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Review

Participation in Sports Activities in People with Epilepsy

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Abstract

Sports activities are of physiological, social, and psychological importance for people with epilepsy as well as for every other person. However, participation in sports activities is less common in people with epilepsy. Patients usually tend to refrain from participating in sports activities for several reasons such as the risk of injuries, the risk of physical exercise inducing seizures, stigmatization, prejudice, or lack of efficient medical advice. In this review, we specified the sports branches with their possible risks, precautions to be taken and their related advice for people with epilepsy. The sports branches are examined in the headings as martial arts, outdoor sports, collective ground sports, and gymnastics. The possible risk of injury, risk of the particular sports branch to precipitate a seizure, and the necessary precautions in each sports branch are discussed separately. A detailed clinical evaluation is required to make an appropriate decision on whether an individual with epilepsy can practice the mentioned sport. The type of sport, the type and frequency of seizures, presence of aura, seizure triggers, drug compliance, presence of efficient supervision, and presence of protective equipment should be evaluated. In this review, we have evaluated these topics for each sports branch separately. When appropriate precautions are taken in patients with epilepsy, sports will be accepted as a therapeutic entity rather than a ban.

Keywords: Collective ground sports, epilepsy, gymnastic, martial arts, outdoor sports, physical exercise, and sports

INTRODUCTION

People with epilepsy (PWE) are generally physically less active, and participation in sports activities is less common.[1-3] Participation in sports activities is less than 25% in PWE.[4] Although the beneficial effects of sports in PWE are known, patients tend to refrain from participating in sports activities for various reasons. Some of these are the fear of that sports activities might cause injuries, or potentially induce seizures, lack of knowledge about the favorable effects of sports, stigmatization, prejudice, and lack of efficient medical advice.[1,2] Studies have shown that most avoided activities are joining a team or a group activity.[5] There are various beneficial effects of regular physical exercise, such as improved quality of life, seizure control, mental and general health, increase in sleep quality, decrease in stress, decrease in cumulative physical and mental fatigue, increased socialization and self-esteem.[1,2,6,7] Considering that most of the epilepsies are well controlled with medication; so that PWE should not be discouraged from participating in sports. Because individuals with epilepsy must deal with many social stigmas, preventing them from sports affects their quality of life even more negatively.

It is recommended that an individual should engage in at least 150 min of moderate-intensity (such as walking or cycling) or 75-minutes of vigorous-intensity (such as running) exercises per week. This situation is similar for individuals with epilepsy.

A reason for lesser participation of PWE in sports is the insufficient knowledge of health professionals on this subject.[8,9] However, in recent years, attitudes have been changing for PWE in favor of doing sports.[3] The ILAE task force on Sports and Epilepsy released a report in 2015, which aims to guide individuals with epilepsy about sports participation. According to this guideline, sports are divided into 3 groups according to their potential risks for injury for PWE. Group 1 sports contain no additional risk for the patient (examples: athletics, bowling, judo, wrestling, skiing, dancing, racquet sports, collective contact sports such as baseball, football, basketball, volleyball), and Group 2 sports have moderate risk for PWE, but not risky for bystanders (examples: archery, triathlon, canoeing, boxing, karate, cycling, fencing, gymnastic, horse riding, skateing, swimming, snowboarding), and Group 3 sports are the ones with major risk of injury/death for PWE and bystanders (aviation, climbing, diving, horse racing, motor sports, parachuting, scuba diving, ski jumping, surfing). However, they have stated that still some sports fall in a gray zone, and a different categorization may be performed in an individual basis.[6]

To improve the biological and psychosocial health of individuals with epilepsy, the most appropriate sports-branch should be selected, necessary education should be provided, and under competent supervision, patients should be encouraged to exercise confidently. A detailed clinical evaluation is required to make an appropriate decision on whether an individual with epilepsy can practice the mentioned sport.

The type of sport, the type and frequency of seizures, presence of aura, seizure triggers, drug compliance, and presence of efficient supervision, and presence of protective equipment should be evaluated (Table 1).

In this review, we specified the sports branches with their possible risks, precautions to be taken and their related advice for PWE.

Sports Branches

1. Martial Arts/Combat Sports

Martial arts can be divided into those with a high risk of injury and those without. However, martial arts in general have favorable effects on mental calmness and self-esteem, which may have a positive influence on epilepsy. Because martial arts are performed indoors and are under uninterrupted supervision, it allows the athlete to be intervened quickly if necessary.

1.1 Boxing

Among the martial arts, boxing seems to be the most risky one for injury and therefore the one with no consensus on it.[3] It is classified in Group 2 by the ILAE report.[6] Head blows are very common in boxing compared to other martial arts. The concern is whether head injury can trigger seizures. Even the association of minor head trauma with seizures is not prominent, the kicks of boxing may be harder and repetitive than other sports. There are animal models showing that repetitive concussions cause progressive phenotypical changes characterized by an initial glutamate increase that is accompanied by glutathione consumption and followed by a dysfunction of parvalbumin-positive interneurons and loss of gamma-aminobutyric acid related inhibitory tone, which supports an increased risk of developing epilepsy.[10] Therefore, there is a common tendency to limit participation to boxing in PWE. It may be evaluated patient based, and if performed, a helmet must be used.

Table 1. Factors affecting decisions of people with epilepsy doing sports

Seizure type
Seizure frequency
Timing of seizures
Duration of epilepsy diagnosis
Presence of aura
Presence of mental retardation
Presence of efficient supervision
Drug compliance
Seizure triggers
Patient preferences/risk tolerance
The risk potential of the particular sports branch

MAIN POINTS

- Sports activities are of physiological, social, and psychological importance for people with epilepsy (PWE) just as for every other person.
- With respect to guidelines of ILAE emerged at this decade, attitudes started to change in favor of encouraging PWE to practise sports even more.
- For clinicians to guide their patients, the decision should solely be tailored patient-based; taking into account of the type and frequency of seizures, presence of aura, seizure triggers and drug compliance.
- As long as the appropriate sports-branch is selected, sport spesific recommemdations are applied, necessary education is given and competent supervision with efficient protective equipment is provided, patients can carry out the exercise confidently.

1.2 Karate

Head and face blows should be in a light and controlled manner in karate. The atheletes wear foot protectors and mitts, which further reduce the severity of the impact. In addition, head blows are not allowed in children under 14 years. This age group should wear a face mask and helmet also.[11] For children between 14-16 years, only skin touch is allowed for kicks, which means touching the target without transferring energy into the head or body. Therefore, it seems safe, especially in children. However, there are subtypes of karate such as 'full contact karate' and 'knockdown karate', which can cause injury. Therefore, if an individual with epilepsy prefers to do karate, he/she should avoid taking part in full-contact karate. Additionally, head protection equipment should be preferred.

1.3 Taekwondo

Taekwondo is performed with protective equipment on the head, trunk, and shin area. By the rules, the kick with the lower part of the ankle can be directed to the chest and head, but the punch can only be thrown to the chest area of the opponent. In professional matches, these protective equipments have sensors and measure opponents strike intensity. Even though head blows and concussions are frequent in teakwondo competitions[12], the use of electronical sensor systems recently has led to more controlled strike intensities. It can be considered safer for PWE compared to other martial arts where a direct punch to the head is allowed.

1.4 Judo

Judo is a branch of martial arts whose rules are determined in order not to cause an injury to the opponent, by its nature. Punches, kicks, other blows, and contact with the face are not allowed, and only throws and grappling are used to control the opponent. Fallings have special techniques that minimize blows to the head and neck.[13,14] In this way, head blows are minimized, and if done professionally and correctly, it can be considered safe for individuals with epilepsy. Studies have shown that the most injured areas in judo and taekwondo are lower extremities.[15]

1.5 Fencing

Fencing is a type of martial art that uses a sword. It is based on the principle of scoring as many points as touched in certain areas of the opponent. Masks are worn on the face as a protective equipment. There are three types of fencing according to the sword type and technique: foil, epee, and sabre. The foil is just a thrusting weapon and the target is trunk, whereas in the sabre, the target is the entire body including the head. Therefore the foil technique may be more appropriate for PWE. It is suitable for individuals with epilepsy as it minimizes head traumas.

1.6 Wrestling

Wrestling is classified as a Group 1 activity according to the ILAE and does not pose any additional risk for PWE.[6] Wrestling may be safe for children with well-controlled seizures or seizures that do not impair consciousness or motor control.[16] Wearing headgear with a frontal pad can also minimize the impact of the forehead and help prevent concussions. Choking techniques in wrestling that make breathing difficult will lower the seizure threshold in these individuals secondary to central hypoxia. Although choking is illegal in professional wrestling, in some types of wrestling, choking can be used as a submission hold for the opponent, which poses a serious risk for PWE.

1.7 Aikido

Aikido is born from armed combat. It is performed without a helmet. It is based on the principle that an opponent initiates the attack within a certain pattern and the other must neutralize it. In this sport, blows from the front and the sides of the head and face pushing are allowed, which render the person in a risk for head blow. In particular, some techniques like shihonage and iriminage may cause the opponent to hit the back of their head to the floor.[17] To minimize the risks, matches can be held without these techniques, if not, a softer and thicker aikido mat may be used and well training of neck muscles beforehand might prevent major injuries. The absence of a free attack practice ensures the next blow to be predictable, so that head protection techniques can be emphasized for an individual with epilepsy.

2. Outdoor Sports

2.1 Walking/Running

Walking and running are considered low-risk activities for PWE. Walking and running are appropriate exercise types which have beneficial effects on the neuropsychological profile and seizure outcomes of PWE.[1] However, running that requires prolonged aerobic capacity, such as marathon or triathlon run, can be risky as they may reveal metabolic disturbances leading to acute symptomatic seizures. The metabolic disturbance associated with prolonged running is hyponatremia. The main risk for hyponatremia is excessive fluid intake during and after the exercise, which may be seen in prolonged exercises such as marathon running and triathlon.[8] In the study of Davis et al.[18] including 26 healthy marathon runners who developed hyponatremia, three with severe hyponatremia (Na <125 mEq/L) developed seizures. The possibility that epileptic individuals being more susceptible to hyponatremia should be considered in this respect. Another physiologic condition during aerobic exercise is hyperventilation. While resting hyperventilation can trigger seizures by causing central hypocapnia and vasoconstriction; hyperventilation during aerobic exercise is a physiological compensation and has been shown not to cause seizure activity.[3] Hypoglycemia may be another trigger for seizures. To avoid the hypoglycemic effect of prolonged aerobic activity, adequate nutrition should be provided before the exercise.[8]

It is recommended that PWE should be accompanied by another person during walking/running; adequate fluid consumption and nutrition are provided before the exercise and they should avoid performing the activities on a treadmill because falling may lead to major injuries.[16,19]

2.2 Mountaineering/Sportive Climbing

Mountaineering can be divided into two categories, the first one is an expeditive style, which is performed at high-altitudes. Another is sportive climbing, which is performed on the rocks or artificial climbing walls. In general, sports performed at heights should be avoided in PWE. Climbing is classified as Group 3 in the ILAE report. Mountaineering in an expeditive style is risky in two ways, firstly, hypoxia from high-altitude can increase the risk of seizures.[8] Secondly seizure during climbing can be life-threatening for both the person and bystanders.[6] Outdoor sportive climbing on the rocks does not involve the risk of hypoxia; however, the risk of severe injury for the patient and bystanders remains. However, it seems safe to climb as an indoor activity to a specifically designed wall for climbers under convenient observation and with a head gear.

Trekking and hiking are safe activities for PWE; however, an electronic localizer device would be beneficial.

2.3 Cycling

Since cycling involves high speeds, the risk of injury is high in case a seizure occurs. Individual risk assessment should be performed. It is not recommended for those with uncontrolled seizures. It can be performed with certain precautions in individuals with seizure control. A helmet must be worn. It is important to use protective pads (knee, elbow, wrist). It is not recommended to cycle in a busy location, on a sloping track and at high speeds.[3] Individuals with epilepsy may prefer 3-wheel bicycles instead of 2-wheel bicycles. In the case of a person with seizures with impaired awareness, to protect the individual while cycling, unique equipment with a loosely adjusted harness and high back may be preferred produced by private companies (Figure 1).

Figure 1. Three wheel bike for people with epilepsy

2.4 Parachuting

Parachuting is considered a high-risk activity for PWE and is not recommended. Any seizure activity that may occur in high-altitude will result in a life-threatening condition. If the person with epilepsy wants to parachute, it is recommended to do a "tandem skydive" (with the group) and with another person in the group who is under surveillance of the situation of the individual. Preferably, these patients should have controlled seizures and seizures without loss of awareness.

2.5 Skiing

ILAE classified cross country skiing in Group 1 but ski jumping in Group 3 activity.[6] Skiers should wear protective gears, especially a helmet. Additionally, sun glasses are important, especially for photosensitive epilepsies. Patients should not be alone in the ski lift. Skiing on high slopes and downhill skiing will pose a risk in the case of a seizure. It is recommended to use an electronic localizer device and have a person accompanying the patient.

2.6 Rafting/Canoeing

Rafting is safe for PWE while taking the safety measures. Wearing a life jacket during the activity, doing it in a group and with a professional, being in the middle rather than the front or back, and wearing an electronic localizer device will reduce the risks in case of any seizure development by providing a rapid first aid. The precautions for canoeing are similar to rafting. All individuals with photosensitive seizures are advised to wear sunglasses. In case of a seizure, the canoe may overturn, the person may get trapped under the canoe, and if awareness is lost, this situation will pose a life-threatening risk. It is recommended to wear lifejackets while performing water sports.[16,19]

2.7 Horse Riding

The ILAE report has classified horse riding in the Group 2; however, horse racing in Group 3.[6] Having a seizure during riding includes severe injury risk. Individual risk assessments should be considered. Horse riding may be permitted for patients with controlled epilepsy with caution. It is recommended that a riding hat is worn. Additionally, an equipment that connects the individual to the horse in order not to fall from height during the seizure is recommended. It should be practiced under close surveillance of a person who knows the condition of the patient.[3,19]

2.8 Swimming

It has been shown that the risk of drowning is increased in PWE while swimming.[20] Patients need to be evaluated according to his/her clinical conditions. While it includes a high risk for individuals with frequent seizures and seizures with impaired awareness: those who are seizure-free for more than 1 year, those who have only nocturnal seizures, and those who do not lose awareness can practice under close supervision. The supervisor should be a trained professional for cardiopulmonary resuscitation.[3] It is recommended to do it as a team, to wear a colored cap that indicates the individual's condition, and to do it in the pool instead of open waters. Individuals with photosensitive seizures caused by refraction of light should wear goggles. Patients should avoid hyperventilating deep fast breaths, or holding breath for swimming underwater for a long time. Individuals with a high frequency of seizures should definitely wear a life jacket. Adequate nutrition should be provided to avoid hypoglycemia.[16,19,21]

2.9 Scuba Diving

Scuba diving includes a high risk for PWE and should be avoided. Apart from scuba diving specific risks such as decompression sickness, oxygen toxicity, and nitrogen narcosis, which can lower the seizure threshold; this activity inherently poses a serious life-threatening risk because if a seizure occurs under the water, it might not be detected, and the rescuer might arrive late.[3,6,22]

2.10 Motor Sports

Whether PWE can drive a motor vehicle or not varies according to the laws of the countries, yet, motor sports are categorized in the risky activity class. In the case of a seizure, the person will risk his life and the lives of the bystanders.[6] Since the activity includes high excitement, this may be another stressing factor that may trigger seizures. The United Kingdom national karting association recommends individuals to be seizure free for 1 year before doing the activity.[19] It is not recommended for people with uncontrolled epilepsy.

3. Collective Ground Sports

3.1 Football

Collective ground sports are generally thought to be safe. General considerations for aerobic sports such as avoiding dehydration, hypoglycemia, and overhydration, should be considered. However, it should be taken into consideration that heading is free in football, which may lead to minor head traumas. Concussion wasnot found to have significance for epilepsy development;[23] but frequent and severe blows should be avoided. It is recommended that teammates and the coach to be aware of the situation and know how to manage the seizure. There was no significant difference found between an individual with epilepsy and a healthy individual to have a seizure while playing football.[24]

3.2 Basketball

It is a safe activity for individuals when the team and coach are aware of the situation, know how to manage the seizure, avoid symptomatic seizure triggers and make the individual with epilepsy rest more frequently than other team players. Attention should be paid to head blows caused by contact sports, and a protective concussion headband or helmet may be worn.

3.3 Volleyball

Although it is considered a contact sport, it differs from other team sports in that it is not in one-on-one struggle with the opposing team player, and the head blow is minimal. It is in the low-risk group for PWE. To minimize the risk of concussion, a protective concussion headband or helmet may be worn, coach and team players should be aware of the situation, and symptomatic seizure triggers must be avoided.

Figure 2. Concussion helmets

3.4 Handball

Although it is in the low-risk group for PWE, it is possible to be exposed to high acceleration and severe head blows during the game. For this reason, it is necessary to wear a protective helmet and a mouthguard (Figure 2).[25]

4. Gymnastics

There are several types of gymnastics such as artistic, rhythmic, and aerobic. Gymnastic movements that are performed on the floor have low risk in case of seizures. Rhythmic and aerobic gymnastic are mostly performed on the floor; however, artistic gymnastic includes high bars, vaults, rings and trampolines, which may be risky for PWE since they are performed on heights. General considerations for aerobic sports should be kept in mind, especially avoiding metabolic disturbances. It is safe for people with controlled epilepsy when safety measures are taken and performed under supervision.[16]

DISCUSSION

Individuals with epilepsy do not sufficiently participate in sports activities due to some reasons arising from the patients and presumptions of the physicians as well. The hesitation of individuals with epilepsy to do sports is mainly originating from the concern that whether sports and physical exercise are triggering factors for epileptic seizures or not, as well as the fact that the potentiality for injury in case a seizure occurs during physical activity.

Risks Associated with Physical Exercise in Terms of Inducing Seizures

Exercise-related precipitant factors may be metabolic disturbances, head trauma, stress of competition, and change in antiseizure drug levels.[8]

1. Metabolic Factors

The development of hyperthermia, hypoglycemia, hyponatremia, hypoxia, and hyperventilation during exercise are the main metabolic disturbances that PWE can face. These may be observed in sports that include prolonged aerobic exercise sessions. The mentioned metabolic disturbances may trigger acute symptomatic seizure; however, there is insufficient evidence that PWE is more prone to those.[3] Among these, hyponatremia due to overhydration in marathon or triathlon runners, and hypoxia in high-altitude climbers seem to harbour much of a significant risk.[8] Hypoxia is not much evident in most exercise activities except for high-altitude climbing. Hyperventilation-related respiratory alkalosis does not occur during moderate-intensity exercise because this is thought to be an adaptive response to metabolic demand. Hyperthermia can induce seizures in specific situations such as febrile convulsions however no association was established between exercise-induced hyperthermia and seizures.[8] Even though rare, it is known that hypoglycemia may induce seizures. To avoid the hypoglycemic effect of prolonged aerobic activity, adequate nutrition should be provided before the exercise.[8]

2. Antiseizure Drugs

Another question is whether exercise can lower antiseizure drug levels by inducing liver enzymes. However, studies have failed to show a significant variation in drug levels during exercise. In the case of clinical necessity, drug levels may be checked.[3,26]

3. Stress

Stress during sports activities may be another precipitant factor for seizures. This may be important, particularly in patients participating in competitive sports activities. Stress may lead to hypothalamic-pituitary adrenal axis dysregulation and increased sympathetic nervous system activity, which together may result in seizure susceptibility.[8] It has been shown that chronic stress can lower the seizure threshold.[27] Therefore, it is important to distinguish between people who do moderate exercise to gain a healthy lifestyle or as a leisure activity, and who do it for professional purposes. Triggering factors should be evaluated by an individual basis in both groups.[3] Competitive sports activities cause stress and fatigue, which might consequently increase the frequency of seizures.[5] For this reason, it may be preferred for individuals with epilepsy to do these activities as a leisure time activity rather than in a high-stress competition environment.

4. Head Trauma

One of the main concerns of individuals with epilepsy in doing sports is the possibility that a head injury may trigger a seizure. It is known that moderate to severe head trauma may cause posttraumatic epilepsy in the later period.[28] However, the relation of minor head trauma and sport-related concussion and seizures are uncertain.[8] Although it has been reported that convulsive attacks may develop after minor head traumas, it has not been directly related to cause epilepsy, eventually.[3] Post-concussive convulsions occur within the seconds of the trauma and lasts for seconds.[29] Semiologically, these convulsion types are mainly tonic stiffening followed by myoclonic jerks or asymmetrical posturing. It has been observed that 68% of these convulsions, which may occur after trauma, are in the form of "posturing". However, after a sports-related concussion, convulsion is the least frequent symptom, while headache and dizziness being the most common symptoms.[29,30] The general opinion is that minor head injury is unlikely to precipitate a seizure.[6,29] Unless trauma is repeated, it is not considered a risk factor for epileptogenic march. In the study of Wennberg et al.[31] including 330 patients with concussion; during 5-10 year follow-up, they have found no increased risk for epilepsy.[32] However, the data about the concussive convulsions and post concussion seizures are limited. There are case reports stating postconcussive seizures during football and wrestling.[33,34] Another point is the impact of repetitive head trauma. Even if the trauma is mild, repetitive head blows may be responsible for epileptogenesis.[10] Thus, it is important to wear a protective headgear in sports with a high risk of head traumas.

Exercise-induced Seizures

However, even very rare, some patients may have seizures precipitated by exercise, which is more common in symptomatic focal epilepsies. Kamel et al.[35] reported 10 patients with exercise-induced seizures, who all had symptomatic focal epilepsies. In the study of Nakken[36] that includes two hundred and four adults with epilepsy, 10% reported exercise as a seizure precipitant, 2% of which reported a clear association with exercise. This is particularly observed in patients with an underlying structural brain lesion. They have reported that the level of physical exertion is correlated with seizure induction in general. The more vigorous the exercise, the more likely it is to trigger a seizure. However, the type of triggering exercise may change according to the patient. The epileptogenic mechanism of how exercise exerts its effect in this minority of patients is not well known. However, it seems like a similar mechanism in reflex epilepsies, rather than being associated with the metabolic effects of exercise. This is supported by the fact that the majority of exercise-induced epilepsies are mostly temporal lobes of origin.[2,35,37] Okadome et al.[38] reported boxing-induced reflex seizure that is precipitated by a specific motion and resolved by avoiding this motion. Even though regular physical exercise has beneficial effects on seizures in general, if a clear exercise-related trigger is described, this should be taken into consideration while evaluating the patient.

Additionally, in rare specific syndromes such as megalencephalic leukoencephalopathy with subcortical cysts and vanishing white matter disease, exacerbation of symptoms including seizures with minor head trauma may be seen.[39,40]

Risk of Injury During Sport When Having a Seizure

Another concern regarding physical exercise and epilepsy is the possibility of injury if the person has a seizure during sports activity. This risk is elevated in patients with frequent seizures, generalized seizures, atonic seizures, and patients with mental retardation.[3] These patients are at a higher risk of injury during normal daily activities as well. However, the most common type of injury during sports activities is soft tissue injuries.[29] Patients with nocturnal seizures and who have aura are at lower risk for injury. In patients with newly diagnosed epilepsy, care should be taken and risky sports should be avoided for a period. The type of sports is also important in this respect. Group 3 sports according to the ILAE report involve high risk of injury, therefore should not be recommended to uncontrolled epilepsies. However, they may be recommended with caution in controlled epilepsy on an individual-based approach.[6]

General Recommendations

It is necessary for the person to wear protective equipment suitable for each sport type (life jacket and goggles for water sports; helmet for martial arts, horse riding, contact sports; wristband that provides vital information and a localizer device of the individual for outdoor sports, harness for cycling and horse riding etc); to take countermeasures for seizure-triggers (for runners hydration, nutrition and appropriate clothing; for climbers adequate oxygenation etc.), and to have a trained supervisor who is educated about the athlete's medical condition and trained for cardiopulmonary resuscitation (Table 2).

A patient-based approach should be followed according to the clinical characteristics of the patient. In patients with frequent seizures, seizures with impaired awareness, recent diagnosis of epilepsy, seizures without aura, and seizures during the day; precautions according to the sports branch should be discussed with them. Seizure triggering factors should be questioned. Patients' drug compliance should be taken into consideration for the final decision. Patients' risk tolerance is another determining factor of the decision (Table 1).

Beneficial Effects of Exercise on PWE

Generally, it has been proven that exercise is good for the cardiovascular system and psychosocial, and physiological well-being. Additionally, it reduces neuronal damage and cell lossand improves the quality of life and neurocognitive outcomes in PWE.[7] It increases cognitive capacity by showing positive effects on attention, memory, and concentration, improves sleep quality, increases self-esteem and improves mood by reducing depression

Table 2. The possible protective equipment for particular sports branches

Helmets/concussion helmets	Martial arts, collective contact sports, cycling, climbing, horse riding
Goggles/sunglasses	Water sports, skiing, and outdoor sports
Life jacket	Water sports
Protective pads	Contact sports and outdoor sports
Electronic localizer device	Mountaineering, hiking, and rafting
Harness	Horse riding, cycling

and anxiety, and protects against osteoporosis. Additionally, it may cause a possible reduction in seizure frequency by several mechanisms. Animal models and clinical studies have shown a decrease in interictal discharges during exercise and additionally seizure occurrence.[2,41-43] Several mechanisms are proposed which include, release of B-endorphins, noradrenaline, and GABA during exercise, release of steroids secondary to stress, increase in melatonin, increase in parvalbumin, and generation of structural changes within the hippocampus.[2] The regular practice of physical exercise enhances the levels of brain-derived neuro factor in the hippocampus, induces neurogenesis, inhibits oxidative stress and reactive gliosis, avoids cognitive impairment, decreases the production of pro-inflammatory and stress biomarkers, and stimulates the production of dopamine in the epileptic brain.[8,44]

CONCLUSION

Traditionally, there has been a tendency to avoid physical activity and sports in PWE. However, this trend has started to change with the recognition of the positive effects of sports on health in PWE. Sports activities are of physiological, social, and psychological importance for individuals with epilepsy and for every other person. To increase the biopsychosocial well-being and social participation of PWE, the most appropriate sports branch should be found, necessary education and training should be given, and people should be encouraged to exercise under competent supervision. People should be in close contact with their physician and should be informed about the necessary practices before, during, and after the activity. When appropriate precautions are taken in patients with epilepsy, sports will be accepted as a therapeutic entity rather than a ban.

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Damage to Liver Tissue Caused by Valproic Acid Used for Treating Epilepsy: Protective Effects of Vitamin B_6

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Abstract

Objective: We intended to determine the vitamin B_6 (Vit B_6) protection on valproic acid (VPA)-induced liver injury.

Methods: Male Sprague-Dawley rats were used. The control group: Vit B_6 (50 mg/kg/day) given rats; VPA (500 mg/kg/day) given rats; VPA and Vit B_6 given rats at the same dose and time for 7 days.

Results: Liver glutathione and total antioxidant capacity were decreased while, lipid peroxidation, advanced oxidized protein products, tumor necrosis factor-alpha, interleukin-6, nitric oxide, total oxidant status, oxidative stress index, reactive oxygen species levels and myeloperoxidase, antioxidant enzyme activities, glucose-6-phosphate dehydrogenase, and adenosine deaminase activities were increased in the VPA group. Vit B_6 eased these parameters in the VPA group. In the histological determinations, nuclei including dense chromatin material, hyperemia, sinusoidal dilation, collagen accumulation in connective tissue, and large and dense granules in the cytoplasm were increased in the VPA group according to the control groups, microscopically.

Conclusion: As a result, Vit B_6 supplementation reversed biochemical results in VPA-induced liver damage by regulating the antioxidant status.

Keywords: Valproic acid, vitamin B_6, hepatotoxicity, oxidative stress, antioxidant effect

INTRODUCTION

2-propyl valeric acid or generally known as valproic acid (VPA) is an effective anticonvulsant and preferred all around the worldwide for treatments of epilepsies for both childhood and adults.[1,2] Although it has been reported for this disease, its side effects have reached a dangerous level. Day by day, there is an increasing number of studies that indicate its unwanted effects on many organs and tissues in both human and experimental rat studies, listed as liver, lung, heart, etc.[3-5]

Albeit with the existence of an unpredictable mechanism for liver toxicity, there is a common opinion for reactive oxygen species (ROS) production because of either VPA-sourced or its metabolites-sourced.[6] This production can be associated with many metabolic pathways. One of these pathways is the interfering effect of VPA on the beta oxidation of fatty acids.[7] Likewise, the electron transferring alterations in the mitochondrial electron transport system (ETC), disrupted ATP generation, and asymptomatic hyperammonemia are the reasons that were related to the hepatotoxic effects of VPA.[6-8] The clinical symptoms for VPA hepatotoxicity during its usage in humans can be numbered as vomiting, jaundice, fatigue, etc.[9] To decrease these effects and find a solution for its serious side effects, researchers have been trying to use different plant extracts or vitamin sourced substances.[10,11]

Vitamin B_6 (Vit B_6) is an important water-soluble vitamin. Its derivatives can be produced at its 4th position, which are named as pyridoxal (with an aldehyde group), pyridoxamine (with an aminomethyl group) and pyridoxine (with an hydroxymethyl group).[12] Their phosphate forms (at 5th position) are also necessary. Vit B_6 is an indispensable cofactor for approximately over a hundred enzymatic reactions in metabolism and the most known reactions are known as transaminationand alpha decarboxylation.[13] Since it isnot produced in humans, it is necessary for being consumed with milk, meat, and various fruits and vegetables.[12] The antioxidant and radical scavenging activities of Vit B_6 have been well proven by Turkyilmaz et al.[14]

Based on this information, we planned to investigate the unique antioxidant capacity of Vit B_6 on VPA-induced hepatotoxicity by evaluating both histochemically and biochemically.

METHODS

Chemicals

All chemicals used were of analytical grade. They were purchased from Sigma-Aldrich and Merck.

Animals and Ethics Statement

In this study, male Sprague-Dawley rats (4-months aged) were preferred, and the ethic permission was taken from the Local Ethics Committee of Animal Research of İstanbul University (number: 2015/09, date: 05.02.2015). All animals were fed with a standard pellet and free access water ad libitum.

Experimental Design

Rats were divided into four groups.

Group 1: Control animals.

Group 2: Animals given Vit B_6 at a dose of 50 mg/kg for 7 days.

Group 3: Animals treated VPA at a dose of 500 mg/kg for 7 days.

Group 4: Animals received Vit B_6 and VPA at the same dose and time for 7 days.

The administration of Vit B_6 was performed by orally (gavage technique), and VPA was intraperitoneally. The doses of Vit B_6 and VPA were referenced according to the study of Tunali.[15] Before the termination of the experiments, the rats were fasted for one night. On 8th day, they were sacrificed under anesthesia. Liver tissue samples were taken for both histologic and biochemical analyses.

Histological Assay

The Bouin's solution was used for fixation of liver tissues. Fixed liver tissues were dehydrated in an ethanol series. It was cleared in xylene and embedded in paraffin. The tissues were cut as 5 µm-thick sections. The sections were stuck on a microscope slide. It was stained with Masson's trichrome for histological determination. The Olympus CX-45 microscope was used for histological analysis (X40 objective and X10 ocular system). The histological score, which has a grade from 0 to 3 as negative (0), weak (1), moderate (2), and strong (3) was used for explanation the results.

MAIN POINTS

- Valproic acid (VPA) is an effective anti-epileptic drug used for the treatments of various seizures and migraine.
- Nevertheless, VPA has many side effects on many organs by triggering oxidative stress.
- Liver is an important organ and contains many macromolecule pathways, but this organ is open to different side effects associated with free radical and oxidative conditions.
- Vitamin B_6 (Vit B_6) is a vital water-soluble vitamin and an important free radical scavenger. This feature leads to this vitamin to be used in preventing toxicities sourced by free radicals.
- The obtained biochemical and histological results from this study support the potential antioxidant feature of Vit B_6 on liver injury induced by VPA.

Biochemical Experiments

Liver tissues were homogenized in cold saline (0.9% NaCl) for preparing 10% (w/v) homogenates. They were centrifuged, and the supernatants were collected. They had been kept at -80 ºC until the biochemical experiments were performed. The reduced glutathione (GSH), lipid peroxidation (LPO), and advanced oxidized protein products (AOPP) levels were performed according to the methods of Beutler[16], Ledwozyw et al.[17] and Witko-Sarsat et al.[18], respectively. Tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) levels were determined as using ELISA kits as the manufacturers' procedure. Myeloperoxidase (MPO) activity and nitric oxide (NO) levels were determined according to the methods as follows Wei and Frenkel[19] and Miranda et al.[20]. Total antioxidant capacity (TAC), total oxidant status (TOS) and oxidative stress index (OSI), and reactive oxygen species (ROS) levels were performed according to Erel[21] and Erel[22], Zhang et al.[23] methods, respectively. Catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione reductase (GR) activities were determined as based on the methods of Aebi[24], Mylroie et al.[25], Wendel[26], and Beutler[27], respectively. Glucose-6-phosphate dehydrogenase (G6PD) and adenosine deaminase (ADA) activities were performed according to the methods of Beutler[28] and Karker[29], respectively.

Statistical Analysis

The statistical analysis of the biochemical results was determined via GraphPad Prism 6.0 (GraphPad Software, San Diego, California, USA). The data were expressed as mean ± standard deviation. The results were assessed with an unpaired t-test and analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. $P<0.05$ was considered significance. The biochemical results were also evaluated using Origin for performing principal component analysis (PCA).

RESULTS

Histological Results

The histological results are presented in Figure 1. The nuclei including dense chromatin material, hyperemia, sinusoidal dilation, collagen accumulation in connective tissue, and large and dense granules in the cytoplasm were increased in the VPA group according to the control group given physiological saline and control group given Vit B_6 in the histological determinations. There was not any alteration in VPA+Vit B_6 group according to the VPA group, microscopically (Figure 1).

Biochemical Results

Figure 2 represents liver GSH, LPO, AOPP, TNF-α and IL-6 levels, MPO activity and NO levels.

After both VPA and VPA+Vit B_6 administration, the alterations in GSH levels were observed as insignificant. LPO and AOPP levels were significantly increased in the VPA group compared to the control group ($^{**}p<0.01$). Vit B_6 reversed LPO and AOPP levels significantly in the VPA group ($^{\#}p<0.01$) (Figure 2).

Liver TNF-α and IL-6 levels, MPO activity and NO levels mentioned in Figure 2 were significantly increased in VPA group compared to the control group ($^{*}p<0.05$, $^{**}p<0.01$, $^{\#\#\#}p<0.001$, respectively). The

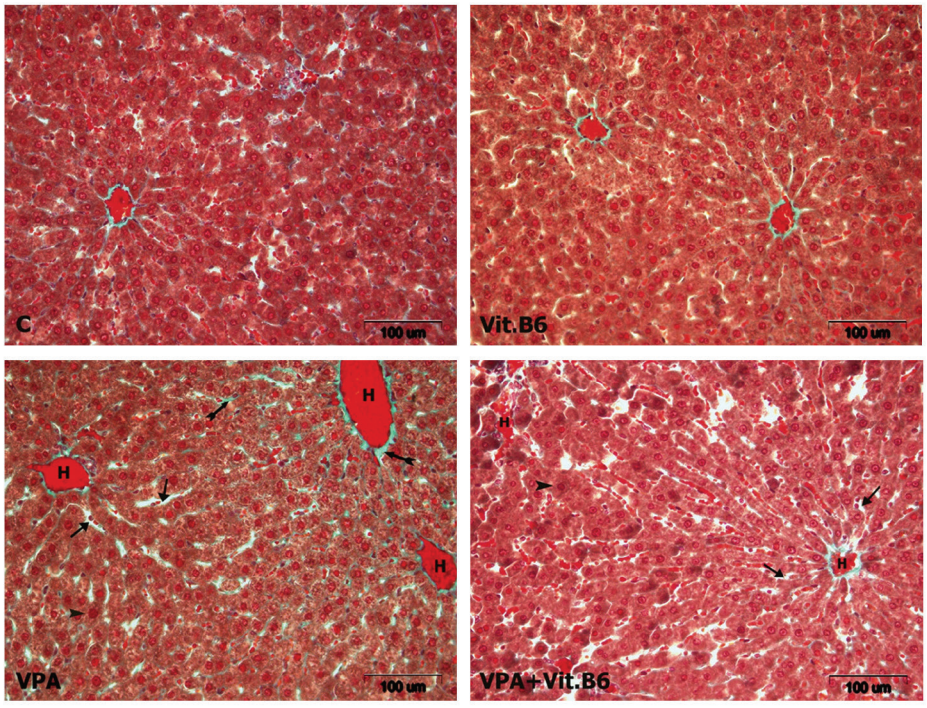

Figure 1. Histological appearance of the liver tissues of all groups.
The control group: C, control group given vitamin B_6 (50 mg/kg): Vit B_6, experimental group given VPA (100 mg/kg): VPA, the experimental group given vitamin B_6: VPA+Vit B_6 (doses were given at the same and concentration). Nuclei including dense chromatin material; ➤, hyperemia; H, sinusoidal dilation; ➔, collagen accumulation in the connective tissue; ➡ can be seen in VPA and VPA+Vit B_6 groups. Masson's trichrome. X40 objective and X10 ocular system
VPA: Valproic acid, Vit B_6: Vitamin B_6

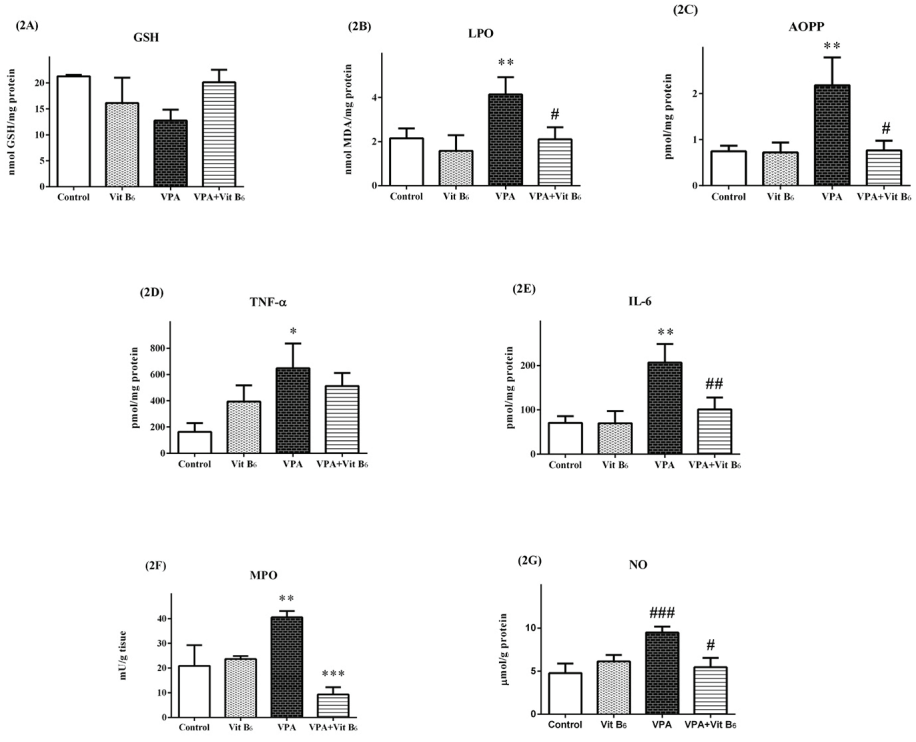

Figure 2. The liver (A) reduced glutathione, (B) lipid peroxidation and (C) advanced oxidized protein products, (D) tumor necrosis factor-α, (E) interleukin-6 levels, (F) myeloperoxidase activity, and (G) nitric oxide levels of all groups. Each column represents mean±standard deviation. The control group: Intact group, Vit B_6 group: animals received 50 mg/kg Vit B_6 per day, VPA group: 500 mg/kg administered animals, VPA+Vit B_6 group: animals received the same doses at the same time. $^{**}p<0.01$ versus control group, $^{\#}p<0.01$ versus VPA group, $^{*}p<0.05$ versus control group, $^{\#\#}p<0.05$ versus VPA group, $^{***}p<0.001$ versus VPA group, $^{\#\#\#}p<0.001$ versus control group
VPA: Valproic acid, Vit B_6: Vitamin B_6

administration of Vit B_6 decreased IL-6, MPO, and NO significantly in the VPA group ($^{\#\#}p<0.05$, $^{***}p<0.001$, $^{\#}p<0.01$, respectively) (Figure 2).

Liver TAC, TOS, OSI and ROS levels, CAT, SOD, GPx and GR activities are presented in Figure 3. Vit B_6 caused a decrease in TAC levels and an elevation in OSI of control group ($^{**}p<0.01$, $^{*}p<0.05$). VPA administration decreased TAC levels ($^{***}p<0.001$) and increased TOS, OSI, and ROS levels significantly as compared the control group ($^{**}p<0.01$, $^{\#\#}p<0.0001$, respectively). In VPA+Vit B_6 group, all the levels given in this Figure 4 were altered significantly compared to the VPA group ($^{****}p<0.0001$, $^{\#}p<0.01$) (Figure 3).

VPA administration increased CAT, SOD, GPx, and GR activities significantly as compared the control group ($^{**}p<0.01$, $^{*}p<0.05$, $^{***}p<0.001$). The administration of Vit B_6 to the VPA group significantly reduced CAT, SOD, GPx, and GR activities ($^{\#}p<0.01$, $^{\#\#\#}p<0.001$) (Figure 3).

Liver G6PD and ADA activities are given in Figure 4. Vit B_6 significantly reduced G6PD in the control group ($^{*}p<0.05$). GP6D activity was significantly increased after VPA administration in the control group ($^{**}p<0.01$). The administration of Vit B_6 decreased G6PD and ADA activities in the VPA group significantly, respectively ($^{****}p<0.0001$, $^{\#}p<0.05$) (Figure 4).

PCA was used to determine the correlation between all biochemical parameters and the results are shown in Figure 4. According to the PCA, the first two components were determined around 83.41% (as total result). PC1 and PC2 values were calculated as 74.60% and 8.81%, respectively. At the first part, MPO, SOD, ADA, GPx, G6PD, GR, OSI, CAT, NO, AOPP, LPO, ROS, IL6, TOS, TNF-alpha data were observed to be clustered together. These parameters were negatively correlated with PON, GSH, and LPO (Figure 4D).

DISCUSSION

VPA and its metabolites can cause mitochondrial oxidative phosphorylation inhibition, impairments of the electron transport chain, and hence disruption of ATP generation.[6] The interruption of energy functioning also affects the pyruvate uptake and transportation in the mitochondrial inner membrane.[30] Systemic insulin resistance alteration and obesity-affected inflammation conditions are the well-documented reasons for VPA hepatotoxicity.[6,30] All the defined reasons are strictly associated with the production of ROS on VPA-induced hepatotoxicity.

After being taken to the organism, Vit B_6 serves at many reactions such as transamination, decarboxylation, etc. as a cofactor. Vit B_6 can form a Schiff base with the amino groups of lysine, which can exist at the active sites of enzymes and then helps electron transfers by stabilizing the reaction intermediates.[31] Its antioxidant capacity on different metabolic disorders has been proved by many researchers.[15]

GSH, a unique tripeptide for the antioxidant system, is capable of detoxifying many toxicants with its thiol (-SH) group. Increased free radical levels have been related to lower GSH levels in different VPA-induced hepatotoxicity models studied by Sokmen et al.[10] Besides, Kiang et al.[32] reported that different VPA metabolites had dramatically depleted GSH levels in rat hepatocytes. In our rat-modelled study, we got diminished GSH levels in the livers of the VPA-treated group compared to the control group. To maintain GSH levels at a constant ratio may help better antioxidant system functioning either regulating GSH-dependent enzymes or total antioxidant status. For this purpose, we administered Vit B_6 to the VPA group. Vit B_6 has been defined as serving like a cofactor for the transsulfuration pathway for the transformation of homocysteine to cysteine, which is necessary for the formation of GSH.[33] As considering this approach, we may say that

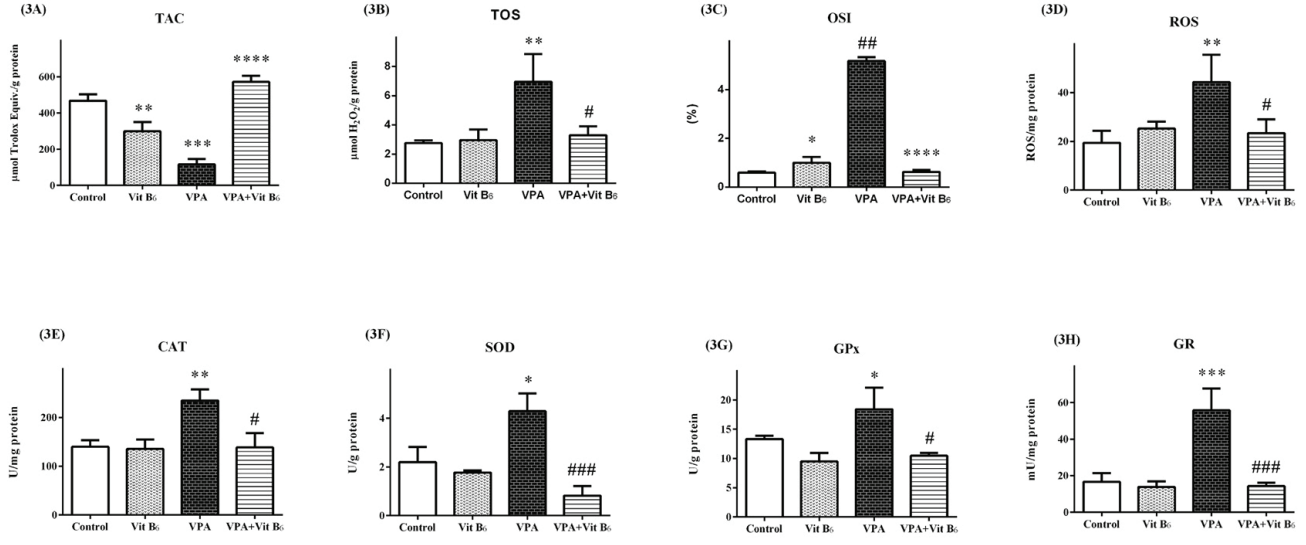

Figure 3. The liver (A) total antioxidant capacity, (B) total oxidant status, (C) oxidative stress index and (D) reactive oxygen species levels, (E) catalase, (F) superoxide dismutase, (G) glutathione peroxidase and (H) glutathione reductase activities of all groups.
Each column represents mean±standard deviation. The control group: Intact group, Vit B_6 group: animals received 50 mg/kg Vit B_6 per day, VPA group: 500 mg/kg administered animals, VPA+Vit B_6 group: animals received the same doses at the same time.$^{**}p<0.01$ versus control group, $^{***}p<0.001$ versus control group, $^{****}p<0.0001$ versus VPA group, $^{\#}p<0.01$ versus VPA group, $^{*}p<0.05$ versus control group, $^{\#\#}p<0.0001$ versus control group, $^{\#\#\#}p<0.001$ versus VPA group
VPA: Valproic acid, Vit B_6: Vitamin B_6

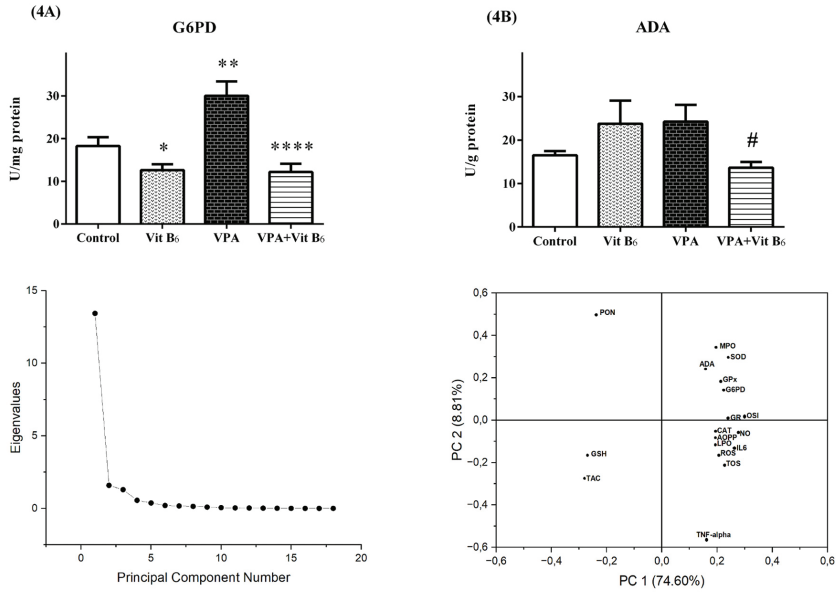

Figure 4. The liver (A) glucose-6-phosphate dehydrogenase and (B) adenosine deaminase activities and principal component analysis (PCA) (C, D) results of all groups.

Each column represents mean±standard deviation. The control group: Intact group, Vit B_6 group: animals received 50 mg/kg Vit B_6 per day, VPA group: 500 mg/kg administered animals, VPA+Vit B_6 group: animals received the same doses at the same time. $^{*}p<0.05$ versus control group, $^{**}p<0.01$ versus control group, $^{****}p<0.0001$ versus VPA group, $^{\#}p<0.05$ versus VPA group. PCA (C, D) results for all biochemical parameters. (C) Plot presentation, (D) the presentation of PCA total result as 83.41% with PC1 and PC2

VPA: Valproic acid, Vit B_6: Vitamin B_6

administration of Vit B_6 elevated GSH levels probably supporting this mechanism and helping scavenge free radicals in the VPA group.

A sign for increased free radical level is LPO. Its elevated level is a major indicator for destructing cell membranes, which could begin with VPA administration. Different concentrations of VPA affect LPO levels in both liver and kidney, by represented by Tong et al.[34] and Chaudhary et al.[35], respectively. In addition, the elevation of LPO may be associated with AOPP levels because proteins can be affected at the same conditions as much as the lipid structure of membranes in cell media with the existence of VPA. Tunali et al.[11] showed that VPA elevated AOPP levels of VPA-induced brain injury by proving the increased ROS levels after VPA administration. Our results are in accordance with this approach, and we got elevated levels of LPO and AOPP in the livers of the VPA-administered group. The administration of Vit B_6 decreased these levels in the VPA group. This diminishing effect of Vit B_6 can be related to the radical scavenging effect of VPA, whose protective effect has also been also indicated in sepsis -induced lung and liver damage by Giustina et al.[36]

Immune system -mediated drug hypersensitivity is another unwanted consequence for the patients who use VPA.[37] Affected energy metabolism is evidence for cytokine-related liver toxicities.[38] VPA increases TNF-α and interleukin gene expression levels in liver tissue.[39] Unfortunately, increasing TNF-α levels lessen ATP levels in cell media and enhances the strong harmful effects of ROS.[37] Likewise, MPO, as forming hypochlorite by using chloride and hydrogen peroxide, which are initiators for the formation of hydroxyl radicals and singlet oxygen and NO, as being a diffusible gas, are important factors for cells.[40,41] Exemplarily, elevation of NO levels is related to increased union with ROS molecules and hence, covalently binding of proteins in mitochondrial respiration complex IV occurs.[42] In our study, TNF-α, IL-6, NO levels and MPO activities were found dramatically increased in VPA group. Our results are parallel with different VPA studies.[39,43,44] However, a diminishment in plasma Vit B_6 levels has been associated with altered inflammation conditions.[45] Taking into consideration of the protective effect of Vit B_6 on both ROS scavenging and stimulation of inflammation, we can assume that Vit B_6 is effective in decreasing TNF-α, IL-6, MPO and NO in liver toxicities.

The lessened GSH levels, increased LPO and AOPP levels, as well as altered inflammatory conditions by VPA, it is inevitable to make a relation with ROS levels. VPA-induced elevation of TOS-ROS levels and diminishment of TAC levels are good evidence for an altered antioxidant system. When we evaluated the activities of CAT, SOD, GPx, and GR, we realized that there had been an increase in these activities in the liver samples of the VPA group. Jafarian et al.[8] reported at their study that VPA-induced ROS generation on isolated mitochondria of the liver would be associated with its harmful effect on mitochondrial ETC system complexes. Pourahmad et al.[46] also revealed that VPA has helped ROS distribution by destabilizing the lysosomal membrane structure, and as H_2O_2 can easily pass, it can form hydroxyl radical at liver tissues. Although we got diminished levels of GSH, we can make a relationship between the elevated activities of GSH-dependent enzymes such as GPx, GR, and increased free radical production. The administration of Vit B_6 may have helped ease all these antioxidant parameters by reducing ROS levels with its antioxidant activity.

G6PD is an important enzyme for the pentose phosphate pathway (PPP), which is a vital source for NADPH production. VPA was reported that it has decreased mitochondrial bioenergetics in yeast. This effect has also been explained with many reasons as the inhibitory function of VPA on some TCA cycle enzymes, an increasing effect on glycolysis. Besides, Salsaa et al.[47] emphasized that 6-phosphogluconic acid levels, related to PPP, were increased by the presence of VPA

because of elevated need for NADPH because of oxidative stress. They also indicated that the elevation of NADPH in cell media would help protect GSH levels for scavenging ROS. Additionally, inflammatory factors have been associated with increased G6PD activities and decreased cAMP levels.[48] Therefore, our results, which we obtained as elevated G6PD activities in the VPA-treated liver may be relate to this approach. Vit B_6 reversed this effect on the VPA group as using its protection against ROS.

ADA is a key enzyme for purine metabolism. It catalyzes the deamination of adenosine. Its excess activity was accompanied by ammonia production. Elevated ammonia levels can be dangerous for causing impairment of energy metabolism and other important macromolecule transformation in the liver. In addition, VPA treatment has been associated to cause asymptomatic hyperammonemia in patients.[7] As parallel to these approaches, our results indicated elevated liver ADA activity in the VPA group. The administration of Vit B_6 decreased this activity by its protective effect.

VPA is a hepatotoxic drug that can be used as a medicine in various diseases such as epilepsy and migraine. However, it shows toxicity in the liver in relation to liver diseases such as steatosis and liver failure. Additionally, in a study, it was shown that administration of VPA to mice exacerbates existing liver damage.[49] Histological changes in liver damage caused by anti-tuberculosis drugs have been shown to be partially improved by the administration of Vit B_6 and it was stated that it is a little toxicity in mice.[50] However, the effects of Vit B_6 against the damage caused by VPA in the liver are unknown. Our results have shown that the damage caused by VPA is not enough to reverse morphological changes by the administration of Vit B_6.

Study Limitations

The study limitation of this study is to fully lighten the beneficial effects of Vit B_6 on liver biochemical and histological parameters, thus further liver disease or toxicity models must be developed and protection of Vit B_6 must be examined on these models.

CONCLUSION

VPA is a widely used anti-antiepileptic drug. Although it has beneficial effects, there are many affected systems and organs due to their serious side effects. The liver is the most affected organ against to toxicity and free radical species exposure. To protect this tissue is a vital target for all research. For this purpose, Vit B_6 was chosen as the protector due to its well-known antioxidant and protective effects. The obtained biochemical and histological results from this study support the protection of Vit B_6 on liver tissue, which has been exposure to VPA.

Ethics

Ethics Committee Approval: The ethic permission was taken from the Local Ethics Committee of Animal Research of İstanbul University (number: 2015/09, date: 05.02.2015).

Informed Consent: Animal experiment.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.B.T., Ş.B., R.Y., Concept: İ.B.T., Ş.B., R.Y., A.K.K., Design: İ.B.T., Ş.B., R.Y., A.K.K., Data Collection or Processing: R.Y., Ş.B., Analysis or Interpretation: R.Y., Ş.B., İ.B.T., Literature Search: R.Y., Ş.B., İ.B.T., Writing: R.Y., Ş.B., İ.B.T., A.K.K.

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Evaluation of the Effect of Anti-seizure Drugs on Cognition in Patients with Idiopathic Generalized Epilepsy by Digital Neuropsychological Test

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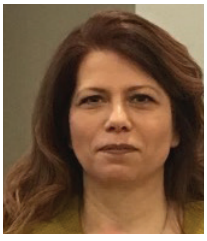

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Abstract

Objective: Cognitive impairment in patients with epilepsy appears as epileptic seizures or side effects of anti-seizure drugs (ASD). The aim of this study was to evaluate the cognitive functions of idiopathic generalized/genetic epilepsy (IGE) patients with digital neuropsychological tests (DNT) and to reveal whether there are differences in test batteries in patients using ASD with monotherapy or polytherapy.

Methods: Thirty-nine individuals diagnosed with IGE syndrome in our clinic, who were diagnosed with IGE in the last decade and had completed at least eight years of education, were included in the study. After the Standardized Mini-Mental Test and Beck Depression Inventory, for neurocognitive evaluation, TestMyBrain (TMB) Number Range, TMB Selective Response Speed Test, TMB Visual Association Pairs Test, TMB Matrix Reasoning and TMB Number Symbol Matching Tests of TMB DNT Battery were applied to all participants.

Results: Among the test categories in the current test battery that measure cognitive functionality in the areas of attention, short-term memory, working memory, visual memory, episodic memory, cognitive processing speed, selective response/inhibition, fluent cognitive skills and perceptual reasoning were applied to the patients and no significant difference was found between the groups receiving monotherapy or polytherapy ($p<0.05$).

Conclusion: It was concluded that the performance status of IGE patients in the sub-category tests included in the TMB DNT Battery and evaluated according to visual material was independent of the number of drugs, but this situation could not be independent of education.

Keywords: Digital neuropsychology, idiopathic generalized epilepsy, cognitive functions

INTRODUCTION

Idiopathic/genetic generalized epilepsies (IGE) account for approximately one-third of all epilepsies and may be of varying phenotypes, depending on age, and are cathegorized as Childhood Absence Epilepsy (CAE), Juvenile Absence Epilepsy (JAE), Juvenile Myoclonic Epilepsy (JME) or IGE with Tonic-Clonic Seizures only.[1] Most of these begin in childhood or adolescence. IGE is characterized by the absence of intellectual disability and focal neurological deficits. However, some studies, mostly consisting of JME patients, have reported impairments in working memory, verbal fluency, response inhibition, sustained attention, and visuospatial reasoning in IGE patients.[2-4]

Cognitive changes seen in epilepsy patients are not only related to seizures, but may also occur as a side effect of anti-seizure drugs (ASDs). Variables including polytherapy being the drug regimen, high level dosage and ASDs' blood levels are also important here. Most major ASDs administered at therapeutic doses do not usually cause cognitive or behavioral impairment. However, individual variability is significant, and some patients cannot tolerate low serum drug levels, while others can tolerate high levels of the same drug without subjective or objective side effects.[5] The aim of this study was to evaluate the potential effect of ASDs on cognition by applying tests that prioritize visual memory and to reveal whether there is a difference between these tests in patients who have been treated with monotherapy or polytherapy.

METHODS

The study group consisted of patients with IGE who were treated in the epilepsy outpatient clinic of the Neurology Department of Marmara University Faculty of Medicine. The study began during the first phase of the Coronavirus disease-2019 (COVID-19) pandemic.

Patients between the ages of 18-48 who had at least 8 years of education were selected from 80 patients who were diagnosed with IGE in our clinic and had been followed up regularly in the last year. Due to the COVID-19 pandemic, 50 patients who met the study criteria were contacted by phone and informed about the test, but 11 of 50 patients refused to participate in the study due to pandemic conditions, and the remaining 39 patients did participated in the study. Of these patients, 35 were JME and 4 were JAA patients. Because of the free use of the TestMyBrain (TMB) Digital Neuropsychology Test (DNT) Battery by McLean Hospital and Harvard University Medical School Brain and Cognitive Health Technologies Laboratory in cooperation with the Many Brains Project during the COVID-19 pandemic, this battery was released to patients after obtaining the necessary permissions. Before participating in the study, all volunteer patients were informed about the study and a voluntary consent form was obtained. Observing the pandemic precautions, the patients were first administered the Beck Depression Inventory (BDI) and the Standardized Mini-Mental Test, and then digital tests that prioritize visual memory. As part of the DNT, participants were asked to complete five tests: TMB Number Range, TMB Selective Response Speed Test, TMB Visual Association Pairs Test, TMB Matrix Reasoning, and TMB Number Symbol Matching Test. The battery included tests for short-term visual, episodic and working memory, attention, processing speed, crystallized and fluid intelligence, response selection/inhibition, and attention.[6] The tests were completed over an average of 40 min.

TMB Digit Span: TMB Digit Span involves recall sequences of digits of increasing length, either in the same order as presented (digit span forward-DSF) or in the opposite order (digit span backward-DSB). TMB Digit Span measures short-term memory, attention, and working memory (backward version).

TMB Choice Reaction Time Test: TMB Choice Reaction Time Test (CRT) is a standard format CRT task. CRT measures processing speed, response selection/inhibition and attention. This test measures both the reaction time (CRT.RT) and accuracy (CRT. ACC).

TMB Visual Paired Associates Test: TMB Visual Paired Associates Test (VIS) is adapted from standard paradigms for assessing context-specific encoding and memory retrieval, which assesses visual memory and episodic memory. The primary result measure of VIS is accuracy, in terms of proportion correct or number correct out of 24 trials.

TMB Matrix Reasoning: TMB Matrix Reasoning (MAT) identifies the image that best completes the pattern in a series, based on a logical rule. This test measures fluid cognitive ability and perceptual reasoning. The main result measure of this test is accuracy, in terms of proportion correct or number correct.

TMB Digit Symbol Matching: TMB Digit Symbol Matching (DSM) involves a symbol-number key. The participants are expected to match as many symbols and numbers as possible within 90 seconds. DSM measures the processing speed. The main result measure of DSM is the number of trials correctly completed within 90 seconds, which is proportionate to the mean response time.

Ethics Committee: The study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Marmara University Faculty of Medicine Clinical Research Ethics Committee approved the study (number: 09.2021.329, date: 09.04.2021).

Statistical Analysis

Data were analyzed with the Statistical Package for the Social Sciences 25 software package. Frequency and percentage values are given for demographic variables. The normality assumption was evaluated with the Shapiro-Wilk test. Independent sample t-test was used for data showing normal distribution and Mann-Whitney U test was used for data not showing normal distribution to evaluate age groups and monotherapy and polytherapy groups. Statistical significance was accepted as p value <0.05.

RESULTS

Of the 39 IGE patients included in the study, 21 (53.9%) were female and 18 (46.1%) were male (Table 1) with a mean age of 23.38±7.10 (minimum=20, maximum=49), 23 of the patients were under 25 years old and 16 of them were 25 years and older. According to their education level, 20.5% of the patients had 8 years, 23.1% had 12 years and 56.4% had more than 12 years of education (Table 1). Epileptiform disorder was seen in 20 of 39 patients' electroencephalographies taken within the last year. Of these patients, 13 were receiving polytherapy and 7 were receiving monotherapy.

The mean values of DSF, DSB, CRT.RT, CRT.ACC, VIS, MAT and DSM in monotherapy and polytherapy groups are shown in Table 2, and no significant difference was found between the two groups in terms of these tests (p>0.05). There was no significant difference between monotherapy and polytherapy groups in terms of BDI results (p=0.872).

Table 1. Demographic characteristics of the participants

The number of participants (n=36)	f	%
Gender		
Female	21	53.9
Male	18	46.1
Age		
<25	23	59
>25	16	41
Education level		
8 years	8	20.5
9-12 years	9	23.1
>12 years	22	56.4

MAIN POINTS

- Cognitive dysfunction is one of the most common complaints in patients with epilepsy.
- When we evaluated executive function, attention and concentration functions in idiopathic/genetic generalized epilepsies patients using the digital neuropsychological test battery, it was found that there was no difference between monotherapy and polytherapy groups.
- However, it has been observed that a high level of education has a positive effect on the success obtained from the tests.

The data of DSF, DSB, CRT.RT, CRT.ACC, VIS, MAT and DSM values according to age groups (<25 years; 25≥) are given in Table 3, and no significant difference was found between the two groups in terms of these tests (p>0.05).

There was no significant difference in DSF, DSB, CRT.RT, CRT. ACC, VIS, MAT and DSM values between sodium valproate, lamotrigine and levetiracetam used in monotherapy (p>0.05).

However, when the patients were categorized as ≤12 years and 12> years according to their education level, there were statistically differences in DSB, CRT.RT, MAT and DSM values, DSF, MAT and DSM values were higher and CRT.RT values were lower in the higher education group, and statistical significance was found at the highest level especially in the MAT evaluation. In line with these results, short-term memory, attention and working memory evaluated by DSF (p=0.02), processing speed performance evaluated by DSM (p=0.03) and perceptual reasoning measured by the MAT test was found to be significantly higher in the high-education group (p=0.0001). In the CRT-RT test, in which attention was evaluated, it was noted that the reaction time was shorter (p=0.047) (Table 4).

It was found that the reaction time was significantly longer in the CRT-RT test, in which attention was evaluated, in patients aged 25 and over who received polytherapy compared to patients who received monotherapy (p=0.021). Relevant data are given in Table 5.

Table 2. Comparison of digital neuropsychological test subcategories between monotherapy and polytherapy groups

Digital NPT	Monotherapy (n=22)	Polytheraphy (n=17)	p value
DSF	5.77±1.65	5.11±1.45	0.205
DSB	4.50±1.65	3.88±1.93	0.290
CRT.RT	1070±325	1262±431	0.165
CRT.ACC	0.97±0.04	0.93±0.14	0.378
VIS	13.63±5.52	12.05±3.59	0.289
MATRIX	20.13±8.14	17.11±7.70	0.248
DSM	40.18±9.81	35.64±10.98	0.182

*p<0.05.
NPT: Neuropsychological Test, DSF: Digit Span Forward, DSB: Digit Span Backword, CRT.RT: Choice Reaction Time.Reaction Time, CRT.ACC: Choice Reaction Time. Accuracy, VIS: Visual Association Pairs Test, MATRIX: Matrix Reasoning Test, DSM: Digit Symbol Matching

Table 3. Differences between age groups

Digital NPT	<25 years	≥25 years	p value
DSF	5.52±1.83	5.43±1.20	0.873
DSB	4.04±2.07	4.50±1.26	0.439
CRT.RT	1167.56±440.13	1135.83±292.17	0.803
CRT.ACC	0.95±0.12	0.96±0.05	0.724
VIS	13.13±4.92	12.68±4.74	0.781
MAT	20.30±8.21	16.68±7.40	0.168
DSM	38.86±9.54	37.25±11.98	0.640

*p<0.05.
NPT: Neuropsychological Test, DSF: Digit Span Forward, DSB: Digit Span Backword, CRT.RT: Choice Reaction Time.Reaction Time, CRT.ACC: Choice Reaction Time. Accuracy, VIS: Visual Association Pairs Test, MAT: Matrix Reasoning Test, DSM: Digit Symbol Matching

In the group under 25 years of age, there was no significant difference between monotherapy and polytherapy groups in the terms of DSF, DSB, CRT.RT, CRT.ACC, VIS, MAT, DSM tests (p>0.05) (Table 5).

DSB values in the group whose education level is over 12 years; when the groups receiving monotherapy and polytherapy were compared, it was found to be significantly higher in those receiving monotherapy (p<0.027) (Table 6). When this comparison was made between those with an education level of 12 years or less, no significant difference was observed between DNTs (p>0.05) (Table 6).

Table 4. Differences according to education level

Education levels			
Digital NPT	**<12 years**	**>12 years**	**p value**
DSF	4.82±1.38	6.0±1.57	0.02*
DSB	3.70±1.31	4.63±2.01	0.09
CRT.RT	1291.74±415.36	1048.53±325.44	0.047*
CRT.ACC	0.95±0.06	0.95±0.12	0.983
VIS	11.29±3.36	14.22±5.38	0.057
MAT	13.76±6.22	22.72±7.04	0.000*
DSM	34.29±7.66	41.22±11.43	0.030*

*p<0.05.
NPT: Neuropsychological Test, DSF: Digit Span Forward, DSB: Digit Span Backword, CRT.RT: Choice Reaction Time.Reaction Time, CRT.ACC: Choice Reaction Time. Accuracy, VIS: Visual Association Pairs Test, MAT: Matrix Reasoning Test, DSM: Digit Symbol Matching

Table 5. Comparison of digital neuropsychological test subcategories between the groups aged 25 and over and those under 25 who received monotherapy and polytherapy

<25 years			
Digital NPT	**Monotherapy (n=12)**	**Polytheraphy (n=4)**	**p value**
DSF	5.58±1.16	5.0±1.41	0.415
DSB	4.50±1.16	4.50±1.73	0.750
CRT.RT	1043.71±212.36	1412.53±354.60	0.021*
CRT.ACC	0.96±0.04	0.95±0.085	0.834
VIS	12.91±5.29	12.00±2.94	0.854
MAT	18.58±7.37	11.00±4.16	0.078
DSM	39.41±10.75	30.75±14.38	0.225
<25 years			
Digital NPT	**Monotherapy (n=10)**	**Polytheraphy (n=13)**	**p value**
DSF	6.0±2.16	5.15±1.51	0.343
DSB	4.50±2.17	3.69±2.01	0.255
CRT.RT	1103.26±435.87	1217.02±454.48	0.577
CRT.ACC	0.98±0.05	0.93±0.15	0.101
VIS	14.50±5.94	12.07±3.88	0.351
MAT	22.00±9.01	19.00±7.64	0.385
DSM	41.10±9.02	37.15±9.93	0.663

*p<0.05.
NPT: Neuropsychological Test, DSF: Digit Span Forward, DSB: Digit Span Backword, CRT.RT: Choice Reaction Time.Reaction Time, CRT.ACC: Choice Reaction Time. Accuracy, VIS: Visual Association Pairs Test, MAT: Matrix Reasoning Test, DSM: Digit Symbol Matching

Table 6. Comparison of digital neuropsychological test subcategories between groups receiving monotherapy and polytherapy for 12 years or less and over 12 years according to education level

>12 years			
Digital NPT	**Monotherapy (n=12)**	**Polytheraphy (n=10)**	**p value**
DSF	6.25±1.76	5.70±1.33	0.479
DSB	5.33±1.55	3.80±2.25	0.027*
CRT.RT	969.85±223.99	1142.95±409.44	0.356
CRT.ACC	0.98±0.022	0.92±0.18	0.396
VIS	15.66±6.11	12.50±3.97	0.220
MAT	24.33±6.61	20.80±7.40	0.261
DSM	43.50±11.80	38.50±10.94	0.322
≤12 years			
Digital NPT	**Monotherapy (n=10)**	**Polytheraphy (n=7)**	**p value**
FDS	5.20±1.39	4.28±1.25	0.115
DSB	3.50±1.17	4.00±1.52	0.608
CRT.RT	1191.89±395.01	1434.38±430.88	0.172
CRT.ACC	0.96±0.06	0.95±0.06	0.731
VIS	11.20±3.67	11.42±3.15	0.844
MAT	15.10±7.06	11.85±4.59	0.434
DSM	36.20±4.68	31.57±10.43	0.261

*p<0.05.
NPT: Neuropsychological Test, DSF: Digit Span Forward, DSB: Digit Span Backword, CRT.RT: Choice Reaction Time.Reaction Time, CRT.ACC: Choice Reaction Time. Accuracy, VIS: Visual Association Pairs Test, MAT: Matrix Reasoning Test, DSM: Digit Symbol Matching

DISCUSSION

Cognitive impairment is one of the most common complaints in people with epilepsy. This disorder is not only associated with seizures, but may also occur as a side effect of ASDs.[7]

Polytherapy, increased dosage and ASD levels have important roles in this side effect profile. The main disorders detected in cognitive functions are decreased reaction and information processing time with changes affecting memory, attention and language. All these effects may adversely affect drug compliance, tolerability and continuity of treatment during long-term treatment.[8]

Most of the newer ASDs are as effective as the older generation ASDs and appear to be better tolerated overall. The newer ASDs may have less impact on cognitive functions and memory. Neuropsychological testing has been the primary method of objectively examining cognitive function related to the use of ASDs; however, methodological differences in the tests cause contradictions in the results. Changes in cognition may reflect an adverse effect of chronic use of ASDs, but the adverse effects of drugs are only one of several factors that can affect cognition. The new ASDs seem to show little or no adverse cognitive effects.[9] Additionally, many studies have revealed that in-utero exposure to ASD may affect the child's cognitive development in later life.[10]

Our current study has the feature of being the first study in our country in which neuropsychological test evaluation of IGE patients in a digital environment was performed. The reason for choosing IGE patients as the study group is that these patients do not have intellectual disability and focal neurological deficits, and the educational status of 56% of the patients in our study group is over 12 years, providing them with the capacity to perform the current digital operation; Although it can be considered bias, this situation was tried to be prevented by choosing a similar feature in the control group. JME patients constitute a large part of our patient group, and when the literature is searched, notably JME patients constitute the patient group especially in such studies, and it reveals that executive functions are impaired in IGE patients.[11,12] Many studies show that individuals with JME perform worse in attention, mental flexibility, inhibition control, working memory, processing speed, and visual-delayed memory functions compared with healthy individuals.[13,14]

Similarly, in our previous study in which we compared this patient group with healthy controls with DNT subtests, it was found that the DSF, DSB, MAT, DSM and MAT scores of the patient group were lower and the CRT.RT score was higher than the healthy group. This shows that cognitive functionality is worse in attention, short-term memory, working memory, visual memory, episodic memory, cognitive processing speed, selective response/inhibition, fluent cognitive skills, and perceptual reasoning in IGE patients.[15] Although it has been reported in the literature that polytherapy, increased dosage and ASD levels have a significant effect on cognitive function in epilepsy patients, such a difference was not observed in polytherapy users in our current study. It is thought that the fact that the patients frequently use two drugs as polytherapy may be a factor, and the low number of patients in our current sample groups may also have affected the statistical data.

Study Limitations

The weaknesses of our study are that patients with JME constitute a large part of the study, the patient groups that make up the other syndromes of IGE were included in a smaller number in this study, and no information was given about the seizure frequency of the patients. Additionally, the measurement tool we use, DNT McLean Hospital and Harvard University Faculty of Medicine Brain and Cognitive Health Technologies Laboratory, in cooperation with the Many Brains Project, has been made available free of charge only during the COVID-19 pandemic, and tests that include only visual tests in this test battery were applied to patients. Since the verbal tests were in English and all of our patients differed in terms of foreign language knowledge, such tests were excluded from the application. This suggests that there may be a factor in the lack of difference between the groups receiving monotherapy and polytherapy.

CONCLUSION

As a result in our study, which included a limited number of IGE patients, it was concluded that in tests measuring cognitive functions such as executive function, attention, and concentration, the use of a single drug or frequent dual drug use had no effect on the cognitive test success, similarly, age did not affect the results, it seems that the high level of education positively affects the success obtained from the tests.

Ethics

Ethics Committee Approval: The study was conducted following the ethical standards of the Declaration of Helsinki. Marmara University Medical Faculty Clinical Research Ethics Committee approved the study (number: 09.2021.329, date: 09.04.2021).

Informed Consent: All volunteer patients were informed about the study and a voluntary consent form was obtained.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.A., İ.M., Concept: E.A., A.F., G.B.K., C.K., İ.M., Design: E.A., A.F., İ.M., Data Collection or Processing: E.A., A.F., G.B.K., C.K., Analysis or Interpretation: E.A., İ.M., Literature Search: E.A., İ.M., Writing: E.A., İ.M.

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Original Article

Etiology, Clinical Characteristics and In-hospital Mortality of Status Epilepticus: Single Center Experience

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Abstract

Objective: Status epilepticus (SE) is a serious neurological emergency that can has high morbidity and mortality rates and requires prompt diagnosis and treatment. There are different etiologies and the prognosis varies multifactorially. The aim of this study was to reveal the etiological causes, clinical features and mortality rates of patients diagnosed with SE at our center.

Methods: The records of 234 patients with a diagnosis of SE over the age of 18 who were followed up and treated at our center between 01.01.2015-01.01.2022 were evaluated retrospectively. Using the hospital information operating system database, we identified people hospitalized with an International Classification of Diseases 10th Revision code G41 for SE as the primary diagnosis. Demographic information, clinical characteristics, and discharge results were obtained from medical records.

Results: One hundred-twenty (51.3%) female and 114 (48.7%) male patients were evaluated. The top 3 most common etiologic causes were: discontinuation of anti-seizure treatments without advice (n=82), cerebrovascular events (n=50), and meningitis or encephalitis (n=39). Motor seizures were detected in 183 (78.2%) patients, and non-motor seizures were detected in 51 (21.8%) patients. Seizures were suppressed by first-line treatment in 24 patients and by second-line treatments in 135 patients. Seventy-five patients whose seizures could not be suppressed were accepted as refractory SE and 9 died. The mean age of all patients was 55, and 63 of the patients died.

Conclusion: In this study, clinical and demographic features, the etiological causes and in the hospital mortality rates of SE followed in a single center in the Turkish population were determined. The most common causes of patients diagnosed with SE were discontinuation of anti-seizure treatments without our recommendation, cerebrovascular diseases and central nervous system infections, respectively. In our center, no relationship was found between age and mortality. The in-hospital mortality rate was 3.9% for all patients (n=234) and 12% for patients with refractory SE (n=75).

Keywords: Status epilepticus, status epilepticus etiology, status epilepticus in-hospital mortality

INTRODUCTION

Status epilepticus (SE) is defined as a seizure that lasts longer than expected, or the recurrence of many seizures without any improvement in the newly developed condition. The duration of sustained seizure activity used for the above definition varied over time. In 2015, the International League Against Epilepsy (ILAE) specified two different temporal concepts for the definition of SE - t1 (five min; time when ongoing seizure activity is abnormally prolonged, unlikely to stop spontaneously, and when treatment for SE should be initiated) and t2 (30 min; when continued seizure activity poses a significant risk of long-term complications). Accordingly, SE is the condition that results from the failure of the mechanisms responsible for seizure termination or the initiation of mechanisms that lead to abnormally prolonged seizures. Depending on the type and duration of seizures, neuronal damage occurs because of neuronal death and neuronal networks change. Semiologically, it is divided into two groups - convulsive and non-convulsive SE. A continuous seizure lasting 5 min or longer, or 2 or more consecutive seizures in which there is no complete recovery of consciousness between, is currently considered generalized convulsive SE. Refractory SE is a condition that does not respond to first-line and second-line medical treatments and exceeds 30-60 minutes. SE is a relatively common medical and neurological emergency that requires prompt evaluation and treatment. There are different SE syndromes, which differ in etiological factors, prognosis, and treatment, as defined by clinical features and electroencephalography (EEG) findings. Optimal evaluation and treatment can only be performed by understanding the type of SE presented and its underlying cause. Causes, risk factors, and prognosis of SE may vary among centres, regions, and countries. In this study, clinical and demographic features, the etiological causes, treatment and mortality of convulsive SE cases followed up and treated in our hospital in the last 7 years were evaluated.

METHODS

Data Source

In this retrospective survey, the hospital information operating system used inpatient and emergency neurology consultation patient medical records. The information provided mandatory information on diagnosis, demographic data, clinical features, anti-seizure treatments, complications, etiologic causes and discharge information (exitus or discharge) for each patient department. Diagnoses are coded according to International Classification of Diseases 10th Revision (ICD-10). Information about the primary diagnosis and main reasons for referral was mandatory and limited to a single diagnosis, whereas additional diagnoses were optional. The type of epileptic seizures and the diagnosis of SE were made by experienced epileptologists according to the 2015 ILAE classification, by evaluating 21 probe pairs of double banana montage EEG images.[1] Hypoglycemia, uremia due to renal failure, electrolyte imbalances, sepsis and liver failure were evaluated as metabolic disorders. Approval for the study was obtained from the Clinical Research Ethics Committee of Bursa Uludağ University Faculty of Medicine with the decision dated 19.04.2022 and numbered 2022-9/10.

Inclusion Criteria

Individuals with a primary diagnosis of SE were identified according to G41 ICD-10 codes (G41.0, G41.1, G41.2, G41.8, G41.9). Patients over the age of 18 who were first diagnosed or discharged between 01.01.2015-01.01.2022 with the primary diagnosis code G41 in the database were included in the study.

Exclusion Criteria

Patients under 18 years of age were not included for the initial evaluation. Then, 313 medical file records were reviewed. 12 patients were excluded from the evaluation due to insufficient data records, 27 because they were followed up in another institution, and 40 because the etiology could not be determined. The remaining 234 patient records were evaluated.

Statistical Analysis

The analysis of the research data was performed using the Statistical Package for the Social Sciences 28 statistical package program in the computer environment. Frequency, percentage, mean and Mann-Whitney U test were used in the analysis of the data.

MAIN POINTS

- In the etiology, cerebrovascular diseases are the most common cause after treatment-related causes.
- Status epilepticus (SE) is a neurological emergency. In the management of SE, rare causes should be noticed, identified, and treated quickly.
- The primary determinant of prognosis is the etiology of SE. In addition, the accompanying complications during the treatment management and the patient's comorbidities also affect mortality. Therefore, a multidisciplinary approach is required to reduce SE mortality.

RESULTS

One hundred-twenty (51.3%) patients were female and 114 (48.7%) were male, and the mean age was 55 (18-90). Motor seizures (focal, generalized or unknown onset, and seizures that begin focally and progress to bilateral tonic-clonic seizures) were detected in 183 (78%) patients, and non-motor seizures (focal, generalized or unknown onset) were detected in 51 (22%) patients. When the etiology of SE in the cohort was examined, the most common causes were reduction or discontinuation of anti-seizure treatments other than our recommendation 35% (n=82), cerebrovascular events 21% (n=50) and acute central nervous system infections or inflammation 17% (n=39) (Table 1). Patients who did not comply with the anti-seizure drug treatment recommendations had different epileptic syndromes and were using different combination therapies. None of the patients who developed SE were due to mono-therapy discontinuation. All patients developed after the discontinuation of dual-therapy. Because of the fact that the previous follow-ups of the patients occurred in more than one external center, the duration of discontinuation could not be evaluated precisely. Half of the patients who developed SE after a cerebrovascular attack had ischemic cerebrovascular disease in the form of major stroke. Subsequently, intracerebral hemorrhage, subarachnoid hemorrhage, subdural hemorrhage and intracranial venous sinus thrombosis were seen, respectively (Table 1). The causes of encephalitis were herpes simplex (n=17), other viral encephalitis (n=8) and limbic encephalitis [GAD antibody (n=3), anti-LGI1 antibody (n=1) and VGKC antibody (n=1)]. There were 9 cases of meningitis, including 1 neurosyphilis, 1 HIV-related diagnosis, and 7 cases of acute bacterial meningitis. The causes of hypoxic ischemic encephalopathy were myocardial infarction (n=6), carbon monoxide intoxication (n=4), respiratory arrest due

Table 1. Etiology of status epilepticus

Etiology			n=234
Reduction or discontinuation of anti-seizure treatments without recommendation			82 (35%)
Cerebrovascular events	Major ischemic stroke	24 (48%)	50 (21%)
	Intracerebral hemorrhage	15 (30%)	
	Subarachnoid hemorrhage	5 (10%)	
	Subdural hemorrhage	3 (6%)	
	Intracranial venous sinus thrombosis	3 (6%)	
Acute central nervous system infections or inflammation	Encephalitis	30 (78%)	39 (17%)
	Meningitis	9 (%22)	
Antibiotics			18 (8%)
Intracranial space-occupying lesions			15 (6%)
Hypoxic ischemic encephalopathy			14 (6%)
Metabolic disregulation			11 (5%)
Idiopathic or first seizure			4 (2%)
After SARS-CoV-2 vaccination (Pfizer/BioNTech)			1

SARS-CoV-2: Severe acute respiratory syndrome-Coronavirus-2

to respiratory tract disease (n=2), and drowning (n=2). Metabolic causes of SE were renal and/or hepatic failure (n=8; 3 renal failure, 3 hepatic failure and 2 patients combined), hyponatremia (n=2) and hypoglycemia (n=1). When the patients who developed SE after the use of antibiotics were evaluated, it was observed that the use of cephalosporin group antibiotics, mostly in the third generation, was observed in all patients. Our patients did not have a history of head trauma, nor had they undergone previous neurosurgery operation. Four cases of SE were evaluated as the first epileptic seizures and subsequently diagnosed as epilepsy.

All patients included in the evaluation (n=234) were treated according to the SE protocol (Table 2). Intravenous benzodiazepine therapy was administered as the first step. Seizures of 24 patients stopped after intermittent diazepam treatment. Subsequently, as a second-line treatment; 183 treatment doses of levetiracetam the, 86 phenytoin and 10 valproic acid were administered intravenously to 210 patients whose seizures continued. Topiramate was administered in 8 patients and lacosamide in 16 patients via the enteral route (with feeding tube). As third-line treatment in 75 resistant cases; 75 treatment doses of midazolam, 18 thiopental and 7 doses of ketamine were administered (Figure 1). Refractory seizures requiring anesthetic treatment developed in 32% (n=75) of the patients. All these patients were followed up with invasive mechanical ventilation. Nine cases (5 female and 4 male, mortality 3.9% for the whole series, 12% for refractory series) died. The average hospital stay was 26 (9-88) days. The mean age of the patients with exitus was 63 (41-87).

Midazolam was the first choice in all patients in terms of anesthetic agents applied to patients with resistant seizures. Additionally, ketamine (n=3) or thiopental sodium (n=1) treatment was administered to all patients who died. Some etiological factors and many accompanying comorbidities were detected in the patients (Table 3). No significant difference was found when the mean age of all SEs and the patients who died were compared (55;63, p>0.05).

DISCUSSION

SE is a life-threatening medical emergency that requires immediate medical treatment and is associated with morbidity and mortality. In published studies, the incidence of SE varies between 10 and 20 or 40 per 100,000.[2] Different results between male and female genders were reported in some studies.[3,4] Causes of SE such as cerebrovascular diseases, anoxia, neurodegenerative diseases and brain tumors increase significantly after the age of 60. Between 6 and 20% of SE patients are diagnosed the first time they experience a seizure in their life.[5] In our series, only 4 (2%) patients were idiopathic or had a first seizure when the group whose cause could not be clarified was excluded. The reason for this low rate may be that our institution is a tertiary hospital and it is a hospital where complicated patients are followed or referred rather than newly diagnosed patients.

The most common causes of SE are inappropriate use of anti-seizure therapy and ischemic stroke.[5] Acute symptomatic causes are more common than chronic symptomatic causes, and of these, a stroke is the most common.[3] A history of at least one epileptic episode was

Table 2. Status epilepticus treatment protocol applied to patients

First line	Second line	The third line	Enteral treatment
Diazepam: IV 10 mg, <5 mg/min bolus, repeated within 5 min at 10 mg doses	Levetiracetam: IV, 30-40 mg/kg up to a maximum of 4000 mg, infusion in 10 min	Midazolam: IV, 0.2 mg/kg bolus, followed by 1-4 mg/kg/hr infusion	Topiramate: 200 mg twice daily followed by a 500-1000 mg loading dose
	Phenytoin: IV, 15-20 mg/kg, 50 mg/min infusion, half the infusion rate in elderly patients	Thiopental: IV, 3-5 mg/kg loading and 1-6 mg/kg/hr infusion/10 mg/kg bolus and 1-3 mg/kg/hr infusion	Lacosamide: 100-200 mg twice a day following a 200-400 mg loading dose
	Valproic acid: IV, 15-20 mg/kg, 5 mg/kg/min infusion	Ketamine: IV, 2 mg/kg bolus followed by 2-4 mg/kg/hr infusion	

IV: Intravenous

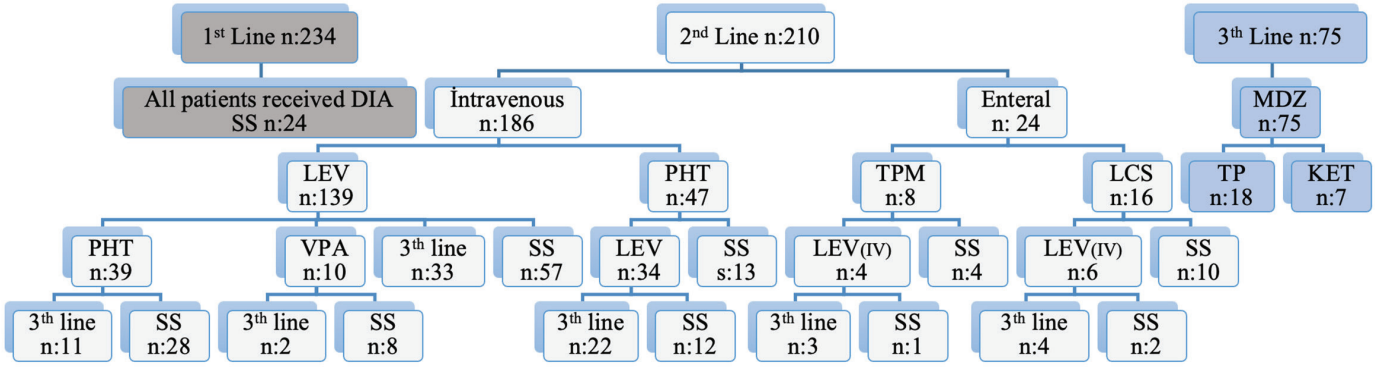

Figure 1. Treatment features
DIA: Diazepam, LEV: Levetiracetam, PHT: Phenytoin, VPA: Valproic acid, TPM: Topiramate, LCS: Lacosamide, MDZ: Midazolam, TP: Thiopental, KET: Ketamine, SS: Seizure suppressed

Table 3. Clinical features of exitus cases due to status epilepticus

Age	Sex F/M	Etiology	Anesthetic treatment	Comorbidity
41	F	Resistant epilepsy	Midazolam	-
68	M	Intracranial mass, limbic encephalitis (LGI)	Midazolam + ketamine	Aspiration pneumonia
65	M	Meningitis, acute kidney failure	Midazolam	Mesothelioma-associated pneumosepsis
81	M	3rd Generation Cephalosporins (ceftriaxone and cefepime) and intracerebral hemorrhage	Midazolam + ketamine	Hypertension, chronic renal failure, rheumatoid arthritis, urosepsis
66	M	Meningitis and hyponatremia	Midazolam + ketamine	Pituitary adenoma
45	M	Cardiac arrest; hypoxic ischemia	Midazolam	Ankylosing spondylitis, chronic kidney failure
87	F	Diabetic ketoacidosis	Midazolam + thiopental sodium	Diabetes mellitus, chronic obstructive pulmonary disease, dementia
41	M	Brain metastasis (of breast cancer)	Midazolam	Sepsis, breast cancer, disseminated intravascular coagulation
73	F	3rd Generation Cephalosporin (ceftriaxone)	Midazolam	Breast cancer, ischemic stroke, epilepsy, covid pneumosepsis, chronic obstructive pulmonary disease

F: Female, M: Male

reported before admission in 35% of patients diagnosed with SE. In general population studies, 12-50% of patients diagnosed with SE are patients with a previous diagnosis of epilepsy.[6] Consistent with the literature in our study, 82 patients (35%) were diagnosed with epilepsy or had at least one epileptic episode before. Etiologies may differ between societies. Central nervous system infections are more common in developing countries.[4] However, the variability of the regional or patient groups included in the studies creates etiological differences in the studies. In our study, the most common (35%) etiology of SE was discontinuation of anti-seizure treatment without our recommendation or use it at inappropriate doses, followed by cerebrovascular diseases (21%) and central nervous system infection/inflammation (17%). Apart from the risk of developing SE and intraparenchymal hemorrhages, no different distribution was found in the literature on cerebrovascular diseases, whereas intracerebral parenchymal hemorrhages were higher than expected in this study as an etiologic cause.[7,8] While the main clinical picture was encephalitis for most of the cases, we found fewer cases of meningitis or meningoencephalitis. We also identified rare causes such as post-vaccination or antibody-associated limbic encephalitis.[9-11] Our case series is largely compatible with the literature for etiological causes. However, we would like to emphasize that the existence of rare factors should not be overlooked and that the etiological evaluation should be conducted in depth.

The etiology of SE is the main determinant of prognosis.[4] As well as the etiology of SE, the problems encountered because of the previous clinical condition of the patient, diagnosis, follow-up and treatment processes have combined and complex effects on mortality. Additionally, SE may not always be easily identified in emergencies, or the underlying cause may not be known. Therefore, the distinction of the cause of mortality cannot be clearly made, and it has been stated in many studies that in some cases it was not possible to establish the real cause of death. The highest mortality risk is seen in acute central pathologies. Mortality due to inappropriate anti-seizure drug intake, toxicity, or metabolic pathologies is relatively low. Additionally, the diagnosis of epilepsy as SE is significantly associated with mortality.[12] Although it was emphasized in some studies that the development of refractory SE is an independent risk factor for mortality in patients followed in the intensive care unit, this relationship is not unclear because it was not possible to evaluate this independently of the cumulative risk of complications.[2,13] While inappropriate anti-seizure therapy has a better prognosis than other etiologies, acute symptomatic SE after a stroke is associated with a higher risk of mortality and morbidity than other SE etiologies. Encephalitis is strongly associated with refractory SE and the risk of developing epilepsy in the follow-up period is quite high. Cryptogenic SE of unknown etiology has been associated with low mortality but a high risk of epilepsy. The patient's age is the third independent risk factor that determines the prognosis, after duration and etiology. Mortality in adult patients ranges increases with age.[5] Prolonged mechanical ventilation with advanced age, coma at admission, hypoxic-ischemic brain injury, accompanying comorbidities, acute symptomatic etiology, and refractory SE are generally associated with higher mortality. However, different results have been reported in many studies in the literature. In this study, the mean age of those who died was found to be older than those in all SEs, but no statistical difference was observed. Additionally, acute symptomatic causes were much more common in this group. However, because of the small number of cases, they were not compared statistically.

When all SE patients were evaluated, mortality varied between 1.9 and 40% in the literature.[2] This rate was 5.6-14% in nonrefractory SE patients, and 17-50% in refractory SE.[6] In our study seven year follow up, 9 patients with a diagnosis of SE died during the hospitalization period. The mortality rate was 3.8% in all patients and 12% in the refractory group. When all cases are evaluated, we think that this rate is good and probably due to the careful evaluation of the diagnosis and treatment processes for the etiology in addition to effective seizure treatment. On the other hand, SE mortality is not only dependent on etiology but is multifactorial due to comorbidities and complications (Table 3). This suggests that serious comorbid diseases, treatments, follow-up in the intensive care unit and complications impact mortality. Considering all these, in the management of SE patients, optimal application of rapid multidisciplinary approaches with teamwork for emergency services, anesthesia and intensive care units and other systemic complications that may accompany may reduce mortality rates. An evaluation of a larger case series with our study methods would further contribute to the literature.

Study Limitations

We planned our study by including individuals with SE using the ICD-10 diagnostic code and presented it as a cohort of 313 cases identified over 7 years. However, 234 patients were evaluated due to insufficient data recording, continued follow-up in another institution, and the etiology could not be concluded with a clear consensus. Additionally, the current search scheme only allows the evaluation of individuals with a definitive diagnosis of SE. All these conditions may be debilitating factors affecting the optimal assessment of the entire SE group.

CONCLUSION

In our single-center observational study of the development of status epilepticus in Turkish society:

1. The 3 most common etiologies in etiology were found to be inappropriate use/stopping of anti-seizure therapy, cerebrovascular diseases, and central nervous system infection/inflammation, respectively. Contrary to expectations, intraparenchymal hemorrhages were more common in etiology. About one in three patients developed refractory SE.

2. In addition to common causes in etiology, rare causes such as anti-GAD, LGI-1, and anti-VGKC, neurosyphilis, HIV-induced central nervous system infections, or Severe acute respiratory syndrome-Coronavirus-2 vaccine (Pfizer/BioNTech) were detected. Rare causes should be considered and evaluated in detail.

3. This study highlights the need to consider the effects of etiologic factors on SE mortality, as well as comorbid conditions and complications. Therefore, in addition to SE treatment, other medical conditions that may develop during this period should be carefully evaluated and treated to reduce mortality rates.

Ethics

Ethics Committee Approval: Bursa Uludağ University Ethics Committee decision no. 2022-9/10 dated 19.04.2022.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.S., A.B.D., İ.B., Concept: F.S., A.B.D., Design: F.S., B.M., Data Collection or Processing: F.S., B.M., Analysis or Interpretation: F.S., A.B.D., Literature Search: F.S., A.B.D., İ.B., Writing: F.S.

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Original Article

A Retrospective Evaluation of the Characteristics of Patients Undergoing Electroencephalography in a Newly Established Pediatric Neurology Clinic

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Abstract

Objective: The aim of this study was to examine the clinical and demographic findings of patients who underwent electroencephalography (EEG) for various clinical indications in a newly established pediatric neurology clinic.

Methods: EEG records in the pediatric EEG laboratory, requested by the pediatric neurology outpatient clinic of Balıkesir University Faculty of Medicine, Department of Pediatrics, between November 2019 and August 2020, were retrospectively reviewed.

Results: 884 EEGs were taken and 450 patients who had EEG for the first time were included in the study. The mean age of the children was 111.11±65.06 months (range 7-216 months). Of the patients who underwent EEG, 224 (49.8%) were female and 226 (50.2%) were male. When grouped by age, the least number of cases was between 0 and 12 months (n=6, 1.3%), while the highest number of cases was in the >12 age group (n=168, 37.3%). The three most common clinical indications for EEG imaging were; diagnosed/suspected epilepsy (n=279, 62%), syncope (n=58, 12.9%) and febrile seizures (n=32, 7.1%). While the EEGs of 314 (69.8%) cases were normal, 43 (9.6%) cases had abnormal EEGs and 93 (20.7%) cases had EEGs with epileptiform character. Localizations of EEGs with epileptiform character; the most common localization was generalized (n=48, 10.7%), secondly focal (n=23, 5.1%) and thirdly multifocal (n=8, 1.8%).

Conclusion: We revealed the profile of a routine EEG laboratory in a newly established pediatric neurology clinic.

Keywords: Children, electroencephalography, epilepsy

INTRODUCTION

Electroencephalography (EEG) has long been used as an important tool in the study of children with various neurological disorders.[1,2] It is also a sensitive detector of diffuse cortical dysfunction seen in toxic, metabolic, and hypoxic encephalopathies.[3,4] Although the diagnosis of seizures and epileptic syndromes is primarily based on clinical findings, EEG provides supportive evidence and assists with seizure classification.[5] Epileptiform abnormalities are detected at EEG in approximately one-third of children and adults presenting with new onset seizures.[6] In some publications, the rate is as high as 56%, and an additional 11% increase in epileptiform abnormalities has been reported with repeated EEG scans.[7]

EEG is also the gold standard method in the differential diagnosis of numerous paroxysmal attacks other than epilepsy, such as syncope and non-epileptic psychogenic seizures with epilepsy. While it is a useful guide in encephalopathies, cognitive or behavioral changes, and neurodegenerative diseases, it can also be diagnostic in cases with specific EEG findings, such as Creutzfeldt-Jakob disease.[8] EEG is also useful in identifying non-convulsive seizures and in the differential diagnosis of seizure-mimicking conditions such as neonatal jitteriness, sleep disturbances, breath-holding spells, startle responses, paroxysmal movement disorders, migraine, syncope, dizziness, masturbation, panic attacks, and non-epileptic seizures.[9]

Although EEG is one of the basic diagnostic methods in pediatric neurology, its use is recommended only in selected cases.[9] The widespread use of EEG raises concerns about the appropriate justification and optimization of EEG requests.[10] Various studies have reported that EEG requests are mostly made by general pediatricians and child psychiatrists, rather than pediatric neurologists.[9] This can affect abnormal

activity detection rates. The aim of this study was to examine the clinical and demographic findings of patients who underwent EEG for various clinical indications in a newly established pediatric neurology clinic, to evaluate normal and abnormal EEG findings, and to present the diagnostic profile of the routine EEG laboratory.

METHODS

EEG records in the pediatric EEG laboratory requested by the pediatric neurology outpatient clinic of the Balıkesir University Faculty of Medicine, Department of Pediatrics, Turkey, between November 2019 and August 2020 were reviewed retrospectively. Scalp electrodes were attached to all patients according to the International 10-20 system consisting of 21 electrodes, and signals were recorded for 30-60 minutes, typically using appropriate standard mounts with a 16-channel Nihon Kohden EEG machine. All the EEGs were evaluated by the same pediatric neurologist. Reasons for requesting EEG, age, gender, birth weight, birth type, gestational age, body weight, height and head circumference percentiles, EEG abnormalities, pathological localizations at EEG, the number of repeated EEG records, family history of febrile convulsion/epilepsy, antiepileptic drugs used, and cranial imaging [magnetic resonance imaging (MRI)] findings were recorded. Approval for the study was obtained from the Balıkesir University Local Ethics Committee (date: 13.01.2021, permission no: 2021/04).

EEGs that could not be evaluated adequately due to artifact or technical reasons were excluded from the study. Standard activation procedures (eye opening, hyperventilation, and photic stimulation) were applied to all patients unless contraindications were present. EEG recordings are noted. Clinical preliminary diagnoses of patients for whom EEG was requested were classified into six groups: 1) suspected/newly diagnosed epilepsy, 2) diagnosed epilepsy, 3) non-paroxysmal epileptic attack, 4) non-epileptic chronic central nervous system (CNS) diseases, 5) acute CNS disorders, and 6) febrile seizure. EEG findings were classified into three groups - normal, abnormal, and epileptiform anomaly. Patients were also grouped by age - <1 year old, 1-3 years, 3-6 years, 6-9 years, 9-12 years, and >12 years. Height and weight were grouped as <3rd percentile, 3rd-97th percentile, and >97th percentile. The head circumference was classified as <-2 standard deviation (SD), between (-2) SD and (+2) SD, and >+2 SD. In terms of gestation weeks, patients were grouped as <28 weeks, 28-32 weeks, 33-37 weeks, and 38-42 weeks. Finally, birth weight classification was classified as <2000 g, 2000-3000 g, 3000-4000 g, and >4000 g.

Seizures in patients with evidence of epilepsy at both clinical examination and EEG were classified according to the International League Against Epilepsy classification.[11]

Statistical Analysis

All analyses were performed on Statistical Package for the Social Sciences (SPSS) version 23.0 software (SPSS, Armonk, NY, USA). Descriptive variables were expressed as percentage, frequency, mean, SD, and minimum and maximum values.

RESULTS

Eight hundred eighty-four EEGs were taken, and 450 patients undergoing EEG for the first time were included in the study. The mean age of the children was 111.11±65.06 months (range 7-216 months). Two hundred twenty-four (49.8%) patients who underwent EEG were female and 226 (50.2%) were male. Mean ages were 108.84±4.85 months (13-216) for girls and 113.89±65.51 months (1-212) for boys. In terms of age, the lowest number of cases was observed at 0-12 months (n=6, 1.3%) while the highest number was in the >12 age group (n=168, 37.3%).

The three most common clinical indications for EEG imaging were diagnosed/suspected epilepsy (n=279, 62%), syncope (n=58, 12.9%), and febrile seizures (n=32, 7.1%). EEG findings were divided into normal, abnormal, and epileptiform anomaly. EEGs were normal in 314 (69.8%) cases, abnormal in 43 (9.6%), and epileptiform in character in 93 (20.7%). EEGs with epileptiform character were most frequently generalized (n=48, 10.7%), followed by focal (n=23, 5.1%), and multifocal (n=8, 1.8%). One hundred fifty-eight (35.1%) patients diagnosed with epilepsy received monotherapy and 55 (12.2%) received polytherapy (2-4). The most commonly used antiepileptic drugs in monotherapy were levetiracetam (n=121, 26.9%), followed by valproic acid (n=50, 11.1%).

Cranial MRI was also performed in 212 (47.1%) cases undergoing EEG. Cranial imaging revealed abnormalities in 45 (21.2%) of these patients. The most common abnormal cranial imaging findings were white matter lesions (n=13, 2.9%), intracranial mass (n=7, 1.6%), and corpus callosum agenesis/dysgenesis (n=6, 1.3%). The clinical and demographic characteristics of the 450 patients who underwent EEG for the first time are shown in Tables 1 and 2.

Arrhythmia was detected in five (1.1%) of the 450 patients who underwent EEG. A total of 435 repeat EEGs were performed during the study. The rate of detection of abnormal findings at repeat EEG was 44.64%.

DISCUSSION

EEG was abnormal/epileptiform in character in 30.2% of the patients undergoing the first EEGs in this study, while abnormal findings were detected at a rate of 44.64% at repeat EEGs. The most frequent indication for EEG was diagnosed/suspected epilepsy (62%).

Jan[1] reported that seizures were the most common reason for requesting EEG (78%). In that study, 32% of EEGs were requested by pediatric neurologists, and EEGs were studied for the first time in 65% of cases. Overall, 55% of EEGs were abnormal, and the likelihood of abnormality at repeat EEG was twice as high as that for the first record.[1] Airoldi et al.[12] reported that 55% of requested EEGs were abnormal, and that 28.6% of patients with definite diagnoses of epilepsy and 6.1% of those with possible seizures

MAIN POINTS

- Electroencephalography (EEG) has been used as an important tool in various neurological disorders.
- EEG is also the gold standard method in the differential diagnosis of many paroxysmal attacks.
- We examined the clinical and demographic findings of patients who underwent EEG for various clinical indications in a newly established pediatric neurology clinic and to reveal the diagnostic profile of the routine EEG laboratory.

Table 1. Characteristics of pediatric patients undergoing EEG for the first time (n=450)

Age	n (%)
0 to 12 months	6 (1.3%)
1 to 3 years	82 (18.2%)
3 to 6 years	65 (14.4%)
6 to 9 years	65 (14.4%)
9 to 12 years	64 (14.2%)
>12 years	168 (37.3%)
Gender	
Female	224 (49.8%)
Male	226 (50.2%)
Height percentiles	
<3rd percentile	1 (0.2%)
3-97th percentile	446 (99.1%)
>97th percentile	3 (0.7%)
Weight percentiles	
<3rd percentile	33 (7.3%)
3-97th percentile	383 (85.1%)
>97th percentile	34 (7.6%)
Head circumference	
<-2 SD	27 (6%)
(-2) SD - (+2) SD	401 (89.1%)
>+2 SD	22 (4.9%)
Gestational week	
<28 weeks	8 (1.8%)
28-32 weeks	26 (5.8%)
33-37 weeks	99 (22%)
38-42 weeks	317 (70.4%)
Birth weight	
<2000 grams	27 (6%)
2000-3000 grams	131 (29.1%)
3000-4000 grams	259 (57.6%)
>4000 g	33 (7.3%)
Delivery type	
NSVR	187 (41.6%)
C/S	263 (58.4%)
Positive family history of epilepsy	97 (21.6%)
Positive family history of febrile seizures	57 (12.7%)

NSVR: Normal spontaneous vaginal route, C/S: Cesarean section, SD: Standard deviation, EEG: Electroencephalography

Table 2. Characteristics of pediatric patients undergoing EEG for the first time (n=450)

Diagnostic classification	
Suspected/newly diagnosed epilepsy	101 (22.4%)
Diagnosed epilepsy	178 (39.6%)
Non-paroxysmal epileptic attack	98 (21.8%)
Non-epileptic chronic CNS diseases	31 (6.9%)
Acute CNS disorders	10 (2.2%)
Febrile seizure	32 (7.1%)
EEG	
Normal	314 (69.8%)
Abnormal	136 (30.2%)
- Non-epileptiform	43 (9.6%)
- Epileptiform	93 (20.7%)
Localization of epileptiform discharges	
Generalized	48 (10.7%)
Multifocal	8 (1.8%)
Focal	37 (8.1%)
- Temporal	12 (2.7%)
- Frontal	9 (2%)
- Other	16 (3.4%)
Cranial MRI	
Normal	167 (37.1%)
Abnormal	45 (10%)
- Encephalomalacia	4 (0.9%)
- Mass	7 (1.6%)
- White matter lesion/gliotic focus	13 (2.9%)
- Hydrocephalus	2 (0.4%)
- Cortical dysplasia	2 (0.4%)
- Calcification	2 (0.4%)
- Demyelinating diseases	2 (0.4%)
- Corpus callosum lesion	6 (1.3%)
- Cerebral atrophy	2 (0.4%)
- Hydranencephaly	1 (0.2%)
- Chiari malformation	2 (0.4%)
- Arachnoid Cyst	2 (0.4%)

CNS: Central nervous system, MRI: Magnetic resonance imaging, EEG: Electroencephalography

exhibited epileptiform discharges at EEG. Some studies have reported that approximately half of the EEG records obtained were normal.[13] In a study involving 300 adults and 59 children presenting with the first seizure, 43% of the initial EEG recordings exhibited epileptiform abnormalities.[14] Shinnar et al.[15] reported that EEG was abnormal in 42% of children presenting with unprovoked seizures. In this study, 69.8% of EEGs were normal, 9.6% abnormal, and 20.6% epileptiform.

In their study published in 2003, Aydin et al.[9] performed EEG tests on 534 children due to clinical seizures (33.8%), definite diagnosis of epilepsy (31.2%), attention deficit hyperactivity disorder (9.1%), headache (8%), syncope (3.5%), learning difficulties (2%), tic disorders (1.4%), or sleep disorders (1.1%), and described 63.8% of all EEGs as normal. Epileptiform activity was detected in 37.1% of definitively diagnosed epilepsy cases in that study, in 13.2% of clinically suspected cases, and in 10% of patients with febrile seizures.[9] Tekin Orgun et al.[10] examined 2045 pediatric EEG records and observed an overall 43.6% rate of abnormalities and 38.2% rate of epileptiform activity at EEG. They reported that definite diagnoses of epilepsy were present in 54.2% of these patients, suspicion of epilepsy in 29.4%, and nonepileptic chronic CNS diseases in 20%. In this study, 39.6% of the patients referred to the EEG laboratory were diagnosed with epilepsy, 22.4% had suspected epilepsy, 21.8% nonparoxysmal epileptic attacks, 7.1% febrile seizures, 6.9% non-epileptic chronic CNS diseases, and 2.2% acute CNS disorders.

Tekin Orgun et al.[10] observed focal abnormal activity in 67.9% of cases with epileptiform activity at EEG, generalized activity in 20.6%, and multifocal activity in 11.9%. In this study, 51.6% cases exhibited generalized activity, 8.6% multifocal, and 39.8% focal epileptic focus. The most common localization in the focal foci was the temporal and frontal regions. In Tekin Orgun et al.'s[10] study, and similarly to this research, 90.5% of EEGs were requested by pediatric neurologists. Those authors also reported that the use of EEG had become more selective in the last decade and that the rate of detection of abnormalities had increased due to a rise in the number of pediatric neurologists.[10]

While the rate of detection of abnormality at the first routine EEG in patients with epilepsy is 30-40%, the detection of epileptiform abnormalities increases with repeated EEG images.[16,17] Jan[1] described repetition of EEGs as a factor that significantly increases the possibility of detection of abnormality at EEG. In Tekin Orgun et al.'s [10] study, the rate of detection of abnormalities with repeated EEGs was 58.2%. Those authors reported that 11.9% of repeated EEGs contributed to the diagnosis. Carpay et al.[7] detected epileptiform abnormalities at a rate of 56% at the first EEG in newly diagnosed patients with epilepsy. Interestingly, and similarly to Tekin Orgun et al.[10] they detected an additional 11% increase in epileptiform abnormalities with repetitive EEG records. In this study, the rate of epileptiform/abnormal feature detection in repeated EEG records was 44.64%, a figure consistent with the previous literature.

Electrocardiogram (ECG) recording during EEG is important for detecting ictal and interictal arrhythmias in paroxysmal disorders of cardiac origin and epilepsy.[18,19] EEG can be requested in some life-threatening arrhythmias due to their seizure-like clinical appearance.[20] A study conducted in 2013 reported that arrhythmia was detected at a rate of 2% with simultaneous ECG recording during routine EEG.[20] A compatible figure of 1.1% was determined in this study.

Brain imaging was performed in 47.1% of the patients who underwent EEG. Abnormal cranial imaging was detected in 45 cases (10% of all patients). The most common abnormal cranial imaging findings were white matter lesion (n=13, 2.9%), intracranial mass (n=7, 1.6%), and corpus callosum agenesis/dysgenesis (n=6, 1.3%). In another study, the most common findings detected during cranial imaging performed due to epilepsy were encephalomalacia due to chronic infarcts (n=18, 6.3%), cerebral atrophy (n=11, 3.8%), neuronal migration disorders (n=11, 3.8%), periventricular leukomalacia (n=9, 3.1%), and hippocampal sclerosis (n=8, 2.8%). However, in contrast to the present research, only cranial imaging findings of patients diagnosed with epilepsy were presented in that study.[21] In our study, the rate of detection of any abnormality was higher with EEG than with cranial MRI.

The rate of abnormality detection gradually changes due to additional factors such as advances in EEG techniques, changes in the time and duration of EEG recording, and the adoption of other simultaneous diagnostic methods such as video EEG. The recent rise in the number of pediatric neurologists has also been reported as a factor.[10]

Study Limitations

The principal limitations of this study can be listed as follows; a) some records were lacking due to its retrospective nature, b) our EEG center is new, and the number of patients admitted to the outpatient clinic was relatively low due to the 2019 Coronavirus disease-19 pandemic, c) EEG was evaluated by only one physician, and interobserver agreement could not be evaluated, and d) the absence of an intensive care unit in our center limited the number of patients with acute encephalopathy.

CONCLUSION

This study aimed to describe the profile of a routine EEG laboratory in a newly established pediatric neurology clinic. We hope that our study will be a useful point of reference for new pediatric neurology clinics to be established due to the increase in the number of pediatric neurology specialists. In conclusion, multi-center, prospective studies with more patients are now needed to better interpret our results.

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Ethics

Ethics Committee Approval: The Balıkesir University Non-Interventional Clinical Research Ethics Committee approval was obtained (date: 13.01.2021, permission no: 2021/04).

Informed Consent: Informed consent was not required because of the retrospective design.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: H.A., S.Y., G.B.A., Design: H.A., S.Y., Data Collection or Processing: H.A., S.Y., G.B.A., Analysis or Interpretation: H.A., S.Y., G.B.A., Literature Search: H.A., S.Y., G.B.A., Writing: H.A., S.Y., G.B.A.

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Archives of Epilepsy

Case Report

The Ongoing Challenge of Diagnosing Non-convulsive Status Epilepticus: What About Generalized Non-reactive Rhythmic Alpha Activity in the Salzburg Criteria?

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Abstract

The ILAE Task Force on Classification released a report in 2015 to clarify the classification of status epilepticus. Non-convulsive status epilepticus (NCSE) was defined as SE without prominent motor symptoms, with or without coma. This diverse entity's electrophysiological diagnosis, which is more consistent in clinical recognition, may be challenging. Some classifications and revisions have been proposed recently, making NCSE diagnosis easier. There are, however, patients who remain in the 'grey zone'. The increasing evidence in patients, who do not meet the Salzburg Consensus Criteria for NCSE diagnosis of 'NCSE' or 'possible NCSE', but whose clinical and electrophysiological features are still suspicious for NCSE, may pave the way for developing more comprehensive criteria. Therefore, we present here the 'generalized non-reactive alpha activity' in the electroencephalogram (EEG) of an elderly patient with no known epilepsy before, who presented with acute confusional state of unexplained cause, which we suspected as NCSE and managed a ccordingly with success. Considering that 'time is brain', early and correct NCSE diagnosis is critical and the NCSE EEG criteria should be more inclusive for the patients in the 'grey zone like the one presented here with 'generalized non-reactive alpha activity'.

Keywords: Non-convulsive status epilepticus, alpha rhythm, Salzburg criteria, grey zone, generalized non-reactive alpha activity

INTRODUCTION

Non-convulsive status epilepticus (NCSE) was defined as SE without prominent motor symptoms, with or without coma.[1] Given the enormous heterogeneity of clinical presentations, diagnosing NCSE is difficult and its electroencephalogram (EEG) findings, also show prominent heterogeneity, are indispensable for diagnosis. Despite extensive collaborative efforts in classification and EEG definitions in the last two decades,[2-4] the diagnosis of NCSE is still challenging and requires paramount experience. New modifications are expected due to some challenging points, such as atypical EEG patterns, underestimation of lateralized periodic discharges, presence of false-negative patients, and lack of definition for the required time interval for the clinical improvement.[5,6] To support these new efforts, herewith we report a case of a suspected NCSE who presented with acute unexplained encephalopathy and had a 'generalized non-reactive rhythmic alpha activity' as an atypical EEG pattern.

CASE PRESENTATION

A 71-year-old, right-handed male patient was admitted to the emergency department with speech difficulties and blurred consciousness which was noticed when he woke up. He had limited cooperation and perseveration with otherwise normal physical and neurological examinations, and there were no neck stiffness and meningeal signs. His relatives denied using any drugs and he had no comorbid diseases, recent infectious disease including Coronavirus disease-19 or vaccination. His history was unremarkable except for mild head trauma at the age of 20 years. He had no family history of epilepsy. His cranial magnetic resonance imaging including diffusion-weighted imaging and computed tomography were unremarkable. There were 12 lymphocytes, 4 polymorphonuclear cells in cerebrospinal fluid (CSF). CSF protein was slightly increased (59 mg/dL), with normal glucose levels. Intravenous (IV) acyclovir 2250 mg/day was administered with a preliminary diagnosis of viral encephalitis, but the viral panel and all blood tests, including liver and renal function tests, ammonia, thyroid hormones turned out to be normal except for slightly increased C-reactive protein. The next day, he was still delayed in responding

and was disorientated. EEG showed spiky contoured, slightly high amplitude, continuous generalized rhythmic alpha activity, non-reactive to eye closure and it was evaluated as consistent with possible NCSE (Figure 1a). After IV diazepam administration, the patient was sedated and the frequency of the abnormal background activity gradually decreased to theta-delta waves (Figure 1b). Levetiracetam 2500 mg/day was administered intravenously and 1000 mg/day maintenance was prescribed. The control cranial magnetic resonance imaging was also normal. CSF cytology and cultures were unremarkable along with the autoimmune panel for anti-neuronal antibodies and paraneoplastic panel including anti-Hu, anti-Yo, anti-Ri, anti-amphyphisin, anti-Tr, anti-PCA-2, anti-Ma, anti CV2-1, anti-ANNA-3 antibodies. He tended to rapidly improve in the following days, correlated with the improvement of subsequent EEG (Figure 1c). On the fifth day, the patient's neurological examination was normal and he was discharged with peroral levetiracetam 1000 mg/day. His neurological examination and EEG (Figure 1d) were completely normal 4 months later.

MAIN POINTS

- Non-convulsive status epilepticus (NCSE) is an important neurological condition that needs to be diagnosed rapidly.
- Electrophysiological findings in the 'grey zone' could sometimes lead to challenges in the diagnosis of NCSE.
- In the presence of diffuse non-reactive alpha-like activity on electroencephalogram in the acute confusional state, we should also suspect NCSE in the differential diagnosis.

DISCUSSION

We present an intriguing case of acute confusional state, whose possible etiological causes were unidentified, with generalized rhythmic alpha activity on EEG that showed electrophysiological improvement after IV diazepam. Considering the modified NCSE criteria,[6] our patient had acute confusion lasting approximately 6 h and other possible causes were excluded as far as we could. His EEG showed generalized rhythmic alpha activity with some minor fluctuations in morphology and frequency, and these rhythms were replaced by delta waves after IV diazepam without rapid clinical improvement. After IV levetiracetam treatment, a gradual but complete clinical improvement was observed in the following days. Unfortunately, this case remained undiagnosed as NCSE with the current state of Salzburg Consensus Criteria for Non-convulsive Status Epilepticus (SCNC).

Defining accurate EEG criteria has become an important milestone for the diagnosis of NCSE. Many studies have been conducted to evaluate the sensitivity and specificity of the diagnostic approach after modification of the SCNC.[5,7] Although SCNC is successful in diagnosing 'Definite NCSE' and 'No-NCSE', it has been argued that there were gray zones in the 'possible NCSE' category.[8] The "continuous" spike-wave activity <10 sec but many epileptic paroxysms filling substantial parts of the epochs, persistent rhythmic delta/theta activity without fluctuations, the fluctuations that do not fully meet the criteria, lateralized periodic discharges, and <2.5 Hz epileptiform discharges (ED) that did not fulfill the secondary criteria could not be diagnosed as 'NCSE' or 'possible NCSE' all causing false negativity according to reports.[5,9]

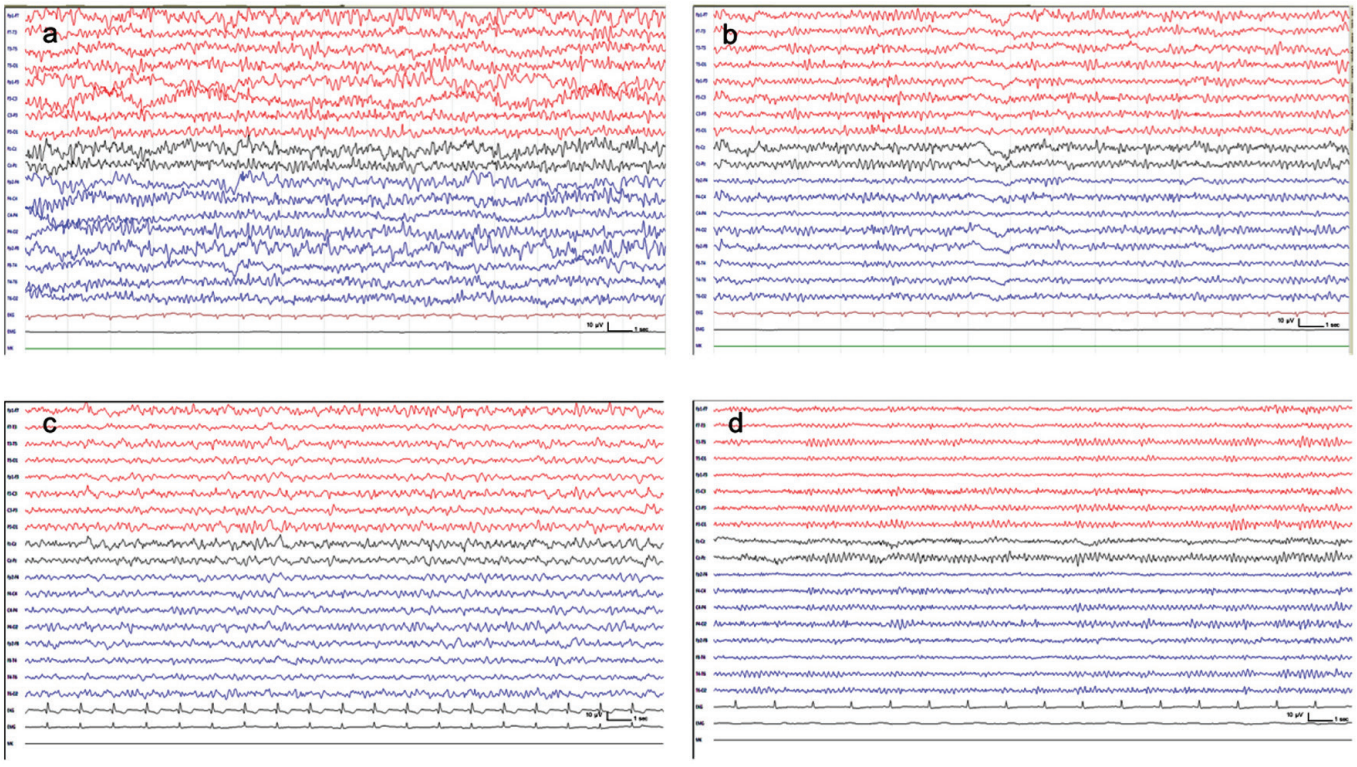

Figure 1. In EEG (high pass filter 0.5 Hz, low pass filter 70 Hz, bipolar longitudinal montage), generalized non-reactive rhythmic alpha activity was detected on the day of admission (a), these rhythms were replaced by theta-delta frequency background activity after IV diazepam without any clear clinical improvement (b). A gradual improvement of the EEG patterns was observed along with clinical improvement on day 2 after levetiracetam treatment (c) and 4 months later, EEG was normal (d)

Ictal generalized rhythmic alpha activity is a rare phenomenon in NCSE. Bauer et al.[6] reported two adult NCSE patients with generalized alpha activity who had known epilepsy but different syndromes. One of them was a 55-year-old male patient with generalized tonic-clonic seizures and impaired cognition and disturbed behavior episodes, which were accompanied by generalized alpha activity in ictal video-EEG recordings. The second patient was a 29-year-old mentally retarded female with a history of infantile spasm; she had episodes of tonic posture in the legs, irregular subtle myoclonia in the arms, hypersalivation and oral automatism, lasting 1-3 days. During these periods, generalized 11-13 Hz ictal activity and sometimes interposed spike and wave complexes in the frontal regions were detected and these episodes were considered NCSE.

It may be wondered why generalized rhythms of alpha frequency were observed instead of well-known ED of the NCSE. Many studies have shown that the sources of electrical events reflected in the scalp EEG as α waves are located in not only the occipital cortex, but also the extra-occipital cortical generators.[10] However, our patient had generalized alpha pattern instead of posterior dominant alpha rhythms of wakefulness. The most well-known cause of generalized alpha-pattern is alpha coma, in which the alpha pattern is located more posteriorly with variability and reactivity in patients with brainstem lesions, whereas the alpha pattern in hypoxic encephalopathies due to cardiac arrest tends to be diffuse spread and non-reactive, more prominent in the frontal regions.[11,12] Some hypotheses have been proposed for the pathophysiological processes of this heterogeneous clinic entity such as the deafferentation of thalamo-cortical circuits releasing autonomous cortical alpha frequency generation in the alpha pattern associated with brainstem lesion, s and a direct effect on cortical alpha frequency generators in the drug intoxication.[13] The neuroimaging findings and metabolic screening were normal, however, a direct or indirect pathophysiological effect of frontal structures on other cortical structures, such as deafferentation of the thalamocortical pathways, may be responsible for this generalized non-reactive 'alpha-like activity' suggestive of NCSE. This speculation needs to be supported by experimental studies and functional imaging techniques.

As a result, our elderly patient is the first case with no epilepsy history before, who was pre-diagnosed with viral encephalitis but unsupported by additional tests such as CSF results and neuroimaging, recovered gradually after antiepileptic treatment along with the symptoms, and diagnosed with NCSE with this unique generalized non-reactive alpha activity.

NCSE's EEG diagnostic criteria have revised several times considering experience and knowledge. Despite this, there are still NCSEs whose diagnosis is doubtful or undiagnosed. Considering that 'time is brain', early and correct NCSE diagnosis is vital and it is inevitable that the guidelines should be more inclusive for patients in the 'grey zone like the one presented here with 'generalized non-reactive alpha activity'.

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Ethics

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: İ.İ.K., B.B., Design: İ.İ.K., B.B., Data Collection or Processing: İ.İ.K., B.B., Analysis or Interpretation: İ.İ.K., B.B., Literature Search: İ.İ.K., B.B., Writing: İ.İ.K., B.B.

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A Case of CADASIL with *NOTCH3* Gene Mutation Presenting with Focal Epileptic Seizure: A Case of CADASIL Presenting with Focal Epileptic Seizure

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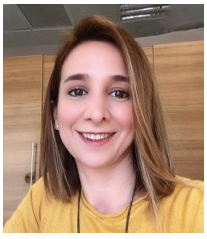

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Abstract

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a hereditary disease of cerebral microvessels with autosomal dominant inheritance due to the *NOTCH3* gene mutation. Epileptic seizures were observed in 5-11% of CADASIL cases. Observation of seizures as an initial clinical observation is a rare condition in patients with CADASIL patients. In this report, we present a patient with temporal lobe seizure, whose condition was diagnosed through gene analysis as CADASIL.

Keywords: CADASIL, focal epileptic seizure, *NOTCH3* gene

INTRODUCTION

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a hereditary disease of autosomal dominant inherited cerebral microvasculature caused by *NOTCH3* gene mutation.[1,2] This condition, in previous literature, was known as "hereditary multi-infarct dementia" or "rapid-progressing Binswanger's disease". Again in 1993, it was reported that the disease gene was discovered on chromosome-19, and three years later, mutations in the *NOTCH3* gene vanished from the disease. However, the *NOTCH3* gene mutation has been shown to be responsible for the condition.[3] This disorder, with a reported prevalence of 2-4 per 100,000, is regarded to be the most prevalent form of hereditary small vessel disease of the brain and is often overlooked or misdiagnosed.[4] As a result of a mutation in the *NOTCH3* gene, the product of this gene, interleukin-1 beta converting enzyme inhibitor the r protein is eliminated, and its functional projection is Fas-mediated cell death, which is involved in intracellular signal transduction.[5] These signal abnormalities cause progressive destruction within the cell.[6] General clinical features can be summarized as recurrent stroke attacks, migraine, or migraine-like headaches, epileptic seizures, and progressive cognitive disorders. Lesions are most commonly seen clinically as migraine, stroke, transient ischemic attacks, cognitive impairment, and mood disorders. Epileptic seizures have been observed in 5-11% of CADASIL cases.[7] We shared our case, who applied to the clinic with a focal tonic seizure in which impairment of awareness and was diagnosed with CADASIL because it is very rare.[8]

CASE PRESENTATION

A 50-year-old female patient presented to the epilepsy clinic complaining of seizures. The patient's history revealed that she had experienced seizures twice. The seizure history consisted of tonic contraction on the left followed by an unpleasant odor and dizziness, lasting 1-2 min, with impairment of awareness and increased anxiety. Postictal urinary incontinence and postictal confusion were not mentioned. There was no mention of postictal urinary incontinence and postictal confusion. There were no features in the family history of the patient consisting of a history of headaches. Neurological examination was evaluated as normal. Routine biochemistry and hematological examinations were normal. Cerebral magnetic resonance imaging (MRI) scan, however, revealed multiple lesions of white matter hyperintensity on

both periventricular white matter, anterior temporal lobes, and outer capsules (Figure 1). The results of an additional planned cardiac echocardiography, carotid and vertebral computed tomography angiography, homocysteine, HIV, VDRL, anti-TPO, anti-cardiolipin, anti-nuclear and anti-beta 2 glycoprotein 1, and extractable nuclear antibody panel was also evaluated as normal. Interictal electroencephalogram was evaluated as consistent with isolated sharp wave activity, which is commonly observed in the anterior regions of the left hemisphere (Figure 2). The patient was put on 500 mg levetiracetam per day, which was increased to 1000 mg per day two weeks later. Neuropsychological test results were considered to be compatible with mild depression. Exon 11 heterozygous mutations were detected in the *NOTCH3* gene. After adding anti-aggregant therapy to her treatment regimen, our patient was been followed-up without seizures for 22 months.

DISCUSSION

Seizure is a rare clinical condition in patients diagnosed with CADASIL.[7] In patients with CADASIL, frequently occurs after a stroke and is often characterized by widespread tonic-clonic seizures.[9,10] Although the exact cause of the epileptic seizure in patients currently on CADASIL is unknown, high-signal-intensity lesions transiently located in the anterior temporal regions in these patients may be associated with epileptogenesis.[11] In the Post-mortem high-resolution 7-T MRI study, multiple cortical and subcortical lesions were also demonstrated in patients with CADASIL.[12] Recently, Gasparini et al.[13] proposed a remarkable hypothesis on the relationship between leukoaraiosis and epileptic seizures. They hypothesized that occult cortical micro-infarcts may be related to epilepsy in patients with leukoaraiosis.[14] In some previous reports, cholinergic denervation has been observed in the cerebral cortex and white matter tract in patients with CADASIL.[15] Cholinergic neurons modulate excitability in the central nervous system. Furthermore, several experimental studies have demonstrated that cholinergic denervation may induce seizures by increasing facilitation.[16] Interestingly, Keverne et al.[17] reported that nine patients with CADASIL had cholinergic neuronal damage mainly along the white matter tracts extending to the frontal cortices.

In the study of Dichgans et al.,[18] 102 patients with CADASIL were evaluated, 10 of them had seizures, nine of the patients with seizures were in the generalized tonic-clonic seizure clinic, and one presented as focal onset seizures. In Another data analysis consisting of CADASIL cases, 6 of 105 patients showed that.[9] Two cases that presented with non-convulsive status epilepticus and recurrent status epilepticus and were diagnosed with CADASIL were reported in the literature. A 30-year-old female patient presenting with focal seizures and diagnosed with CADASIL was reported by Velizarova et al.[7] In our case, our patient had bilateral generalized tonic-clonic seizures with focal onset. In these two cases, seizure clinic and electrophysiological findings were consistent with temporal lobe seizures. Co-occurrence of focal seizures and CADASIL is very rare, and three cases have been reported in the literature together with our case.

Although seizures are more likely to occur following a stroke in patients with CADASIL, seizures may rarely happen in these patients. CADASIL should be suspected when encountering patients with new-onset of seizures with unexplained white matter lesions on a brain MRI scan. Furthermore, the precise mechanism of seizure development remains unclear. This necessitates additional research with more patients with CADASIL, to investigate the association of CADASIL with seizure types.

MAIN POINTS

- Seizure is a rare clinical condition in patients diagnosed with CADASIL. It is hypothesized that occult cortical microinfarctions in patients with leukoaraiosis may be associated with epilepsy. In some previous reports, cholinergic denervation has been observed in the cerebral cortex and white matter tract in patients with CADASIL.
- Focal seizures and CADASIL are very rare, and three cases have been reported in the literature together with our case. CADASIL should be suspected when encountering patients with new-onset of seizures with unexplained white matter lesions on a brain MRI scan.

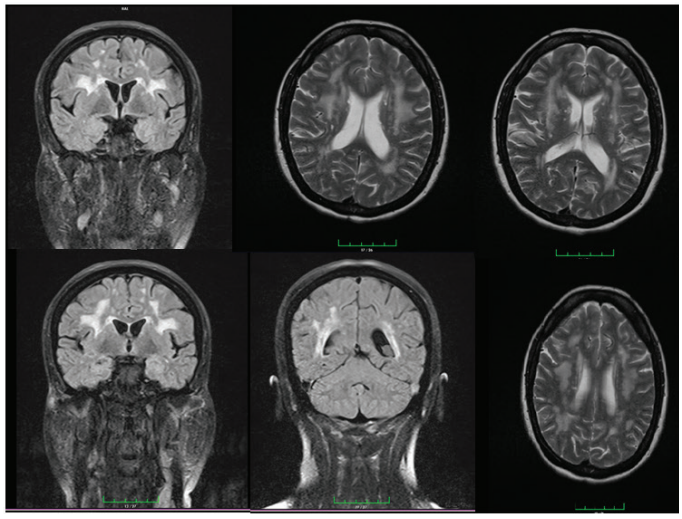

Figure 1. Cerebral magnetic resonance imaging: multiple lesions of white matter hyperintensity on both periventricular white matter, anterior temporal lobes, and outer capsules

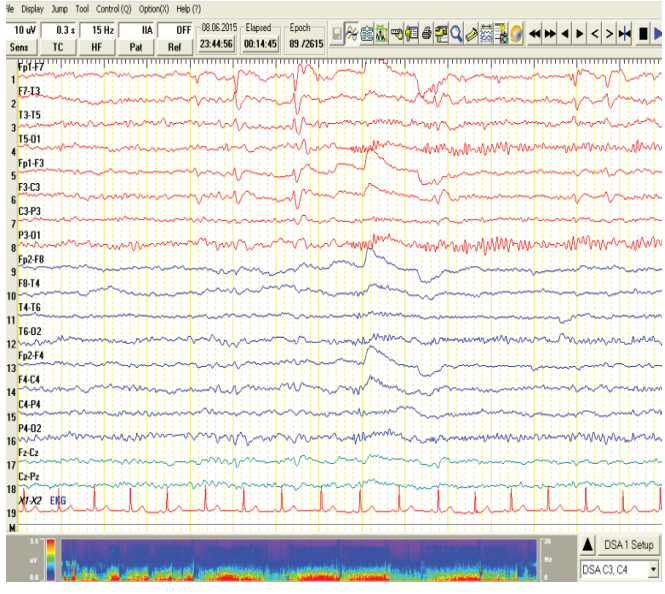

Figure 2. Electroencephalogram: isolated sharp wave activity, which is commonly observed in the anterior regions of the left hemisphere

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.İ.A., O.O.E., D.Ö.A., Concept: D.İ.A., O.O.E., D.Ö.A., Design: D.İ.A., O.O.E., D.Ö.A., Data Collection or Processing: G.U., D.İ.A., Analysis or Interpretation: G.U., D.İ.A., Literature Search: G.U., D.İ.A., Writing: G.U., D.İ.A.

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