Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandar in on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Considering temporality in causal relationship between seizure worsening and psychological stress in patients with epilepsy during the COVID-19 pandemic: A systematic review

Naoto Kuroda a,b,⇑, Ayataka Fujimoto c

a Department of Pediatrics, Wayne State University, Detroit, MI, USA
b Department of Epileptology, Tohoku University Graduate School of Medicine, Sendai, Japan
c Comprehensive Epilepsy Center, Seirei Hamamatsu General Hospital, Hamamatsu, Japan

Abstract

Objective: To investigate whether published studies that identified a causal relationship between psychological stress and seizure worsening in patients with epilepsy during the coronavirus disease 2019 (COVID-19) pandemic considered the temporality of Hill’s criteria.

Method: A systematic review approach was used to comprehensively search MEDLINE, CENTRAL, EMBASE, and ClinicalTrials.gov databases for relevant studies. Studies that reported an association between psychological stress and seizure worsening in patients with epilepsy during the COVID-19 pandemic were included accordingly. The quality of assessments in each study was evaluated and an assessment for considering temporality in the causal relationship between the two events in each study was carried out.

Results: Seventeen studies were included in the analysis. Most (14/17) were cross-sectional studies and only four out of these 17 studies (23.5%) considered temporality in the causality. Further, these four studies did not consider temporality in the study design, they only described it as a limitation.

Conclusion: We found that many articles reported a causal relationship between psychological stress and seizure worsening without considering temporality. As both researchers and readers, we need to consider temporality when interpreting the causal relationship between increased psychological stress and seizure worsening in patients with epilepsy during the COVID-19 pandemic.

1. Introduction

Worldwide, the coronavirus disease 2019 (COVID-19) pandemic has strongly influenced societies, including patients with epilepsy [1]. Indeed, there are many studies being conducted to examine seizure control in patients with epilepsy during this pandemic.

Abbreviations: COVID-19, coronavirus disease 2019; DASS-21, Depression, Anxiety, and Stress Scale 21 items; PSQI, Pittsburgh Sleep Quality Index; GAD-7, General Anxiety Disorder-7; HADS, Hospital Anxiety and Depression Scale; BAI, Beck Depression Inventory Scale II; IES-R, Impact of Event Scale-Revised; CS, Cross-sectional study; CH, Cohort study; PwE, patients with epilepsy; VNS, vagus nerve stimulation; ANOVA, analysis of variance; N.D., not described; PS, psychological stress; SW, seizure worsening.

⇑ Corresponding author at: Department of Pediatrics, Wayne State University, 3901 Beaubien St, Detroit, MI 48201, USA.
E-mail address: naoto.kuroda@wayne.edu (N. Kuroda).

https://doi.org/10.1016/j.yebeh.2021.108184
1525-5050/© 2021 Elsevier Inc. All rights reserved.
2. Materials and methods

2.1. Searching strategy

We conducted a search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [3]. This review protocol has not been previously registered. The MEDLINE (accessed from PubMed), CENTRAL (accessed from the Cochrane Library), and EMBASE databases were systematically searched for studies published up to March 20, 2021. In the PubMed database, the following key words were searched: (“Epilepsy”[MeSH Terms] OR “Epilepsy”[Title/Abstract] OR “seizure disorder”[Title/Abstract]) AND (“COVID-19”[MeSH Terms] OR “COVID-19”[Title/Abstract] OR “2019 ncov infection”[Title/Abstract] OR “SARS-CoV-2”[Title/Abstract] OR “2019 novel coronavirus”[Title/Abstract]). The following keywords were searched in the Cochrane libraries: ([mh Epilepsy] OR Epilepsy:ti,ab OR “seizure disorder”:ti,ab) AND ([mh COVID-19] OR [mh SARS-CoV-2] OR COVID-19:ti,ab OR “2019 ncov infection”:ti,ab OR SARS-CoV-2:ti,ab OR “2019 novel coronavirus”:ti,ab). In the EMBASE, the following key words were searched: (“Epilepsy”/exp OR Epilepsy:ti,ab OR “seizure disorder”:ti,ab) AND (“COVID-19”/exp OR “SARS-CoV-2”/exp OR COVID-19:ti,ab OR “2019 ncov infection”:ti,ab OR SARS-CoV-2:ti,ab OR “2019 novel coronavirus”:ti,ab). We also used ClinicalTrials.gov to search for unpublished, ongoing, terminated, or completed studies to minimize the influence of publication bias. We screened the reference lists of all identified articles for additional relevant studies.

2.2. Eligibility and risk-of-bias assessment

Studies were included based on the following criteria: (1) studies that investigated seizure worsening in patients already diagnosed with epilepsy; (2) studies that investigated the increased psychological stress or new-onset psychiatric disorders during the COVID-19 pandemic (including anxiety, depression, and sleep disturbance); (3) studies that investigated the association between seizure worsening and psychological stress in patients with epilepsy (or their caregivers) during the COVID-19 pandemic; and (4) studies that performed statistical analyses. We did not include studies focused on patients with epilepsy during the pandemic, which reported only the number or proportion of patients with epilepsy who had pre-existing psychiatric disorders as demographic data and did not assess anxiety, depression, or stress during the pandemic. This was because the existence of pre-existing psychiatric disorders before the COVID-19 pandemic did not reflect the influence of COVID-19 on patients with epilepsy. We excluded studies (1) that were not yet recruiting, currently recruiting, or were withdrawn according to Clinical.Trials.gov; and (2) studies that reported patients diagnosed with psychogenic nonepileptic seizures. Studies written in languages other than English were excluded accordingly. We did not limit the search by article type.

To assess the quality of the included articles, we scored the level of risk of bias using the risk of bias instrument for cross-sectional surveys of attitudes and practices contributed by the CLARITY group at McMaster University [4] and Joanna Briggs Institute checklist for cohort studies [5].

---

**Fig. 1.** Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of this research.
| Authors, year | Country | Study period | Participants' study design | Statistical design | Stress associated with seizure worsening | Seizure worsening | Cause | Consequence | Consideration of temporality | Quality score |
|--------------|--------|--------------|--------------------------|--------------------|------------------------------------------|------------------|-------|-------------|----------------------------|--------------|
| Rosengard et al. [6] | NY, USA | Mar 1–May 31, 2020. | CS 177 PwE | Mann–Whitney U test between seizure worsening group and non-seizure worsening group | Increased/worsened stress due to the COVID-19 pandemic | Difference in reported seizure frequency between 2019 and 2020 | PS | SW | Discussed as limitation | 3/5 |
| Abokalawa et al. [7] | Kuwait | Jan 8–Oct 8, 2020 | CS 151 PwE | Multivariate logistic regression analysis | DASS-21/PSQI | Worsening of seizures during the pandemic (Yes/No) | PS | SW | Discussed as limitation | 3/5 |
| Grande et al. [8] | Italy | Apr–May, 2020 | CS 30 PwE who underwent VNS surgery | Student's t-test/ Wilcoxon's test | BAI II/GAD-7/PSQI | Difference in reported seizure frequency for 50 days between before and after 3/11/2020 | PS | SW | Discussed as limitation | 4/5 |
| Tedrus et al. [9] | Brazil | Aug 1–Sep 10, 2020 | CS 114 PwE | N.D. | Likert questions (self-reported nervousness) | Increase in the number of seizures in the COVID-19 pandemic | PS | SW | Discussed as limitation | 3/5 |
| Huang et al. [10] | China | Feb 23–Mar 5, 2020 | CS 362 PwE | Multivariate logistic regression analysis | Worries about the adverse effect of the outbreak on overall seizure-related issues | Experienced an increased number of seizures (Yes/No) | PS | SW | None | 4/5 |
| Alkhotani et al. [11] | Saudi Arabia | Apr, 2020 | CS 156 PwE | ANOVA | Self-reported stress/ change in sleep during the pandemic | Change in seizure control after the pandemic | PS | SW | None | 2/5 |
| Aledo-Serrano et al. [12] | Spain | Apr 7–Apr 11, 2020 | CS 277 caregivers of individuals with genetic developmental and epileptic encephalopathies | Multivariate logistic regression analysis | Anxiety and depression | New-onset anxiety | PS | SW | None | 3/5 |
| Conde Blanco et al. [13] | Spain | N.D. | CS | N.D. | Anxiety and depression | Increased seizure frequency | PS | SW | None | 1/5 |
| Assenza et al. [14] | Italy | Apr 11–Apr 16, 2020 | CS 456 PwE | Multivariate logistic regression analysis | PSQI | Number of seizures | PS | SW | None | 4/5 |
| Nakamoto et al. [15] | HI, USA | Apr 22–May 18, 2020 | CS 67 PwE | N.D. | New or worsening depression/anxiety/ sleep problems | Worsened outcomes | PS | SW | None | 3/5 |
| Fonseca et al. [16] | Spain | Mar 16–Apr 17, 2020 | CS 255 PwE | Multivariate logistic regression analysis | Insomnia (sleep disturbance) | Changes in seizure frequency | PS | SW | None | 3/5 |
| Koh et al. [17] | Malaysia | Jun 7–Jul 5, 2020 | CS 461 PwE | Multivariate logistic regression analysis | Anxiety/inadequate sleep | Seizure worsening (Yes/No) | PS | SW | None | 3/5 |
| Millevert et al. [18] | Belgium | Jul 26–Dec 3, 2020 | CS 407 participants (337 PwE and 70 caregivers) | Multivariate logistic regression analysis | HADS | Seizure frequency (increased/decreased/no change/not applicable) | PS | SW | None | 3/5 |
| Rathore et al. [19] | India | Sep 26–Oct 6, 2020 | CS 325 PwE | Multivariate logistic regression analysis | More worried about your epilepsy control during the pandemic | Worsening of seizures during the pandemic | SW | PS | None | 3/5 |
| Sanchez-Larsen et al. [20] | Spain | May 17–Jun 7, 2020 | CH 100 PwE | Multivariate logistic regression analysis | Changes in stress/ anxiety | Increase of >50% of seizure frequency | PS | SW | None | 6/11 |
| d’Orsi et al. [21] | Italy | Jan–Jun, 2020 | CH 102 PwE | Multivariate logistic regression analysis | Student’s t-test | Seizure frequency | PS | SW | None | 4/11 |
| Giordano et al. [22] | Italy | Mar–Apr, 2020 | CH 40 progressive PwE (18/ 40: generalized epilepsy, 22/40: focal epilepsy) | Wilcoxon signed-rank tests | IES-R (Intrusion and avoidance) | Number of seizures | PS | SW | None | 9/11 |
2.3. Data extraction and outcome measurements

Two reviewers (NK and AF) independently screened the titles and abstracts and evaluated the full texts of the selected articles. Any disagreements were resolved through discussion between the reviewers (NK and AF). The following variables were extracted: author, publication year, country, study period, study design, number of participants, statistical design, measurement of stress and seizure worsening in the study, cause/consequence in the study, and the consideration of temporality.

We defined outcome measurement in this study the temporality between psychological stress and worsening of seizures in patients with epilepsy. This was measured by reviewing whether each article considered the causality between psychological stress and worsening of seizures. Consideration of the causal relationship between psychological stress and seizure worsening was defined as follows: (1) the study investigated the existence of psychological stress prior to the worsening of seizure control; (2) the study investigated the occurrence of worsening of seizure control prior to psychological stress; or (3) the study discussed the limitations of the study and stated that the study findings were not sufficient to prove causality due to the lack of examination of psychological stress or seizure worsening, either one preceding the other. The outcomes were independently reviewed by two reviewers (NK and AF). Any disagreements or discrepancies between the reviewers regarding outcomes were resolved through discussion.

3. Results

A total of 802 studies were retrieved (217 papers from MEDLINE, 0 papers from CENTRAL, 583 papers from EMBASE, and two studies from ClinicalTrials.gov) up to March 20, 2021. After removing duplicates and screening the titles and abstracts, 44 studies were identified for the review. The full-text screening of these studies led to the exclusion of 27 studies that did not meet the inclusion criteria. A total of 17 studies finally fulfilled the eligibility criteria for inclusion in the systematic review [6–22]. The selection process is outlined in Fig. 1. Table 1 summarizes the findings of the included studies. Regarding cause and consequences, we recorded whether these were discussed or concluded in the studies. We also recorded whether statistical design implied the cause and consequences.

As mentioned above, we found that 17 studies reported the relationship between psychological stress and seizure worsening in patients with epilepsy during the COVID-19 pandemic. Among them, 14 studies utilized a cross-sectional design, while three studies utilized a cohort design.

Sixteen of the 17 studies concluded that psychological stress due to the COVID-19 pandemic could cause seizure worsening in patients with epilepsy, while one article stated that seizure worsening could cause psychological stress. Among them, no study had examined the temporality of these changes. Only four (23.5%) studies stated that their study had limitations in concluding the causality between these changes.

4. Discussion

Our systematic search method found that 13 (76.5%) studies did not consider temporality in the causal relationship between seizure worsening and psychological stress during the COVID-19 pandemic.

According to Hill’s criteria [2], in addition to statistical significance, we needed to confirm nine points to prove causality: (1) strength, (2) consistency, (3) specificity, (4) temporality, (5) biological gradient, (6) plausibility, (7) coherence, (8) experiment, and (9) analogy. In this study, we focused only on the temporality of these nine points. This was to prevent the potentially critical misleading conclusion that there is a causal relationship in the opposite direction of the truth, as would have occurred without considering temporality.

As mentioned above, when an association is found between stress and seizure worsening, the cause and consequences must be carefully determined. Our study found that most of the included studies (64.7%) were cross-sectional studies based on patient interviews or surveys. A cross-sectional study cannot consider temporality because outcomes and variables are measured simultaneously. Therefore, the discussion in these studies should include the limitation that which of stress and/or seizure worsening is the cause and which is the consequence that cannot be identified. However, only 4/14 (28.6%) of the included cross-sectional studies mentioned this limitation. We must remember that it is known that psychological stress also can cause seizure worsening [23,24], while seizure worsening also can increase stress in patients with epilepsy [25]. This means that either of them can be considered as the cause or consequence in a cross-sectional study. In contrast, three studies used a cohort design. A cohort study is a longitudinal observational study that allows us to consider the temporality between variables/exposures and outcomes. None of the cohort studies considered the temporality between psychological stress and worsening of seizures. This could be due to the unpredictable nature of the COVID-19 pandemic, which did not allow us to consider longitudinal data acquisition prior to its occurrence.

Such caution is important because we should focus on treating the cause. If seizure worsening causes psychological stress, seizures should be controlled in patients with epilepsy, which will improve their psychological health. If psychological stress causes seizure worsening, we should treat the psychological stress of patients with epilepsy or their caregivers, which will help control their seizures.

Further prospective studies are hence required to determine the cause and consequences of psychological stress and worsening of seizures.

5. Conclusion

We found that many articles concluded that there was a causal relationship between psychological stress and seizure worsening without considering temporality. It should be noted that the statistical association between the two events is not sufficient for causality. Without considering temporality, we might conclude that there is a causal relationship in the opposite direction of the truth. As both researchers and readers, we need to consider temporality when interpreting causality between increased psychological stress and seizure worsening in patients with epilepsy during the COVID-19 pandemic.

Financial Disclosures

No disclosures.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.
References

[1] Kuroda N. Epilepsy and COVID-19: updated evidence and narrative review. Epilepsy Behav 2021;116:107785.

[2] Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58(5):295–300.

[3] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol, 2009;62(10):e1-34. doi: 10.1016/j.jclinepi.2009.06.006.

[4] Distiller SR. Risk of Bias instrument for Cross-sectional survey of attitudes and practices, https://www.evidencepartners.com/resources/methodological-resources/risk-of-bias-instrument-for-cross-sectional-surveys-of-attitudes-and-practices-distillersr; 2021 [accessed 6 May 2021].

[5] The University of Adelaide. Critical appraisal tools, https://jbi.global/critical-appraisal-tools; 2020 [accessed 6 May 2021].

[6] Rosengard JL, Donato J, Ferreiraano V, Zhao D, Molinero I, Boro A, et al. Seizure control, stress, and access to care during the COVID-19 pandemic in New York City: The patient perspective. Epilepsia 2021;62(1):41–50.

[7] Abokalawa F, Ahmad SF, Al-Hashel J, Hassan AM, Arabi M. The effects of coronavirus disease 2019 (COVID-19) pandemic on people with epilepsy (PwE): an online survey-based study. Acta Neurol Belg 2021:1–8.

[8] Grande E, Tufo T, Ciavarro M, Di Muccio I, Fuggetta F, Silvestri M, et al. The impact of COVID-19 lockdown on people with epilepsy and vagal nerve stimulation. Front Neurol 2021;12:640581.

[9] Tedrus GMAS, Silva JFCPD, Barros GS. The impact of COVID-19 on patients with epilepsy. Arq Neuropsiquiatr. 2021:S0004-282X2021005003201.

[10] Huang S, Wu C, Jia Y, Li G, Zhu Z, Lu K, et al. COVID-19 outbreak: The impact of stress on seizures in patients with epilepsy. Epilepsia 2020;61(9):1884–93.

[11] Alkhodari A, Siddiqui MI, Almutashari F, Baethman R. The effect of COVID-19 pandemic on seizure control and self-reported stress on patient with epilepsy. Epilepsy Behav 2020;112:107323.

[12] Áleo-Serrano Á, Mingorance A, Jiménez-Huete A, Toledano R, García-Morales I, Anciones C, et al. Genetic epilepsies and COVID-19 pandemic: Lessons from the caregiver perspective. Epilepsia 2020;61(6):1312–4.

[13] Conde Blanco E, Manzanares I, Centeno M, Khawaja M, Bérdón O, Donaire A, et al. Epilepsy and lockdown: A survey of patients normally attending a Spanish centre. Acta Neurol Scand 2021;143(2):206–9.

[14] Assenza G, Lanzone J, Brigo F, Coppola A, Di Gennaro G, Di Lazzaro V, et al. Epilepsy care in the time of COVID-19 pandemic in Italy: risk factors for seizure worsening. Front Neurol 2020;11:737.

[15] Nakamoto M, Carrazana E, Vierk A, Liow K. Epilepsy in the time of COVID-19. Acta Neurol Scand 2021;143(3):333–5.

[16] Fonseca E, Quintana M, Lallana S, Luís Restrepo J, Abraira L, Santamarina E, et al. Epilepsy in time of COVID-19: A survey-based study. Acta Neurol Scand 2020;142(6):545–54.

[17] Koh MY, Lim KS, Fong SL, Khor SB, Tan CT. Impact of COVID-19 on quality of life in people with epilepsy, and a multinational comparison of clinical and psychological impacts. Epilepsy Behav 2021;117:107849.

[18] Millevert C, Van Hees S, Siewe Fodjo JN, Wijtvliet V, Faria de Moura Vilela E, Rosso B, et al. Impact of COVID-19 on the lives and psychosocial well-being of persons with epilepsy during the third trimester of the pandemic: Results from an international, online survey. Epilepsy Behav. 2021:116:107800.

[19] Rathore C, Baheti N, Bansal AR, Jabeen SA, Copinath S, Jagtap S, et al. Impact of COVID-19 pandemic on epilepsy practice in India: A tripartite survey. Seizure 2021;86:60–7.

[20] Sanchez-Larsen A, Gonzalez-Villar E, Diaz-Maroto I, Layos-Romero A, Martinez-Martin Á, Alcabat-Rodriguez C, et al. Influence of the COVID-19 outbreak in people with epilepsy: Analysis of a Spanish population [EPICVID registry]. Epilepsy Behav 2020;112:107396.

[21] d’Orsi G, Mazzeo F, Ravida D, Di Claudio MT, Sabetta A, Lalla A, et al. The effect of quarantine due to Covid-19 pandemic on seizure frequency in 102 adult people with epilepsy from Apulia and Basilicata regions, Southern Italy. Clin Neurol Neurosurg 2021;203:106592.

[22] Giordano A, Siciliano M, De Micco R, Sant’Elia V, Russo A, Tedeschi G, et al. Correlates of psychological distress in epileptic patients during the COVID-19 outbreak. Epilepsy Behav 2021;115:107632.

[23] van Campen JS, Jansen FE, Pet MA, Otte WM, Hillegers MH, Joels M, et al. Relation between stress-precipitated seizures and the stress response in childhood epilepsy. Brain 2015;138(Pt 8):2234–48.

[24] Hingray C, McGonigal A, Kotwas I, Alcabat-Rodriguez JA. The relationship between epilepsy and anxiety disorders. Curr Psychiatry Rep 2019;21(6):40.

[25] Moon HJ, Seo JC, Park SP. Perceived stress and its predictors in people with epilepsy. Epilepsy Behav 2016;62:47–52.