

Up to 30% of stroke patients have abnormal EEG

EEG in stroke

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Abstract

Aim: EEG is an accessible, sensitive and informative method for recording changes in the bioelectrical activity of the brain in routine neurological clinical practice in a number of acute and chronic neurological diseases. However, the method is not used as the main one in the diagnosis of ischemic stroke due to the lack of evidence from the studies carried out to date on correlations between clinical and imaging findings with those of the EEG recording, the method is considered non-informative and non-specific.

Material and Methods: We conducted an epidemiological study on acute stroke patients in order to find early epileptic seizures with the establishment of EEG changes in 51 patients. We also grouped the results of qualitative EEG changes as abnormal and general non-specific, and divided them by patients' normal EEG activity.

Results: By analyzing the results, we can conclude that up to 30% of stroke patients have abnormal EEG changes, fully consistent with the clinical and imaging pathological findings, as well as readiness for the development of early seizures.

Discussion: This creates a need for prophylaxis with antiepileptic drugs. After enrollment in therapy, none of the patients who were monitored developed structural epilepsy in the subsequent subacute period. Therefore, it can be assumed that EEG is a method with a more prognostic role in stroke patients with early onset of epileptic seizures and bioelectrical changes. This information can be used to incorporate early antiepileptic prophylaxis and prevent the complications associated with structural epilepsy.

Keywords

Predictors, Seizures, Cerebrovascular Diseases, Stroke, Screening, EEG Biomarkers.

Introduction

EEG (Electro-encephalography) is not widely used in the diagnosis of cerebral stroke, since this diagnosis is clinical, and EEG lacks specific signs of this disease. Nevertheless, in acute and chronic cerebral ischemia, the lack of oxygen and metabolites causes EEG changes of different nature and intensity [1]. EEG remains the main diagnostic method of epilepsy. A quantitative electroencephalogram (qEEG) is a test that analyzes the electrical activity of the brain to measure and display patterns that may correspond to diagnostic information and/or cognitive deficits. qEEG involves analyzing brain wave patterns to understand brain function. In stroke, qEEG has been explored to assess brain damage, predict outcomes, and guide rehabilitation strategies. Research suggests that qEEG can detect abnormalities in stroke patients, aiding in prognosis and treatment planning [2]. Regarding post-stroke epilepsy, studies have investigated qEEG's role in predicting and diagnosing seizures. Monitoring brain activity through qEEG might help identify individuals at risk for developing epilepsy after a stroke and assist in early intervention [3]. Pharmacological strategies for stroke and post-stroke epilepsy continue to evolve. Medications targeting seizure prevention in post-stroke epilepsy aim to minimize neuronal hyperexcitability. Drugs for stroke management focus on preventing secondary complications and promoting recovery. Recent reviews may delve deeper into these areas, potentially highlighting advancements in qEEG technology, its application in stroke-related conditions, and emerging pharmacological approaches [4].

Aim

The aim is to conduct an epidemiological study of early epileptic seizures in the acute phase of stroke finding the EEG changes.

Material and Methods

Prospectively acute stroke patients, who were treated in our clinic and met the inclusion and exclusion criteria (Table 1) were enrolled. Forty-three biological, clinical, laboratory and instrumental variables were evaluated (Table 2).

Each patient underwent an instrumental Electroencephalography (EEG) examination on the second day of the onset of the stroke. EEG was done with Neuron-Spectrum-64 Neurosoft EEG/EP device, with the following characteristics: Channels: 25; ADC: 24 bit; Frequency range for EEG channels: 0 Hz - 600 Hz; Sensitivity for EEG channels: 0.01 - 10000000 $\mu\text{V/mm}$; Sampling frequency: 1000 Hz. The research is performed in an electrophysiological laboratory with preliminary preparation according to the approved standards and the international system 10/20 (Available at: https://www.mh.gov.mk/bg/media/filer_public/2015/11/18/nervni-bolesti.pdf). Applying a NOTCH filter was done using a specific type of filter designed to eliminate or reduce a particular frequency or frequencies, typically 50 or 60 Hz. These frequencies often correspond to electrical interference or noise originating from power sources like mains electricity. When a NOTCH filter is applied during EEG analysis, it indicates that the filtering process aimed to remove or significantly reduce the interference caused by these specific frequencies. This filtering helps to clean the EEG signal by attenuating or eliminating the noise from power lines or other environmental sources, allowing a clearer view of the

brain's electrical activity. The application of a NOTCH filter is a common practice in EEG analysis to improve the quality of the recorded brain signals by reducing unwanted external interference, ensuring that the focus remains on the brain's electrical activity without contamination from environmental noise at these specific frequencies [5]. A common standard for EEG recordings is to maintain electrode impedances below a certain threshold to ensure accurate and reliable signals. The impedance levels used for this study were within the range of 5 to 10 k Ω (kilohms). Maintaining electrode impedances below this range helps to minimize noise, ensure good signal quality, and enhance the accuracy of the recorded brain activity [5].

The data was analyzed manually by a neurophysiology researcher, who processed the recorded data without relying extensively on automated or computer-based algorithms. Analyzing EEG data manually involves visual inspection, in which the expert examines the raw EEG signals, looking for specific patterns, anomalies, or events of interest. This visual inspection might involve identifying characteristic waveforms (such as alpha, beta, theta, or delta waves), spikes, sharp waves, or other abnormalities. The event marking process includes noting and marking specific events or occurrences within the EEG recording, such as the onset of seizures, artifacts, or changes in brain activity. Artifact rejection is a very important step to be done by human to identify and exclude artifacts caused by external interference (movement, electrical noise, etc.) or physiological sources (muscle activity, eye blinks, etc.) from the analysis. Data segmentation was done by dividing the EEG recording into segments based on different experimental conditions, time frames, or specific activities for further analysis. Quantification and interpretation is the final step of the manual data analysis which involves measuring and quantifying specific EEG features or parameters manually, such as frequency bands, amplitudes, or durations of certain brain activities. This process might involve using rulers or digital tools to make precise measurements. Manual analysis of EEG data allows for a detailed and nuanced understanding of the recorded brain activity. It permits the expert to identify subtle patterns or abnormalities that automated algorithms might miss, especially in complex or atypical cases [6].

To achieve the goal of the study, we determined and grouped the qualitative changes in the EEG, considering as abnormal only the focal or generalized epileptic graph elements such as sharps, spikes and sharp-slow complexes or focuses of theta and delta rhythms (Table 3). All other changes in the type of oscillations, phase amplitude coupling, phase to phase coupling, amplitude to amplitude coupling, cross-frequency phase coupling and inter-hemisphere bands, are defined as general non-specific changes. The normal EEG results are according to the reference values of the software analysis, reported by us earlier [7]. Understanding the functional significance involves considering the implications.

While general nonspecific changes and moderate disorganization in brain bioelectrical activity might not directly indicate epilepsy or focal seizure tendencies, they could reflect generalized disturbances in brain function. Conversely, epileptic graph elements like spikes, sharp waves, or specific rhythmic patterns often carry more diagnostic and prognostic

significance, indicating a higher likelihood of epilepsy or focal brain abnormalities [8].

Finally, each evaluated patient was counted in excel by determined type of EEG findings. Statistical processing is in accordance with the developed criteria [9].

Although medication effects and acute stroke treatments were controlled and unified across the entire patient sample, the study may still encounter potential confounding factors and unaddressed influences on EEG patterns. While the standardized medication regimen and therapy offer a level of control, variations in individual responses to medications, potential interactions between drugs, or underlying comorbidities might introduce subtle yet impactful differences in EEG manifestations [10].

Ethical Approval

This study protocol was reviewed and approved by Local Ethics Committee of Trakia University - Stara Zagora city, Bulgaria (Date: 2020-01-02, No: 14). All patients voluntarily signed an informed consent form prior to inclusion in the study.

Results

The enrolled patients are 51. The men/women ratio is 25/26 with age from 41 to 88 (average of 67) with Gaussian-Laplace, symmetric distribution shape. NIHSS score is from 2 to 20 (average 7 - moderate stroke) with right skewness exponential distribution shape. The provided information describes the distribution of cases based on EEG findings and suggests a statistically significant difference among the groups (Figure 1). The majority of patients, comprising 56.9% (29 patients), exhibited general nonspecific changes and moderate disorganization in the bioelectrical brain activity (2nd column). Following this group, 29.4% (15 patients) displayed abnormal EEG results (3rd column). The smallest proportion, 13.7% (7 patients), showed normal EEG values (1st column). The variable “Type of EEG” is characterized as a qualitative

variable with three levels (normal, nonspecific changes with moderate disorganization, and abnormal results) and two degrees of freedom, indicating that it contains three categories and provides two contrasts within the groups. The statement suggesting a statistically significant difference between groups at the 0.05 significance level implies that, based on the analysis conducted, there is strong evidence to support that the distribution of patients among the three EEG categories is not occurring purely by chance. Instead, it suggests that there’s a likely association or difference among the groups regarding their EEG findings that is beyond random variation. This finding is statistically significant, meaning it’s likely not due to random fluctuations in the data but rather reflects a meaningful difference between the categories in terms of EEG patterns. In examining the collective findings from the entire cohort of 15 patients exhibiting abnormal EEG results, a notable trend emerges in their combined clinical and laboratory profiles. It appears that the severity of the stroke, irrespective of the scale employed, emerges as a pivotal determinant in the onset of post-stroke epilepsy. Specifically, a heightened susceptibility to epileptogenesis seems linked to certain factors: infarction within the anterior cerebral artery territory, notably in the dominant cerebral hemisphere and in close proximity to the cortex; a lower age correlating with an increased risk; INR levels at or below 1.11; and cholesterol levels equal to or greater than 4mmol/l.

Discussion

In this article, we reported our results related to patients, diagnosed with stroke and their EEG changes in the post-stroke recovery period. EEG, as a predictor of post-stroke recovery, is currently largely based on the initial behavioral changes, although the recovery outcomes could differ significantly from the initial clinical similarities. A personalized and healing strategy pointed to the maximal efficient recovery [11].

Table 1. Including and excluding criteria

Inclusion criteria	Exclusion criteria
Patient with pyramidal signs	Patient without signs of stroke
Patient at acute phase of stroke	Patient at subacute phase of stroke
Patient who can understand written and verbal information and able to sign the Informed Consent	Patient who can` t understand written and verbal information and unable to sign the Informed Consent
Patient who is able to collaborate during the EEG	Patient who is unable to collaborate during the EEG
Patient who have no story of seizures	Patient who has story of seizures

Table 2. Evaluated biological, clinical, laboratory and instrumental variables

Variables	
Biological	Gender (m/f); Age (years)
Clinical	Type and location of cerebrovascular disease (LMCA Stroke; RMCA Stroke; VBS Stroke; Hemorrhage in left brain hemisphere; Hemorrhage in right brain hemisphere; Hemorrhage in Cerebellum; SAH from ACA; SAH from MCA); NIHSS (score); Seizures (y/n); Arterial hypertension (y/n); Atrial fibrillation (y/n); Heart failure (y/n); Rhythm disorders (y/n); Diabetes (y/n); Bronchial asthma (y/n); Kidney failure (y/n); Dyslipidemia (y/n); Anemia (y/n); Epilepsy (y/n); Systolic blood pressure (mmHg); Diastolic blood pressure (mmHg); Average blood pressure (<60; 60-160; >160 mmHg); Outcome (discharged/mortal)
Laboratory	Leukocytes (x10~9/L); Hemoglobin (g/l); Hematocrit (l/l); Erythrocytes (x10~12/L); Platelets (x10~9/L); Glucose (mmol/L); Urea (mmol/L); Creatinine (mmol/L); Potassium (mmol/L); Sodium (mmol/L); Cholesterol (mmol/L); INR (INR);
Instrumental	Mean amplitude of the alpha rhythm in the left hemisphere (µV); Mean amplitude of the alpha rhythm in the right hemisphere (µV); Interhemispheric asymmetry of the alpha rhythm (%); Dominant frequency of the alpha rhythm (Hz); Mean amplitude of the low - frequency beta rhythm (µV); Mean amplitude of the high - frequency beta rhythm (µV); Mean amplitude of the delta rhythm (µV); Dominant frequency of delta rhythm (Hz); Decrease in the alpha rhythm index in EO (%); Decrease in the alpha rhythm index in HV (%)

Table 3. Functional implications and clinical significances of determined qualitative changes in the EEG

	General Nonspecific Changes and Moderate Disorganization	Epileptic EEG Elements (e.g., Spikes, Sharp Waves, Theta/Delta Rhythms)
Functional Implication	These changes might indicate diffuse alterations in brain activity that are not specifically indicative of epileptic activity. They could stem from various factors, including medication effects, metabolic disturbances, or nonspecific alterations in brain function.	These elements often represent more focal or specific abnormal electrical discharges within the brain. Spikes, sharp waves, or focal theta/delta rhythms are commonly associated with epileptic activity or a predisposition to seizures.
Clinical Significance	While these changes might not directly signify epilepsy, they could reflect underlying neurological issues or indicate a state of altered brain function that might contribute to cognitive or behavioral abnormalities. However, these changes might lack the clear-cut diagnostic value associated with specific epileptic patterns.	Their presence can indicate a higher likelihood of epilepsy or a seizure disorder. Focal epileptic elements may suggest a specific area of brain pathology or hyperexcitability, potentially guiding treatment decisions or providing insights into the localization of seizure foci.

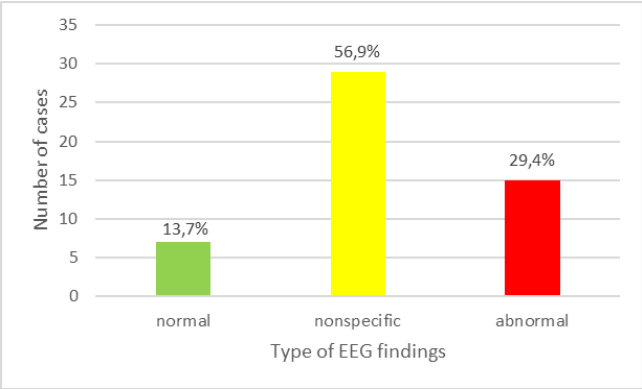


Figure 1. Number of cases and type of EEG findings

In their 2017 study, Philips et al. [12] proposed an EEG beta band-based network model of biomarkers aimed at evaluating stroke rehabilitation.

Current studies show that oscillation in the infra-frequency bands could be reliable for assessing brain abnormality after stroke.

Cross-frequency coupling (CFC) presents new perspective to understanding brain activity after stroke. Many researched performed test related to phase amplitude coupling (PAC), phase to phase coupling (PPC), and amplitude to amplitude coupling (AAC) [13]. Some combined the with EMG signals. So far, it has been reported that CFC abnormalities were registered in the whole brain area scale (divided into low- and high-frequency and low- and low-frequency). According to Bin Ren et al. [14], abnormal cross-frequency phase coupling could be highly related to the delta-band since delta band can reflect injury and recovery of neurons. According to Yan et al, 2013 [15] brain's internal communication of the affected hemisphere and inter-hemisphere in inter-frequency bands (like beta) is also disturbed. The CFC analyses could further reveal that the information exchange in the non-lesion hemisphere is affected (which could not be seen in intra-frequency bands).

CFC shows advances in understanding the impact of numerous neurological diseases such as Alzheimer's disease [16], epilepsy and multiple sclerosis [17].

Potential limitations within the study: The study included a relatively small sample size of acute stroke patients (up to 51). While the results provide insights, the small sample might limit the generalizability of findings to broader stroke populations. A larger, more diverse sample might offer a more comprehensive understanding of EEG changes post-stroke.

The research was conducted in a single clinic, potentially limiting the variability and representation of stroke patient populations. Multi-center studies with diverse patient demographics could offer a more comprehensive perspective on post-stroke EEG changes.

While manual EEG analysis offers detailed insights, it's subject to interpretation biases and might lack the objectivity of automated algorithms. Providing inter-rater reliability measures or comparisons with automated analyses could strengthen the study's methodology. The study primarily focused on classifying EEG changes into abnormal, nonspecific, and normal categories based on specific elements (spikes, sharp waves, theta/delta rhythms). This classification might overlook nuanced EEG patterns or miss subtleties that automated or alternative analyses could capture. While mentioning CFC and its potential, the study did not directly employ these advanced analyses. Incorporating CFC or other advanced EEG analysis methods could further enrich the understanding of brain activity post-stroke and reveal additional insights beyond the traditional EEG classification used in this study.

Conclusions

Our findings suggest that about 30% of stroke patients exhibit abnormal EEG results, signifying a predisposition to early seizures. Consequently, early administration of antiepileptic drugs becomes crucial for this subgroup. It is advisable to screen a larger proportion of stroke patients using EEG to promptly identify bioelectrical alterations, initiate early antiepileptic prophylaxis, and prevent the development of structural epilepsy-related complications. The findings underscore a critical association emergence of post-stroke epilepsy and certain factors such as infarction location within the anterior cerebral artery territory, proximity to the dominant cerebral hemisphere cortex, younger age, lower INR levels, and elevated cholesterol appear pivotal in influencing the risk of post-stroke epileptogenesis.

Clinical Implications: The observed distribution of EEG patterns in post-stroke patients, characterized by a predominant presence of nonspecific changes and moderate disorganization in bioelectrical brain activity, highlights the complexity of post-stroke neurophysiological alterations. These findings underscore the need for nuanced clinical evaluations beyond initial assessments, acknowledging that a substantial proportion of patients exhibit non-specific EEG changes that might not align directly with classical epileptic elements.

Diagnostic Considerations: Identifying a significant percentage of patients displaying abnormal EEG results and a smaller subset demonstrating normal EEG values suggests the variability in post-stroke brain activity presentations. This calls for a comprehensive diagnostic approach that considers the diverse EEG patterns seen in stroke recovery, emphasizing the necessity of precise and individualized diagnostic interpretations beyond a binary classification of abnormal or normal EEG findings.

Treatment Strategies and Prognosis: Understanding the distribution of EEG patterns following stroke could have implications for prognosis and treatment planning. The prevalence of nonspecific EEG changes might signal a need for tailored rehabilitation strategies targeting these particular neurophysiological alterations. Moreover, the subset displaying abnormal EEG results could prompt closer monitoring for potential epileptic tendencies or secondary complications.

Research Directions: Further research should delve into the long-term implications of these observed EEG distributions in post-stroke patients. Investigating how these varied EEG patterns correlate with functional outcomes, cognitive recovery, or predisposition to long-term neurological conditions could offer deeper insights into prognostic markers and guide more refined therapeutic interventions in stroke rehabilitation.

Overall Impact: These findings contribute to the evolving understanding of post-stroke neurophysiological changes, emphasizing the necessity of nuanced EEG assessments. Recognizing the spectrum of EEG alterations in post-stroke populations is pivotal in advancing our comprehension of recovery trajectories and tailoring interventions to optimize neurological outcomes in these patients.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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