



Social Relevance and Post-stroke Epilepsy Prevention

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Abstract

BACKGROUND: Stroke is an important cerebrovascular disease resulting in long-term disability and death. A rare consequence of stroke is structural epilepsy.

AIM: Here, we discuss the importance of post-stroke epilepsy prevention.

METHODS: We look into the occurrence of stroke and epilepsy in the general population, the risk factors and severity of those conditions, and the significance of early seizure prevention after the stroke. We analyze published research papers and reviews dealing with this problem.

RESULTS: In brief, there is a diagnostic problem leading to ineffective treatment. On one hand, preventing seizures could expose the patients under known side effects of treatment. On the other hand, if you do not treat them, there is a risk of developing seizures in the future.

CONCLUSION: Here, we propose ways to select patients for treatment and refine the diagnostic considerations for early start of anti-seizure therapy.

Edited by: Mirko Spiroski

Citation: Naydenov C, Parashkevova-Simeonova B, Mancheva V. Social Relevance and Post-stroke Epilepsy Prevention. Open Access Maced J Med Sci. 2022 Sep 30; 10(B):2345-2350. <https://doi.org/10.3889/oamjms.2022.10680>

Keywords: Stroke; Epilepsy; Risk factors; Early prophylaxis

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Received: 13-Jul-2022

Revised: 09-Aug-2022

Accepted: 20-Sep-2022

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Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

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Introduction

Cardiovascular conditions are considered socially significant diseases. It is important because of: High mortality rates, especially in working age populations; high prevalence and incidence with adverse dynamics in this age group; high and increasing healthcare and rehabilitation cost; and high social, economic, psychological, etc. cost for the patients and their families. Stroke is a cerebrovascular disease, which is a leading cause of disability and death. The treatment, rehabilitation, and reintegration of the patients with stroke are especially costly in low- and middle-income countries. Big help in this aspect is the action of nongovernmental organizations such as Angels Initiative, which has for main goal the decrease of post-stroke disabilities. A rare complication following stroke is the symptomatic/structural epilepsy, estimated to be 12.3% of all cases [1]. If there are approximately 15 million people in the world, suffering stroke annually, according to the World Stroke Organization, this makes around a million and a half patients having seizures at the time or following a stroke [2]. There is also a significant heterogeneity in the ratio of the patient with seizures during stroke, caused by the heterogeneous design used in the research papers, as well as because of the frequent use of electroencephalography as a method for stroke diagnosis [3].

Objective, Materials, and Methods

The objective of the current paper is to propose ways for the prevention of seizures following cerebrovascular disease. We aim to achieve this by exploring the following topics: Discuss the prevalence and incidence of the stroke and epilepsy in the general population; discuss the risk factors leading to stroke; discuss the severity of the disease at different occasions; and present ways for effective prevention of post-stroke epilepsy. We have used descriptive analysis of published scientific papers and reviews regarding this problem.

Overview and Discussion

Occurrence and prevalence

Stroke is the second most frequent cause of death in the Western world after cardiovascular diseases and cancer [4], which makes 10% of the overall mortality in the world. In Bulgaria, stroke is the main cause of death followed by cancer and ischemic heart disease. According to the (Bulgarian) National Center for Analysis of the Public Health in 2019, the stroke mortality was 296.2/100 000, cancer was 262.3, and ischemic

heart disease was 188.1. By hospitalization rate, the cardiovascular conditions are number one in the country. The risk of stroke increases after the third decade of life, due to different causes [5]. There is a straight proportionality between age and stroke frequency, as the risk increases with age [6], [7]. This does not preclude a stroke diagnosis in younger age, even in childhood. Males are 25% more likely to suffer stroke than females [7]. Even so, 60% of stroke fatalities occur in females, due to their higher life expectancy [7]. This despite specific risk factors related to pregnancy, giving birth, menopause, and hormone replacing therapies.

Epilepsy is one of the common neurological conditions [8], afflicting around 65 million people [9], with prevalence increasing in direct proportion with age [10], and slightly more common in males than in females [11], [12]. Epilepsy frequency in the developed countries stands at 5–10% annually [8], [12]. At the same time, the frequency in the developing countries is 50% higher compared to the developed countries. This implies poverty as a bigger risk factor than social status and nationality. Age distribution of epilepsy is also different with mostly young and elderly people in the developed countries and mainly young people and children in the developing countries, due to higher traumatism and exposure to infection diseases in the third world [11]. Around the year 2003, however, the frequency of epilepsy in children is decreasing, compared to people in higher age groups [8]. Bulgaria does not have an official statistic for the epilepsy cases, but according to the Center for Epilepsy Surgery at “Saint Ivan Rilski” hospital in 2020, there has been close to 75,000 epilepsy cases in the country. Half of the epilepsy cases are combined with psychiatric conditions such as depression, anxiety, and psychoses [13], [14], [15]. A reciprocal relationship is also viable [15]. Depression correlates with seizures with frontal lobe foci, mainly in the dominant hemisphere [14], [15], [16], [17]. These symptoms are transitory and disappear in the time span of several weeks [15], [18]. Roughly, half of the epilepsy patients have depression too [15]. This is in contrast with the frequency of psychoses, which count for about 4–10% of the psychiatric complications [19], [20], [21]. Part of those are caused by the side effects of anti-seizure medications, used in preventive epilepsy treatment following stroke.

Risk Factors

Risk factors for epileptogenic ischemia: The severity of stroke is the main factor for epilepsy, regardless of the stroke scale level [22], [23], [24], [25]. Anterior cerebral artery infarcts are linked to highest risk of epilepsy [23], [26], [27], [28]. The extent of the cortical area injured and also correlates with increased risk [22], [27], [29] while involvement

of the parietotemporal cortex makes it even higher [22], [27], [30], [31]. Small vessels disease is also a factor. Lacunar infarcts make up for around 11% of epilepsy cases following ischemia [32]. Seizures not only can be caused by ischemic stroke, but used as biomarkers [33], [34], [35]. A large study [36] in the U.K. finds that late inception of epilepsy increases the risk of a new stroke. Vascular risk factors, myocardial infarction, peripheral vascular disease, hypertension, high cholesterol, or left ventricular hypertrophy are linked to late epilepsy by means of “silent infarctions” [35], [37]. There is also a frequent association between epilepsy and leukoaraiosis, found in elderly patients (Epilepsy Associated with Leukoaraiosis, EAL) [38], [39].

Risk factors for epileptogenic hemorrhage: Size and location of the hemorrhage, cortex involvement, and patient’s age are the main risk factors for seizures [40]. Extravascular bleeding and hemorrhagic infarctions also increase the chances for seizures [25], [26], [41], [42]. Hemorrhagic stroke presents a much higher risk of seizures compared to the ischemic. Another risk factor is the location of the lesion in the dominant hemisphere [42].

Cerebrovascular Disease Causes Epileptic Seizures

Cerebral hemorrhages are either results of trauma or spontaneous in nature. They start with headaches and nausea combined with seizures and focal neurological deficit. Between 2.8% and 18.7% of the patients with cerebral hemorrhage have seizures, more often compared to the ischemic patients [40], [42], [43]. According to a 2006 study of the Istanbul Medical University, this percentage is 3.6% [32], [42]. Parenchymal hemorrhages are located in the cerebral tissue [42]. In case of a larger size lesion and close proximity to the ventricular system, blood can reach the cerebrospinal fluid causing fast developing impairment of consciousness and tonic extension seizures [42].

In subarachnoid hemorrhage, bleeding reaches the subarachnoid space causing generalized brain damage. Signs of meningeal syndrome follow. Patients, suffering subarachnoid hemorrhage develop generalized seizures in 5%–25% of cases. Seizures in late stages of the disease can signal renewed hemorrhages [42].

Ischemic stroke: Seizures can indicate ischemic stroke and early seizures can be early signs and biomarkers for the beginning of post-stroke epilepsy [33], [34], [35]. A newly diagnosed epilepsy in elderly patients can be a harbinger of a future stroke in 4–10-year period. This, so called “vasculogenic epilepsy,” leads to stroke in 5%–20%. When seizures follow a stroke, they are defined as late symptomatic

seizures. They frequently appear 6 months–2 years later [43], [44]. In a 2016 study of stroke patients from Stara Zagora region, early seizures are not recorded but these patients did not get the long-term follow-up, which could have detected late seizures [42]. Early treatment aimed at preventing symptomatic epilepsy lower its frequency in the long run [41], [42], [45]. Research focused on active prevention continues [46], alongside the improvement of the patient quality of life and social integration [42]. The younger the patient the more reactive its nervous system is and the more likely is developing seizures during an impending stroke [23], [41], [42], [47]. On the other hand, the closer the lesion is to the cortex the likelier seizures are [42], [48]. Chances for seizures are even higher when the injury is close to the anterior and middle cerebral arteries [31], [42], [44], [49].

Disease severity

Disease severity determines the social consequences of the stroke: Mortality, disability, rehabilitation, and reintegration in society as well as significant economic burden. Epilepsy itself has neurologic, cognitive, and psychological as well as social consequences for over 50 million people worldwide. Because of the increasing number of stroke survivors and the increased life expectancy, the number of epilepsy patients will be increasing too. Epilepsy exerts a heavy toll on the physical, social, and psychological well-being of patients and their families. Almost 80% of those patients live in low- to middle-income countries making treatment problematic, despite the high effectiveness and low cost of anti-seizure medications. Bulgaria ranks first in Europe in mortality from cerebrovascular diseases. Early post-stroke seizures have high mortality too, especially in the acute and subacute phases. Late developing seizures in old age patients are more likely caused by chronic cerebrovascular disease. The frequency of early seizures is not well established, mainly because of their relatively rare occurrence, < 10% of all strokes, and most of them cardioembolic in nature. Other risk factors for seizures are cerebral hemorrhage, young age, and Rankin scale level greater than 1. Race was studied and later disproved as a risk factor [50]. Epilepsy patients are 4 times more likely to die compared to the general population, not only because of seizures, but also because of traumas, suicide attempts, sudden death, or epileptic status [51], [52], [53], [54]. Late unprovoked seizures are not only signs of symptomatic epilepsy, but also harbingers for an upcoming stroke [24], [36]. Mortality rate in these patients is also high [22], [55], [56], [57]. Seizures make for a poor prognosis [58]. Even worst as diagnostic sign is the epileptic status. By itself, it cannot be an outcome but rather a forerunner for a following stroke [59], [60], [61], [62], [63]. The mortality rate of epileptic status following stroke is also much higher compared to other medical conditions.

Ways for preventing seizures: To deal with the epilepsy burden globally, early prevention is paramount. This can be achieved by acting on the main risk factors such as perinatal injuries, infections, traumas, and strokes, which together make up for 25% of the epilepsy cases. We aim here to focus on one frequent and potentially avoidable cause of epilepsy – the stroke. Seizures in stroke survivors correlate with high mortality rates, disabilities, and high cost of treatment. The severity of this medical condition is different among different countries and regions of the world. Wide preventive measures are warranted especially in maternal healthcare, infection diseases, and trauma care, along with cardiovascular and cerebrovascular prevention in reducing risk factors. Understanding the specific mechanisms of seizures following stroke is also of importance for making secondary prevention works. Diagnostic difficulties can impair prevention. Neurological diagnosis is predicated on anamnesis, clinical as well as laboratory data, along with connected data from various instruments and using algorithmic approach. Some of the medical condition, however, do not have a morphologic signature easily detected by imaging or laboratory methods. Even when abnormalities are found, it may be too late for prevention with disabilities already present. Developing screening methods to help early detection and treatment is there for all the more important. Still million and a half people worldwide experience early seizures after or during stroke. With early seizure surveillance, structural epilepsy is preventable. However, because of the specific side effects from medications, not every stroke patient can receive early treatment. Selecting the right patients for seizure prevention is a challenge even with the wider use of EEG. This is difficult to achieve given the labor intensity and the specific requirements of this method. It is also hard to be done in emergency. Consequently, a diagnostic problem leads to lack of timely treatment for eligible patients. This is a dilemma of seizure prevention on one side for patients, who have never had them before with the use of anti-seizure drugs with well-known side effects. Withholding these drugs, however, puts them in risk of seizures and all the long-term consequences for their health in the future. Here, we propose expanding the use of EEG in stroke patients, especially those with early seizures and organizing their prevention. EEG examination of as much patients as possible gives them a chance for complex treatment, as well as databases and archive creation, used by researchers in the future, for the advancement of neurological science in this particular area. Investigation of the phenotype variables as an expression of genotype may also be helpful.

Conclusions

Combining all the scientific data with regards of post-stroke seizures shows the importance of screening

as part of complex early detection system. The aim is to develop expert systems in the future based on traditional tools of medicine – anamnesis, status, laboratory, and image methods that can help resolve the dilemmas in diagnosis and treatment of this medical condition. Poor prevention and early treatment, especially in low- and middle-income countries, leads to deteriorating health outcomes, rising disabilities and health expenses, and lack of social integration for the patients. Bigger investments in research and development in the future will be needed.

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