	Mean ±SD	8.1±4.6		14.9±4.1		7.1	<0.001**
	Range	(2-20)		(5-20)			
Family history of epilepsy	-ve	67	75.3	14	48.3	7.41	0.006*
	+ve	22	24.7	15	51.7*		
Family history of migraine	-ve	42	47.2	14	48.3	0.9	0.01
	+ve	47	52.8	15	51.7		
Family history of both epilepsy &migraine	-ve	64	71.9	17	58.6	1.79	0.18
	+ve	25	28.1	12	41.4		
EEG changes	Absence	11	12.4	0	0.0	5.75	0.056
	Sharp-slow	75	84.3	26	89.7		
	Polyspike-slow	3	3.4	3	10.3		
Response to treatment	- Improved	11	12.4	2	6.9	2.09	0.35
	- Controlled	42	47.2	11	37.9		
	- Intractable	36	40.4	16	55.2		
AEDs	Monotherapy	73	82.0	13	44.8	15.3	<0.001**
	Polytherapy	16	18.0	16	55.2*		

Table 6. The prevalence of bronchial asthma and its clinical presentation

		No	%
Prevalence of B.A	-ve	89	75.4
	+ve	29	24.6
Sex	- Male	14	48.3
	- Female	15	51.7
Age at B.A onset	Mean ±SD	5.1±2.5	
	Range	(2-10)	
Relation between epilepsy onset & B.A onset	- Before epilepsy	22	76.0
	- Same year	5	17.2
	- After epilepsy	2	6.8
Duration(years)	Mean ±SD	5.3±4.6	5.3±4.6
	Range	(1-14)	(1-14)
Seizure type	GTCS	20	68.9
	Tonic	5	17.4
	Myoclonic	3	10.3
	Absence	1	3.4
Severity	Intermittent	8	27.6
	Mild	10	34.5
	Moderate	8	27.6
	Sever	3	10.3
Temporal association	- Interictal	10	34.5
	- Preictal	2	6.9
	- Postictal	17	58.6

Table 6 in this table we noticed that the bronchial asthma comorbidity in our patients was with a more prominent onset before epilepsy (76%). It also showed that the mild asthma was the more common form and it was commonly postictally.

Table 7 illustrated that epileptic patients comorbid with B.A had a significantly higher positive family history of both epilepsy & B.A than epileptic patients without B.A comorbidity. It also illustrated that monotherapy of AEDs was statistically significant higher in epileptic patients without B.A than epileptic patients comorbid with B.A (P= 0.04).

Table 8 demonstrated that onset of eczema was commonly prior to that of epilepsy & it occurred in a mild form usually interictally.

Table 7. A comparison between epileptic patients with and without bronchial asthma comorbidity

		Epilepsy without B.A (n=89)		Epilepsy with B.A (n=29)		X^2	P
		NO	%	NO	%		
Sex	- Male	52	58.4	14	48.3	0.9	0.33
	-female	37	41.6	15	51.7		
Age at epilepsy onset:	Mean ±SD	9.6 ±5.1		10.3±6.3		t o.66	0.5
	Range	(2-20)		(2-20)			
Family history of epilepsy	+ve	38	42.7	18	62.1	*3.29*	0.069
	-ve	51	57.3	11	37.9		
Family history of B.A	+ve	24	27.0	13	44.8	3.24	0.07
	-ve	65	73.0	16	55.2		
Family history of both B.A and epilepsy	+ve	17	19.1	20	69.0*	25.27	<0.001**
	-ve	72	80.9	9	31.0		
EEG changes	Absence	9	10.1	2	6.9	0.52	0.77
	Sharp-slow	75	84.3	26	89.7		
	Polyspike-slow	5	5.6	1	3.4		
Response to treatment	- Improved	11	12.4	2	6.9	1.05	0.59
	controlled	38	42.7	15	51.7		
	intractable	40	44.9	12	41.4		
AEDs	monotherapy	69	77.5	17	58.6	3.96	0.04*
	polytherapy	20	22.5	12	41.4		

Table 8. The prevalence of atopic eczema and its clinical presentation

		No	%
Prevalence of eczema	-ve	80	67.8
	+ve	38	32.2
Sex	- Male	20	52.6
	- Female	18	47.4
Age of eczemz onset	Mean ±SD	4.5±2.6	
	Range	(2-7)	
Relation between epilepsy onset & eczema onset	Before epilepsy	31	81.6
	Same year	5	13.2
	After epilepsy	2	5.2
Duration (years)	Mean ±SD	5.7±4	
	Range	(1-15)	
Severity	Mild	26	64.8
	Moderate	9	23.7
	Sever	3	7.9
Temporal association	Interictal	38	100
	Preictal	0	0.0
	Postictal	0	0.0

Table 9 showed that epileptic patients comorbid with atopic eczema had a significantly higher positive family history of both epilepsy & atopic eczema than epileptic patients without atopic eczema comorbidity (P<0.001).

Table 10 illustrated that epileptic patients with multiple comorbidities were on polytherapy of AEDs more than those without or with one comorbid illnesses (p= 0.0012).

Table 9. A comparison between epileptic patients with and without atopic eczema

		Epilepsy without eczema (n=80)		Epilepsy with eczema (n=38)		X^2	P
		No	%	No	%		
Sex	Male	46	57.5	20	52.6	0.25	0.61
	Female	34	42.5	18	47.4		
Age at epilepsy onset	Range	(2-20)		(2-20)		t 0.94	0.34
	Mean ±SD	9.4±5.5		10.4±5.2			
Positive family history of eczema	+ve	24	30.0	13	34.2	0.21	0.64
	-ve	56	70.0	25	65.8		
Positive family history of epilepsy	+ve	39	48.8	17	44.7	0.17	0.68
	-ve	41	51.2	21	55.3		
Positive family history of both eczema and epilepsy	+ve	5	6.3	21	55.3*	36.17	<0.001**
	-ve	75	93.7	17	44.7		
EEG changes	Absence	7	8.8	4	10.5	0.1	0.94
	Sharp-slow	69	86.3	32	84.2		
	Polyspike-slow	4	5.0	2	5.3		
Response to treatment	Improved	10	12.5	3	7.9	2.5	0.28
	Controlled	32	40.0	21	55.3		
	Intractable	38	47.5	14	36.8		
AEDs	Monotherapy	60	75.0	26	68.4	0.56	0.45
	Polytherapy	20	25.0	12	31.6		

Table 10. EEG changes, type and response to AEDs of studied epileptic patients without and with comorbidities(one,multiple comorbidities)

		Epilepsy without comorbidity (n=52)		Epilepsy with one comorbidity (n=41)		Epilepsy with multiple comorbidities (n=25)		Significance	
		No	%	No	%	No	%		
EEG changes	Absence	6	11.5	4	9.6	1	4.0	X^2	p
	Sharp-slow	44	84.6	34	82.9	23	92.0	1.82	0.76
	Polyspike-slow	2	3.8	3	7.3	1	4.0		
AEDs	monotherapy	42	80.8	33	80.5	11	44.0	13.39	0.0012*
	polytherapy	10	19.2	8	19.5	14	56.0*		
Response to treatment	improved	8	15.4	3	7.3	2	8.0	2.63	0.6
	controlled	20	38.5	21	51.2	12	48.0		
	intractable	24	46.2	17	41.5	11	44.0		

4. Discussion

Comorbidities in epilepsy are common but poorly understood and often remain unaddressed. The prevalence of comorbid conditions is considerably higher in epilepsy than seen in the general population [7].

Comorbid condition(s) can arise before, concomitant with, or after epilepsy onset; they may be cause or consequence of epilepsy, or they can be associated with epilepsy because they share common pathologic risk factors (genetic, environmental, molecular, or morphologic), or a pathogenic process, or they can be discordant conditions [8].

Average prevalence of migraine in the general population about 15% [9]. In our study we found that the prevalence of migraine among our epileptic patients was 24.6% (29 patients out of 118 patients).This is in agreement with Ottman and Lipton [10], Syvertsen et al. [11], Shyam et al. [12], Ottman et al. [5], Kelley et al. [13], Winawer et al. [14], Mainieri et al. [15], Elmassry et al. [16] who found that the prevalence of migraine with epilepsy in their studies was: 24%, 20%, 26%, 27.9%, 25%, 25,2%, 26.3% and 21.83% respectively. Weatherburn et al. [17] in their study found that migraine was strongly associated with epilepsy (adjusted prevalence odd ratio 2.36).

Average prevalence of BA in children about 4%-20% [18]. In our study, we found that the prevelance of asthma in our epileptic patients was 24.6% (29 patients out of 118 patients). This is in accordance with Kobau et al. [19], Elliott et al. [20], Ottman et al. [5], Russ et al. [21] and Kadima et al. [22] who found that the prevalence of asthma with epilepsy was: 20%(15.3%-26.4%), 21.9%(18.2%-26.2%), 20.7%, 18% and 19.2%(15.2%-24.0%) respectively.

About 20% of all children develop symptoms of atopic dermatitis at some point in their lives [23]. In our study, we found that the prevalence of eczema in our epileptic patients was 32.2% (38 patients out of 118 patients). Frediani et al. [24] illustrated that the prevalence of eczema in their patients was 19.4% (14 patients out of 72 patients). Russ et al. [21] showed that the prevalence of allergic disease including atopic eczema in patients with history of epilepsy and seizures was 43% vs 26% in patients without history of epilepsy and seizures. Silverberg et al. [25] illustrated that the prevalence of atopic eczema in their study was (OR 1.73 [95% CI 1.17–2.56], P = 0.0006). Strom and Silverberg [26] domenstrated that seizures were significantly associated with eczema (aOR, 1.37; 95% CI, 1.13-1.67; P =. 002). Silverberg [27] demonstrated that persons with atopic eczema appeared to be at high risk of developing seizures.

Epileptic patients without comorbidity had a statistically significant (P=0.012) higher male sex prevalence than those with one comorbidity and multiple comorbidites (male/female(M/f) ratio 37/15,18/23,11/14 respectively). This is in agreement with Elmassry et al. [16] who found that epilepsy without comorbidity male/female ratio 30/2 while epilepsy with migraine comorbidity the ratio was 7/12.

In our study, the ages of patients with IGE with multiple comorbidities were statistically significant higher (P<0.001) than those without or with one comorbid illness. The mean ages were (13.1±5.8*, 9.6±4.7, 8.3±5.0 respecively). This is in contrast to Elmassry et al. [16] who found that the epileptic patients without comorbidity had an older mean age±SD than the` epileptic patients comorbid with migraine and the epileptic patients comorbid with depression (34±6.1, 23±2.4, 22±1.6 respectively). Our finding is just a finding in our sample.

Regarding the age of onset of epilepsy, we found that the comorbid epileptic patients had an older age of onset of epilepsy than epileptic patients without comorbidity (7.6±3.7 vs 6.3±4.1 years). This is in contrast to Elmassry et al. [16] who found that the comorbid patients had significantly younger age of onset than epileptic patients without comorbidity. Also our finding is a mere finding in our sample and we can not justify it.

As regard the duration of epilepsy,the comorbid epileptic patients had a statistically significant longer duration of epilepsy than epileptic patients without comorbidity (7.6±3.7 vs 6.3±4.1 years) (P= 0.02*). This comes in agreement with Velioğlu et al. [4] who found that epileptic patients comorbid with migraine had longer duration of epilepsy than epileptics without migraine comorbidity. Mainieri et al. [15] also found that epileptic patients with posictal headache had a longer duration of epilepsy than patients without postictal headache (21; 12-29 vs 20; 11-32 years).

In the present study, we found that IGE patients with multiple comorbidities receiving a polytherapy of AEDs were statistically signuficant higher (P= 0.0012) than those without comorbidity and with one comorbidity. This comes in agreement with Velioğlu et al., [4] who domenstrated that epileptic patients with comorbid illness (migraine) were usually using a polytherapy of AEDs for achieving remission when compared with epileptic patients without comorbidity.

On studying the type of seizures, we found no statistically significant difference between epileptic patients with and without comorbidity. This is in accordance with Yamane et al., [28] who had the same results.

On studying the frequency of the seizures, we found no statistically significant difference in the frequency of the seizures between epileptic patients with and without comorbidity. Velioğlu et al. [4] showed that epileptics comorbid with migraine had a higher frequency of seizures than epileptics without comorbidity.

Regarding the response to and compliance to AEDs, epileptcs with comorbidities showed a lesser response to treatment (less number of improved patients, 5 vs 8 patients) and higher non compliance to AEDs(57.6% vs 42.3%) than epileptics without comorbidities. This is in accordance with Velioğlu et al., [4] who illustrated that epileptics with comorbidity had a lower treatment response, and a higher incidence of medication problems than epileptics alone without comorbidity.

The migraine comorbidity in our epileptic patients was more common in female (20 patients out of 29 patients), female/male(F/M) ratio 20/9.This is in accordance with many studies like Schon and Blau [29], Ottman and Lipton [5], Ito et al. (1999), Tonini et al. [30] Winawer et al. [14] and Nahid and Hakimeh [31] where F/M ratio in their studies was: 61/39; 60 %/40 %; 73/36; 338/154; 445/285 and 11/4 respectively.

MA was the commonest in our patients (23out of 29 patients). This is in accordance with Ludvigsson et al. [32] who illustrated that the prevalence of MA was higher among children with a first unprovoked seizure when compared to age-matched controls in Iceland. Brodtkorb et al. (2008) found that the prevalence of active epilepsy increased among individuals with MA. Winawer et al. [14] found that MA was significantly increased in enrolled epileptic participants with ≥2 additional affected first degree relatives.

Regarding the relation between migraine onset and epilepsy onset, we found in our study that migraine onset after epilepsy was the commonest and it was found in 11 patients out of 29 patients (48.2%), migraine onset before epilepsy was found in 7 patients (31%) and migraine onset in the same year of epilepsy onset was found in 5patients (20%). This is in agreement with Toldo et al. [33] who found that epilepsy onset preced migraine onset in 71% of their cases. El-Senousey et al. (2012) found that epilepsy onset before the migraine onset was the commonest in their patients and it was found in 66.66% (4 patients out of 6 patients) but headache onset in the same year of epilepsy had the same result as headache onset before epilepsy 16.76% (1 patient out of 6 patients for both), this difference could be explained by the small number of epileptic patients comorbid with headache (only 6 patients) in their study. Also Elmassry et al. [16] found in their study that migraine onset after epilepsy was the commonest and was found in 12 patients out of 19 patients (63.16%), and migraine onset before epilepsy in 7 patients (36.84%).

Regarding the temporal relationship between migraine and epilepsy, in the present study we found that interictal migraine was the commonest 44.8%(13 out of 29) followed by postictal migraine 34.5%(10 out of 29) and

preictal migraine20.7%(6 out of 29).This is in agreement with Vujisic et al. (2012) who found that the interictal migraine was the commonest type 52% followed by the postictal migraine in 28% and preictal migraine in 20%. Mainieri et al. [15] found also that the interictal migraine was the commonest 47.06% followed by postictal migraine 37.25% and preictal 18.63%, and Nahid and Hakimeh [31] illustrated that the interictal headache was the commonest 42.52% followed by the postictal 31.48% and preictal 25.92%.

On comparing epileptic patients with migraine comorbidity with those without, in our study we found that epileptic patients with migraine comorbidity had a statistically significant (P= 0.0018) higher female sex and older mean age±SD of epilepsy onset(P<0.001) than patients without migraine comorbidity. Elmassry et al. [16] had the same results of higher female sex in the epileptic patients comorbid with migraine than epileptic patients without comorbidity. This could be explained by the higher frequency of migraine among women rather than general population [31].

In our study, a positive family history of epilepsy was more common in epileptic patients with migraine comorbidity (51.7%) than epileptic patients without migraine comorbidity (P = 0.006), which is slightly higher than the results of Toldo et al. [33] and El-Senousey et al. (2012) who found that a positive family history of epilepsy was present in 39%, 35.71% respectively in their epileptic patients comorbid with migraine. These results could suggest that epilepsy and migraine are comorbid conditions and may share a common genetic pathophysiological mechanisms.

In the present study, we found that epileptic patients with multiple comorbidites had a statistically significant older age of onset of bronchial asthma and longer duration of asthma than epileptic patients with asthma comorbidity alone (P= 0.02,0,14 respectively).

In the present study, bronchial asthma comorbidity was slightly more common in female (51.7%) (15 out of 29 patients). Bilan and Ghaffari [34] in their study had 26 asthmatic patients comorbid with epilepsy (15 male and 11 female).

On studying the seizure type in epileptic patients comorbid with asthma, GTCS were the commonest (20 patients) followed by the tonic seizures (5 patients) then myoclonic seizures (3 patients) with the least common absence seizures (1 patient). Czubkowska et al. [35] demonstrated that they had 8 patients (out of 9 patients) had GTCS and 1 patient had absence seizure, El-Taweel et al. [36] found that 20% of their asthmatic patients had seizures of whom 62.5% suffered from generalized tonic-clonic and 25% had myoclonic seizures. Bilan and Ghaffari [34] illustrated that GTCS were the commonest type of seizures in their patients (21 out of total 26 asthmatic patients comorbid with epilepsy) followed by absence seizures(5 out of 26 patients).

In our study, mild asthma was the commonest form of asthma (34.5%) followed by moderate asthma (27.6%) with a less common severe asthma (10.3%).

Bilan and Ghaffari [34] in their study compared the prevalence of epilepsy in various stages of asthma (from the aspect of severity) and found no meaningful difference.

On studying the temporal relationship between asthma and epilepsy, we found that the postictal asthma was the commonest (58.6%) followed by interictal asthma (34.5%) with a less common preictal (6.9%).

Regarding the family history of epilepsy, epileptic patients comorbid with asthma were highly associated with positive family of epilepsy than epileptics without asthma comorbidity (62.1% vs 42.7%). They also had a statistically significant higher positive family history for both asthma and epilepsy than epileptics without asthma comorbidity (P<0.001). This result could suggest that epilepsy and asthma are comorbid conditions and share a common genetic pathophysiological mechanisms.

In our study, atopic eczema comorbidity is slightly higher in male (52.6%), with a more common onset before epilepsy onset (81.6%) followed by onset in the same year of epilepsy onset (13.2%) with a less common onset after epilepsy onset (5.2%).

Regarding eczema severity, the mild form of eczema is the commonest form (64.8%) followed by the moderate form (23.7) with the least common sever form (7.9%). Atopic eczema occurred mainly interictally.

In our study, we found that epileptic patients with multiple comorbidites had a statistically significant longer duration of atopic eczema than epileptic patients with atopic eczema comorbidity alone (P= 0.016).

On revealing the family history of both epilepsy and eczema,the epileptic patients comorbid with atopic eczema had a statistically significant higher positive family history for both eczema and epilepsy than epileptic patients without eczema comorbidity (P<0.001). This result could suggest that epilepsy and atopic eczema are comorbid conditions and may share a common genetic pathophysiological mechanisms.

5. Summary

We found that:

- IGE was more common in male than female (55.9% vs 44.1 %). Atopic eczema was the most frequent comorbid illness (32.2%) followed by migraine (24.6%) and bronchial asthma (24.6%).
- The female sex and older age of patients were statistically significant in patients with IGE with comorbidity than those without comorbidity (P= 0.003, P 0.009 respectively).
- Family history of epilepsy was more in epileptic patients with comorbidity than IGE patients without comorbidities,but the difference was not statistically significant.
- IGE patients with multiple comorbidities had a statistically significant older age of onset than IGE patients with one comorbidity and without comorbidities (P= 0.001).
- IGE patients with multiple comorbidities were on polytherapy of AEDs more than those without or with one comorbid illnesses (p= 0.0012).
- Average prevalence of migraine in the general population about 15%.Migraine comorbidity in our study was present in 24.6% of epileptics with female preponderence (69%). MA was more common (79.3%). Migraine onset occurred after that of epilepsy in 48.2% . Mostly migraine attacks occurred interictally.

- IGE patients comorbid with migraine had a statistically significant higher female sex, mean age of epilepsy onset and positive family history of epilepsy than epileptic patients without migraine comorbidity (P = 0.0018, <0.001, 0.006 respectively).
- A polytherapy of AEDs was more commonly used in IGE patients comorbid with migraine.
- Average prevalence of bronchial asthma in children about 4%-20%.In our study bronchial asthma was present in about 24.6% of our IGE patients. Bronchial asthma comorbidity in our patients was with a more prominent onset before epilepsy (76%). It also showed that the mild asthma was the more common form and it was commonly postictally.
- IGE patients comorbid with B.A had a significantly higher positive family history of both epilepsy & B.A than epileptic patients without B.A comorbidity.
- About 20% of all children develop symptoms of atopic dermatitis at some point in their lives .In our study atopic eczema was present in about 32.2% of our IGE patients. Eczema comorbidity in our patients was with an onset more commonly prior to that of epilepsy & it occurred in a mild form usually interictally.
- Epileptic patients comorbid with atopic eczema had a significantly higher positive family history of both epilepsy & atopic eczema than epileptic patients without atopic eczema comorbidity (P<0.001).

6. Conclusion

Epilepsy, migraine, bronchial asthma and atopic eczema were comorbid conditions in our study.

Migraine was frequently (24.6%) comorbid with epilepsy especially MA, with an onset usually after epilepsy and most of its attacks occur interictally.

Bronchial asthma was commonly (24.6%) comorbid with epilepsy, with a predominent onset before epilepsy and most of its attacks occur postictally in a common mild form.

Atopic eczema was comorbid with epilepsy(32.2 %), with a predominent onset before epilepsy and it occurred in a mild form usually interictally.

IGE patients with multiple comorbidities were on polytherapy of AEDs more than those without or with one comorbid illnesses.

Family history of epilepsy was more in epileptic patients with comorbidity than IGE patients without comorbidities.

The prevalence of these diseases among patients with IGE was more than that encountered in the general population. This may be due to more association of these diseases with IGE, possibly due to more genetic link association and sharing underling some inherited pathophysiological mechanisms. This is suggested by the presence of higher family history for these diseases than epileptic alone. Also polytherapy is needed in those patients to attain remission in epilepsy.

7. Recommendations

- Better identification of epilepsy comorbidity is important from several aspects:

- it could affect the prognosis (comorbid epileptic patients were associated with less compliance and a polytherapy of AEDs).
- it could affect treatment plan treat two conditions with a single drug (e.g., valporate or topiramate may treat both epilepsy and migraine) or by imposing therapeutic limitations (e.g., tricyclic antidepressants may lower seizure threshold).
- it may provide insight into pathogenesis by revealing shared neurobiologic mechanisms underlying multiple disorders.

- Further studies will be needed for better understanding of the precise mechanisms underlying epilepsy and comorbid conditions.

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