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EDITORIAL

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S. Naz Yeni, M.D., Prof.
Editor-in-Chief

Evaluation of *Toxoplasma gondii* in the Etiology of Cryptogenic Epilepsy: A Case-control Study

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Abstract

Objectives: This study was conducted to evaluate the relationship between toxoplasmosis and cryptogenic epilepsy (CE) by comparing the rate of *Toxoplasma gondii* seropositivity identified in CE patients with those without any neurological disorder.

Methods: The study included 200 cryptogenic patients and 164 individuals without neurological disorders. *T. gondii* seropositivity was studied in individuals included in the study using the *T. gondii*-IgG ELISA kit.

Results: The study found *T. gondii* IgG in 15.50% of CE patients and 28.66% of individuals without any neurological disorder. The difference between the two groups was determined to be statistically significant.

Conclusion: Toxoplasmosis did not increase the risk of epilepsy in the region where this study was conducted. However, for a better understanding of the CE-*T. gondii* relationship, we believe that seroprevalence studies should be conducted in larger populations.

Keywords: Cryptogenic epilepsy, dopamine, GABA, neurology, toxoplasmosis

INTRODUCTION

Epilepsy is one of the most common neurological disorders after stroke and Alzheimer's disease, and it has a global prevalence of approximately 1%. The underlying cause of epilepsy is unknown in two-thirds of patients, and this type of epilepsy is called cryptogenic epilepsy (CE).[1] Infectious diseases, especially those associated with the central nervous system (CNS), are assumed to play an important role in epilepsy.[2]

Toxosoplasma gondii (*T. gondii*) is an intracellular zoonotic parasite. The prevalence of this parasite varies depending on the cultural structures of the societies and especially their eating habits, and it has been reported that approximately one-third of the world's population is infected with this parasite.[3] Using the Trojan horse strategy, *T. gondii* may penetrate into non-immune organs such as dendritic cells and monocytes, as well as the testicles, eyes, and notably the brain. It may infect many cell types in the brain, including neurons, Purkinje cells, and microglial cells in the amygdala, hippocampus, cerebral cortex, and basal ganglia regions.[3,4] It may lead to changes in the cognitive and psychological state of the host by disrupting the electrical activity of the cells in which it settles.[3] In addition, a study on mice reported that *T. gondii* chronic infection increased brain dopamine levels by up to 15%. Therefore, the neurobehavioral and neurological symptoms assumed to be associated with *T. gondii* infection may be associated with potential dopamine modulation in the host brain.[5] Based on these studies, the *T. gondii* positivity rate was reported to be higher in patients with various neuropsychiatric disorders, such as schizophrenia, CE, bipolar disorder, obsessive-compulsive disorder, unipolar depression, substance use disorder, suicides, murders, generalized anxiety disorder and panic disorder, personality disorders, and mood disorders, than in healthy controls.[3,4,6] Current studies consistently support the relationship between *T. gondii* and schizophrenia, although it is necessary to conduct more detailed studies on other disorders.[5]

This study was conducted to evaluate the relationship between toxoplasmosis and CE by comparing the rate of *T. gondii* seropositivity identified in CE patients with patients without any neurological disorder and by performing a meta-analysis of the results of studies that previously discussed the relationship between *T. gondii* and CE.

METHODS

Study Population and Sample Collection

This study was conducted on 200 patients diagnosed with CE and followed up at the University of Health Sciences Turkey, Van Training and Research Hospital between August 2021 and October 2022 in Van province, Turkey. Also included as the control group were 164 healthy individuals without neurological disease. The patient group included CE patients with normal brain magnetic resonance imaging and no history of head trauma, brain surgery, meningitis, encephalitis, or alcohol dependence; the control group included healthy subjects in the same age range as well as the patient group without any neurological complaint. To provide similar populations of the patient and control groups, people not residing in Van were not included in the study. For the routine examinations of the individuals included in the study, the remaining blood samples that they gave to the biochemistry laboratory were used in the study. Serum was separated from the collected blood samples and stored at -20 °C.

Serological Antibody Detection

The presence of anti-*T. gondii* IgG antibody in sera was determined using an ELISA IgG kit (DRG, Germany). The serum samples were allowed to thaw at room temperature before testing. The procedure was performed according to the manufacturer's instructions.

Statistical Analysis

The Minitab 14 package program was used for statistical analysis of the seroprevalence study with the control group. The Z test and Fisher's exact tests were used to determine statistical significance and $p<0.05$ was considered significant.

RESULTS

The ratio of females to males in the patient and control groups was 95/105 and 100/64, respectively. The mean age of the patients was 31.05±12 years (minimum 19-maximum 72), whereas in the control group was 42.27±20.12 years (minimum 19-maximum 80) (Table 1).

MAIN POINTS

- Current studies consistently support the link between *T. gondii* and schizophrenia. However, more detailed studies are needed for other disorders such as cryptogenic epilepsy (CE).
- Studies have reported that neurological disorders of toxoplasmosis depend on the localization of tissue cysts in the central nervous system. *T. gondii* infections may not be associated with all types of epilepsy but only some types of epilepsy and only some strains, not all *T. gondii* strains, may lead to epilepsy.
- Toxoplasmosis did not increase the risk of CE in the region where this study was conducted.

The study found *T. gondii* IgG in 31 (15.50%) of 200 CE patients and 47 (28.66%) of 164 non-epileptic individuals. Based on the statistical analysis, the higher rate in non-epileptic individuals compared with CE patients was determined to be statistically significant (p=0.003).

The distribution of *T. gondii* IgG positivity rates by age and gender is shown in Table 2. When the positivity rates of CE patients and non-epileptic individuals by age were statistically compared, no significant difference was found in individuals under 35 years of age (p=0.47) but a significant difference was found in individuals over 35 years of age (p=0.001).

DISCUSSION

It is estimated that 30% of people worldwide are infected with *T. gondii*. However, *T. gondii* seropositivity may vary among countries, different regions within the same country, and communities of different ethnic origins living in the same region.[5] Studies conducted in Turkey in the last decade have determined *T. gondii* seropositivity to be 26.8-32.4% in the general population.[7] *T. gondii* seropositivity was found to be 29% in the control group of a study investigating the relationship between schizophrenia and toxoplasmosis in Van province,[6] and 28% in the control group of a study investigating *T. gondii* seropositivity in hemodialysis patients.[8] This study also showed 28.66% positivity in individuals without any neurological disease selected as the control group. This study and previous studies have demonstrated that approximately one in three people in Turkey are exposed to *T. gondii*. Therefore, studies on the pathogenicity of this protozoon are important.

Toxoplasma gondii may cause serious illnesses in humans, particularly in congenitally infected children and those with a weakened immune system or immunocompromised.[7] In particular, it has been discussed that individuals may develop behavioral and neurological disorders due to latent toxoplasmosis. Studies have reported that *T. gondii* with an increasing prevalence recently may be associated with some neurological disorders such as Parkinson's disease, Alzheimer's disease, schizophrenia, and epilepsy.[3,4,6] While there is consistency in the results of studies on schizophrenia,[5] there is no clear information about the role of *T. gondii* in the etiology of neurological disorders such as epilepsy. There are studies reporting that there is no statistically significant difference between the *T. gondii* seropositivity rate of epileptic patients and that of the healthy control group,[9,10] as well as studies reporting that the seropositivity rate is higher in epileptic patients.[11,12] Researchers also evaluated the seroprevalence of *T. gondii* in patients with CE, a type of epilepsy with unknown etiology.

Table 1. Comparison of demographic characteristics of the patient with CE and control groups

	CE patient group	Control group	p
Mean age±SD	31.05±12	42.27±20.12	0.001
Gander			
Female	95 (47.50%)	100 (60.98%)	0.01
Male	105 (52.50%)	64 (39.02%)	

CE: Cryptogenic epilepsy, SD: Standard deviation

Table 2. Distribution of *T. gondii* IgG positivity rates by age and gender

Veriable	CE patient group		Control group		p
	Number (%)	Seropositivity to *T. gondii* (%)	Number (%)	Seropositivity to *T. gondii* (%)	
Gender					
Female	95 (47.50)	15 (15,79)	100 (60.98)	28 (28.00)	**0.037**
Male	105 (52.50)	16 (15.24)	64 (39.02)	19 (29.69)	**0.031**
Age					
≤35	144 (72.00)	25 (17.36)	77 (46.95)	17 (22.08)	0.407
>35	56 (28.00)	6 (10.71)	87 (53.05)	30 (34.48)	**0.001**
Total	200 (100.00)	31 (15.50)	164 (100.00)	47 (28.66)	**0.003**

CE: Cryptogenic epilepsy, IgG: Immunoglobulin G

Table 3. Characteristics of studies investigating the relationship between cryptogenic epilepsy and toxoplasmosis

Authors	Country	Age groups	CE patient group		Control group	
			N	n (%)	N	n (%)
El-Tantawy et al.[13]	Egypt	Child age group	132	80 (60.06)	60	26 (43.33)
Abd El-Aal et al.[14]	Egypt	2-46 age	72	25 (34.72)	60	7 (11.67)
Eraky et al.[15]	Egypt	Child age group	40	8 (20.00)	20	2 (10.00)
Khatab et al.[16]	Egypt	Child age group	30	12 (40.00)	20	2 (10.00)
Zibaei et al.[17]	Iran	All ages	85	12 (14.12)	85	4 (4.71)
Babaie et al.[10]	Iran	18-64 age	262	94 (38.88)	63	24 (38.09)
Yazar et al.[18]	Turkey	All ages	50	27 (54.00)	50	9 (18.00)
Akyol et al.[19]	Turkey	11-60 age	100	31 (31.00)	50	10 (20.00)
This study	Turkey	All ages	200	31 (15.50)	164	47 (28.66)

N: total number of individuals.
n: number of *T. gondii* seropositive individuals.
CE: Cryptogenic epilepsy

While seven studies (Table 3)[13-19] revealed *T. gondii* seropositivity in CE patients to be higher than in the control group, Babaie et al.[10] study and this study showed seropositivity to be high in the control group. We believe that the relationship between *T. gondii* infection and CE will be more clearly understood when larger patient populations are studied and well-matched control groups are selected. Having found the seropositivity rate to be higher in the control group than in epileptic patients in Iran, Babaie et al.[10] also suggested conducting prospective studies with large sample sizes consisting of well-matched control groups to clarify the effect of *T. gondii* on the occurrence of epilepsy. The sample size included in this study was higher than that of the other eight studies (Table 3),[13-19] and attention was paid to ensure that the region where the individuals selected for the control group lived was compatible with the patient group.

It should be examined the mechanisms of the occurrence of epilepsy and how *T. gondii* infection affects the neurological system to interpret the toxoplasmosis-CE relationship. Epileptic activity is particularly caused by repetitive synchronous hyperactivity of cortical and hippocampal neurons. Epileptiform discharges are caused by decreased extracellular magnesium, increased extracellular potassium (K) concentration, inhibition of the sodium pump, or antagonism of GABA receptors.[3] *T. gondii*, as a carbon source, may lead to epileptic seizures by using GABA, the neurotransmitter primarily responsible for preventing the onset of seizures.[20] Brooks et al.[20] reported that glutamic acid decarboxylase 67 (GAD67), a key enzyme catalyzing GABA synthesis in the brain, was affected in mice infected with the type 2 ME49 *T. gondii* strain, but not in mice infected with the type 3 CEP strain. The study highlighted that the regulation of GABAergic synapses may be due to polymorphic parasitic factors, and the brains of mice also had tachyzoite and activated microglia and astrocytes as well as numerous cysts.

It is also known that epileptic activity may result from changes in the brain dopamine level. The genome of *T. gondii* contains two regions of aromatic amino acid expiration. These amino acids provide the synthesis of the L-DOPA enzyme and thus affect the biosynthesis of dopamine and serotonin. It increases the parasite K^+ ion level in dopaminergic cells, thereby causing dopamine to be released three times more. Dopamine levels were also found to be high in brain tissue with *T. gondii* cysts. Dopamine levels and concentrations increase when the parasite settles in the amygdala region.[3]

To sum up, studies have reported that neurological disorders of toxoplasmosis depend on the localization of tissue cysts in the CNS, *T. gondii* infections may not be associated with all types of epilepsy but only some types of epilepsy[9] and that only some strains, not all *T. gondii* strains,[20] may lead to epilepsy. Thus, we believe that the relationship between *T. gondii* and CE may vary from region to region, to different communities within the same region, and from individual to individual within the same community. In addition, the higher *T. gondii* seropositivity in the control group can be partially explained by the fact that the control group was older.

Because *T. gondii* seroprevalence increases with age as a result of cumulative seropositivity. In a study, it was determined that *T. gondii* seroprevalence increased at a rate of 1.09% with each year of age.[21]

Study Limitations

The main limitation of the study is that it was conducted in a single hospital; therefore, the patient population was from a single region. In addition, the fact that *T. gondii* IgM levels were not measured in the patients is also a limitation of the study.

CONCLUSION

Toxoplasma gondii seropositivity in CE patients included in the study was lower than that in the control group. According to these results, toxoplasmosis did not increase the risk of CE in the region where this study was conducted. However, for a better understanding of the CE-*T. gondii* relationship, the role of different *T. gondii* strains in the etiology of CE, the importance of the immune system of individuals infected with *T. gondii* in the occurrence of CE, and the *T. gondii*-CE-dopamine relationship should be examined. In addition, seroprevalence studies should be conducted in larger populations and in different countries.

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Ethics

Ethics Committee Approval: The ethical approval for this study was obtained from the Non-invasive Ethics Committee of Van Yüzüncü Yıl University (09/07/2021-2021/08-15).

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

Author Contributions

Concept: Z.T.C., S.A., M.T.A., Ö.S.T.A., Design: S.A., Z.T.C., H.Y., Data Collection or Processing: Ö.S.T.A., M.K., C.B., Analysis or Interpretation: S.A., M.T.A., H.Y., Literature Search: S.A., M.T.A., Writing: S.A., Z.T.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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Archives of Epilepsy

Original Article

Health Equity Consideration in Cochrane Systematic Reviews and Primary Studies on Add-on Therapy for Refractory Focal Epilepsy Treatment

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Abstract

Objective: Health equity is defined as the absence of unequal and avoidable factors in health differences among populations. Several add-on treatments have been suggested for refractory epilepsy and epilepsy unresponsive to usual treatments in systematic reviews. The current study assessed equity concerns in Cochrane systematic reviews and original studies on additive therapies used for refractory focal epilepsy because identifying the reasons for injustice is the first step in eradicating health inequality.

Methods: Cochrane systematic reviews and their primary studies on add-on therapy for treatment-resistant focal epilepsy in adults published in the Cochrane library in the last 10 years (until the end of 2022) were gathered. Two researchers independently reviewed the PROGRESS criteria in the studies based on the guide for each of the primary and review studies.

Results: In the present study, 7 systematic reviews and 54 primary studies were included. based on the findings of our study, all review studies and 81.5% of the original studies were conducted in high-income countries. none of the articles mentioned the issue of justice in health or PROGRESS criteria. However, all of the articles mentioned gender distribution and patients' place of residence, and about 35% of the original articles also mentioned patients' race. None of these factors were analyzed as a criterion for group comparison or as a criterion for influencing the treatment process.

Conclusion: The Cochrane-related reviews confirm that PROGRESS criteria are rarely considered in trials of interventions linked to add-on therapies for treatment-resistant focal epilepsy.

Keywords: Health equity, refractory focal epilepsy, systematic reviews

INTRODUCTION

Epilepsy is one of the most common and serious neurological diseases that affects approximately 70 million people worldwide. Epilepsy occurrence has a two-fold pattern, and the highest risk of occurrence is in infants and the elderly; Emergence of epilepsy depends on a combination of environmental risk factors and underlying genetic predisposition.[1] Despite the existence of more than 20 types of anti-epileptic drugs, seizures are still not well controlled in approximately 30% of patients.[2] Drug-resistant epilepsy does not respond to two or more antiepileptic drugs prescribed as monotherapy or polytherapy for a sufficient time.[3] Before further consideration, conditions that mimic drug resistance, such as misdiagnosis, insufficient dosage, inappropriate medication, and low patient compliance, must be ruled out and then referred to specialized epilepsy centers.[3] Because drug-resistant epilepsy can be dangerous and greatly affect patients' quality of life, early diagnosis, referral, and treatment are essential.[4] So far, many research and clinical trials have been conducted on add-on therapies for drug-resistant focal epilepsies, and various drugs such as felbamate, lamotrigine, zonisamide, clonazepam, rufinamide, etc., and the effects of each on epilepsy have been investigated.[5-8]

Health equity is the absence of unfair and avoidable factors in health between and within populations, and it is a priority for health-related research.[9] Health justice includes access to health care and equal opportunities to achieve health.[10] Differences in receiving medical and health services between groups may be due to inequality in factors such as social and economic characteristics. Health disparities in

almost all health problems persist and are worsening, both within and between countries. For example, people living in the poorest countries have at least 30 years less life expectancy than people living in the richest countries. In low- and middle-income countries, the under-five mortality rate is 64.6 deaths per 1,000 births among the poor and 31.3 per 1,000 births among the wealthy.[11] According to the Global Child Mortality Update, the disparity in under-five mortality between high- and low-income regions is widening as sub-Saharan Africa is estimated to bear 60% of the global burden of under-five mortality by 2050.[12,13]

The World Health Organization established the Commission on Social Determinants of Health in 2006 and published its final report in 2008 to assess the evidence for reducing health inequalities.[14] Health inequality is defined as the "poor health of the poor" within and between countries due to the "unequal distribution of power, income, goods and services, globally and nationally, resulting in immediate and visible injustice in their access to health care and education, working and leisure conditions, homes, communities, towns or cities-and their chances of living a flourishing life".[14] Such health inequalities are not only for moral and ethical reasons but also for economic reasons, and should be considered.[15] Increasing evidence of the effectiveness of interventions to reduce health inequalities, both within and between countries, as well as methods for assessing health equity in systematic reviews, such as the Cochrane Handbook chapter about justice and specific populations.[16]

Health justice and related studies are becoming a big and fundamental pillar of research. According to the review of such articles on other topics, it has been seen that this principle has not been valued as much as it should be. Regarding the treatment of drug-resistant focal epilepsies, according to the clinical trials of various types of drugs, there is no mention of observing the principles of justice and equality in these cases. According to the abovementioned cases, attention to health justice has a special place among this category of patients. By studying this field and knowing these factors, we can obtain results that can be adapted to most people or societies and have a higher value by eliminating or controlling these inequalities in studies and experiments and helpful in health-related policies.

MAIN POINTS

- Health equity involves the absence of unfair and avoidable differences in health within and between populations. Health justice encompasses access to healthcare and equal opportunities to achieve health.
- Disparities in healthcare access and outcomes persist globally, with significant differences observed between countries and within populations. Social and economic factors influence these disparities.
- Despite the growing importance of health equity, studies, including clinical trials on drug-resistant epilepsy treatments, often overlook the principles of justice and equality. This highlights the need for greater attention to health justice in research and healthcare policies.
- Addressing health inequalities in research and clinical practice can generate results and policies that benefit most people and societies, ultimately leading to more equitable healthcare outcomes.

METHODS

The Cochrane systematic review articles on treatments related to add-on therapies for refractory focal epilepsy in adults from 2011 to 2021 were included in the study. Studies on other diseases in the age range other than adults were excluded from the study.

We also extracted and considered the studies included in each of these review articles as primary studies; based on the location of the study and World Bank classification, we divided the country conducting the study into two groups: high income and low income. Information related to the type of study, sample size, results, location, and budget was also extracted from each study. Two researchers independently reviewed the PROGRESS criteria (Table 1) separately based on the guide (O'Neil reference) for each of the primary and review studies.[17] The contradiction between the extracted data among the researchers was resolved by a third member.

The study protocol was approved by the Ethics Committee of the Iran University of Medical Sciences under the ethical approval code IR.IUMS.FMD.REC.1400.200, date: 20.06.2021.

Table 1. PROGRESS criteria

Place of residence	It is classified as rural, urban, and poor urban areas; It also includes high, middle, and low-income countries.
Race/ethnicity/ culture	Refers to the patient's ethnic, racial, and cultural background as well as language. Race is defined from a biological point of view, while ethnicity and culture include social aspects. Biological differences are not considered unfair unless their manifestation is avoidable.
Occupation	It includes various conditions such as unemployment, part-time jobs, informal workers, and unsafe work environments.
Gender	It includes all social, economic, and cultural characteristics and opportunities and it is a type of role. which are determined for both sexes, male and female (based on the phenotype and appearance of the person). This measure includes socially constructed rules and other characteristics that society associates with gender.
Religion	The belief path of people is called religion. This criterion considers the injustices that limit access to health services for a specific subgroup of the population with a specific religious orientation or without any religious orientation.
Education	It refers to the degree of education obtained from reputable educational institutions such as schools and universities. It is important because it affects the type of employment and consequently the income of the person. Also, educated people have more knowledge about health and preventive measures.
Socio-economic level	Objectively measured based on a person's job, education, and income. This factor determines the adequacy of many components affecting health, such as living conditions and access to fresh and healthy food.
Social capital	It includes the level of trust between community members, civil participation, and the desire of members of a community to help each other and strengthen their political relationships. In general, it includes the amount of support from people around and at the community level.

In general, PROGRESS includes: P: Place of residence, R: Race/ethnicity/culture, O: Occupation, G: Gender, R: Religion, E: Education, S: Socio-economic level, S: Social capital

Statistical Analysis

We used Statistical Package for the Social Sciences version 22 software for statistical analysis of the data. The results for quantitative variables are expressed as mean±standard deviation and for qualitative variables as percentages.

RESULTS

A total of 7 systematic reviews of add-on therapy for refractory focal epilepsy and 54 primary studies were examined. Information on each systematic review included is presented in Table 2.

The results obtained are that all the articles mentioned the two criteria of patients' gender and place of residence; in 19 studies (35.18%), in addition to gender and place of residence, race was also mentioned, but other PROGRESS criteria were not mentioned in any study (Table 3).

DISCUSSION

There is growing evidence that systematic reviews of the best available evidence are the main source of information for determining evidence-based policy and practice and that systematic reviews are a useful basis for decision-making because they reduce the likelihood of bias and are a reliable source for clinical practice.[24,25]

In this study, we examined a total of seven systematic reviews and 54 articles used in the review studies. All review studies were conducted in high-income countries, and 81.5% of the original studies were also conducted in high-income countries, and only 18.5% of them were multi-centric and included low-income countries. None of the studies were conducted only in low-income countries. Based on the findings of our study, none of the articles mentioned the concept of health equity or PROGRESS criteria. However, all the articles mentioned the factors of gender and place of residence of the patients in their findings, and approximately 35% of the original articles also mentioned the race of the patients in addition to the place of residence and gender.

Our findings were consistent with previous studies in the field. As in the study of Tugwell et al.[26] about rheumatoid arthritis and its related interventions, among early studies, gender was the most mentioned variable, followed by education level and race/ethnicity. PROGRESS dimensions were mentioned in less than 50% of systematic reviews. Disadvantaged communities were mentioned in only 5% of the primary studies. In general, in early studies on interventions in the field of rheumatoid arthritis, few variables of health inequality criteria were mentioned. In the study by Evans et al.[27] on equity related to systematic reviews and primary studies on cataracts, among 85 studies, only one considered the PROGRESS criteria as an inclusion. Overall, the PROGRESS factors that indicate equality were not mentioned in these studies. The same results were found in Cochrane systematic reviews related to HIV infection.[28] In another study, it was found that in the studies that conducted strategies to improve the quality of life of diabetic patients, less than one-third of the trials were concerned with the inclusion of health equity criteria.[29]

The PROGRESS framework was first proposed by Evans et al. in 2003.[27] Although there are several other frameworks available for assessing equality, we chose this framework because it is recommended by the Campbell and Cochrane Equity Methods Group and included in the reporting guidelines for systematic reviews in 2012 and intervention studies in 2017.[30,31] However, not all components of the PROGRESS framework are relevant to all systematic reviews or primary studies. For example, if all participants are from the same place and have similar ethnicities or languages/religions, inequality on these dimensions may not be a concern. However, sometimes people are excluded from studies for reasons such as language or inability to participate; therefore, a higher awareness of equality issues on the part of trial conductors is important.[32]

One of the benefits of conducting such studies is to assess the extent to which researchers consider factors related to health equity; however, we were unable to analyze the impact of equity-related factors on study outcomes. The effectiveness of interventions often varies depending on the participating population and the existing health system. Based on the limited primary data we have from targeted and public trials, it is difficult to draw firm conclusions about which health equity interventions or strategies are effective or ineffective in reducing health disparities and/or improving health outcomes for disadvantaged groups.

Table 2. Information on included systematic reviews

Title	Number of included studies	Sample size	Country of origin
Felbamate add-on therapy for drug-resistant focal epilepsy[18]	4	236	HIC
Topiramate add-on therapy for drug-resistant focal epilepsy[19]	11	1650	HIC
Vigabatrin add-on therapy for drug-resistant focal epilepsy[20]	11	756	HIC
Pregabalin add-on for drug-resistant focal epilepsy[21]	11	3949	HIC
Carisbamate add-on therapy for drug-resistant focal epilepsy[22]	4	2211	HIC, LIC
Zonisamide add-on therapy for focal epilepsy[8]	7	1636	HIC
Tiagabine add-on therapy for drug-resistant focal epilepsy[23]	6	948	HIC

HIC: High-income countries, LIC: Low-income countries

Table 3. The PROGRESS dimensions considered in systematic reviews and primary studies

Progress	Reviews	Primary studies
Place of residence	7 (100%)	54 (100%)
Race/ethnicity/culture	0	18 (33.3%)
Occupation	0	0
Gender	7 (100%)	54 (100)
Religion	0	0
Education	0	0
Socioeconomic status	0	0
Social capital and networks	0	0

Study Limitations

The study's limitations include a restricted focus on Cochrane systematic reviews and their primary studies within the past decade, potentially excluding relevant research from other databases or earlier periods. Moreover, the predominant inclusion of studies conducted in high-income countries limits the generalizability of findings to diverse global populations. Despite assessing studies for health equity using PROGRESS criteria, the absence of explicit consideration for health justice and limited analysis of factors such as race or socioeconomic status may overlook important determinants of health disparities.

CONCLUSION

In conclusion, the findings of this study on Cochrane systematic reviews and their primary studies indicate a significant lack of health equity and thus considerable improvement in the proportion of studies that examine equality and the range of equality factors that can be reported and analyzed. Therefore, health equity dimensions can be routinely considered during clinical intervention and randomized controlled trial studies in addition to the usual items of age, gender, comorbidities, and place of residence.

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Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of the Iran University of Medical Sciences under the ethical approval code IR.IUMS.FMD.REC.1400.200, date: 20.06.2021.

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

Authorship Contributions

Surgical and Medical Practices: Z.M., Concept: Z.M., B.S., Design: Z.M., B.S., Data Collection or Processing: S.S., P.M., R.M., Analysis or Interpretation: S.S., B.S., Literature Search: S.S., P.M., R.M., Writing: S.S., Z.M., P.M., R.M.

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Does the Frequency and Etiology of Status Epilepticus Change During the SARS-CoV-2 Pandemic?

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Abstract

Objective: There are limited data regarding the development of status epilepticus (SE) in epilepsy patients during the Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) pandemic. In Turkey, no study has investigated the frequency and etiology of SE in patients with epilepsy during the pandemic period. We aimed to evaluate the etiologies, clinical features, treatment, and prognosis of patients who were followed up with a diagnosis of SE in our neurology clinic and intensive care unit during the pandemic period.

Methods: In this study, 59 patients (mean age 51.7±2.7 years), 32 males (54.2%) and 27 females (45.7%), who were monitored and treated in the Bursa City Hospital Neurology Clinic and Neurology Intensive Care Unit between March 11, 2020 and December 31, 2022, were retrospectively included.

Results: When etiologic factors leading to SE were analyzed; it was considered that 16 patients had ischemic stroke (27.1%), 8 had intracranial tumor (13.5%), 4 had intracerebral hemorrhage (6.7%), 4 had medication discontinuation (6.7%), 4 had SARS-CoV-2 infection (6.7%), 3 had other infections (5.0%), 2 had SARS-CoV-2 vaccination (3.3%), 4 had previously diagnosed refractory epilepsy (6.7%), and 8 had NORSE (13.5%). In the present study, 18 patients (30%) received IV levetiracetam, 8 patients (13.5%) received levetiracetam + valproic acid, and 6 patients (10.1%) received levetiracetam + phenytoin infusion for SE. We had 28 patients who needed general anesthesia. Ten patients (16.9%) died.

Conclusion: In the etiology of SE in our patients monitored during the pandemic period, it was found that ischemic stroke, cryptogenic causes, cerebral hemorrhage, intracranial tumors, SARS-CoV-2 and other infections, and irregular drug use were the most common causes.

Keywords: SARS-CoV-2, COVID-19, epilepsy, status epilepticus, pandemic, etiology

INTRODUCTION

Status epilepticus (SE) is defined as a single seizure that lasts longer than 5 min or repetitive seizures in which the patient does not return to the previous state.[1] In cases where seizure activity is still present despite first-line benzodiazepine and second-line intravenous (IV) antiseizure medication, the patient is considered to have developed refractory SE (RSE). RSE is observed in approximately 9-43% of all SE cases, and the mortality rate has been reported to be between 15% and 33%. The mortality rate increases as the duration of SE increases.[2]

In the neurological spectrum of Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) infection; there are many neurological symptoms, including delirium, loss of smell and taste, encephalopathies, stroke, epileptic seizures, and SE.[3] It has been reported that SARS-CoV-2 may cause neurological symptoms due to its neuroinvasive and neurotropic properties and that the inflammatory response (cytokine storm) related to SARS-CoV-2 infection may lead to increased circulating cytokine levels and immune cell hyperactivation, which may cause secondary organ dysfunction and a life-threatening systemic inflammatory syndrome.[4] SARS-CoV-2 may trigger a systemic inflammatory response and result in stroke, epileptic seizures, and SE. Acute symptomatic seizures and SE are the most commonly reported clinical conditions related to SARS-CoV-2 infection, and the mortality rate is high (5-39%).[5] Although vaccines are generally safe for patients with epilepsy, they may lead to seizures, particularly with live vaccines. Although the effects of SARS-CoV-2 vaccines on seizures are still unknown, They have rarely been observed to increase epileptic seizures.[5] It was found that there was a further increase in seizures after vaccination in patients with frequent seizures.[5,6] In a cross-sectional study by Özdemir et al.[6], it was reported that SARS-CoV-2 vaccines were well tolerated in patients with epilepsy, and more seizures than normal were observed in a small group of patients. In rare cases, SE cases after SARS-CoV-2 vaccination in people without epilepsy have also been reported.[7]

Several studies have evaluated the situation of epilepsy patients during the SARS-CoV-2 pandemic. However, data on SE are limited.[8-10] Furthermore, no study has investigated SE in patients with epilepsy during the pandemic period in Turkey. It was considered that there might be an increase in the frequency of epilepsy seizures and the prevalence of SE in patients with epilepsy during the SARS-CoV-2 pandemic period because of the inability of patients with epilepsy to use their medications on a regular basis, failure to perform neurologic follow-up appropriately, and the possible seizure risk of SARS-CoV-2 infection and vaccines. This retrospective study evaluated the demographic characteristics, etiologies, and whether there was a relationship with SARS-CoV-2 infection in SE patients who were hospitalized in our hospital during the SARS-CoV-2 pandemic.

METHODS

Patients who were hospitalized, monitored, and treated in the Neurology Clinic and Intensive Care Unit of Bursa City Hospital between March 11, 2020 and December 31, 2022 were scanned. Patients with a diagnosis of SE were extracted from the hospital data processing system and analyzed.

Study inclusion criteria:

1. Patients must be over 18 years of age,

2. Patients in whom seizures were consistent with the International League Against Epilepsy SE diagnostic criteria (continuous clinical and/or electrographic seizure activity that lasts longer than 5 min or recurrent seizure activity that does not return to baseline).

We excluded patients under 18 years of age and those with a single clinical seizure with a duration of less than 5 min.

If SE developed in the first 3 weeks after SARS-CoV-2 vaccination (patients without any underlying etiologic cause and without a history of epilepsy), it was a possible vaccine-associated SE.

During the pandemic period, 59 patients (mean age 51.7±2.7 years), 32 males (54.2%) and 27 females (45.7%), were hospitalized, monitored, and treated in our hospital. Data on age, gender, previous history of epilepsy, comorbidities, SE occurrence, SE etiology, brain computed tomography and magnetic resonance imaging findings, electroencephalography (EEG) findings, laboratory findings, SE treatments, and SE prognosis were evaluated.

For this study, ethics committee approval number: 2023-8/5, date: 10.05.2023 was obtained from the Bursa City Hospital Ethics Committee.

MAIN POINTS

- Status epilepticus is an important life-threatening neurological condition that may occur during the clinical course of Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) infection.
- In the SARS-CoV-2 pandemic, epilepsy patients could not go for regular controls because of fear of infection and various other reasons.
- Ischemic stroke, cerebral hemorrhage, intracranial tumors, SARS-CoV-2 and other systemic infections, and medication discontinuation were the common etiological factors of status epilepticus in our patients who were followed up during the SARS-CoV-2 pandemic.

Statistical Analysis

All statistical analyses were performed using MedCalc® (Mariakerke, Belgium) software. Comparisons between groups were performed using the chi-square test and independent two-sample t-test. $P<0.05$ was considered statistically significant.

RESULTS

A total of 59 patients (mean age 51.7±2.7 years), 32 males (54.2%) and 27 females (45.7%) were retrospectively included in the study.

Ischemic stroke was the most common underlying etiologic cause of SE in our study group of 16 patients (27.1%). It was found that there is intracranial tumor in 8 patients (13.5%), intracerebral hemorrhage in 4 patients (6.7%), medication discontinuation in 4 patients (6.7%), SARS-CoV-2 infection in 4 patients (6.7%), other infections in 3 patients (5.1%), possible vaccine-associated in 2 patients (3.3%), drug-resistant epilepsy in 4 patients (6.7%), autoimmune encephalitis in 1 patient (1.6%), neurodegenerative disease in 1 patient (1.6%), and no identified cause in 8 patients (13.5%) (Table 1). The most common factors triggering the onset of SE were epilepsy after stroke, hemorrhage and intracranial tumours, medication discontinuation, epilepsy secondary to Coronavirus disease-2019 (COVID-19) infection, and other systemic infections. The underlying causes of SE in our patients are listed in Table 1.

Considering the drugs used for treating SE; 18 patients (30%) received levetiracetam (LEV), 8 patients (13.5%) received LEV + valproic acid, and 6 patients (10.1%) received LEV + phenytoin infusion. In 27 patients (45.7%), other anti-seizure drug combinations were used. Additionally, there were 28 patients (47%) who needed general anesthetics such as midazolam, ketamine, thiopental, and propofol. Thirty-one patients (53%) did not receive general anesthetics. It was seen that only 15 (25%) of the patients could undergo EEG and the remaining 44 patients could not undergo EEG due to pandemic conditions. Considering the EEG findings; 6 patients had generalized slow wave paroxysms, 1 patient had generalized epileptic abnormality, 2 patients had focal epileptic abnormality, 1 patient had focal epileptic abnormality with secondary generalization, and 5 patients had normal EEG findings. EEG was performed in all patients after the seizures ended (Table 2). When the mortality rates were evaluated, 10 of the 59 patients were lost (16.9%). The mortality period ranged between 5 and 137 days.

Table 1. Main underlying causes in SE cases

	Number of cases	Percentage (%)
Acute/remote stroke	16	27.1%
Brain metastasis	8	13.5%
Intracranial hemorrhage	4	6.7%
Epilepsy inadequate medication	4	6.7%
COVID-19 pneumonia	4	6.7%
Drug resistant epilepsy	4	6.7%
After vaccination	2	3.3%
Other infections	3	5.0%
Other causes	6	10.2%
Unknown	8	13.5%

SE: Status epilepticus, COVID-19: Coronavirus disease-2019

Table 2. Demographic and clinical data of patients

Gender	Male	32	54.2%
	Female	27	45.7%
Age	Arithmetic mean	51.7±2.7	
	Median	54	
History of epilepsy	Yes	33	55.9%
	No	26	44.0%
Comorbidity	Yes	50	84.7%
	No	9	15.3%
Intubated	Yes	27	45.7%
	No	32	54.3%
Relation with vaccination	Yes	2	3.3%
	No	57	96.6%
Exitus	Yes	10	16.9%
	No	49	83.1%
EEG	Yes	15 (25.4%)	Normal 5
			Abnormal 10
	No	44 (74.6%)	

EEG: Electroencephalography

DISCUSSION

Several studies have been conducted to investigate the situation in epilepsy patients during the SARS-CoV-2 pandemic. In these studies, the effects of the pandemic on epilepsy were evaluated.[11-15] There are limited studies investigating SE in patients with epilepsy during the pandemic period.[13-16] To our knowledge, there is no study on SE during the pandemic period in Turkey. It has been reported that there was an increase in seizure frequency with an increase in fatigue, irritability, and anxiety in patients with epilepsy during the SARS-CoV-2 period.[9] Another study showed that the course of epilepsy was generally stable in pediatric patients during the pandemic period. It has been emphasized that sleep irregularities are also more frequent in patients with worsening seizures.[11]

In a study by Emami et al.[9], newly developing seizure cases without a history of epilepsy were reported in critically ill patients with SARS-CoV-2. The reasons for this were hypoxia, metabolic disorders, organ failure, and neuroinvasion of the virus. In one survey study, it was observed that approximately 5% of patients with epilepsy decreased the doses of anti-seizure medications or discontinued the medication during the pandemic period due to lack of access to anti-seizure medications and difficulty in communication with their physicians.[12] In this study, 55.9% of our patients had a previous history of epilepsy. In 6.7% of our patients, we thought that SE developed because of inadequate drug intake due to pandemic conditions. SE due to intracranial mass was observed in 13.5% of our patients. In a study by Arik et al.[17], it was stated that SE due to intracranial tumor was observed in 7% of all SE cases before the pandemic period. The rate of SE due to intracranial tumors was higher in our study. This was thought to be due to patients' SARS-CoV-2 fear of going to the hospital. Furthermore, an increase in cerebral edema as a result of decreased access to treatment in patients with cerebral masses may be another reason for the development of SE.

Status epilepticus is a neurologic condition that may occur during the clinical course of SARS-CoV-2 infection. The exact mechanism of the relationship between SE and SARS-CoV-2 is not known, but it may be related to the systemic inflammatory response due to cytokine release.[13] SARS-CoV-2 pneumonia was present in 6.7% and other infectious conditions in 5.0% of the patients with SE in our study. It is thought that the systemic inflammatory response secondary to infection may have triggered epileptic attacks.[9,13] New-onset RSE (NORSE) has been reported as a SARS-CoV-2-related condition. It was observed as the most common type of SE in this patient population, and a positive correlation was found between the advanced age of the patients and SE severity score.[13] Kheradmand et al.[14] reported that severe hyponatremia, ischemic stroke, and meningoencephalitis were causes of seizures in 3 of 5 cases of SARS-CoV-2-related SE. No specific cause of epileptic seizures was identified in the two cases. Three of the five patients died because of advanced age and accompanying comorbidities. The cause could not be determined in 13.5% of our patients with SE in our study. Post-stroke SE was found at a rate of 27.1%, which is higher than the prevalence of post-stroke SE found in previous studies during the pandemic period.[18]

In a multicenter retrospective study conducted by Kohle et al.[19] in Germany, cases with SE before and during the pandemic were compared. It has been suggested that SARS-CoV-2 is not directly related to SE. There are differences in the causes of SE, and it has been reported that cryptogenic and anoxic-induced SE are more common. Likewise, we found that ischemic stroke, brain metastasis, and cryptogenic SE were more frequent in our study. Several hypotheses have been proposed to explain the possible underlying causes of SARS-CoV-2-related SE. One controversial hypothesis is that SARS-CoV-2 is capable of direct invasion into the central nervous system (CNS). Because of its neuroinvasive and neurotropic properties, the virus may lead to SE.[20] In addition, it may enter the nervous system directly through neural pathways or indirectly through the ACE2 receptor. The entry of proinflammatory cytokines into the nervous system or the production of these cytokines by microglia and astrocytes may lead to disruption of the blood-brain barrier, increase in glutamate and aspartate, decrease in GABA levels, and consequently epileptic seizures.[21]

In epidemiologic studies, it was observed that the incidence of SE during the pandemic was consistent with the overall SE incidence recorded in the previous 5 years. Our results were also similar. However, difficulties in the use of EEG and other examinations may have led to a significantly lower recognition of NKSE.[22]

In patients older than 60 years with SARS-CoV-2, new-onset neurological symptoms, seizures, CNS infections, and stroke are frequently reported.[23] There are increasing data on the relationship between ischemic stroke and SARS-CoV-2. The association between SARS-CoV-2 and ischemic stroke is thought to be most prominent in cases involving anterior circulation and male gender. In these cases, cardioembolic strokes were observed more frequently.[24] Ischemic stroke was found in approximately 0.5-1.3% of hospitalized SARS-CoV-2 patients. It was suggested that

there was a 3- to 4-fold relative risk increase in ischemic stroke in hospitalized SARS-CoV-2 patients. Increased D-dimer levels, history of ischemic stroke, presence of diabetes mellitus, and additional vascular risk factors have shown that the likelihood of stroke increases in patients with SARS-CoV-2.[25] there is a risk of epileptic seizures and SE development after stroke.[26] In one study that investigated the etiology of SE, stroke-related SE was found to be 14.5%.[27] We found that 27.1% of patients developed SE after stroke in our study, and this rate was quite high. Although it is thought that the increased risk of stroke during the SARS-CoV-2 period may play a role in this, the data are not sufficient.

Although all vaccines, including the SARS-CoV-2 vaccine, are safe in patients with epilepsy, seizures can sometimes occur after vaccination. Although SARS-CoV-2 vaccines are recommended to patients with epilepsy considering the risk-benefit ratio. In a study, it was found that there may be an increase in seizures after vaccination in patients with frequent seizures.[6] A few cases of SE after SARS-CoV-2 vaccination in people without epilepsy have been reported.[8,17] Encephalopathy and NKSE were reported in two cases after the SARS-CoV-2 vaccine.[17] Post-SARS-CoV-2 vaccine SE was observed in approximately 3.3% (2 cases) of our patients with SE during the pandemic period in our study, and its relation to the vaccine is not clear.

Study Limitations

The limitations of our study is that EEG recordings could not be performed or performed with a delay during the pandemic period. therefore, we may have missed non-convulsive conditions. In addition, the course of COVID-19-related SE could be better understood using a multicenter status epilepticus study.

CONCLUSION

As a result, ischemic stroke, cerebral hemorrhage, intracranial tumors, SARS-CoV-2 and other systemic infections and medication discontinuation were found to be at the forefront of the etiology of SE in our patients who were followed up during the pandemic. It has been suggested that the development of SE, seen mainly in post-stroke patients during the pandemic, may be attributed to the multisystemic involvement of SARS-CoV-2 infection.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of the Bursa City Hospital under the ethical approval number 2023-8/5, date: 10.05.2023.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: S.G., Ö.K., Concept: S.G., Ö.K., A.Ö., Design: S.G., Ö.K., A.Ö., Data Collection or Processing: S.G., Ö.K., C.H., M.A.A., G.M., G.Ö., Analysis or Interpretation: S.G., Ö.K., C.H., M.A.A., G.M., G.Ö., Literature Search: S.G., Ö.K., C.H., M.A.A., G.M., G.Ö., Writing: S.G., Ö.K., C.H., M.A.A., G.M., G.Ö.

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From Shadows to Diagnosis: Unraveling L-2 Hydroxyglutaric Aciduria in Adulthood

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Abstract

L-2-hydroxyglutaric aciduria (L2HGA) is a rare autosomal recessive metabolic disorder that causes central nervous system dysfunction. We present the case of a 33-year-old woman with macrocephaly, developmental delay, cerebellar ataxia, pyramidal signs, and seizures. Despite typical clinical features and suggestive magnetic resonance imaging findings, the diagnosis was not made. Genetic analysis revealed a homozygous missense mutation in the L-2-hydroxyglutarate dehydrogenase (*L2HGDH*) gene. Treatment with riboflavin and L-carnitine was initiated. L2HGA should be considered in the differential diagnosis, even in adults, when suggestive imaging findings are present. Early diagnosis is crucial for better outcomes.

Keywords: Epilepsy, L2-hydroxyglutaric aciduria, cranial MRI, genetic mutation

INTRODUCTION

L-2-hydroxyglutaric aciduria (L2HGA) is an autosomal recessive inborn metabolic error. It occurs because of a deficiency in the L-2-hydroxyglutarate dehydrogenase (L2HGDH) enzyme.[1] It is a type of cerebral organic aciduria that causes central nervous system dysfunction. Psychomotor developmental delay, intellectual disability, cerebellar dysfunction, pyramidal-extrapyramidal signs, macrocephaly, and seizures are the hallmarks of the disease.[2] The age of symptom onset may be heterogeneous. Like many other inborn errors of metabolism, milder or juvenile forms can be diagnosed in late adulthood.[3] Although many patients are diagnosed in infancy or childhood, diagnosis in some cases may be considerably delayed because of vague symptoms. Here we present a 33-year-old female patient with macrocephaly, developmental delay, cerebellar ataxia, pyramidal signs, and seizures. Despite typical clinical features and suggestive magnetic resonance imaging (MRI) findings, the diagnosis was overlooked.

CASE PRESENTATION

A 33-year-old right-handed female patient, born to a consanguineous marriage, was admitted to our clinic for seizure control. Her medical history revealed that her generalized onset tonic-clonic seizures had started at the age of 3 years and ceased after anti-seizure medication (ASM) treatment. Two years later, her ASM was discontinued, and she was seizure-free until 22 years of age when generalized onset tonic-clonic seizures reappeared. She was put on 3000 mg/day levetiracetam (LEV). Phenytoin and topiramate were also prescribed, but she could not continue because of side effects such as dizziness and somnolence. Her parents noticed that infections precipitated her seizures. Otherwise, she was seizure-free.

Personal history revealed macrocephaly and delayed motor and language skills, in addition to seizures. The patient underwent surgery for congenital cataract and congenital dysplasia of the hip. She was diagnosed with cerebral palsy and treated symptomatically. Family history was unremarkable. Her physical examination revealed dysmorphic features such as a long face, deeply located eyes, up-slanting palpebral fissures, thin lips, and macrocephaly. The metacarpophalangeal and interphalangeal joints were rigid. On neurological examination, the

patient had cognitive impairment, scarce verbal output, dysarthria, and extremity ataxia. She also had mild motor deficit and spasticity and could not walk independently.

Her routine blood tests were normal. There was mild diffuse background slowing in the EEG. Brain MRI demonstrated symmetric T2 and FLAIR high signal intensity and T1 low signal intensity of the subcortical and deep white matter (U-fibers) with relative sparing of the periventricular regions and brain atrophy. White matter involvement had a centripetal pattern, starting in the U-fibers and extending to the deeper white matter (see Figure 1 for detailed description).

Basic metabolic scans were ordered because of highly suggestive cranial MRI findings. Urine organic acid analysis by gas chromatography-mass spectrometry showed a 5-fold increase in 2-hydroxy glutaric acid (2HGA) excretion. We performed *L2HGDH* gene analysis, which revealed a homozygous missense c.164G>A (p. Gly55Asp) mutation in exon 2 of the *L2HGDH* (NM_024884.3) gene. Riboflavin and levo-carnitin were added to her ASM and supportive therapy.

DISCUSSION

L2HGA is a rare genetic metabolic disorder that mainly affects the central nervous system. The first case was reported by Duran et al.[4] in 1980. Mutations in the L2HGDH enzyme, which is involved in the oxidation of L-2-hydoxyglutarate (L2HG) to alpha-2-ketoglutarate, cause the disease. In 2004, Topçu et al.[5] mapped the disorder to chromosome 14q22.1 by homozygosity mapping in Turkish families. This gene is primarily expressed in the central nervous system. Mutations in the *L2HGDH* gene result in the accumulation of L-2HGA in the cerebrospinal fluid (CSF), plasma, and urine.[6] This leads to white matter toxicity via myelin vacuolation.

Macrocephaly must alert clinicians to the possibility of cerebral organic aciduria, especially in epilepsy clinics, as status epilepticus might be the first symptom of the disease.[7] Seizures are usually well controlled with ASMs. EEG may show irregular background activity and slowing, focal or generalized spikes, and slow wave discharges.[2] Radiological hallmarks of the disease are predominant subcortical white matter abnormalities and involvement of dentate nuclei and basal ganglia. These findings become symmetrical, and atrophy ensues with increasing disease duration.[8] Subependymal pseudocysts, delayed cerebral maturation, callosal agenesis, and enlargement of the lateral ventricles are other clues suggesting L2HGA.[9] It can be diagnosed with increased levels of 2-HGA in blood, CSF, or urine via gas chromatography-mass spectrometry or genetic analysis. In Turkey, the most common variants in the *L2HGDH* gene are c.164G>A (p. Gly55Asp) and c.1115delT (p. Met372fs). The c.164G>A mutation was previously reported only in Turkish patients.[10] Thus far, there has been no definitive treatment. Some patients may benefit from Riboflavin and L-carnitine (even in adulthood), physical therapy, and rehabilitation.[11]

MAIN POINTS

- Epileptic seizures may be the first sign of metabolic disorders.
- L-2-hydroxyglutaric aciduria is a rare genetic disorder affecting the central nervous system that presents with intellectual disability, developmental delay, and seizures.
- Here, we present a case of a patient diagnosed with L-2-hydroxyglutaric aciduria at the age of 33 years and emphasize the need for heightened awareness in adults.

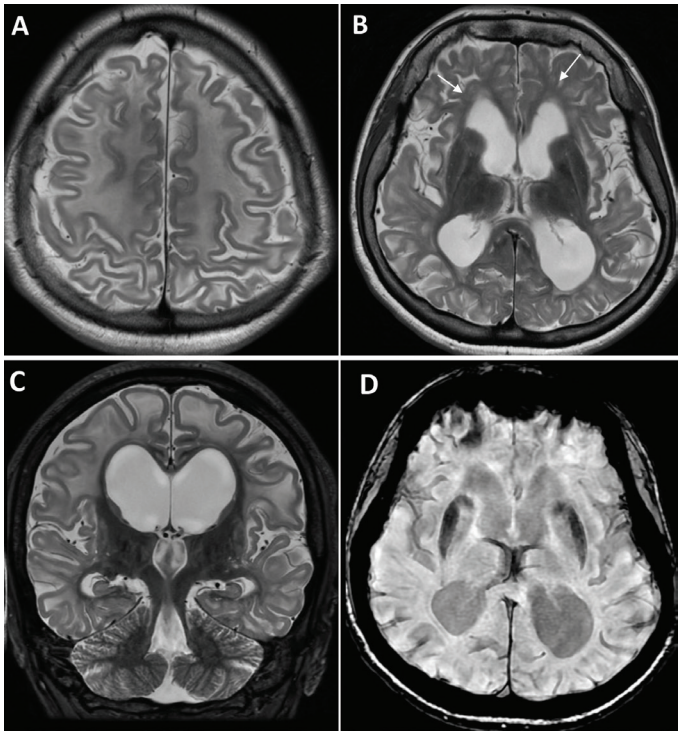

Figure 1. A-D) Brain magnetic resonance ımaging. Axial (A, B, D) and coronal (C) sections. T2-weighted images show high signal intensity of the subcortical white matter (U-fibers) (A), with relative sparing of the periventricular white matter (B, C) and hypointense and atrophic basal ganglia. Susceptibility-weighted image (D) reveals susceptibility effects in the caudate and putamen

L-2HGA has a chronic progressive highly variable clinical course and lacks acute exacerbations, unlike other organic acidurias.[11] Therefore, diagnosis is often delayed. In milder forms, subtle clinical findings may not be noticed until adulthood. Several publications have reported delayed diagnosis in adult patients in their late 40s and 50s.[3] Cases diagnosed in the third and fourth decades of their lives were also reported in the studies of Zübarioğlu et al.[12] from Turkey.

CONCLUSION

In conclusion, patients with epilepsy, developmental delay, and cognitive impairment should be examined carefully, and cranial MRI should be performed without delay. If the imaging findings are suggestive, inborn errors of metabolism should be considered in the differential diagnosis, even in adult patients.

Ethics

Informed Consent: The consent form was filled out by the parent of the patient.

Authorship Contributions

Surgical and Medical Practices: E.D.Ö., J.N., H.T.A., A.D., R.G., N.D., Concept: N.D., Design: N.D., Data Collection or Processing: E.D.Ö., J.N., D.Y.Y., A.D.,

Analysis or Interpretation: E.D.Ö., H.T.A., D.Y.Y., A.D., R.G., N.D., Literature Search: E.D.Ö., H.T.A., N.D., Writing: E.D.Ö., H.T.A., D.Y.Y., N.D.

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