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EC NEUROLOGY
Review Article

Metabolic Syndrome in Patients with Epilepsy

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Received: September 26, 2024; **Published:** October 28, 2024

Abstract

Metabolic syndrome (MetS) refers to the group of several interconnected risk factors that collectively double the risk of cardiovascular disease. Epilepsy is linked to MetS across all age groups, though its prevalence differs across various studies. This can be understood from the perspective of seizure-related metabolic abnormalities, long-term antiepileptic drugs (AEDs) use, and a more sedentary lifestyle due to epilepsy. The factors that are considered in developing MetS for patients with epilepsy (PWE) are age, residence, level of physical activity, food intake status, epilepsy subtype, epilepsy duration, current (AEDs) use, drug responsiveness status, body-mass index (BMI), total cholesterol and LDL-cholesterol levels. A deeper understanding of the epilepsy-AED-MetS connection and the exploration of lifestyle interventions hold the promise of significantly improving the overall health and well-being of PWE. Clinicians managing PWE should closely monitor various risk factors for developing MetS and consider them when selecting AED treatment.

Keywords: *Metabolic Syndrome; Epilepsy; Dyslipidemia; Antiepileptic Drugs*

Introduction

Metabolic syndrome (MetS) refers to the group of several interconnected risk factors that collectively double the risk of cardiovascular disease. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition is among the most commonly utilized criteria for diagnosing metabolic syndrome. According to this definition, metabolic syndrome is diagnosed if at least three of the following five criteria are met:

- Waist circumference over 40 inches for men or 35 inches for women
- Blood pressure exceeding 130/85 mmHg
- Fasting triglyceride (TG) levels above 150 mg/dl
- Fasting high-density lipoprotein (HDL) cholesterol levels below 40 mg/dl for men or 50 mg/dl for women
- Fasting blood sugar levels over 100 mg/dl [1].

In 2022, a team of Polish researchers introduced a new definition for MetS. This definition includes the presence of obesity along with at least two of the following three conditions: high blood pressure, impaired glucose metabolism, and elevated levels of non-high-density lipoprotein (non-HDL) cholesterol, indicative of atherogenic dyslipidemia [2]. The factors that are considered in developing MetS for patients with epilepsy (PWE) are age, residence, level of physical activity, food intake status, epilepsy subtype, epilepsy duration, current antiepileptic drugs (AEDs) use, drug responsiveness status, body-mass index (BMI), total cholesterol and LDL-cholesterol levels.

Epilepsy is linked to MetS across all age groups, though its prevalence differs across various studies. In a study conducted by Nair., *et al*. nearly one-third of adults under 50 years old with epilepsy who were undergoing antiepileptic therapy had MetS [3]. Beyene-Kassaw and colleagues conducted a cross-sectional study and found that the prevalence of MetS, based on the NCEP ATP III definition, was 25.5% in adult PWE, compared to 13.7% in the control group [4]. Ndayambaje and colleagues studied 1,076 adult epilepsy patients using AEDs and found a prevalence rate of 30.6%, with the highest rate observed in the 46 - 60 age group [5]. We have highlighted the most frequently mentioned mechanisms connecting MetS and epilepsy.

Metabolic disturbances

Adipokines are bioactive molecules secreted by adipose tissue that have various effects on health and disease. Leptin, a crucial regulator of metabolic balance, controls glucose homeostasis both centrally and peripherally, with pancreatic β-cells being the primary peripheral targets [6]. High levels of leptin have been observed in PWE, leading to impaired glucose tolerance, which is mainly due to effects of valproic acid (VPA) [7]. Adiponectin is another significant adipokine involved in regulating glucose and lipid metabolism, and it also possesses anti-inflammatory and antioxidant properties. VPA suppresses the gene expression of adiponectin in mature adipocytes, leading to hypoadiponectinemia, which is strongly linked to weight gain and insulin resistance [8-10]. The literature also mentions involvement of the hypothalamus, whether through damage to the nuclei themselves by epileptic seizures and the resulting imbalance between energy intake and consumption, or excessive activation of the hypothalamus-pituitary-adrenal axis [4].

Behavioral factors

In addition to the influence of antiepileptic therapy, the most frequently associated causative factors of metabolic syndrome in PWE are those related to behavior, especially physical activity, and dietary habits. The impact of physical activity on health has been extensively studied in medicine in general, which is the case with PWE as well. It is well established that lack of physical activity is one of the leading risk factors for noncommunicable diseases (NCDs) and it ranks as the fourth leading cause of death globally, which is why it presents a major public health issue [11]. Although evidence suggests that regular physical activity has a positive effect on physical and mental well-being, as well as the quality of life, PWE are less physically active compared to the general population, which may lead to numerous metabolic disturbances, such as weight gain, insulin resistance, hyperlipidemia, etc. The reason for this, for the most part, lies in the fear of injuries, seizure induction, insufficient knowledge among healthcare professionals, and stigma [12]. In a large Canadian population-based study with over 400.000 participants, of which 2.555 were PWE, it was shown that PWE were 1.4 times more likely to be physically inactive compared to the general population [13]. Jalava and colleagues demonstrated that PWE had significantly poorer physical fitness than the control population [14]. Cui., *et al*. analyzed data from the 2010 cross-sectional National Health Interview Survey (NHIS) which included 27.139 adults and revealed that those with epilepsy were significantly less likely to follow recommended physical activity guidelines compared to the adults without epilepsy [15]. PWE spend more hours sitting during the day and less time walking, with some data showing that a sedentary lifestyle is almost two times more prevalent in this population, compared with controls [16,17]. They are often discouraged from engaging in sports activities by family, friends and even physicians [18]. In 2016, the International League Against Epilepsy (ILAE) published a consensus paper that offered general guidance and promoted safe participation of PWE in sports activities due to possible positive effect on seizure control, in addition to overall physical and mental health, emphasizing the importance of individual risk assessment for each patient [19].

Research on the dietary habits of individuals with epilepsy is sparse, with the majority of studies focusing on the impact of the ketogenic diet on drug-resistant epilepsy. A group of Latvian scientists showed that children and adolescents with epilepsy tended to prefer meals high in carbohydrates and fat over protein, as well as frequently drank soda and juice [20]. Consequently, children with epilepsy display lower levels of omega-3 which decreases plasma triglyceride levels, as well as modulates cholesterol levels [21]. Similar data apply to the adult epileptic population as well. PWE consume more soda, fat, and sodium than healthy people, as shown by Szałwińska., *et al* [17]. Elevated carbohydrate, protein, and saturated fatty acid intake, as well as lower daily intake of unsaturated fatty acids, has been observed in this group, which carries a higher risk of cardiovascular disease, through their impact on serum triglyceride levels, cholesterol levels, as well as expression of proinflammatory and proatherogenic mediators [22].

An additional factor that contributes to the higher prevalence of metabolic syndrome in PWE is cigarette smoking, as a proven risk factor for the development of peripheral arterial disease, which is more prevalent in this population than in the general population [23-25].

The role of antiepileptic drugs (AEDs)

AEDs have a great influence on lipid and hormonal status in patients with epilepsy by affecting various enzymes inside the body. It has been proven that AEDs have an effect as enzyme inhibitors, or their inducers, that increase the level of lipids in the blood, which increases the risk of atherosclerosis [26]. Most of the papers refer to the influence of VPA on the occurrence of hypertriglyceridemia and hypercholesterolemia, especially in increasing low-density lipoprotein cholesterol (LDL-c), and decreasing high-density lipoprotein cholesterol (HDL-c). VPA has long been used as an AED and is the drug of choice for certain types of epilepsy. However, with long-term use of VPA, there comes an increase in oxidative stress, hyperinsulinemia and insulin resistance as shown by Nisha., *et al* [27]. Due to the mentioned changes, as well as the VPA effect on the increased appetite for carbohydrates, restricted energy expenditure, most patients gain weight and their BMI increases. The exact mechanism of weight gain remains unknown, but it is believed that hyperinsulinemia and an increase in leptin, ghrelin and neuropeptide Y levels lead to the aforementioned changes. One of the possible mechanisms of weight gain is that VPA is a derivative of fatty acids and inhibits βoxidation, which leads to an increase in insulin in the blood and insulin resistance [28,29]. The exact mechanism of the increase in leptin and thus neuropeptide Y in the blood is yet to be elucidated, both central and peripheral pathways are suspected. An increase in body weight mediated by VPA can lead to reduced compliance in the pediatric population, due to its negative psychological effect [30]. In addition to the above, long-term use of VPA in children can lead toa significant increase in thyroid hormones, and serum leptin concentration, causing metabolic diseases besides epilepsy [31]. VPA in adolescents, as demonstrated by George., *et al*. often leads to an increase in liver transaminases and the occurrence of nonalcoholic fatty liver disease (NAFLD). Additionally, VPA can also lead to the appearance of hirsutism, and menstrual abnormalities, which can present a problem for females of reproductive age who want children. This is why close monitoring is very important in such patients to avoid unwanted effects on the reproductive system of women [32]. In a study that involved forty patients divided in three groups, who were treated with monotherapy with carbamazepine (CBZ), VPA, and lamotrigine (LTG), CBZ and VPA treatment caused a noteworthy increase in the concentrations of triglycerides, cholesterol, and LDL-c compared with LTG treatment and the control group [26]. Furthermore, it has been proven that therapy with certain antiepileptic drugs during pregnancy, such as valproate and carbamazepine, carries a risk of major congenital anomalies [33]. Mintzer and colleagues demonstrated that changing the therapy regime from phenytoin (PHT) and CBZ to noninducing AEDs such as levetiracetam (LEV) and LTG may substantially decrease several vascular risk parameters, such as triglycerides, atherogenic cholesterol, C-reactive protein, and homocysteine, thus decreasing the risk for cardiovascular and cerebrovascular disease [34].

Of particular interest is the study which included 126 adult patients with focal onset epilepsy and nonalcoholic fatty liver disease (NAFLD). The patients were divided into two groups, zonisamide (ZNS) group who received ZNS monotherapy or adjunctive therapy, and

the control group who were not receiving ZNS therapy. The ZNS group experienced a significant reduction in body weight and metabolic parameters, including serum levels of HbA1c, triglycerides, and hs-CRP. These results suggest that ZNS provides benefits in patients with obesity and metabolic syndrome at high vascular risk. The authors proposed several mechanisms by which ZNS may have contributed to the amelioration of NAFLD symptoms, such as the central hypothalamic effect on appetite and the inhibition of lipogenesis utilizing the mitochondrial carbonic anhydrase inhibitory activity of ZNS [35].

Conclusion

MetS is a group of conditions that together increase the risk of cardiovascular disease, type 2 diabetes, and stroke. It can lead to other health problems as well, like conditions related to plaque buildup in artery walls (atherosclerosis) and consequently organ damage. In this paper, we explored correlations of epilepsy, AEDs, and MetS. The factors that are considered in developing MetS for PWE are age, residence, level of physical activity, food intake status, epilepsy subtype, epilepsy duration, current AED use, drug responsiveness status, BMI, total cholesterol, and LDL-cholesterol levels. Reading through literature many studies indicated a higher prevalence of MetS in PWE. This can be understood from the perspective of seizure-related metabolic abnormalities, long-term AEDs use, and a more sedentary lifestyle due to epilepsy. It has also been studied how epileptic seizures damage specific brain nuclei in the hypothalamus and lead to changes of serum levels of some neurotransmitters and hormones, which leads to an imbalance of food intake and energy expenditure with subsequent weight gain [34]. AEDs have a great influence on lipid and hormonal status in patients with epilepsy by affecting various enzymes inside the body. AEDs such as PHT, CBZ, and VPA due to their effect as enzyme inhibitors/inducers have more influence in developing MetS than noninducing AEDs such as ZNS, LEV, and LTG, which can substantially decrease several vascular risk parameters, such as triglycerides, atherogenic cholesterol, C-reactive protein, and homocysteine, thus decreasing the risk for cardiovascular and cerebrovascular disease.

In the end, we would like to emphasize that a deeper understanding of the epilepsy-AED-MetS connection and the exploration of lifestyle interventions hold the promise of significantly improving the overall health and well-being of PWE. Clinicians managing PWE should closely monitor various risk factors for developing MetS and consider them when selecting AED treatment.

Author Contributions

All authors stated above have made substantial contributions to this paper. Conceptualization Ž.P.G. and A.H.; literature research B.Đ.I., A.H. and M.B.; data interpretation - Ž.P.G; A.B.K; B.Đ.I. writing - Ž.P.G., A.H.; B.Đ.I..; critical revision - Ž.P.G., A.B.K; writing, review, and editing - all authors.

All authors have read and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Volume 16 Issue 11 November 2024