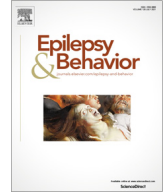




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Brief Communication

COVID-19 among patients with epilepsy: Risk factors and course of the disease

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ABSTRACT

Introduction: The study assessed the prevalence and risk factors for SARS-CoV-2 infection in patients with epilepsy (PWE). Additionally, the course of COVID-19 and its impact on seizure control was investigated.

Material and methods: Subjects with definite (confirmed by positive RT-PCR nasopharyngeal swab or serum anti-SARS-CoV-2 antibodies) and probable COVID-19 were identified via telephone survey among PWE treated at the university epilepsy clinic.

Results: Of 252 screened subjects, 17 (6.7%) had definite and 14 (5.5%) probable COVID-19. The percentage of PWE with definite COVID-19 was much higher than the percentage of subjects with confirmed COVID-19 in Polish general population (3.65%). In the heterogeneous population of PWE, including patients with drug-resistant epilepsy, physical/intellectual disability, and comorbidities, we were not able to identify any risk factors for contracting COVID-19. The course of infection was mild or moderate in all subjects, not requiring oxygen therapy or respiratory support. The most common symptoms were fever, fatigue, headaches, muscle aches, and loss of smell/taste and continued for approximately 7–21 days, except for loss of smell/taste which lasted usually several weeks. Seizure exacerbation was noted in only one pregnant patient with confirmed COVID-19 and it was likely related to decreased serum level of levetiracetam in the third trimester.

Conclusion: The study provided reassuring findings related to the low risk of seizure exacerbation in PWE during the course of COVID-19. Patients with epilepsy may be at increased risk of SARS-CoV-2 infection. Epilepsy characteristics are not likely to modify the risk of COVID-19.

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1. Introduction

Although the most typical manifestations of COVID-19 are fever and respiratory illness, up to one-fifth of patients may develop neurological symptoms, including new-onset seizures [1]. Moreover, electroencephalographic abnormalities have been reported in 90% of patients with SARS-CoV-2 infection [2]. A number of studies reported severe psychological distress, limited access to face-to-face epilepsy care, and difficulties in obtaining antiseizure medications in patients with epilepsy (PWE), resulting in seizure exacerbation in many cases [3–6]. Otherwise, the data on the prevalence of COVID-19 in PWE and the impact of infection on the course of epilepsy are limited [3,7]. Patients with chronic disorders seem to be at higher risk of COVID-19 and the severe course

of the disease [8]. Epilepsy is the one of the most prevalent chronic neurological conditions and PWE are likely to have somatic and psychiatric comorbidities, thus subject with epilepsy may be more predisposed both to COVID-19 and its more severe course. Furthermore, COVID-19 symptoms, especially fever may lower seizure threshold and increase seizure frequency [9].

Thus, we decided to study the prevalence and risk factors for SARS-CoV-2 infection in PWE. Additionally, we investigated the course of COVID-19 and its impact on seizure control in the cohort of PWE treated in a university epilepsy clinic.

2. Material and methods

Adult PWE who had been followed up for at least one year and were seen in the university epilepsy clinic (Kraków, Poland) between July 1, 2019 and December 31, 2021 were eligible. Patients with progressive neurological disorders and with psychogenic nonepileptic seizures were excluded. The following data were collected by means of the structured questionnaire: age,

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sex, age at onset of epilepsy, epilepsy characteristics and its treatment, seizure frequency (seizure freedom was defined as lack of seizures within the past 12 months) the presence of physical or intellectual disability, comorbidities, and employment status. The following COVID-19-related information was collected via telephone calls: symptoms, duration of symptoms, treatment, and impact of SARS-CoV-2 infection on seizure control. Additionally, the access to healthcare during the pandemic was evaluated by means of telephone survey among subjects or caregivers (in case of aphasia or intellectual disability) after their oral informed consent was obtained. The survey was conducted by neurologists and neurology residents. Definite COVID-19 was diagnosed in patients with symptoms and positive RT-PCR nasopharyngeal swab or serum anti-SARS-CoV-2 IgM/IgG antibodies. Probable COVID-19 was diagnosed in following cases: (a) in patients with at least four typical symptoms (fever, fatigue, cough, shortness of breath or difficulty breathing, muscle or body aches, headache, sore throat, congestion or runny nose, new loss of taste or smell, nausea or vomiting, diarrhea); (b) in patients with at least two symptoms including new loss of taste or smell; (c) in patients with at least two symptoms and laboratory confirmed SARS-CoV-2 infection in a household member. These criteria were based on WHO case-definition with one additional feature required [10]. Seizure control had been evaluated from the beginning to the end of COVID-19 symptoms, excluding long-lasting loss of smell/taste and fatigue. The study was approved by the university ethics committee.

Variables were characterized either as a median with interquartile range (q_1 – q_3), or as percentages. The significance of the differences between groups of PWE infected with SARS-CoV-2 and others were analyzed using the χ^2 test or Fisher exact test or with Mann–Whitney U -test.

Firstly, univariate analysis of factors that differ between PWE with and without COVID-19 was made. Then, analysis of independent factors that influenced the occurrence of COVID-19 (dependent variable) was performed by logistic regression modeling.

Models were created using stepwise method: backward selection with determining criterion likelihood ratio for variables selection. A p -value of less than 0.05 was considered statistically significant for parameters in the final model.

3. Results

3.1. Patients

Of 333 eligible patients, 75 could not be reached and 6 refused to participate. Finally, 252 PWE completed the survey. The median age of the study participants was 33 (27–42) years. The majority of patients had focal epilepsy and most of them had drug-resistant epilepsy. The most commonly prescribed antiseizure medication (ASM) were levetiracetam (LEV), valproate, and lamotrigine. Sixty six (26.2%) subjects had physical and/or intellectual disability and one third of the cohort had at least one comorbid condition. Demographic and clinical features of the studied group are described in Table 1.

3.2. The course of SARS-CoV-2 infection and its risk factors

Seventeen patients had COVID-19 confirmed in all but one with positive RT-PCR test. Detailed demographic, epilepsy-related, and SARS-CoV-2 infection characteristics of PWE with definite COVID-19 are presented in Table 2. The most common symptoms were fever, fatigue, headaches, muscle aches, and loss of smell/taste and continued for approximately 7–21 days, except for loss of smell/taste which lasted usually several weeks. Additionally, 14 patients had probable COVID-19 with fatigue (9/14), headaches (9/14), fever (8/14), cough (8/14), and loss of smell/taste (5/14), shortness of breath (4/14), muscle aches (4/14), sore throat (3/14), and diarrhea (1/14). The course of infection was mild or moderate and all but one patient were treated at home with nonsteroidal anti-inflammatory

Table 1
Comparison of demographic and epilepsy characteristics, disability, comorbidities, and employment status between patients with definite, definite and probable COVID-19 infection, and patients with no history of COVID-19 infection.

Variable	All subjects N = 252	Definite COVID-19 N = 17 (6.7%)	Definite and probable COVID-19 N = 31 (12.3%)	Patients without COVID-19 N = 221 (87.7%)	P-value ¹ Patients with definite COVID-19 vs. patients without COVID-19	P-value ¹ Patients with definite and probable COVID-19 vs. patients without COVID-19
Gender (female)	154 (61.1%)	14 (82.3%)	21 (67.7%)	133 (60.2%)	0.07	0.42
Age	33 (27–42)	33 (30–40)	33 (28–39)	33 (26–42)	0.82	0.87
Age at onset	16 (10–22)	16 (13–25)	16 (12–25)	16 (9–21)	0.24	0.50
Type of epilepsy						
Generalized	46 (18.2%)	3 (17.6%)	7 (22.6%)	39 (17.6%)	1.0	0.50
Focal	189 (75.0%)	11 (64.7%)	20 (64.5%)	169 (76.5%)	0.28	0.15
Mixed or unknown	17 (6.8%)	3 (17.6%)	4 (12.9%)	13 (5.9%)	0.09	0.14
Number of AEDs						
0	2 (0.8%)	0	0	1 (0.4%)	–	–
1	121 (48.0%)	12 (70.6%)	20 (64.5%)	101 (45.7%)	0.07	0.049
2	83 (32.9%)	4 (23.5%)	6 (19.3%)	77 (34.8%)	0.43	0.08
3	39 (15.5%)	1 (5.9%)	3 (9.7%)	36 (16.3%)	0.48	0.43
4–5	7 (2.8%)	0	2 (6.4%)	5 (2.7%)	1.0	0.21
Polytherapy	129 (51.2%)	5 (29.4%)	11 (35.5%)	118 (53.4%)	0.08	0.06
Seizure freedom	94 (37.3%)	8 (47.0%)	13 (41.9%)	81 (36.6%)	0.39	0.57
Employed	106 (42.1%)	10 (58.8%)	16 (51.6%)	90 (40.7%)	0.14	0.25
Intellectual disability	44 (17.5%)	1 (5.9%)	2 (6.4%)	42 (19.0%)	0.32	0.13
Physical disability	47 (18.6%)	1 (5.9%)	5 (16.1%)	42 (19.0%)	0.32	0.81
Comorbidities	91 (36.1%)	5 (29.4%)	8 (25.8%)	83 (37.5%)	0.60	0.20

¹ χ^2 test (or Fisher exact test where appropriate) except for age (Mann–Whitney U -test).

Table 2
Demographic, epilepsy characteristics and COVID-19 symptoms in patients with laboratory confirmed infection.

	Sex/age/age at onset	Epilepsy type/remission/ number of ASM	Additional clinical information	COVID-19 symptoms
1	F/43/24	f/Y/1 (LEV)		fever, fatigue, cough, muscle aches, diarrhea, loss of smell/taste, tachycardia
2	M/27/19	f/N/2 (CBZ, LEV)		fatigue, cough, headaches
3	F/23/13	g/Y/1 (LEV)		fever, headaches, muscle aches, loss of smell/taste
4	F/44/15	m/Y/1 (CBZ)	comorbidities	fever, fatigue, headaches, muscle aches, diarrhea, loss of smell/taste
5	F/55/15	f/Y/1 (LEV)		fever, fatigue, shortness of breath, muscle aches, body aches, loss of smell/taste
6	M/64/59	f/Y/2 (VPA, LEV)	comorbidities	fatigue, cough, shortness of breath, loss of smell/taste, loss of appetite
7	F/33/25	m/Y/1 (LEV)		fever, fatigue, cough, shortness of breath, headaches, muscle aches, diarrhea, vomiting, loss of smell/taste
8	M28/1	f/N/2 (LEV, LCM)	ID/PD/comorbidities	fever, fatigue, headaches, muscle aches
9	F/30/23	f/N/1 (LCM, GBP)		fever, fatigue, cough, headaches, muscle aches
10	F/31/11	f/Y/1 (LEV)	comorbidities	fever, fatigue, muscle aches
11	F/33/12	f/N/3 (LEV, LCM, TPM)		fever, fatigue, cough, headaches, chest pain
12	F/39/14	m/N/1 (LTG)		fever, fatigue, cough, headaches, muscle aches, loss of smell/taste
13	F/40/38	f/Y/1 (LEV)		fever, fatigue, sore eyes, loss of smell/taste
14	F/19/9	f/N/1 (CBZ)		fever, fatigue, headaches, sore throat, loss of smell/taste
15	F/30/16	g/N/1 (LEV)	comorbidities	headaches, loss of smell/taste
16	F/34/30	f/N/1 (LEV)		fever, fatigue, loss of smell/taste, conjunctivitis
17	F/33/13	f/N/1 (LEV)		fever, diarrhea, loss of smell/taste

Abbreviations: M-male, F-female, f-focal, g-generalized, m-mixed or unknown, ASM-antiseizure medication, CBZ-carbamazepine, GBP-gabapentin, LCM-lacosamide, LTG-lamotrigine, LEV-levetiracetam, TPM-opiramate, VPA-valproate, ID-intellectual disability, PD-physical disability.

drugs and antibiotics. Patient no. 8 with comorbid hepatitis B, treated with tenofovir, was hospitalized at the department of infectious diseases for 3 weeks with mild symptoms and required neither oxygen therapy nor respiratory support.

Among patients with definite COVID-19 five subjects worked at hospital (two nurses, one medical assistant, one medical secretary, one laboratory technician).

Increased seizure frequency was reported by one patient with definite COVID-19. A 31-year-old woman, who was seizure-free until the 33rd week of pregnancy (patient no. 10) experienced 4 tonic-clonic seizures within 2 weeks after positive RT-PCR test. Levetiracetam dosage was increased with subsequent seizure-freedom and she delivered a healthy daughter at term.

Among patients with probable COVID-19, a 28-year-old male with Unverricht-Lundborg disease experienced slight and transient increase in myoclonus frequency related to fever.

The subgroups of PWE with definite COVID-19 and separately with definite and probable COVID-19 were compared with patients without COVID-19 in terms of age, sex, age at onset of epilepsy, epilepsy type, seizure frequency (seizure freedom versus drug-resistant epilepsy), pharmacotherapy, the presence of physical or intellectual disability, comorbidities, and employment status (Table 1), but no significant difference was found. Regression models did not reveal any significant predictor of COVID-19 in the studied cohort.

3.3. Access to healthcare

The majority of PWE (178, 70.6%) reported limited access to health services during the pandemic, including: difficulties in obtaining antiseizure medications (92, 36.5%), limited access to general practice services (81, 32.1%), specialist consultations (60, 23.8%), or diagnostic studies (24, 9.5%). Most general practice services and specialist consultations were provided by means of telemedicine. Follow-up consultations at our epilepsy center were provided from March 11 to May 31 via telephone calls, and initial appointments were postponed to June. From June onward we offered face-to-face visits and teleconsultations on patients' request.

4. Discussion

In this study, we aimed to evaluate the prevalence and risk factors for SARS-CoV-2 infection in PWE.

Since the identification of the first case of SARS-CoV-2 infection in March 2020, the total number of confirmed COVID-19 cases in Poland reached 1 404 905 at the time of last evaluation in our study (January 13, 2021), which represents 3.65% of Polish population [11]. The prevalence of definite and definite and probable COVID-19 was much higher in our cohort – 6.7% and 12.3%, respectively. These results suggest that PWE may be at increased risk of COVID-19. We believe that this finding should be regarded with caution due to the relatively small sample and the lack of plausible biological explanation for the direct association between those two conditions. It rather seems to reflect the greater number of comorbidities among PWE or different strategies of testing against potential COVID-19 in the population studied and the general population. In this regard, it is worth mentioning that five out of 17 patients with confirmed COVID-19 were hospital staff, put at increased risk of SARS-CoV-2 infection. Further studies are needed to investigate the role of underlying conditions, comorbidities or more frequent use of healthcare resources in potentially increased risk of COVID-19. Previous studies on COVID-19 prevalence among PWE are few and provide conflicting results. Suspected COVID-19 was found in 10.2% of surveyed PWE in New York City [3] and Cabezudo-Garcia et al. reported a higher cumulative incidence of COVID-19 in PWE than in patients without epilepsy [12], while the risk of contracting COVID-19 was not increased in PWE in the Iranian study [13].

The results of our study are consistent with available reports suggesting that seizures in PWE are infrequently worsened by COVID-19 [3,14,15]. We noted seizure exacerbation in only one out of 17 patients with confirmed COVID-19. However, increase in seizure frequency in a pregnant woman was likely related to decreased serum level of LEV in the third trimester. Even though somatic comorbidities associated with more severe COVID-19 course (e.g., cardiovascular disease, diabetes mellitus, chronic respiratory disease) were present in the substantial proportion of our patients, the course of infection was mild or moderate in all subjects. It might be explained by the fact that the median age of the studied patients was 33 years and young age was found to be associated with an asymptomatic or mild course. We were not able to identify any risk factors for contracting COVID-19. It may be related to a relatively small number of studied subjects. Otherwise, our cohort was heterogenous in terms of epilepsy type, seizure frequency, pharmacotherapy, the presence of disabilities, comorbidities, and employment status. Similarly to other studies [3,6,14–16],

majority of patients reported limited access to health care during the pandemic.

We acknowledge several limitations related to our findings and their interpretation. Firstly, the cohort of studied patients was relatively small. Secondly, our study did not comprise the control group. Thirdly, subjects answered many questions retrospectively; thus seizure counts and the recall of the COVID-19 course may not have been entirely reliable. Finally, our cohort involved subjects followed up in tertiary epilepsy clinic, thus patients with more severe course of epilepsy in terms of seizure frequencies, polytherapy, and comorbidities were overrepresented.

5. Conclusion

Patients with epilepsy may be at increased risk of COVID-19, but the risk of seizure exacerbation in PWE during the course of COVID-19 is low. Epilepsy characteristics are not likely to modify the risk of COVID-19. Future studies are needed to investigate the prevalence and risk factors for SARS-CoV-2 infection in PWE.

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Conflicts of Interest

MB received honoraria for publications from Sanofi; honoraria for lectures, travel expenses, and conference fees from Sanofi, Adamed, Teva Pharmaceutical, Neuraxpharm, Glenmark, UCB Pharma, Zentiva.

IM and KW have nothing to declare.

AS received honoraria for lectures from Bayer, Boehringer Ingelheim, Novartis, Polpharma, Bristol-Myers Squibb, Novartis, Biogen, Teva Pharmaceutical, Medtronic; for the participation in advisory meetings from Bayer, Boehringer Ingelheim, Novartis.

WT received honoraria for publications from Sanofi-Genzyme; honoraria for lectures, travel expenses, and conference fees from Shire, Takeda, CSL Behring, and Merck.

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