Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Dec 05; 10(B):2505-2508.
https://doi.org/10.3889/oamjms.2022.10895
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Neurology*

Early Seizures during Stroke

Christiyan Naydenov[1]*, Velina Mancheva[1], Lachezar Manchev[1], Antoaneta Yordanova[2]

[1]Department of Neurology, Medical Faculty, Trakia University, Stara Zagora City, Bulgaria; [2]Department of Health Care, Medical college, Trakia University, Stara Zagora city, Bulgaria

Edited by: Mirko Spiroski
Citation: Naydenov C, Mancheva V, Manchev L, Yordanova A. Early Seizures during Stroke. Open Access Maced J Med Sci. 2022 Dec 05; 10(B):2505-2508. https://doi.org/10.3889/oamjms.2022.10895
Keywords: Predictors; Seizures; Cerebrovascular diseases; Stroke; Prevention; Screening
***Correspondence:** Christiyan Naydenov, Department of Neurology, Medical Faculty, Trakia University, Armeyska 11 str., Stara Zagora city, 6000, Bulgaria. E-mail: kristiyan.naydenov@trakia-uni.bg
Received: 01-Sep-2022
Revised: 04-Nov-2022
Accepted: 28-Nov-2022

Funding: This study was supported through the project grant MU21-FMI-015 of NPD at the University of Plovdiv Paisii Hilendarski.
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: The connections between seizures and stroke, their characteristics, and features are barely developed and also very important for the outcome. The diagnostic problem leads to ineffective treatment due to difficult selection of patients who are subject to prevention with antiepileptic drugs (AEDs) on one hand. On the other hand, it is impossible to exam every stroke patient by EEG. We need an algorithm for screening indicated patients and conducting the EEG. After that, we can include properly AED as a prevention. Their low frequency makes them time consuming to study.

AIM: The aim of the study was to conduct an epidemiological study of early epileptic seizures at the acute stroke phase and to derive principles for screening, diagnosis, and behavior for prevention.

METHODS: To achieve the goal, we have researched retrospective patients, totally amounting to 656.

RESULTS: The factors identified so far in the genesis of seizures such as age, type, and location of cerebrovascular accident and proximity to the cortex do not act alone, but in combination with undiscovered ones.

CONCLUSIONS: There are no clear criteria to outline the rules for the AED prophylactic in patients with cerebrovascular disease (CVD). The most important indicator is the systematic assessment of the risk of seizures in the course of the disease. Patients at high risk of triggering seizures and developing epilepsy in CVDs are suitable for EEG examinations with a view to timely diagnosis and treatment.

Introduction

The subject of the study was early seizures during stroke as a complication. It means that the main diagnose (stroke) is already present and the possible complication is in the asymptomatic phase which allows us to do secondary prevention at this stage. The relative share of these patients is extremely small, which makes the problem unattractive to scientists and is poorly defined. The risk is below 10%. However, assuming that about 15 million people/year worldwide suffer from stroke, according to the World Stroke Organization, this means that about 1.5 million patients have seizures during or after a stroke [1]. This is a significant number of patients, which makes it a very important topic for study despite the little published data. The diagnostic problem leads to ineffective treatment due to difficult selecting of patients who are subject to prevention with AEDs. On one hand – prevention of seizures among patients who never show such and exposing them to the risk of side effects, and on the other hand – lack of prevention of seizures among patients who are at risk and show this complication in the future with disability and necessary of tertiary prevention.

Aim

The aim of the study was to conduct an epidemiological study of early seizures during the acute phase of stroke and to derive principles for screening, diagnosis, and behavior for secondary prevention.

Theoretical research and nature of the problem

The “seizure” symptom is considered a harbinger of a stroke, such as in the course of a vascular accident and seizures as residual symptoms after experiencing an acute phase of stroke (early and late) [2]. The connections between seizures and stroke their characteristics and features are also considered. The focus of the scientific literature so far is the seizures in cerebral hemorrhage. The larger number of cerebral hemorrhages makes the research more reliable. Seizures are significantly less affected in cases of cerebral infarction, which necessitates in-depth research on them. Their low frequency makes them time consuming to study. The severity of clinical stroke, regardless of the scale used, is a major factor in the development of post-stroke epilepsy [3], [4], [5], [6], [7]. Particularly, high risk for genesis of seizure is infarction in the anterior cerebral

artery blood supply [4], [8], [9], [10]. The extent of cortical involvement is the next most important risk factor [3], [9], [11], as the involvement of the parietal-temporal cortex increases it [3], [9], [12], [13]. Small vessels disease also has an effect. Lacunar infarcts form about 11% of post-ischemic epilepsy [14]. Epileptic seizures can be caused by ischemic stroke or can be biomarkers for it [15], [16], [17]. A large study [18] in the United Kingdom reported that late-onset epilepsy was associated with a risk of later stroke. Vascular risk factors, including a history of myocardial infarction, peripheral vascular disease, hypertension, elevated total serum cholesterol, and left ventricular hypertrophy, have been associated with late onset of "silent infarction" epilepsy [17], [19]. The younger the patient, the more reactive his nervous system is and the more likely he is to have a seizure in the course of an ongoing stroke [20], [21], [22], [23], [24]. Early prevention of symptomatic epilepsy reduces its incidence in the long run [25], [26], [24]. Studies continue to reveal effective prevention [27] to reduce disability and improve the quality of life of patients with cerebrovascular disease as a socially significant disease [24].

Contingent and variable

Design

The population at risk are all of the included retrospective patients with acute stroke passed through our clinic from March 2017 to February 2018, amounting to 656. Each patient was evaluated by biological, clinical, and laboratory indicators, which was systematized in a database and has subjected to statistical processing by the method of classification and regression tree with the main dependent variable – "seizures". The data were obtained through the general hospital electronic archive – retrospectively. Their processing and storage are in accordance with the requirements set out in the Code of Ethics [28].

Methods

Classification and regression tree (CART) have been developed and proposed various variants [29], [30], [31], [32], as well as hybrid methods [33]. CART is a hybrid model based on logistic regression [33]. A new regression methodology is the proposed hybrid CART-MARS method [34]. This method is able to classify and predict values for a given dependent variable by identifying the main influencing and most strongly independent variables [35]. The data processing is non-parametric and does not suggest the distribution of the dependent variable. The created tree can be considered as a kind of multidimensional distribution of data [37]. It is successful in cases of missing data on important predictors. Another advantage is that it works well with both small and large data sets, and the results are easy for everyone to interpret. The CART method is defined as a recursive-dividing regression in which data are divided into relatively homogeneous end nodes to obtain a predicted value that is the average observed value for each end node [37]. Homogeneity is expressed as a low standard deviation by the least squares method.

Results and Discussion

Correlation analysis

From the correlation analyzes, it is clear that there is no relationship between the compared variables, as demonstrated in studies of symptomatic epilepsy in men and women [38]. The ratio of the individual types and locations of cerebrovascular diseases is preserved and the connection with the manifested seizures is weak, which is an applicable conclusion for all 26 variables. Each variable individually does not have the power to influence the manifestation or not of fainting, but this does not exclude the possibility of a combination of individual factors to have a strong impact. The purpose of the correlation analysis is to emphasize that the factors identified so far in the genesis of seizures such as age, type, and location of cerebrovascular accident and proximity to the cortex do not act alone, but in combination with undiscovered internal and external ones.

Classification and regression tree

The data processing program simulates multiple variants of a classification and regression tree with different numbers of end nodes and automatically finds the number of end nodes with the lowest statistical error. The tree tracks the patients who have seizures and divides them based on the strongest factor in the daughter nodes, followed by a new division or not at the end nodes. All patients grouped in one end node have similar combination of characteristics and risk factors and it can be concluded that they have the same degree of risk for seizures. Through the model developed in this way, based on laboratory standard tests of all future patients with cerebrovascular diseases, they can be classified and recognized to any of the end nodes, which can be used for screening by EEG. In other words, the indications for electroencephalography can be expanded and the indications for the inclusion of antiepileptic prophylaxis with the future reduction of disability and improvement of quality of life can be determined.

Patients at high risk of seizures and indicated for EEG examination have the following combination of characteristics: The severity of the clinical stroke, regardless of the scale used, is a major factor in

the development of post-stroke epilepsy [1], [28], [29], [30], [31]. Particularly, high risk for epileptogenesis is infarction in the anterior cerebral artery basin [28], [32], [33]. Young age; cerebral hemorrhage or embolic infarction in the dominant cerebral hemisphere and near the cortex; INR ≤1.11; Cholesterol ≥4 mmol/l.

Conclusions

It is recommended to cover as many cases of cerebrovascular diseases with EEG as possible to give them a chance for complex treatment, but also because more information of science is needed; creating a publicly available database of neurological research environments, sharing archives, and engaging more researchers on the topic of the problem. It is also necessary to study the phenotypic variables as a manifestation of the genotypic influence.

Acknowledgments

The first author would like to thank Prof. Dr. Ivan Manchev, MD, ScD and the last author would like to expresses gratitude for the project grant MU21-FMI-015 of NPD at the University of Plovdiv Paisii Hilendarski.

Statement of Ethics

This study protocol was reviewed and approved by Local Ethics Committee of Trakia University – Stara Zagora city, Bulgaria, approval number 14/02 OCT 2020. All patients voluntarily signed an informed consent form before inclusion in the study.

Author Contributions

C. Naydenov – constructing the aim and the design, processing the research, writing the overview, and introduction. V. Mancheva – scientific supervisor, writing the discussion, and conclusions. L. Manchev – coordinating the process and creating local environment and writing the abstract. A. Yordanova – creating the database and statistical processing of the results.

Data Availability Statement

The datasets generated and analyzed in the present study are available from the corresponding author on reasonable request.

References

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, *et al*. Global and regional burden of stroke during 1990-2010: Findings from the global burden of disease study 2010. Lancet. 2014;383:245-54. https://doi.org/10.1016/s0140-6736(13)61953-4
   PMid:24449944
2. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the commission on classification and terminology of the international league against epilepsy. Epilepsia. 1981;22(4):489-501. https://doi.org/10.1111/j.1528-1157.1981.tb06159.x
   PMid:6790275
3. Bladin CF, Alexandrov AV, Bellavance A, Bornstein N, Chambers B, Coté R, *et al*. Seizures after stroke: A prospective multicenter study. Arch Neurol. 2000;57(11):1617-22. https://doi.org/10.1001/archneur.57.11.1617
   PMid:11074794
4. Zhang C, Wang X, Wang Y, Zhang JG, Hu W, Ge M, *et al*. Risk factors for post-stroke seizures: A systematic review and meta-analysis. Epilepsy Res. 2014;108(10):1806-16. https://doi.org/10.1016/j.eplepsyres.2014.09.030
   PMid:25454500
5. Jungehulsing GJ, Heuschmann PU, Holtkamp M, Schwab S, Kolominsky-Rabas PL. Incidence and predictors of post-stroke epilepsy. Acta Neurol Scand. 2013;127(6):427-30. https://doi.org/10.1111/ane.12070
   PMid:23398544
6. Arntz R, Rutten-Jacobs L, Maaijwee N, Schoonderwaldt H, Dorresteijn L, van Dijk E, *et al*. Post-stroke epilepsy in young adults: A long-term follow-up study. PLoS One. 2013;8(2):e55498. https://doi.org/10.1371/journal.pone.0055498
   PMid:23390537
7. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Epileptic seizures after a first stroke: The Oxfordshire community stroke project. BMJ. 1997;315(7122):1582-7. https://doi.org/10.1136/bmj.315.7122.1582
   PMid:9437276
8. Roivainen R, Haapaniemi E, Putaala J, Kaste M, Tatlisumak T. Young adult ischaemic stroke related acute symptomatic and late seizures: Risk factors. Eur J Neurol. 2013;20(9):1247-55. https://doi.org/10.1111/ene.12157
   PMid:23581284
9. Hsu CJ, Weng WC, Peng SS, Lee WT. Early-onset seizures are correlated with late-onset seizures in children with arterial ischemic stroke. Stroke. 2014;45(4):1161-3. https://doi.org/10.1161/STROKEAHA.113.004015
   PMid:24595587
10. Heuts-van Raak L, Lodder J, Kessels F. Late seizures following a first symptomatic brain infarct are related to large infarcts involving the posterior area around the lateral sulcus. Seizure. 1996;5(3):185-94. https://doi.org/10.1016/

s1059-1311(96)80034-3
PMid:8902919

11. Leone MA, Tonini MC, Bogliun G, Gionco M, Tassinari T, Bottacchi E, *et al*. Risk factors for a first epileptic seizure after stroke: A case control study. J Neurol Sci. 2009;277(1-2):138-42. https://doi.org/10.1016/j.jns.2008.11.004
PMid:19059614
12. Benbir G, Ince B, Bozluolcay M. The epidemiology of post-stroke epilepsy according to stroke subtypes. Acta Neurol Scand. 2006;114(1):8-12. https://doi.org/10.1111/j.1600-0404.2006.00642.x
PMid:16774620
13. Giroud M, Gras P, Fayolle H, André N, Soichot P, Dumas R. Early seizures after acute stroke: A study of 1,640 cases. Epilepsia. 1994;35(5):959-64. https://doi.org/10.1111/j.1528-1157.1994.tb02540.x
PMid:7925167
14. Chadehumbe MA, Khatri P, Khoury JC, Alwell K, Szaflarski JP, Broderick JP, *et al*. Seizures are common in the acute setting of childhood stroke: A population-based study. J Child Neurol. 2009;24(1):9-12. https://doi.org/10.1177/0883073808320756
PMid:18923086
15. Brigo F, Tezzon F, Nardone R. Late-onset seizures and risk of subsequent stroke: A systematic review. Epilepsy Behav. 2014;31:9-12. https://doi.org/10.1016/j.yebeh.2013.11.003
PMid:24291522
16. Cleary P, Shorvon S, Tallis R. Late-onset seizures as a predictor of subsequent stroke. Lancet. 2004;363(9416):1184-6. https://doi.org/10.1016/S0140-6736(04)15946-1
PMid:15081649
17. Pitkänen A, Roivainen R, Lukasiuk K. Development of epilepsy after ischaemic stroke. Lancet Neurol. 2016;15(2):185-97. https://doi.org/10.1016/S1474-4422(15)00248-3
PMid:26597090
18. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. Lancet. 2008;371(9624):1612-23. https://doi.org/10.1016/S0140-6736(08)60694-7
PMid:18468545
19. World Health Organization. The World Health Report: 2004: Changing history. Geneva: World Health Organization; 2004. Available from: https://www.apps.who.int/iris/handle/10665/42891 [Last accessed on 2022 Jun 20].
20. Kopyta I, Sarecka-Hujar B, Skrzypek M. Post-stroke epilepsy in polish paediatric patients. Dev Med Child Neurol. 2015;57(9):821-8. https://doi.org/10.1111/dmcn.12711
PMid:25692742
21. Graham NS, Crichton S, Koutroumanidis M, Wolfe CD, Rudd AG. Incidence and associations of poststroke epilepsy: The prospective South London stroke register. Stroke. 2013;44(3):605-11. https://doi.org/10.1161/STROKEAHA.111.000220
:23370202
22. Tanaka T, Yamagami H, Ihara M, Motoyama R, Fukuma K, Miyagi T, *et al*. Seizure outcomes and predictors of recurrent post-stroke seizure: A retrospective observational cohort study. PLoS One. 2015;10(8):e0136200. https://doi.org/10.1371/journal.pone.0136200
PMid:26309124
23. Werhahn KJ, Klimpe S, Balkaya S, Trinka E, Krämer G. The safety and efficacy of add-on levetiracetam in elderly patients with focal epilepsy: A one-year observational study. Seizure. 2011;20(4):305-11. https://doi.org/10.1016/j.seizure.2010.12.015
PMid:21257324
24. Naydenov C, Manolova T, Chavdarov S, Manchev I. Cerebrovascular Diseases and Seizures. Vol. 5. Bulgaria: Trakia University; 2018. p. 84-6.
25. Tanaka T, Ihara M. Post-stroke epilepsy. Neurochem Int. 2017;107:219-28. https://doi.org/10.1016/j.neuint.2017.02.002
PMid:28202284
26. Pezzini A, Grassi M, Del Zotto E, Giossi A, Volonghi I, Costa P, *et al*. Complications of acute stroke and the occurrence of early seizures. Cerebrovasc Dis. 2013;35(5):444-50. https://doi.org/10.1159/000348704
PMid:23735811
27. Zelano J, Larsson DA, Kumlien E, Åsberg S. Pre-stroke seizures: A nationwide register-based investigation. Seizure. 2017;49:25-9. https://doi.org/10.1016/j.seizure.2017.05.010
PMid:28544888
28. Republic of Bulgaria Commission of Personal Data Protection. Personel Data Protection Act/01/JAN/2002. 2002. Available from: https://www.cpdp.bg/en/index.php?p=element&aid=1194 [Last accessed on 2022 Jun 20].
29. Steinberg D, Golovnya M. CART 6.0 User's Guide. San Diego, CA: Salford Systems; 2007.
30. Kass GV. An exploratory technique for investigating large quantities of categorical data. J R Stat Soc Ser C Appl Stat. 1980;29(2):119-27. https://doi.org/10.2307/2986296
31. Biggs D, De Ville B, Suen E. A method of choosing multiway partitions for classification and decision trees. J Appl Stat. 1991;18(1):49-62. https://doi.org/10.1080/02664769100000005
32. Wilhelm A. Data and knowledge mining. In: Härdle W, Mori Y, Gentle JE editors. Handbook of Computational Statistics. Heidelberg: Springer; 2004. p. 789-820.
33. Steinberg D, Cardell NS. The hybrid CART-Logit Model in Classification and Data Mining. Keystone, CO: American Marketing Association. In: Eighth Annual Advanced Research Techniques Forum; 1998b.
34. Voynikova D. Linear model of the output power of CuBr laser using CART. 2013;2:15-20. Available from: http://fmi.uni-plovdiv.bg/gocheva/Avtoreferat%20Voynikova_Author's%20summary%20PhD%20dissertation.pdf [Last accessed on 2022 Jun 20].
35. Steinberg DL, Colla P. CART: Tree-Structured Non Parametric Data Analysis. San Diego, CA, United States: Salford Systems; 1995.
36. Breiman L, Friedman JH, Olshen RA, Stone CJ. Classification and Regression Trees. Monterey, CA, US: Wadsworth and Brooks; 1984.
37. Breiman L. Random forest. Mach Learn. 2001;45:5-32. https://doi.org/10.1023/A:1010933404324
38. Ranjbar S, Anderies BJ, Singleton KW, Johnston SK, Rickertsen CR, Sharma A. Sex differences in seizure at presentation in glioma population. 2019. https://doi.org/10.1101/718791