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Risk estimation of SUDEP during COVID-19 pandemic era in a tertiary referral center

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ABSTRACT

Objective: No data exist regarding the impact of the lockdown due to the COVID-19 pandemic on the risk factors of sudden unexpected death in epilepsy (SUDEP). This study aimed to stratify risk factors of SUDEP in relation to COVID-19 lockdown, among patients with epilepsy (PWE) in Cairo University epilepsy unit (CUEU). Therefore, we can detect risk factors and mitigate such factors in the second wave of the virus.

Methods: an observational, cross-sectional study carried on 340 Egyptian patients with active epilepsy. Individual risk identification and stratification was done by using The SUDEP and seizure Safety Checklist, after which sharing risk knowledge to PWE and their caregivers was undertaken.

Results: The mean age of patients was 29.72 ± 12.12 . The median of the static factors was 4 (IQR 3–5) whereas, the median of the modifiable factors was 2 (IQR 1–3). Epilepsy emergencies (serial seizures or status epilepticus) were reported in 24.1 % of patients, for which non-compliance was the commonest cause, followed by deferral of epilepsy surgery for patients with drug resistant epilepsy (DRE). Stepwise logistic regression analysis showed that use of anxiolytic medications, non-compliance, keeping patients with DRE on dual anti-seizure medications (ASMs), or adding third medication increased the odds of increased seizure frequency by 2.7, 3.5, 16.6 and 6.1 times, respectively.

Conclusion: Some COVID-19 related issues had influenced the risk of seizure worsening including postponing epilepsy surgery for patients with DRE, non-compliance, and psychiatric comorbidities. Special attention should be paid to these issues to mitigate the risk of SUDEP.

1. Introduction

Sudden unexpected death in epilepsy (SUDEP) is the most common cause of epilepsy related deaths. Its incidence varies, it affects 0.09–1.2/1000 person-years in general epilepsy population and 9.3/1000 person-years in epilepsy surgery candidates (Keddie et al., 2016; Tomson et al., 2008). Many risk factors are associated with SUDEP. Some are modifiable and others are non-modifiable. Increased seizure frequency especially generalized tonic clonic seizures, nocturnal seizures, polytherapy are among the modifiable risk factors. While male gender, younger age of onset, longer epilepsy duration, intellectual disability are among non-modifiable risk factors (Hesdorffer and Tomson, 2013; Watkins et al., 2018). Identification of modifiable risk factors for SUDEP is essential to detect individuals who are at risk. So that risk factors can be mitigated and SUDEP can be prevented. (Whitney and Donner, 2019)

Coronavirus disease 2019 (COVID-19) is affecting many countries of the world. Africa is the last continent to be affected but it is the most

vulnerable. The first case of COVID-19 in Egypt was confirmed on 14th of February 2020 (Lone and Ahmad, 2020). Some studies expected the COVID-19 peak in Egypt to be in the middle of June 2020 (Anwar and AbdelHafez, 2020; El Desouky, 2020).

The lockdown imposed by the Egyptian government due to the pandemic, may impede patients' access to our epilepsy clinic in Qasr Al-Ainy, which is the oldest tertiary center in Middle East region to receive their regular follow up and to dispense anti-seizure medications (ASMs). On the other hand, patients with drug resistant epilepsy (DRE) whose presurgical evaluation was deferred due to the COVID-19 lockdown, present another major problem. Also, stress and anxiety may add to the increased seizure frequency during the pandemic especially in patients with epilepsy (PWE) with premorbid psychiatric disorders (Alkhotani et al., 2020).

The patients with epilepsy and their families have the right to understand the risks of their condition and to be involved in the decision-making and treatment. According to the 2012 National Institute of

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Health and Care Excellence (NICE) guidelines, tailored information about SUDEP, the patient's individual SUDEP risk and measures to reduce this risk should be discussed with patient (Excellence, 2012 accessed June 2016).

The aim of this study was to stratify risk factors of SUDEP among PWE in Cairo University epilepsy unit (CUEU) in relation to COVID-19 lockdown, by using The SUDEP and Seizure Safety Checklist paving the way for discussing the modifiable factors and future strategies with patients, in order to mitigate such factors in the second wave of the virus.

2. Methods

2.1. Study design and participants

The current study was an observational, cross-sectional study, conducted on 340 Egyptian patients with active epilepsy, who were currently on ASMs and had one or more seizures in the past year (Zack and Kobau, 2017). The study targeted PWE, of any age and both sexes, who were following up with us in the epilepsy clinic of Cairo University Epilepsy Unit (CUEU) before the emergence of the epidemic in Egypt. The patients were recruited in the period of August 15 to September 15, 2020.

With the emergence of the epidemic in Egypt, the CUEU applied the following strategy: Activating some means of Telemedicine that were appropriate to our patients' capabilities, in the form of communicating with the epilepsy team via mobile or WhatsApp, although it was of limited use before. Medications were dispensed every two months instead of every month to reduce the crowdedness and overflow in the outpatient clinic during pandemic. We emphasized with the patients, on the importance of compliance to their ASMs in seizure control. For all patients with DRE, epilepsy surgery had been postponed. Patients with DRE either were kept on double ASMs or received a third drug, according to the patient's preference. All included patients in this study were submitted to this strategy.

2.2. Data collection tools

The SUDEP and seizure Safety Checklist (Shankar et al., 2013) was conducted during face-to-face interviews with each patient or caregiver if patients were adolescents or had an intellectual disability. The SUDEP and Seizure Safety Checklist is an evidence-based tool of 19 modifiable and non-modifiable factors. Static factors are male sex, epilepsy duration (15–30 years), unclear treatment history, generalized tonic-clonic seizures, and intellectual disability. Young age (<45 years) represents a moderate risk static while early onset of epilepsy (<15 y) represents the established risk static one. Modifiable factors are increase severity of seizures (serial fits or status epilepticus), three or more ASMs, non-compliance issues, frequents ASMs prescribing changes, sub-therapeutic ASMs level, carbamazepine intake, reported alcohol intake, psychiatric comorbidities, anxiolytic medications and increase seizure frequency. The later represents the established risk modifiable one if increased more than 25 %. In case of nocturnal seizures, sleeping in prone position and no night surveillance represent the moderate risk modifiable factors.

After finishing the checklist, sharing risk knowledge to PWE and their caregivers was undertaken including individual risk identification, risk stratification and its modification if possible. At the end of discussion, the patient or the caregiver was asked this question "After the SUDEP information, please describe any positive, negative consequences or indifference?" Some examples for positive consequences were a patient's promise to adhere to treatment or interact more with the physician through the available telemedicine services. On the other hand, fear or crying expressed negative consequences.

2.3. Sampling

All PWE who visited the epilepsy clinic of CUEU during the recruitment period and fulfilled the eligibility criteria were included in the study (340 patients).

3. Ethical considerations

The ethical committee of the Faculty of Medicine, Cairo University, approved the study proposal. The study design was consistent with the requirements of Revised Helsinki Declaration of biomedical ethics.

3.1. Statistical analysis

SPSS (statistical package for social sciences) version 18.0 was used for data management and data analysis. Mean \pm standard deviation (SD) described quantitative variables and median with interquartile range (IQR) when appropriate (distribution did not follow normality). Number and percentages described qualitative data and Chi-square or / Fisher exact-tested proportion independence. Also Chi-square test for Goodness of fit was used to test an observed binomial distribution to an expected one. For comparing mean values of 2 independent groups, parametric and non-parametric *t*-test were used. Stepwise logistic regression analysis was used to detect independent variables of having increase seizure frequency as compared to not having. The likelihood of increase seizure frequency was expressed as odds ratio (OR) and 95 % confidence interval (CI). *P* value is always 2 tailed and significant at 0.05 level.

4. Results

4.1. Demographics and clinical characteristic of the study population

The present study included 340 PWE, with mean age of 29.72 \pm 12.12. The majority of patients were females (178, 52.4 %) versus 162 males (47.6 %). Regarding the etiology, (109, 32 %) patients had idiopathic, (151, 44.4 %) had symptomatic, and (80, 23.6 %) had unknown etiology. Only 116 (34.1 %) patients had DRE, 66 of them had lesional DRE (56.9 %) while 50 patients (43.1 %) had non-lesional DRE.

4.2. Static and modifiable risk factors of SUDEP among the study population

The median risk factors of SUDEP was 6 per patient with IQR 4–8. The median of the static factors was 4 with IQR 3–5 whereas, the median of the modifiable factors was 2 with IQR 1–3. Distribution of different static and modifiable risk factors listed in the SUDEP and Seizure Safety Checklist among the study population was shown in Table 1.

4.3. Consequences after individual risk identification and risk stratification

After individual risk stratification by using the SUDEP and Seizure Safety Checklist, the majority of the study population (259, 76.2 %) showed positive consequences; while 50 patients (14.7 %) had negative consequence and only (31, 9.1 %) had indifference.

4.4. Epilepsy emergencies during the COVID-19 pandemic

During the pandemic, 82 PWE (24.1 %) of our sample had epilepsy emergencies either in the form of serial fits or status epilepticus (SE), for which non-compliance was accused in the majority of them (65.8 %), while deferral of epilepsy surgery for patients with DRE was the cause in 34.2 %.

Table 1
Distribution of static and modifiable risk factors of SUDEP among the study population.

n (%)	
1-Static factors	
Male sex	162 (47.9 %)
Epilepsy duration > 15 y	164 (48.2 %)
Unclear treatment history	67 (19.7 %)
Generalized tonic-clonic seizures	273 (80.3 %)
IQ < 70	72 (21.2 %)
Younger age < 45 y	299 (88 %)
2- Modifiable factors	
Increase severity of seizures	82 (24.1 %)
Three or more ASMs	84 (24.7 %)
Non-compliance	86 (25.3 %)
Frequent ASMs prescribing changes	59 (17.3 %)
Sub therapeutic ASMs level	29 (8.5 %)
Carbamazepine	133 (39.1 %)
Reported alcohol problem	4 (1.2 %)
Depression	47 (13.8 %)
Anxiolytic medications	22 (6.4 %)
3- Moderate Risk-Modifiable Factors*	
No surveillance at night	56 (16.4 %)
Sleeping in prone position	57 (16.8 %)
4- Established Risk Static Factors	
Early onset of epilepsy < 15y	214 (62.6 %)
5-Established Risk Modifiable Factors	
Increase seizure frequency	(25 %)

IQ: intelligence quotient, ASM: anti-seizure medications.

* Only 183 patients had nocturnal seizures.

4.5. Factors in relation to increased seizure frequency during the COVID-19 pandemic

Several factors were significantly associated with increase in seizure frequency (Table 2). Stepwise logistic regression analysis was performed for prediction of having increased seizure frequency using the following variables in the model : age, depression, DRE strategy of giving dual therapy, DRE strategy of giving triple therapy, non-compliance, DRE lesional or not, sex, nocturnal seizures, early onset of epilepsy, sub therapeutic ASMs level, and, anxiolytic medications.

Age, DRE strategy of giving dual therapy or giving triple therapy, non-compliance, and anxiolytic medications were retained as independent risk factors associated with increased seizure frequency (Table 3).

Use of anxiolytic medications, non-compliance, keeping patients with DRE on dual ASMs or adding third medication were associated with increased the odds of increased seizure frequency by 2.7, 3.5, 16.6 and 6.1 times, respectively (Table 3).

5. Discussion

This is the first study to measure the impact of COVID-19 pandemic era on risk factors of SUDEP. It is important to identify modifiable factors contributing to the high risk of SUDEP due to this pandemic, so that we can work to minimize them in the second wave of the virus. We totally believe that future changes to improve seizure risk outcomes is a shared responsibility with clinicians and PWE, which was facilitated by using the SUDEP and Seizure Safety Checklist.

Although, the median risk factors of SUDEP was apparently high per patient (6, IQR 4–8), the weight of the static factors (Median 4, IQR 3–5) was higher compared to that of the modifiable factors (Median 2, IQR 1–3).

This study showed that 25.3 % of patients were not compliant. Non-compliance issues may occur because of the difficulty of obtaining medications or lack of motivation associated with underlying psychiatric comorbidities. This can be alleviated during the expected second wave by expanding telemedicine service, purchasing prescription drugs for a longer duration, and special care of PWE with psychiatric comorbidities. However, the use of telemedicine is limited in developing

Table 2
Comparison between patients with increase seizure frequency and those without regarding different risk factors.

	No increase in seizure frequency (n = 255)	Increase in seizure frequency (n = 85)	P value
Age (mean ± SD)	30.6 ± 12.2	27 ± 11.3	0.01
Sex	Males	112 (43.9 %)	50 (58.8 %)
	Females	143 (56.1 %)	35 (41.2 %)
Early onset of epilepsy	>15 y	103 (40.8 %)	23 (27.1 %)
	< 15y	152 (59.2 %)	62 (72.9 %)
Epilepsy duration	< 15 y	130 (51 %)	46 (54.1 %)
	>15 y	125 (49 %)	39 (45.9 %)
IQ	> 70	207 (81.2 %)	61 (71.8 %)
	< 70	48 (18.8 %)	24 (28.2 %)
Generalized tonic-clonic seizures	No	47 (18.4 %)	20 (23.5 %)
	Yes	208 (81.6 %)	65 (76.5 %)
Sleep related epilepsy	No	127 (49.8 %)	30 (35.3 %)
	Yes	128 (50.2 %)	55 (64.7 %)
DRE	No	195 (76.5 %)	28 (32.9 %)
	Yes	59 (23.5 %)	57 (67.1 %)
DRE*	Not lesional	25 (42.4 %)	26 (45.6 %)
	Lesional	34 (57.6 %)	31 (54.4 %)
DRE strategy	Dual ASMs	14 (23.7 %)	18 (31.6 %)
	Triple ASMs	45 (76.3 %)	39 (68.4 %)
Etiology	Idiopathic	83 (32.6 %)	27 (31.8 %)
	Symptomatic	109 (42.7 %)	42 (49.4 %)
Carbamazepine	Unknown	63 (24.7 %)	16 (18.8 %)
	No	158 (62 %)	49 (57.6 %)
Non-compliance	Yes	97 (38 %)	36 (42.4 %)
	No	199 (78 %)	55 (64.7 %)
Frequent ASMs prescribing changes	Yes	56 (22 %)	30 (35.3 %)
	No	224 (87.8 %)	57 (67.1 %)
Sub therapeutic ASMs level	Yes	31 (12.2 %)	28 (32.9 %)
	No	239 (93.7 %)	72 (84.7 %)
Reported alcohol problem	Yes	16 (6.3 %)	13 (15.3 %)
	No	252 (98.8 %)	84 (98.8 %)
Depression	Yes	3 (1.2 %)	1 (1.2 %)
	No	225 (88.2 %)	67 (78.8 %)
Anxiolytic medications	Yes	30 (11.8 %)	18 (21.2 %)
	No	243 (95.3 %)	75 (88.2 %)
	Yes	12 (4.7 %)	10 (11.8 %)

SD: standard deviation, IQ: intelligence quotient, DRE: drug resistant epilepsy, ASMs: anti-seizure medications.

* 116 patients had DRE.

Table 3
Independent predictors of increased seizure frequency during the pandemic by stepwise logistic regression.

	B	P value	Odds ratio	95 % CI
Age	-0.03	0.02	0.97	0.95 to 0.99
DRE on dual ASMs	2.8	<0.001	16.6	6.9–39.4
DRE on triple ASMs	1.8	<0.001	6.1	3.2–11.5
Non-compliance	1.24	0.002	3.5	1.8 to 6.7
Anxiolytic medications	1	0.048	2.7	1 to 7.4
Constant	-1.62	<0.001		

R square 0.3.

CI: Confidence interval, DRE: drug resistant epilepsy, ASMs: anti-seizure medications.

countries, and its expansion is a challenge where the some people's culture lacks the use of technology (Combi et al., 2016). This study revealed that non-compliance was associated with increased the odds of seizure frequency by more than three times.

The most affected group during the epidemic is the DRE group, who were preparing for epilepsy surgery and deferred due to the epidemic circumstances. In this study, the majority of patients with DRE (71.8 %) were on three ASMs, although adding third ASM opposes the definition of DRE (Jobst, 2015). Nevertheless, the strategy of adding a third ASM was associated with increasing the odds of increasing seizure frequency

by only 6 times while the odds were increased to 16 times by maintaining the same dual ASMs. For the expected second wave, some bridge therapies that do not necessitate hospitalization must be raised as options for patients with DRE, as ketogenic diet (Williams and Cervenka, 2017) and intermittent fasting (Hartman et al., 2013). However, the real risk of proceeding and the real risk of deferral on epilepsy surgery should be considered case by case. Even if these bridge therapies are not implemented, the addition of a third drug will be the best scenario as a temporary solution.

Escalating COVID-19 crises may exacerbate mental stress in PWE with underlying psychiatric comorbidities via exaggerated fear of infection, lifestyle disturbances, economic insecurity, social distance, or changes in medication compliance, all of which may affect the frequency of seizures (Kuroda, 2020). Indeed, use of anxiolytic medications was associated with increase the likelihood of increasing seizure frequency by 2.7 times during the pandemic. For the expected second wave, collaboration with psychiatric team should be revitalized with proper awareness and delivering correct information to reduce unnecessary anxiety and stress in this vulnerable group.

In this study, the most common reported cause of SE occurrence was the non-compliance (65.8 %), while deferral of epilepsy surgery for patients with DRE was the second cause in 34.2 %. A previous study conducted in our center 2 years ago, revealed that lesional DRE was the most common cause of SE cases (Othman et al., 2020). This confirms that the extent of non-adherence to ASMs among PWE increased during the epidemic period.

Ultimately, the emotional consequences of the patients or their relatives had to be evaluated after educating the patients about SUDEP. However, the positive consequences reported by the majority of our patients (76.2 %) are very promising. This reflects patients' willingness to cooperate with us in order to modify the factors that contributed to the increased risk of SUDEP. Patients who have developed panic should be given special psychiatric care, otherwise the study will be counter-productive. For example, some people may decide to discontinue their treatment as long as death awaits them.

The main limitation of this study was its cross-sectional design, assessing the current risk of SUDEP without putting into consideration the baseline risk before the pandemic. Follow up of our patients to assess changes in SUDEP risk during the coming second wave is mandatory.

6. Conclusion

Seizure frequency might be aggravated by factors associated with COVID-19 lockdown as postponing epilepsy surgery for patients with DRE, non-compliance, and psychiatric comorbidities. More efforts are needed to eliminate such barriers, with the ultimate goal of reducing the risk of SUDEP.

Declaration of Competing Interest

Neither of the authors has any conflict of interest to disclose.

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