Kerbala Journal of Pharmaceutical Sciences

ISSN: 2221-7207(Print) / **ISSN**: 3006-7189 (Online)

Assessment of The Level of Protein S100B as a Potential Clinical Biomarker for Epilepsy and Correlation with HBA1C Level

Athraa Al-Jaffer[1] *, Ghusoon Kaem[1] , Haider Shafi[1 2]

[1] Department of Clinical Laboratories, College of Applied Medical Science, University of Kerbala, Karbala, Iraq
[3] Al-Kafeel Hospital, Karbala, Iraq

***Corresponding Author**
Athraa Al-jaffer:athoora.hh@gmail.com

Received: 01/05/2025
Accepted: 12/06/2025
Published: 30/06/2025

Keywords: *protein-S100B; HBA1C; epilepsy*

DOI: 10.62472/kjps.v16.i26.230-239

Abstract

Background

Epilepsy is a chronic brain disorder marked by a tendency for recurrent seizures and associated neurobiological, psychological, and social effects. Seizures are sudden, stereotyped episodes reflecting abnormal brain activity. Epilepsy can be primary (genetic causes affecting neurotransmission and ion channels) or secondary (due to brain injuries like trauma, stroke, infections, or tumors). The protein S100B, mainly produced by astrocytes, is elevated in the serum or CSF of epilepsy patients. HbA1c, a key marker for glucose control, is also relevant, as blood sugar fluctuations can trigger seizures. This study aimed to assess serum S100B and HbA1c levels in epilepsy patients and explore their correlation.

Methods

The study enrolled 90 subjects grouped as primary epileptic patients which have the disease due to genetic reasons, secondary epileptic patients which have the disease due to acquired reasons such as fall in blood sugar level and an age-gender matched control group (n=30). The serum samples were collected at the six-month interval and were analyzed for protein S100B using ELISA.

Results

The results showed a significantly decreased levels of HBA1C in patients with secondary epilepsy in comparison with control and primary epilepsy. Suggest that blood sugar levels should be taken into consideration when developing a treatment plan for a patient with epilepsy. Also, there were statistically significant differences in the level of protein S100B biomarker between the control group and patients with primary and secondary epilepsy as well as the comparation between patient groups primary and secondary are statistically significant with higher protein S100B level in the secondary group. S100B also shows a negative correlation with HBA1C levels which means that as S100B increases, the HBA1C levels decrease.

Conclusion

Serum protein S100B levels are a useful tool to assess and diagnose patients with epilepsy as well as blood HBA1C levels are useful in diagnosing and making treatment plan for epileptic patients

تقييم مستوى البروتين S100B كمؤشر حيوي سريري محتمل للصرع وارتباطه بمستوى الهيموغلوبين السكري HBA1C

عذراء الجعفر، غصون غانم، وحيدر شافي

الخلاصة

المقدمة

الصرع مرض دماغي، يتميز بميل مستمر للإصابة بنوبات، وتُعدّ التبعات العصبية الحيوية والمعرفية والنفسية والاجتماعية لتكرار النوبات من السمات المميزة للصرع. تُعرّف النوبات الانتيابية المتكررة، أو نوبات الصرع، باضطرابات سلوكية نمطية تُشير إلى الآليات الدماغية الكامنة وراء المرض. هناك العديد من الاضطرابات السريرية التي تُدرج في التشخيص التفريقي للصرع، وتتميز بتغيرات وجيزة في الوعي و/أو السلوك. يُصنف الصرع حسب سبب المرض إلى صرع أولي قد يحدث نتيجة لتغيرات جينية. يمكن أن تؤثر هذه الطفرات على إطلاق النواقل العصبية، والقنوات الأيونية، والمرونة المشبكية، وآليات بيولوجية أخرى. أما الصرع المكتسب (الصرع الثانوي) فيشير إلى اضطرابات النوبات التي تتطور نتيجة لإصابات أو أمراض دماغية محددة، مثل إصابات الدماغ الرضحية، والسكتة الدماغية، والالتهابات، والأورام.

Protein S100Bهو بروتين رابط للكالسيوم، يُعبَّر عنه بشكل أساسي في الخلايا النجمية. يمتلك مرضى الصرع مستويات أعلى من التعبير عن S100B في مصل الدم أو سائل السائل الدماغي الشوكي مقارنةً بالأشخاص الأصحاء. يُعد الهيموغلوبين السكري (HbA1c) أحد المؤشرات الحيوية المهمة لتقييم التحكم طويل الأمد في مستوى الجلوكوز لدى مرضى السكري. يساعد رصد HbA1c في تشخيص المرضى الذين يعانون من نوبات صرع، حيث يكون الارتفاع أو الانخفاض غير الطبيعي في سكر الدم أحد أسبابها. هدفت الدراسة إلى تقدير تركيز بروتين S100B في مصل دم مرضى الصرع، وتحديد مستويات HBA1C وارتباطها بمستويات.S100B

العينات وطرق العمل

شملت الدراسة 90 مريضًا، مُصنَّفين إلى مجموعتين: مرضى صرع أولي (لأسباب وراثية)، ومرضى صرع ثانوي (لأسباب مكتسبة مثل انخفاض مستوى سكر الدم)، ومجموعة ضابطة متطابقة من حيث العمر والجنس (عددهم 30). جُمعت عينات المصل بفاصل ستة أشهر، وحُللت للكشف عن بروتين S100B باستخدام تقنية.ELISA

النتائج

أظهرت النتائج انخفاضًا ملحوظًا في مستويات HBA1C لدى مرضى الصرع الثانوي مقارنةً بالمجموعة الضابطة والمجموعتين الأوليتين. تشير هذه النتائج إلى ضرورة أخذ مستويات سكر الدم في الاعتبار عند وضع خطة علاجية لمريض الصرع. كما وُجدت فروق ذات دلالة إحصائية في مستوى المؤشر الحيوي لبروتين S100B بين المجموعة الضابطة ومرضى الصرع الأولي والثانوي. كما أن المقارنة بين مجموعتي المرضى الأوليين والثانويين كانت ذات دلالة إحصائية مع ارتفاع مستوى بروتين S100B في المجموعة الثانوية. كما أظهرت الدراسة ارتباطًا سلبيًا مع مستوياتHBA1C ، مما يعني أنه مع زيادةS100B ، تنخفض مستويات.HBA1C

1. Introduction

The epilepsies are chronic neurological disorders in which clusters of nerve cells, or neurons, in the brain sometimes signal abnormally and cause seizures. Many neurons fire (signal) simultaneously during a seizure, up to 500 times per second, which is far quicker than usual. *(National Institute of Neurological Disorders and Stroke. (2022).* In addition to causing involuntary actions, sensations, emotions, and behaviors, this simultaneous spike in excessive electrical activity may also result in a temporary loss of consciousness (Shorvon et al., 2011). Epilepsy can have many different causes, including acquired (secondary epilepsy) and genetic factors (primary epilepsy). Genetic mutations are a significant contributor. For example, in severe childhood epilepsy, mutations in the CACNA1E gene cause calcium channels in neurons to be disrupted, which results in excessive electrical activity and seizures (Macdonald et al., 2010; Staněk et al., 2018). Some adult epilepsies, including temporal lobe epilepsy, are also influenced by somatic mutations that develop after conception. Certain genetic pathways, such as the RAS/MAPK pathway, which is also linked to cancer, may be impacted by these mutations (Beltrán-Corbellini et al., 2022; Montanaro et al., 2023). Additionally, research has identified the TMEM184B gene as a possible factor in epilepsy, as its absence or alteration can cause neurons to fire excessively, affecting normal neural communication (Beltrán-Corbellini et al., 2022; Gesche & Beier, 2022; McCormack et al., 2020). Numerous conditions that also impact the structure and function of the brain can result in epilepsy. Because they can cause aberrant electrical activity in the brain, neurological disorders like stroke, traumatic brain traumas, and brain tumors are important causes of epilepsy. Seizures can also be caused by illnesses that inflame the brain or surrounding tissues, such as encephalitis or meningitis. Another component may be autoimmune disorders, in which the brain is mistakenly attacked by the immune system, resulting in epileptic episodes. Additionally, epilepsy has been connected to vascular abnormalities and degenerative diseases like Alzheimer's disease especially in older people. These secondary causes frequently draw attention to epilepsy as a sign of more serious underlying problems (Kenney & Mann, 2013; O'Neill et al., 2020). A calcium-binding protein called protein S100B is mostly expressed by astrocytes in the central nervous system (CNS). Its participation in intracellular and extracellular regulatory functions makes it an important biomarker for a number of neurological disorders. Increased S100B serum levels have been used in clinical settings to gauge the degree of traumatic brain injury (TBI) and are suggestive of astrocytic damage. S100B has been used as a screening tool in the treatment of TBI patients, which has been noteworthy since it helps with patient outcome prediction and monitoring (Mondello et al., 2021; Zimmer et al., 2023). S100B has been studied in relation to epileptic seizures in addition to TBI. According to research, S100B may contribute to the pathophysiology of epilepsy by playing a part in the neuroinflammatory processes linked to the condition. S100B may be a biomarker for epileptic activity because elevated levels of the protein have been seen in seizure patients (Reddy & Volkmer, 2017; van Vliet et al., 2017; Zimmer et al., 2023). One indicator of long-term blood glucose levels, hemoglobin A1c (HbA1c), has been linked to epilepsy treatment and prognosis. Increased seizure intensity and recurrence have been linked to elevated HbA1c levels, which are a sign of inadequate glycemic control. In research, individuals with hyperglycemia diabetes who had their first seizure had significantly higher HbA1c levels if they had another seizure (11.8% vs. 8.6%, $p<0.05$) than those who did not. Additionally, patients who had HbA1c levels higher than 9% were more likely to experience seizure clustering and recurrence (Bellon et al., 2017; He et al., 2023; Phoswa & Mokgalaboni, 2023). Seizures can also occur in individuals with low hemoglobin A1c (HbA1c)

levels, primarily due to hypoglycemia. Hypoglycemia, defined as blood glucose levels falling below normal, can lead to neurological symptoms, including seizures. While seizures are relatively uncommon, they are more likely to happend when glucose levels fall significantly. A study found that generalized tonic-clonic seizures occurred when serum glucose levels fell below 2.0 mM, and focal seizures were noted at glucose levels as high as 3.3 mM. (He et al., 2023; Phoswa & Mokgalaboni, 2023; Reddy & Volkmer, 2017; Zimmer et al., 2023). Additionally, lower HbA1c levels have been linked to a higher risk of severe hypoglycemia and hypoglycemic coma, which includes seizures, in young patients with type 1 diabetes. But with time, patients with lower HbA1c levels had a lower relative risk of severe hypoglycemia, maybe due to improved management strategies. Furthermore, HbA1c has been investigated as a possible biomarker for tracking systemic ketosis and diet adherence in individuals with drug-resistant epilepsy on ketogenic diets. Higher blood ketone levels were linked to lower HbA1c levels, indicating its potential use in the management of such dietary treatments (Gulati & Panda, 2019; Teng et al., 2022). This study aims to Comparison between primary and secondary types of epilepsy by measure the level of PROTEIN S100 B biomarker and its role in patients with epilepsy. Measurement level of HBA1C and its effect in patients with epilepsy. Measure progression after the condition is established and reduce the cost of clinical trials of potential ant epileptogenic interventions by enriching the trial population with patients at high risk for developing epilepsy.

2. Patients & Methods

The study enrolled 90 subjects grouped as primary epileptic patients which have the disease due to genetic reasons, secondary epileptic patients which have the disease due to acquired reasons such as fall in HBA1C level and an age-gender matched control group (n=30). The serum samples were collected at the six-month interval and were analyzed for protein S100B using ELISA.

2.1. Detection of HBA1C

2.1.1. Principles

When the sample is added to the sample port on the test card, HbA1c and Hb in the sample combines with mouse anti-human HbA1c and Hb monoclonal antibodies which are coupled to fluorescent particles to form fluorescent particles - antibody - antigen complexes. This immune complex reaches the test area (T) along the nitrocellulose membrane and binds with the pre-coated mouse anti-human HbA1c monoclonal antibody, The amount of HbA1c in the sample is directly correlated with its fluorescence intensity. A quality control line is created when the remaining fluorescent antibody particle reaches the quality control area (C) and combines with the pre-coated goat anti-human Hb monoclonal antibody. The ratio of HbA1c to Hb was calculated by the fluorescence signal intensity. The test area (T) will not appear fluorescence, if the sample does not contain HbA1c.

2.1.2. Procedure

Bring all reagents to room temperature (18-25℃) before use.

1. Startup: Click “STD Mode” in the main menu to enter the measurement interface, click “Item” to select the desired test item and click “Type” to select the sample type.
2. Click “Lot No.” to enter the card swiping interface, put mag card of the corresponding item into the magnetic induction zone and when hearing a “di” sound this mean that the mag card is swiped successfully. Make sure the mag card and the test card are from the same batch.

3. Sampling: Add 10μL of whole blood into a centrifuge tube with 1000μL of the sample diluent, mix for 1 minute. Take 100μL diluted sample, drop vertically to the sample port directly on the test card and start timing.
4. Insert it into the analyzer's test slot (the sample port ends toward the inside). Click "Measure", the instrument will detect and print out the results automatically after 15 minutes (If using "Fast Mode", keep it for 15 minutes and quickly insert into the analyzer's test slot)

2.2. Determination of Protein S100-B

2.2.1. Principle

The kit is an Enzyme-Linked Immunosorbent Assay (ELISA). The plate has been pre-coated with Human S100B antibody. S100B present in the sample is added and binds to antibodies coated on the wells. And then biotinylated Human S100B Antibody is added and binds to S100B in the sample. Then Streptavidin HRP is added and binds to the Biotinylated S100B antibody. After incubation unbound Streptavidin-HRP is washed away during a washing step. Then added substrate solution, and color develops in proportion to the amount of Human S100B. The reaction is terminated by addition of acidic stop solution and absorbance is measured at 450 nm.

2.2.2. Calculation of Results

Construct a standard curve by plotting the average OD for each standard on the vertical (Y) axis against the concentration on the horizontal (X) axis and draw a best fit curve through the points on the graph. These calculations can be best performed with computer-based curve-fitting software and the best fit line can be determined by regression analysis.

3. Results and Discussion

3.1. Demographic Characteristics of Study Groups

The current study was conducted on (90) people suffering from epilepsy and healthy people. This study takes 30 samples from patients suffering from primary epilepsy (group1), 30 samples from secondary epilepsy (group2), and 30 samples as a control, Table1.

Table1: Demographic Characteristics of Study Groups

Category	Groups	N
Patients	Group-1: primary epilepsy	30
	Group-2: secondary epilepsy	30
Healthy	Control	30

3.2. Protein S100B in Epileptic Patients and Control

There were statistically significant differences in the level of protein S100B biomarker between the control group and other groups (group 1 and 2 of patients); (43.161 ±9.267 VS 50.537 ±2.711, 64.206 ±9.534), P-value was 0.00032, Table2.

Table2: Comparison of the Research Parameter of All Patients Compared with Control Group

Parameters	Control		Patient primary		Patient secondary		P value
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	
Protein S100B	43.161	9.267	50.537	2.711	64.206	9.534	0.00032

In Table3 and Fig.1 the comparation between patient groups primary and secondary are statistically significant (50.537 ±2.711VS 64.206 ±9.534), the P-value was 0.00005, indicating a highly significant difference between the groups with higher protein S100B level in the secondary group.

Table3: Comparison of the Research Parameters Between Patients in Primary Compared with Secondary Group

Parameters	Patient primary		Patient secondary		P value
	Mean	Std. Deviation	Mean	Std. Deviation	
Protein S100B	50.537	2.711	64.206	9.534	0.00005

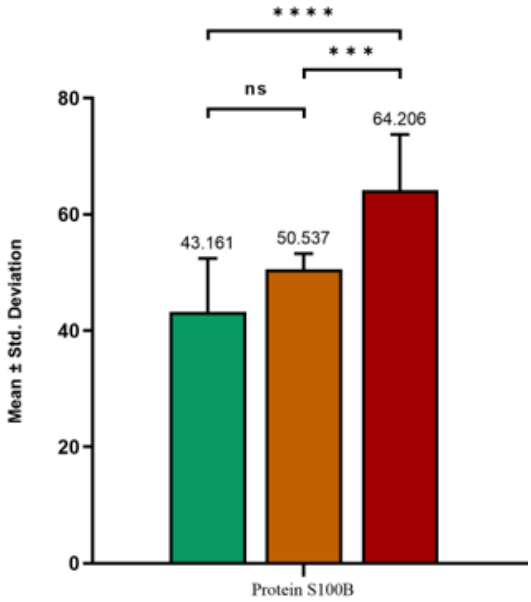

Figure1: Comparison of Serum Protein S100B Levels (Mean ± Standard Deviation) Among Control Subjects, Patients with Primary Epilepsy, And Patients with Secondary Epilepsy
Statistical analysis shows a significant increase in Protein S100B levels in secondary epilepsy patients compared to both control and primary epilepsy groups (***p < 0.001, ****p < 0.0001), while the difference between control and primary groups was not statistically significant (ns).

Beyond just acting as a marker, S100B plays an active involvement in the pathophysiology of epilepsy. S100B promotes neuronal survival and function at physiological concentrations, but when levels are high, it can cause neurotoxicity by triggering stress-induced enzymes and pro-inflammatory cytokines, which can lead to neuronal apoptosis and worsen epileptic disorders. Additionally, the development of neuroinflammatory responses has been linked to S100B's interaction with the receptor for advanced glycation end products (RAGE), underscoring its dual function of neuroprotection and neurodegeneration contingent on its concentration (Liang et al., 2019; Seçen et al., 2023). The table's results are consistent with findings from other research studies. Patients with epilepsy exhibited significantly higher serum S100B levels than healthy controls, according to a systematic review and meta-analysis of

18 studies with 1,057 individuals. The pooled effect size was Hedges g = 1.568 (95% CI = 1.431–1.706, P < 0.001). This lends credence to the idea that elevated S100B levels are linked to epilepsy. Additionally, case-control research on mesial temporal lobe epilepsy (MTLE) revealed that patients had significantly higher plasma S100B levels than healthy controls (P = 0.018), which may indicate that raised S100B levels are a biomarker for MTLE." Furthermore, serum S100B levels were significantly higher in patients with epileptic seizures (SMD = 0.80; 95% CI 0.18 to 1.42), according to a meta-analysis looking at blood-based brain biomarkers in these patients. This suggests that S100B levels are higher in epileptic patients than in healthy controls (Chen et al., 2015; Keshavarz & Amiri, 2019; Lipatova et al., 2018; Seçen et al., 2023; Xu et al., 2012).

3.3. HBA1C In Primary and Secondary Epilepsy:

The result showed the difference of the HBA1C between the patients of primary and secondary epilepsy and control group (6.877 ±0.564 mg/dl, 5.320 ± 1.851 mg/dl VS 6.613 ±0.580 mg/dl) was significant. The P-value of 0.00603 shows a significant difference in HBA1C levels, especially between the primary and secondary groups, Table4.

Table4: Comparison of the HBA1C Level of All Patients Compared with Control Group

Parameters	Control		Patient primary		Patient secondary		P. value
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	
HBA1C	6.613	0.580	6.877	0.564	5.320	1.851	0.00603

The comparison between primary and secondary patient groups (table 4-5) showed that the primary group had (6.877 ±0.564 mg/dl) while the secondary group had a lower mean of (5.320 ± 1.851 mg/dl), this difference was statistically significant, with a P-value of 0.00300.

Table5: Comparison of the HBA1C Level Between Patients in Primary Compared with Secondary Group

Parameters	Patient primary		Patient secondary		P value
	Mean	**Std. Deviation**	**Mean**	**Std. Deviation**	
HBA1C	6.877	0.564	5.320	1.851	0.00300

These findings agreed with a study that was published in the Journal of Epilepsy in 2017. The study found that patients who had poor glycemic control (HbA1c > 9%) were much more likely to experience generalized seizures (46.7% vs. 7.7%, p < 0.05). The importance of your findings is supported by the suggestion that raised HbA1c levels are linked to an increased risk of seizures (Mondello et al., 2021). Furthermore, an investigation that was published in the Seizure: European Journal of Epilepsy (2010) discovered a correlation between a significant increase in HbA1c levels and occipital lobe seizures. This lends more credence to the link between high HbA1c levels and seizures (Zimmer et al., 2023).

3.4. Correlation Coefficient Among Parameters According to Research Parameters

The correlation analysis presented in Table6 explains the relationships between various biological and clinical parameters in epilepsy patients. A notable finding is the negative correlation between S100B and HBA1C levels (r = -0.302, p = 0.019), suggesting a potential link between S100B and altered metabolic or mineral states in epilepsy patients.

Table6: Correlation Coefficient Among Parameters According to Research Parameters

Parameters	Value	Protein S100B	HBA1C
Protein S100B	R. value	1.000	-.302*
	P. value		.019
HBA1C	R. value		1.000
	P. value		

A study published in Diabetes Research and Clinical Practice investigated the relationship between glycemic control and S100B levels in diabetic patients. Higher S100B levels were linked to better glycemic control, according to the study, which also identified a negative correlation between S100B levels and HbA1c levels. This study indicates a possible association between S100B and metabolic parameters that may be pertinent to individuals with epilepsy, even though it was carried out on diabetic patients (Celikbilek et al., 2014; Katsanou et al., 2018; Ruchkin et al., 2022).

4. Conclusion

significantly decreased levels of HBA1C in patients with secondary epilepsy in comparison with control and primary epilepsy. Suggest that blood sugar levels should be taken into consideration when developing a treatment plan for a patient with epilepsy. Also, there were statistically significant differences in the level of protein S100B biomarker between the control group and patients with primary and secondary epilepsy as well as the comparation between patient groups primary and secondary are statistically significant with higher protein S100B level in the secondary group. S100B also shows a negative correlation with HBA1C levels which means that as S100B increases, the HBA1C levels decrease.

References

Bellon, M. L., Barton, C., McCaffrey, N., Parker, D., & Hutchinson, C. (2017). Seizure-related hospital admissions, readmissions and costs: Comparisons with asthma and diabetes in South Australia. *Seizure*, *50*. https://doi.org/10.1016/j.seizure.2017.06.005

Beltrán-Corbellini, Á., Aledo-Serrano, Á., Møller, R. S., Pérez-Palma, E., García-Morales, I., Toledano, R., & Gil-Nagel, A. (2022). Epilepsy Genetics and Precision Medicine in Adults: A New Landscape for Developmental and Epileptic Encephalopathies. In *Frontiers in Neurology* (Vol. 13). https://doi.org/10.3389/fneur.2022.777115

Celikbilek, A., Akyol, L., Sabah, S., Tanik, N., Adam, M., Celikbilek, M., Korkmaz, M., & Yilmaz, N. (2014). S100B as a glial cell marker in diabetic peripheral neuropathy. *Neuroscience Letters*, *558*. https://doi.org/10.1016/j.neulet.2013.10.067

Chen, W., Tan, Y., Ge, Y., Chen, Y., & Liu, X. (2015). The Effects of Levetiracetam on Cerebrospinal Fluid and Plasma NPY and GAL, and on the Components of Stress Response System, hs-CRP, and S100B Protein in Serum of Patients with Refractory Epilepsy. *Cell Biochemistry and Biophysics*, *73*(2). https://doi.org/10.1007/s12013-015-0683-8

Gesche, J., & Beier, C. P. (2022). Drug resistance in idiopathic generalized epilepsies: Evidence and concepts. In *Epilepsia* (Vol. 63, Issue 12). https://doi.org/10.1111/epi.17410

Gulati, S., & Panda, P. K. (2019). Evolution of Dietary Therapies in Treatment of Childhood Drug Resistant Epilepsy: an overview of nine studies including six randomized controlled trials accomplished over last twelve years in a tertiary care teaching hospital in North India (P5.6-052). *Neurology*, *92*(15_supplement). https://doi.org/10.1212/wnl.92.15_supplement.p5.6-052

He, Y., Huang, Z., Wei, C., & Chen, J. (2023). Case Report: Abruptio placentae and epileptic seizure after occurrence of perinatal hyperglycaemia in woman with gestational diabetes mellitus and hypertriglyceridemia-induced acute pancreatitis. *Frontiers in Endocrinology*, *14*. https://doi.org/10.3389/fendo.2023.1220957

Katsanou, P., Tentolouris, N., Perrea, D., Katsanos, S., Ntova, V., Antrian, V., Konstantopoulos, P., & Politis, A. (2018). S100B Levels in Patients with Type 2 Diabetes Mellitus and Co-Occurring Depressive Symptoms. *Depression Research and Treatment*, *2018*. https://doi.org/10.1155/2018/5304759

Kenney, M. K., & Mann, M. (2013). Assessing Systems of Care for US Children with Epilepsy/Seizure Disorder. *Epilepsy Research and Treatment*, *2013*. https://doi.org/10.1155/2013/825824

Keshavarz, M., & Amiri, A. (2019). The role of S100B and nitric oxide in the apoptotic action of pentylenetetrazole on astrocytes. *Physiology and Pharmacology (Iran)*, *23*(4).

Liang, K. G., Mu, R. Z., Liu, Y., Jiang, D., Jia, T. T., & Huang, Y. J. (2019). Increased serum S100B levels in patients with epilepsy: A systematic review and meta-analysis study. In *Frontiers in Neuroscience* (Vol. 13, Issue MAY). https://doi.org/10.3389/fnins.2019.00456

Lipatova, L. V., Serebryanaya, N. B., & Sivakova, N. A. (2018). The role of neuroinflammation in the pathogenesis of epilepsy. In *Nevrologiya, Neiropsikhiatriya, Psikhosomatika* (Vol. 10). https://doi.org/10.14412/2074-2711-2018-1S-38-45

Macdonald, R. L., Kang, J. Q., & Gallagher, M. J. (2010). Mutations in GABAA receptor subunits associated with genetic epilepsies. In *Journal of Physiology* (Vol. 588, Issue 11). https://doi.org/10.1113/jphysiol.2010.186999

McCormack, M., McGinty, R. N., Zhu, X., Slattery, L., Heinzen, E. L., Costello, D. J., Delanty, N., & Cavalleri, G. L. (2020). De-novo mutations in patients with chronic ultra-refractory epilepsy with onset after age five years. *European Journal of Medical Genetics*, *63*(1). https://doi.org/10.1016/j.ejmg.2019.01.015

Mondello, S., Sorinola, A., Czeiter, E., Vámos, Z., Amrein, K., Synnot, A., Donoghue, E., Sándor, J., Wang, K. K. W., Diaz-Arrastia, R., Steyerberg, E. W., Menon, D. K., Maas, A. I. R., & Buki, A. (2021). Blood-Based Protein Biomarkers for the Management of Traumatic Brain Injuries in Adults Presenting to Emergency Departments with Mild Brain Injury: A Living Systematic Review and Meta-Analysis. In *Journal of Neurotrauma* (Vol. 38, Issue 8). https://doi.org/10.1089/neu.2017.5182

Montanaro, F. A. M., Mandarino, A., Alesi, V., Schwartz, C., Sepulveda, D. J. C., Skinner, C., Friez, M., Piccolo, G., Novelli, A., Zanni, G., Dentici, M. L., Vicari, S., & Alfieri, P. (2023). PTCHD1 gene mutation/deletion: the cognitive-behavioral phenotyping of four case reports. *Frontiers in Psychiatry*, *14*. https://doi.org/10.3389/fpsyt.2023.1327802

O'Neill, D. G., Phillipps, S. A., Egan, J. R., Brodbelt, D., Church, D. B., & Volk, H. A. (2020). Epidemiology of recurrent seizure disorders and epilepsy in cats under primary veterinary care in the United Kingdom. *Journal of Veterinary Internal Medicine*, *34*(6). https://doi.org/10.1111/jvim.15881

Phoswa, W. N., & Mokgalaboni, K. (2023). Immunological Imbalances Associated with Epileptic Seizures in Type 2 Diabetes Mellitus. In *Brain Sciences* (Vol. 13, Issue 5). https://doi.org/10.3390/brainsci13050732

Reddy, D. S., & Volkmer, R. (2017). Neurocysticercosis as an infectious acquired epilepsy worldwide. In *Seizure* (Vol. 52). https://doi.org/10.1016/j.seizure.2017.10.004

Ruchkin, M. P., Markelova, E. V., Fedyashev, G. A., & Krasnikov, V. E. (2022). The role of innate immune system mediators in the development of retinal neurodegeneration in type 2 diabetes mellitus. *Rossiiskii Oftal'mologicheskii Zhurnal*, *15*(4). https://doi.org/10.21516/2072-0076-2022-15-4-72-76

Seçen, A. E., Akçalı, D. T., & Kurt, G. (2023). The S100B Protein in Epilepsy. In *Archives of Epilepsy* (Vol. 29, Issue 2). https://doi.org/10.4274/ArchEpilepsy.2023.231289

Shorvon, S. D., Andermann, F., & Guerrini, R. (2011). The causes of epilepsy: Common and uncommon causes in adults and children. In *The Causes of Epilepsy: Common and Uncommon Causes in Adults and Children*. https://doi.org/10.1017/CBO9780511921001

Staněk, D., Laššuthová, P., Štěrbová, K., Vlčková, M., Neupauerová, J., Krůtová, M., & Seeman, P. (2018). Detection rate of causal variants in severe childhood epilepsy is highest in patients with seizure onset within the first four weeks of life. *Orphanet Journal of Rare Diseases*, *13*(1). https://doi.org/10.1186/s13023-018-0812-8

Teng, L. Y., Lee, V. W. M., Murugesu, S., Lee, J. X., Ibrahim, N. S., Ishak, M. F., Mohamed, A. R., & Khoo, T. B. (2022). Glycemic biomarkers in children with drug-resistant epilepsy on various types of ketogenic diet therapies: A cross-sectional study. *Epilepsia*, *63*(8). https://doi.org/10.1111/epi.17292

van Vliet, E. A., Dedeurwaerdere, S., Cole, A. J., Friedman, A., Koepp, M. J., Potschka, H., Immonen, R., Pitkänen, A., & Federico, P. (2017). WONOEP appraisal: Imaging biomarkers in epilepsy. In *Epilepsia* (Vol. 58, Issue 3). https://doi.org/10.1111/epi.13621

Xu, J. Y., Chen, G., & Xiao, C. H. (2012). Change and its significance of levels of serum protein S100B, high sensitivity C-reactive protein and neuron-specific enolase in epilepsy patients and pseudoseizure patients. *Journal of Clinical Neurology (China)*, *25*(2).

Zimmer, L., McDade, C., Beyhaghi, H., Purser, M., Textoris, J., Krause, A., Blanc, E., Pavlov, V., & Earnshaw, S. (2023). Cost-Effectiveness of Blood-Based Brain Biomarkers for Screening Adults with Mild Traumatic Brain Injury in the French Health Care Setting. *Journal of Neurotrauma*, *40*(7–8). https://doi.org/10.1089/neu.2022.0270