RESEARCH ARTICLE

Serum Leptin levels in newly diagnosed Epileptic Patients

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Abstract

Objective: To compare leptin levels in newly-diagnosed treatment-naive epileptic patients and healthy controls.
Method: This case-control study was conducted from January 10 to September 15, 2022, at the Dow University of Health Sciences, Karachi, and comprised newly-diagnosed epileptic patients age 12-35years who had no comorbidity. The subjects were enrolled from the Neurology out-patient department of Civil Hospital, Karachi. Healthy individuals matched for age, gender and body mass index were also enrolled as controls. Blood samples were collected between 8am and 10am for the evaluation of serum leptin levels using enzyme-linked immunosorbent assay. Data was analysed using SPSS 26.
Results: Of the 100 subjects, 64(64%) were males and 36(36%) were females. There were 50(50%) cases with mean age 19.34±5.65 years, and 50(50%) controls with mean age 19.76±5.67 ($p=0.614$). 100% of 50 individuals in control group did not have any family history of epilepsy,while 18% of cases (9) reported a positive family history. Mean leptin level in cases was 31.03±19.37 compared to 5.25±4.03 in the controls ($p<0.05$).
Conclusion: Serum leptin levels were elevated in newly-diagnosed epileptic patients compared to healthy controls.

Key Words: Epilepsy, Leptin, Leptin resistance.
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Introduction

Chronic, treatable, non-communicable epilepsy is characterised by recurrent episodes of strong, jerky convulsions that can last from a few seconds to several minutes. It affects people of all ages and genders, and causes behavioural, social, health and economic problems for the patients and their families[1]. Epilepsy affects people all over the world. Incidence rates range from 49 per 100,000 per year in high-income countries (HICs) to 139 per 100,000 per year in low-income countries (LICs), affecting about 70 million people worldwide. In developing nations, people with epilepsy encounter the most significant obstacles to receiving high-quality healthcare. Globally, there persists a problem of seizures being inadequately acknowledged, resulting in delays in diagnosis and treatment. This challenge arises from issues related to stigma, public awareness, fundamental healthcare access, and the education of healthcare professionals. In various geographical areas, individuals may encounter obstacles, such as language, economic constraints, and technological limitations, impeding the prompt identification and management of seizures. Even after diagnosis, individuals with epilepsy frequently encounter shortcomings in achieving optimal seizure management through the utilisation of anti-seizure medications[2]. Epilepsy affects more than 2.2 million people in Pakistan, with a prevalence rate of 0.98%[3]. It constitutes 1% of the overall global health burden[4]. The International League Against Epilepsy (ILAE) revised the definition of epilepsy, which now comprises any of the following conditions; at least 2 unprovoked seizures occurring >24 hours apart, one unprovoked seizure with a relevant abnormal electroencephalographic (EEG) pattern or brain scan suggesting a high probability of a second seizure, and diagnosis of an epilepsy syndrome. Four types of epilepsy are recognized; focal, generalised, combined focal-generalised, and unknown[1]. Although several underlying disease mechanisms can cause epilepsy, the cause is still unknown in 50% of cases worldwide. Epilepsy is not a contagious condition[5].

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Neurotrophic factors, such as leptin, are chemical mediators that help in the survival of neurons, called neurogenesis and neuroprotection[6]. Due to its close relationship with the control of neuronal excitability in numerous brain regions, it has been proposed that leptin has a shielding effect in epilepsy for excessive neuron stimulation. Leptin is a polypeptide hormone, containing 167 amino acids, and is produced by adipose tissue, pituitary gland, skeletal muscle, gastrointestinal tract (GIT) and placenta[6]. Its receptors are distributed throughout the brain including hypothalamus and mesolimbic areas. The hypothalamus uses leptin to regulate both energy intake and expenditure. Leptin frequently penetrates the choroid plexus of the brain tissue, and is associated with both convulsant and anticonvulsant properties in the hippocampus. It appears to act as a neurotrophic factor that promotes the growth of nervous tissue[7]. Leptin, having anticonvulsive effects, may have a protected role against exaggerated excitability during epilepsy, therfore current study was planned to compare leptin levels in newly-diagnosed epileptic patients and healthy controls.

Patients and methods

The case-control study was conducted from January 10 to September 15, 2022, at the Dow University of Health Sciences (DUHS), Karachi, and comprised newly-diagnosed epileptic patients of age 12-35years who had no comorbidity. The subjects were enrolled using nonprobability purposive sampling technique from the Neurology out-patient department at DUHS and RuthPfau Civil Hospital, Karachi (CHK). Healthy individuals matched for age, gender and body mass index (BMI) were also enrolled as controls. After approval from the institutional ethics review boards, the sample size was calculated using the finite population correction factor.[8]

Blood samples were collected between 8am and 10am for the evaluation of serum leptin levels using enzyme-linked immunosorbent assay (ELISA) kit.

Data was analysed on SPSS 26. and nonprobability purposive sampling technique was used.The demographic variable,age was described by mean +-Sd values,gender ,family history and seizure history by frequency and percentages.The normal distribution of continuous variable (age) was checked using the shaipro-wilktest (p-value,0.05). Maa-Whitney U-test was applied to asses the difference between age and study groups and Chi square/Fisher's Exact test was performed to assess the association between categorical variables and study groups.P-value P<0.05 was considered significant.

Results

Of the 100 subjects, 64(64%) were males and 36(36%) were females. There were 50(50%) cases with mean age 19.34±5.65 years, and 50(50%) controls with mean age 19.76±5.67 (p=0.614). 100% of 50 individuals in control group didnot have any family history of epilepsy,while 18% of cases (9) reported a positive family history. Seizure type, duration and pattern of the cases were noted in detail (Table 2). Mean leptin level in cases was 31.03±19.37 compared to 5.25±4.03 in the controls (p<0.05) (Figure).

Table-1: Baseline characteristics (n=100).

Variables	Cases n (%)	Controls n (%)	*p*-value
Mean Age in years	19.34 ± 5.65	19.76 ± 5.67	0.614*
Gender			
Male	32 (64.0)	32 (64.0)	1.000
Female	18 (36.0)	18 (36.0)	
Family history			
Yes	9 (18.0)	0 (0.0)	<0.05
No	41 (82.0)	50 (100.0)	

*p-value calculated using Mann Whitney test.
p-value calculated using chi-square/Fisher's exact test.

Table-2: Seizure history among Epileptic patients (n=50).

Variables	n	%
Seizure frequency since incidence (1 year)		
1 time seizure	2	4.0
2-time seizure	43	86.0
3-time seizure	5	10.0
Seizure Duration		
Up to 30 seconds	19	38.0
Up to 60 seconds	27	54.0
Up to 120 seconds	4	8.0
Seizure Type		
Myoclonic	4	8.0
Tonic Colonic	46	92.0
Recent Seizure		
Same day	16	32.0
One week	27	54.0
One month	7	14.0

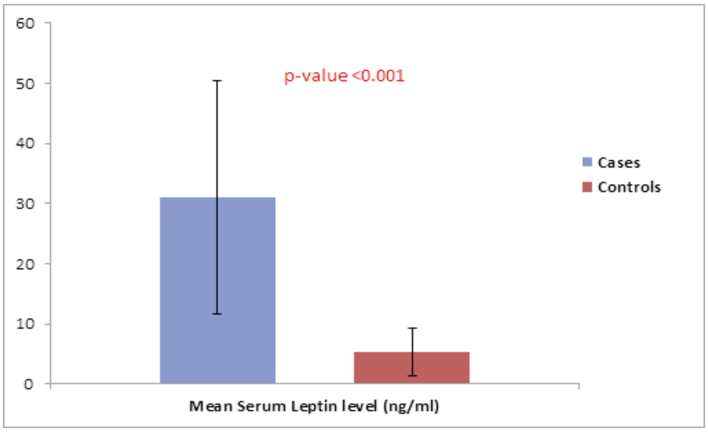

Figure: Leptin levels between cases and controls.

Discussion

Leptin, a hormone originating from adipose tissue, holds a pivotal role in the regulation of energy balance and metabolism. Differences in leptin levels have been discerned across a spectrum of diseases, spanning metabolic disorders, such as obesity, and neurological disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD), major depressive disorder (MDD), panic disorders and epilepsy. Leptin has been identified as a neuroprotective agent[9]. The present study reported serum leptin levels of adolescent (12-19) and young adults (19-35) adults who were newly-diagnosed and treatment-naive epileptic patients, and compared the levels with those of healthy individuals. To our knowledge, the current study is the first of its kind.

Family history of epilepsy was found to be a significant factor in epileptic patients ($p<0.05$) compared to controls. Other studies have also reported similar findings[10,11].

In the current study, generalised epilepsy cases were more common in men (64%) than in women (36%), indicating male gender to be prone to developing generalised tonic-clonic seizures compared to females. The finding is supported by other studies.[11, 12] Moreover, a review article reported that in majority of low- and middle-income countries (LMICs) the most commonly documented seizure types were generalised tonic-clonic seizures[13], which was in agreement with the present findings (92%).

On the global scale, epilepsy is the 5th most prevalent neurological disorder, following stroke, migraine, dementia and meningitis[4]. Epileptogenesis refers to the exaggerated transformation of a typically functioning brain, resulting in the onset of epilepsy[14]. This process induces molecular modifications in the hippocampus, including changes in neurogenesis and heightened levels of neurotrophic factors and proteins.[14] Leptin is a neurotropic factor, and it contributes to the growth, maturation and viability of neurons within the brain. Leptin receptors are expressed in widespread regions of the brain, such as the hippocampus, hypothalamus and cortex[15]. Within these areas, leptin stimulates neurogenesis, generates new neurons, and improves neuronal longevity. Additionally, leptin exerts influence on synaptic plasticity, impacting the dynamic strengthening or weakening of synapses over time, consequently influencing learning and memory functions[16].

In the current study, serum leptin levels were increased in the newly-diagnosed epileptic patients, and these were significantly elevated compared to healthy individuals (Figure). It is interesting to speculate that the increase in leptin levels were in response to a protective mechanism for the neurons during vigorous epileptic seizures.

The present research provides an insight into the connection between leptin levels and epilepsy, and the consequences of elevated leptin levels in epilepsy remains a matter of focus, requiring further exploration. A few in vivo studies have indicated that elevated levels of leptin could be linked to improved management of seizures in rodents with epilepsy[17].

The mechanisms underlying the elevated leptin levels in epilepsy are not fully understood. One possible explanation is that seizures themselves can induce changes in leptin production. It has been observed that seizures can lead to alterations in glucose metabolism and insulin resistance[18], which can, in turn, affect leptin secretion. Additionally, inflammation and oxidative stress, which are commonly observed in epilepsy, may contribute to the dysregulation of leptin production and signalling. Epilepsy has been reported to be frequently correlated with metabolic aberrations, like obesity and metabolic syndrome[19]. Moreover, these conditions are closely connected to leptin, and elevated levels of leptin could signal potential underlying metabolic irregularities. These accompanying health issues can have adverse effects on overall wellbeing, and might influence the treatment of epilepsy.

Furthermore, the increased leptin levels found in the present study might be due to leptin resistance. Leptin resistance is a complex metabolic problem that has attracted increasing attention in recent times. Central leptin resistance relates to various neurological problems, such as AD and PD[20]. A case-control study reported that epileptic patients in the sodium valproate group exhibited a significant increase in serum leptin levels[21]. Sodium valproate is a widely utilised broad-spectrum antiepileptic medication.

Increases in leptin levels in epilepsy could be due to various underlying biochemical processes that need to be further explored. It is tempting to deduce that modulating leptin levels may affect the seizure outcomes in treatment-naive cases of epilepsy.

Conclusion

Serum leptin levels were found to be significantly elevated in newly-diagnosed epileptic patients compared to healthy controls. This increase in leptin levels could be due to leptin resistance and measures need to be taken to address leptin resistance to get the anticonvulsant activity of Leptin in epileptic patients.

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References

1. Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. Lancet 2019;393:689-701. doi: 10.1016/S0140-6736(18)32596-0.
2. Pellinen J. Treatment gaps in epilepsy. Front Epidemiol 2022;2:976039. Doi: 10.3389/fepid.2022.976039
3. Mogal Z, Aziz H. Epilepsy treatment gap and stigma reduction in Pakistan: A tested public awareness model. Epilepsy Behav 2020;102:106637. doi: 10.1016/j.yebeh.2019.106637.
4. Zhang YJ, Kong XM, Lv JJ, Yang CH, Li XY, Yang XT, et al. Analysis of the global burden of disease study highlights the global, regional, and national trends of idiopathic epilepsy epidemiology from 1990 to 2019. Prev Med Rep 2023;36:e102522. doi: 10.1016/j.pmedr.2023.102522.
5. GBD 2016 Epilepsy Collaborators. Global, regional, and national burden of epilepsy, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:357-75. doi: 10.1016/S1474-4422(18)30454-X.
6. Casado ME, Collado-Pérez R, Frago LM, Barrios V. Recent Advances in the Knowledge of the Mechanisms of Leptin Physiology and Actions in Neurological and Metabolic Pathologies. Int J Mol Sci 2023;24:1422. doi: 10.3390/ijms24021422.
7. Diano S, Horvath TL. Anticonvulsant effects of leptin in epilepsy. J Clin Invest 2008;118:26-8. doi: 10.1172/JCI34511.
8. Cochran WG. Sampling techniques, 3rd ed. Hoboken, New Jersey: John Wiley & Sons, 2007; pp 76.
9. Zou X, Zhong L, Zhu C, Zhao H, Zhao F, Cui R, et al. Role of Leptin in Mood Disorder and Neurodegenerative Disease. Front Neurosci 2019;13:e378. doi: 10.3389/fnins.2019.00378.
10. Ghiasian M, Daneshyar S, Khanlarzadeh E, Bolouri Novin M. Investigating the relationship of positive family history pattern and the incidence and prognosis of idiopathic epilepsy in epilepsy patients. Caspian J Intern Med 2020;11:219-22. doi: 10.22088/cjim.11.2.219.
11. Kishk N, Mourad H, Ibrahim S, Shamloul R, Al-Azazi A, Shalaby N. Sex differences among epileptic patients: a comparison of epilepsy and its impacts on demographic features, clinical characteristics, and management patterns in a tertiary care hospital in Egypt. Egypt J Neurol Psychiatry Neurosurg 2019;55:1-8. Doi: 10.1186/s41983-019-0078-7.
12. Hu Y, Shan Y, Du Q, Ding Y, Shen C, Wang S, et al. Gender and Socioeconomic Disparities in Global Burden of Epilepsy: An Analysis of Time Trends From 1990 to 2017. Front Neurol 2021;12:e643450. doi: 10.3389/fneur.2021.643450.
13. Beghi E, Giussani G, Abd-Allah F, Abdela J, Abdelalim A, Abraha HN, et al. Global, regional, and national burden of epilepsy, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology. 2019 Apr 1;18(4):357-75. Reference no 5 and 13 are same.
14. Sumadewi KT, Harkitasari S, Tjandra DC. Biomolecular mechanisms of epileptic seizures and epilepsy: a review. Acta Epileptologica 2023;5:28. Doi: 10.1186/s42494-023-00137-0
15. Irving AJ, Harvey J. Leptin regulation of hippocampal synaptic function in health and disease. Philos Trans R Soc Lond B Biol Sci 2013;369:20130155. doi: 10.1098/rstb.2013.0155.
16. Harvey J. Food for Thought: Leptin and Hippocampal Synaptic Function. Front Pharmacol 2022;13:e882158. doi: 10.3389/fphar.2022.882158.
17. Xu L, Rensing N, Yang XF, Zhang HX, Thio LL, Rothman SM, et al. Leptin inhibits 4-aminopyridine- and pentylenetetrazole-induced seizures and AMPAR-mediated synaptic transmission in rodents. J Clin Invest 2008;118:272-80. doi: 10.1172/JCI33009.
18. de Melo IS, Pacheco ALD, Dos Santos YMO, Figueiredo LM, Nicacio DCSP, Cardoso-Sousa L, et al. Modulation of Glucose Availability and Effects of Hypo- and Hyperglycemia on Status Epilepticus: What We Do Not Know Yet? Mol Neurobiol 2021;58:505-19. doi: 10.1007/s12035-020-02133-8.
19. Nazish S. Obesity and metabolic syndrome in patients with epilepsy, their relation with epilepsy control. Ann Afr Med 2023;22:136-44. doi: 10.4103/aam.aam_139_22.
20. Casado ME, Collado-Pérez R, Frago LM, Barrios V. Recent Advances in the Knowledge of the Mechanisms of Leptin Physiology and Actions in Neurological and Metabolic Pathologies. Int J Mol Sci 2023;24:1422. doi: 10.3390/ijms24021422.
21. Rehman T, Sachan D, Chitkara A. Serum Insulin and Leptin Levels in Children with Epilepsy on Valproate-associated Obesity. J Pediatr Neurosci 2017;12:135-7. doi: 10.4103/jpn.JPN_152_16.