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ORIGINAL RESEARCH

Application Value of Serum Metabolic Markers for Cognitive Prediction in Elderly Epilepsy

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Background and Study Aims: Elderly epilepsy is the third most common chronic disease that affects metabolism either alone or through antiepileptic drugs (AEDs). Here, we focus on whether neurocognitive profiles in elderly epilepsy and its treatment are linked to metabolic conditions.

Patients and Methods: Elderly patients with epilepsy without cognitive impairment (n = 78) and with cognitive impairment (n = 75) were enrolled. C-reactive protein (CRP) and metabolic markers (triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL-c), low-density lipoprotein (LDL-c), albumin, fasting glucose (Glu) and glycosylated hemoglobin (HbA1c)) were measured. Serum markers were modeled using logistic regression analysis.

Results: TG, TC, fasting glucose, HbA1c and CRP were significantly increased ($p < 0.05$, 0.05, 0.001, 0.001, 0.01, respectively) in elderly epilepsy, whereas HDL-c, LDL-c and serum albumin were decreased ($p < 0.001$, 0.001, 0.001) in elderly epilepsy. TG, TC, fasting Glu, HbA1c and CRP were significantly elevated ($p < 0.05$, 0.001, 0.001, 0.001, 0.001, respectively) in epilepsy with cognitive impairment, whereas HDL-c, LDL-c and serum albumin were decreased ($p < 0.001$, 0.001, 0.001). The abnormal glycolipid profile was predominated in AED-treated patients. The regression model combined with TG, LDL-c, HDL-c and albumin performed better (area under the ROC curve was 0.824) in AED-treated patients.

Conclusion: The relevant relationship between glycolipid profile and cognitive impairment with epilepsy was described, and the logistic regression model based on serum TG, LDL-c, HDL-c and albumin is reported and may serve as promising diagnostic markers for elderly epilepsy with cognitive impairment. Additionally, a specific emphasis on the complex role of altered lipid metabolism and AEDs is made.

Keywords: elderly epilepsy, glycolipid metabolic, logistic regression, AED

Introduction

With advances in healthcare and an aging population, the number of the elderly with epilepsy is set to rise substantially across the world. Epilepsy is the third most common neurological disorder and affects 65 million people with a peak incidence that is higher in the older population over 65 years of age.[1,2] A continuous epileptogenic process could irreversibly damage the brain, causing persistent cognitive impairment.[3] Recent findings show an important bidirectional link between cognitive function and epilepsy. Comorbid condition could arise before, concomitantly, or after an epilepsy diagnosis; they may be caused by or a consequence of epilepsy or may be associated with epilepsy because they share common pathologic risk factors or pathogenic process, or they may be discordant conditions.[4,5] Epidemiological findings show that individuals with epilepsy and people with cognitive impairment share common risk factors.[6]

The epileptic cognitive impairment theory was first put forward, indicating that cognitive impairment and epilepsy may result from the same underlying impairment.[6] There is a complex interplay between comorbidities in elderly epilepsy, especially elderly epilepsy with cognitive impairment. The elderly epilepsy identified a threshold of over 65 years of age as likely to be the most optimal.[7] Only one detailed report is available on cognitive function in people who first developed epilepsy after the age of 65.[8] Importantly, some findings also suggest that elderly patients with epilepsy

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are at a higher risk of developing cognitive impairment and ultimately dementia.[9] Indeed, markers for cognitive impairment in epilepsy might not be unique to epilepsy but rather reflect mixed pathologies. Shared markers may be due to the fact that cognitive impairment may share underlying pathological mechanisms with epilepsy. Alternatively, seizures might trigger pathological changes that make the brain more vulnerable to developing cognitive impairment. Thus, molecular cascades important in both seizure generation and cognitive impairment might converge within epileptogenic tissue in elderly patients.[10] Animal models of cognitive impairment provided possible insights into commonalities of network disruption in cognitive impairment and epilepsy.[11] Two important candidate pathologies in elderly epilepsy have been implicated in dementia: small vessel cerebrovascular disease and tau or amyloid deposition, both of which affect brain networks that subserve cognition on a large scale.[6] Levetiracetam, an antiepileptic drug (AED), reduced amyloid plaques in the model.[12] However, we note that there has been little investigation specifically of cognitive impairment in elderly epilepsy.

Evidence is emerging that inflammation might be a consequence as well as a cause of epilepsy.[13,14] Over the last decade, a study has shown a bidirectional communication between inflammation and epilepsy by using in vivo and in vitro experimental models, indicating that seizures may generate an inflammatory response, which could in turn modulate epilepsy.[13] Several studies demonstrated that proinflammatory cytokines are overexpressed in brain areas of seizure generation. Elevated blood levels of CRP have also been observed in patients with epilepsy.[15] However, the relationship of inflammation occurrence in elderly epilepsy and impaired cognition remains unknown.

In addition to inflammation, glycolipid metabolism has been shown to be associated with cognitive impairment in epilepsy. Several metabolic indicators appear to be involved in cognition,[16] although a relationship between glycolipid metabolism profiles and cognitive impairment in elderly epilepsy remains inconclusive. AEDs have also been linked with a myriad of metabolic disorders and their chronic use has been associated with a significant change in the lipid profile, as well as CRP levels.[17] Despite the availability of a wide range of AEDs, currently AEDs are mainly used to treat symptoms and prevent seizures but do not affect the underlying pathology or the progression of the disorder.[18,19] We are not aware of any observations on the potential different effects of AEDs on serum markers in elderly epilepsy with or without cognitive function.

The aim of the present study was to characterize the inflammatory pattern and metabolic profiles of elderly epileptic patients. Inflammatory and metabolism markers are provided to understand the relationship and the role of AED monotherapy in epilepsy and cognitive impairment.

Materials and Methods

Participants

The group consisted of 233 participants including 80 healthy volunteers and 153 epilepsy patients. Based on neuroimaging data, clinical and EEG features (see Table S1), all patients were diagnosed as epilepsy. Inclusion criteria were age 65–80 years and a first-recognized, unprovoked seizure. Patients were excluded if seizures were provoked (ie, associated with trauma, cerebrovascular factor, infection, mass lesion or toxin). Care was taken to ensure that the control population did not have any inflammatory or infectious diseases, such as fever and upper respiratory tract infection in the last 2 weeks, which may alter levels of glycolipids. Glycolipid biomarkers were collected from epilepsy patients at baseline and grouped according to the MMSE score, such that the elderly epilepsy patients were divided into two groups. MMSE >25 were elderly epilepsy individuals without cognitive impairment (n = 78), and MMSE $\leq$ 25 were the elderly epilepsy individuals with cognitive impairment (n = 75). In addition, the 80 healthy, sex-matched volunteers without underlying health conditions were enrolled as the control group.

This study was carried out at the Affiliated ZhongDa Hospital. It was approved by the Ethics Committee. Informed consent was obtained from all patients and control subjects.

Laboratory Analyses

Routine fasting blood samples were analyzed for TC, TG, LDL-c, HDL-c, serum albumin, fasting Glu, HbA1c and CRP in patients with non-epileptic seizures.

Statistical Analyses

Continuous variables were compared using Student's *t*-test. Statistical analyses were performed using SPSS software. A p-value <0.05 was considered significant for all statistical analysis.

Results

Patients and Clinical Findings

Table 1 presents the baseline characteristics of the 80 healthy people, 78 epilepsy subjects without cognitive impairment and 75 epilepsy subjects with cognitive impairment. No significant differences were determined between the groups in terms of mean age or sex.

Of the epilepsy participants without cognitive impairment, 35.90% (n = 28) were on levetiracetam (LEV) monotherapy, 24.36% (n = 19) were on oxcarbazepine (OXC) monotherapy, 21.79% (n = 17) were on sodium valproate (VPA) monotherapy, and 17.95% (n = 14) were taking biotherapy. Of the epilepsy participants with cognitive impairment, 56% (n = 42) were on LEV monotherapy, 5.33% (n = 4) were on OXC monotherapy, 8% (n = 6) were on VPA monotherapy, and 30.67% (n = 23) were taking biotherapy.

Analysis of Serum Markers

Within the inflammatory markers measured, CRP concentrations were higher in epileptic patients (Figure 1). Considering markers of metabolism, the epileptic patient group had a significant increase in TG, TC, fasting Glu and HbA1c, with a

Table 1 Clinical Demographic Data

Characteristic	Control (n=80)	Epilepsy		*P* value
		Elderly Epilepsy without Cognitive Impairment (n=78)	Elderly Epilepsy with Cognitive Impairment (n=75)	
Sex (M/F)	40/40	33/45	43/32	0.076
Age (years)	69.90±4.21	69.51±4.10	71.41±5.33	0.014
MMSE scores	29.06±0.90	28.58±1.17	15.13±2.88	0.000
Duration (years)	–	1.35±0.73	1.41±0.48	0.551
Focal epilepsy /Generalized epilepsy	–	51/27	46/29	0.619
AEDs use (100%) LEV OXC VPA Two AEDs	–	 28 19 17 14	 42 4 6 23	
TC	2.98±0.95	3.05±0.92	3.77±0.83	0.000
TG	1.23±0.48	1.28±0.41	1.55±1.03	0.033
LDL-c	2.80±0.58	2.45±0.69	1.78±0.63	0.000
HDL-c	1.61±0.40	1.48±0.33	1.14±0.29	0.000
Serum albumin	46.32±3.44	37.60±2.19	34.03±4.13	0.000
Fasting Glu	5.17±0.71	5.45±1.14	6.87±1.60	0.000
HbA1c	5.14±0.55	5.46±0.57	6.10±0.83	0.000
CRP	1.57±0.83	3.11±6.67	14.78±21.60	0.000

Abbreviations: AEDs, antiepileptic drugs; LEV, levetiracetam; OXC, oxcarbazepine; VPA, valproate; TC, total cholesterol; TG, triglyceride; LDL-c, low-density lipoprotein; HDL-c, high-density lipoprotein; HbA1c, glycosylated hemoglobin; CRP, c-reactive protein.

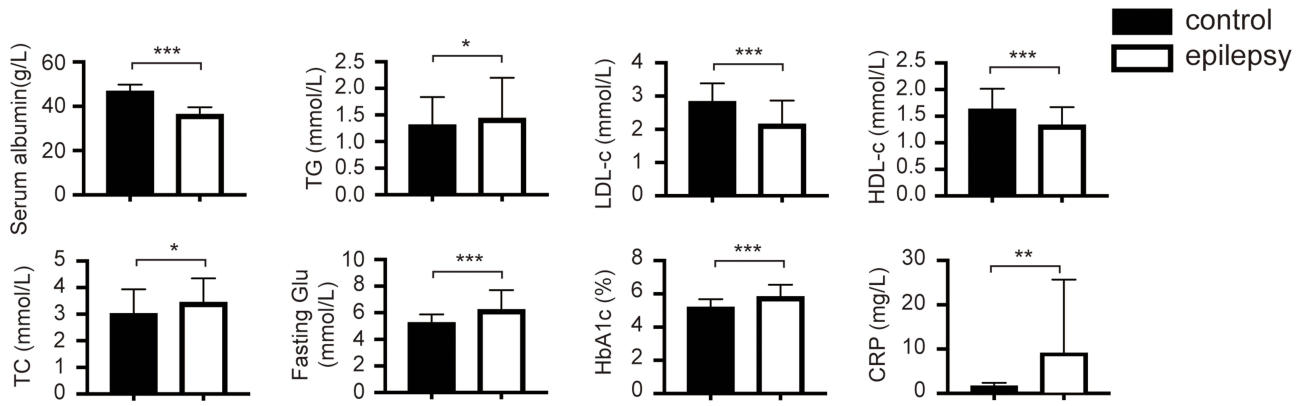

Figure 1 Group situation of two groups. The levels of TC, TG, LDL-c, HDL-c, serum albumin, fasting Glu, HbA1c and CRP in healthy control group and elderly epilepsy group. *p < 0.05, **p < 0.01, ***p < 0.001.

decrease in HDL-c, LDL-c and serum albumin (Figure 1). Then, the serum markers in the patients with or without cognitive impairment were analyzed. As shown in Figure 2, TG, TC, fasting Glu and HbA1c were significantly elevated in elderly epilepsy with cognitive impairment, whereas HDL-c, LDL-c and serum albumin were decreased compared with the elderly epilepsy without cognitive impairment.

Elevated levels of lipid metabolism were noted in the noncognitive impairment group, and patients with cognitive impairment also had elevated markers of lipid metabolism. Epileptic patients had reduced levels of glycometabolism in the noncognitive impairment group and in cognitive group. Changes were predominated among the group of patients with cognitive impairment compared to the noncognitive impairment group (Table 2).

Logistic Regression Analysis

Seventy-eight elderly epileptic patients without cognitive impairment and 75 elderly epileptic patients with cognitive impairment were selected to establish the logistic regression model. The 9 markers, including TG, TC, fasting Glu, HbA1c, HDL-c, LDL-c, serum albumin, CRP and LEV, were analyzed using forward logistic stepwise regression analysis (Table 3). Only four variables, LDL-c, HLD-c, TG and albumin, were chosen in the equation. The partial regression coefficients were −2.308, −3.259, −3.767 and −0.346, and the corresponding p values were 0, 0, 0, 0.002, respectively.

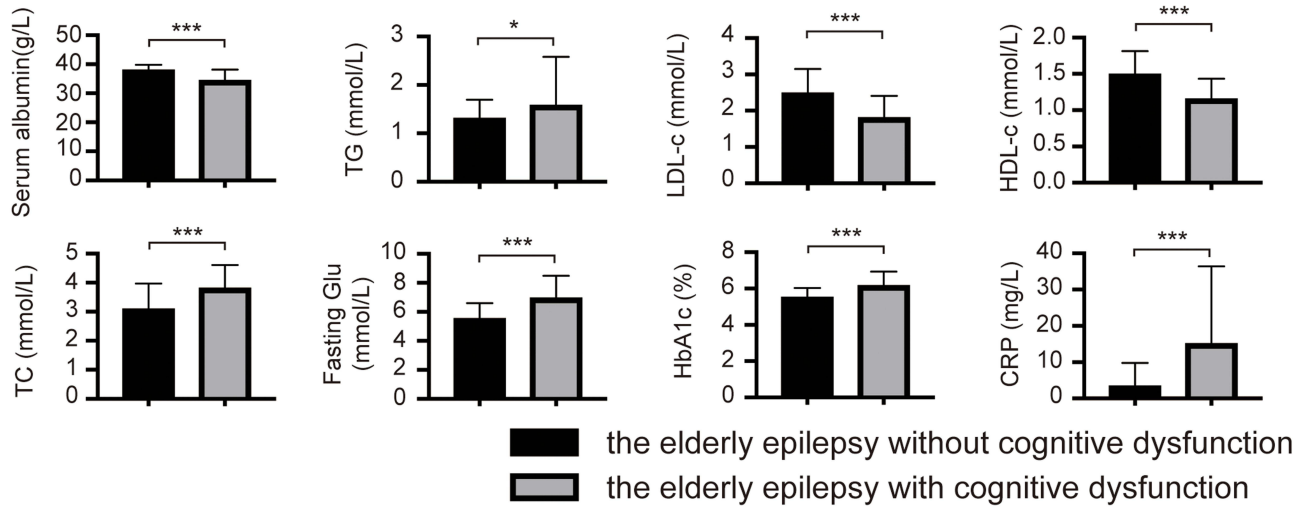

Figure 2 Group situation of two groups. The levels of TC, TG, LDL-c, HDL-c, serum albumin, fasting Glu, HbA1c and CRP in the elderly epilepsy without cognitive impairment group and the elderly epilepsy with cognitive impairment group. *p < 0.05, ***p < 0.001.

Table 2 Number of Patients with Epilepsy Having Abnormal Serum Markers Balance in Relation to Different AEDs Utilized (Elderly Epilepsy Without Cognitive Impairment/Elderly Epilepsy with Cognitive Impairment)

N=78/75	Total	LEV (28/42)	OXC (19/4)	VPA (17/6)	Polytherapy (14/23)
TC (high)	33/37	5/17	14/4	7/5	7/11
TG (high)	44/25	6/6	12/4	16/6	10/9
LDL-c (high)	37/34	6/13	15/3	12/5	4/13
HDL-c (high)	46/38	11/17	17/3	5/5	13/13
Albumin (low)	40/39	10/21	12/3	5/3	13/12
Fasting Glu (low)	45/15	6/6	18/2	16/4	5/3
HbA1c (low)	41/40	8/22	11/3	16/5	6/10
CRP (high)	9/24	1/9	4/3	0/1	4/11

Notes: The number before / in the first row indicates the number of people taking the drug in the elderly epilepsy without cognitive impairment, the number after / indicates the number of people taking the drug in the elderly epilepsy with cognitive impairment.
Abbreviations: AEDs, antiepileptic drugs; LEV, levetiracetam; OXC, oxcarbazepine; VPA, valproate; TC, total cholesterol; TG, triglyceride; LDL-c, low-density lipoprotein; HDL-c, high-density lipoprotein; HbA1c, glycosylated hemoglobin; CRP, c-reactive protein.

Table 3 The Logistic Regression Analysis

	B	SE	Wald	Sig.	Exp (*B*)
LDL-c	−2.308	0.408	32.049	0.000	0.099
TG	−3.259	0.673	23.470	0.000	0.038
HDL-c	−3.767	0.931	16.382	0.000	0.023
Albumin	−0.346	0.109	10.052	0.002	0.708

Notes: Variable used in step1: LDL-c. Variable used in step2: TG. Variable used in step3: HDL-c. Variable used in step4: serum albumin.
Abbreviations: B, beta; SE, standard error; LDL-c, low-density lipoprotein; TG, triglyceride; HDL-c, high-density lipoprotein.

ROC Curve Analysis

The model discrimination was measured by the area under the receiver operating characteristic (AUC-ROC) curve (Figure 3 and Table 4). Subsequently, the AUC was evaluated with the combined detection, which had the best diagnostic value. In conclusion, the model with the four combined markers was the best model for diagnosing elderly epilepsy with or without cognitive impairment.

Discussion

In this article, the relationship between cognitive impairment in epilepsy and glycolipid profile was evaluated. Elderly epilepsy patients were divided into groups based on the presence or absence of cognitive impairment and nine serum markers were selected to build a logistic regression model and ROC curves. OXC, LEV and VPA monotherapy are determined to be significantly associated with cognitive impairment in elderly patients with epilepsy, albeit via different underlying mechanisms.

Several lines of evidence suggest that in experimental models of epilepsy, changes in metabolism and activation of specific cellular inflammatory pathways are associated with cognitive decline. Because the same signaling pathways are often critical regulators of cellular mechanisms underlying synaptic plasticity, their detection may become a promising approach for identifying the risk of cognitive comorbidities following epileptogenic brain injuries. This study provides a comprehensive analysis of glycolipid metabolism profiles and common clinical markers in the elderly patients with epilepsy.

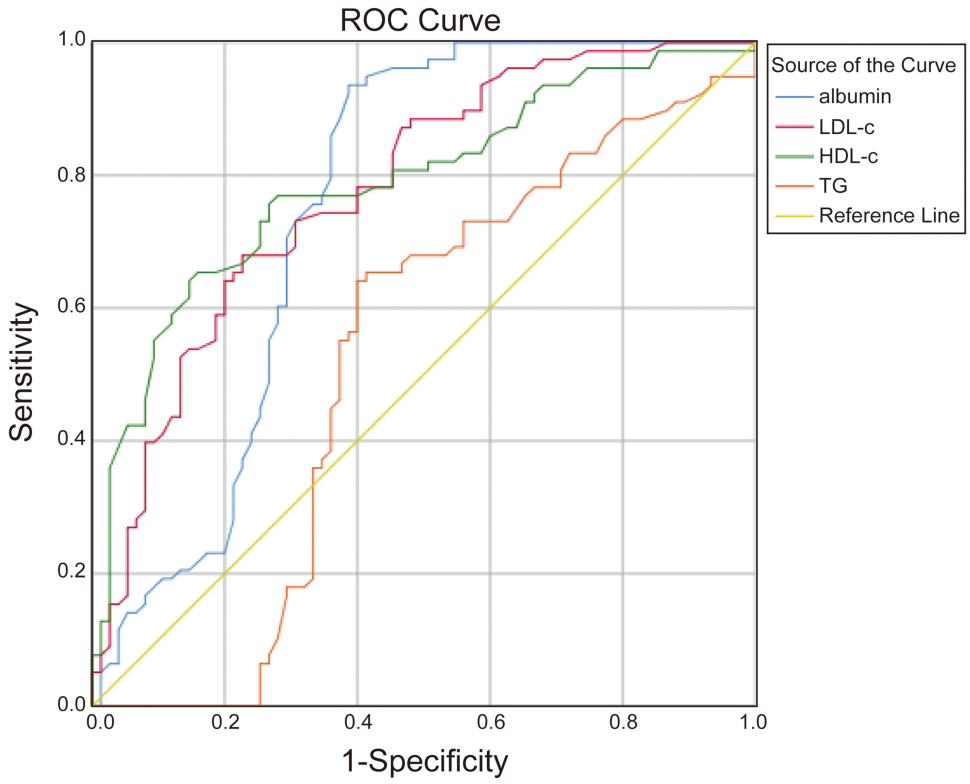

Figure 3 The ROC curves of four markers.

The results showed that, compared to healthy controls, elderly epileptic patients exhibited abnormalities in glycolipid metabolism and inflammation. When searching for factors associated with abnormal cognition in epilepsy, attention classically turns to variables, such as epilepsy syndrome, duration of epilepsy, seizure frequency and severity, and related disorder-specific measures.[20] However, markers of inflammation and metabolic health are of considerable interest in the general aging and cognition.[21] The data herein also show that the markers of inflammation and metabolic health are significantly associated with cognition. The higher degree of dysregulation in lipid metabolism observed in elderly epileptic patients with cognitive impairment may be due to the differences in the levels of LDL-c, HLD-c, TG and albumin. In conclusion, the four indicators selected may serve as predictors of elderly epilepsy with cognitive impairment. Moreover, single markers cannot fully explain the change and development of the disease due to the complex pathophysiological process. Thus, the ROC curves of the four markers were analyzed and compared and showed that the AUC based on the four indicators showed the best diagnostic value.

A rapidly growing body of evidence has demonstrated that currently available AEDs may modify lipid profiles. However, little is known about the precise nature of such changes in elderly patients with epilepsy with cognitive impairment. The largest observed effect of AEDs reported that the lower CRP concentrations are associated with VPA use.[22] It is possible that these AEDs have some effect on CRP concentrations, but the size of the effect was not large enough for diagnosing alterations in cognition in elderly epileptic patients. The results herein showed that the CRP concentration was significantly below the

Table 4 Comparison of the AUC

Indexes	Albumin	LDL-c	HDL-c	TG	Combined
AUC	0.753	0.779	0.788	0.522	0.824
Sensitivity	0.613	0.773	0.853	0.600	0.853
Specificity	0.936	0.680	0.641	0.641	0.910

Abbreviations: AUC, the area under the receiver operating characteristic; LDL-c, low-density lipoprotein; HDL-c, high-density lipoprotein; TG, triglyceride.

normal average range in two groups of elderly epileptic patients on AEDs monotherapy. The effects of VPA on changes in lipid profiles remain controversial.[23,24] In the present results, more than half of the patients showed an increase in lipid metabolism and a decrease in glymetabolism in both groups on VPA monotherapy. Interestingly, changes in the levels of glycolipids in the elderly epileptic patients with or without cognitive impairment with different AEDs. Consistent with many studies, the majority of epilepsy patients taking AEDs had higher lipid metabolism and lower glymetabolism in the present study, with the LEV treatment group showing a lower degree of glycemic disorders.[25,26] To our knowledge, this is the first report of changes in metabolism in elderly epileptic patients with or without cognitive impairment, despite the type of AEDs utilized or the degree of control on AEDs. However, the current study has the sample limitations that interfere with determining the cause of these changes.

An urgent need exists for determining if changes in the measured markers correlate with cognitive outcome with sufficient specificity to provide a more clinically accessible marker of future risk of cognitive impairment in elderly epileptic patients. Moreover, determining whether cognitive impairment is causative or a direct or indirect consequence from a common origin is not clear and requires further investigations.

Conclusion

In this study, AED efficacy was assessed by determining changes in glycolipid metabolism. The elderly epilepsy was grouped as elderly epilepsy without cognitive impairment and elderly epilepsy with cognitive impairment. Based on these, 4 serum indicators were identified as being significantly different between the two groups, and the logistic regression model based on these four serum markers holds promise for predicting cognitive outcomes and for achieving a better prognosis for elderly epileptic patients.

Abbreviations

AEDs, antiepileptic drugs; CRP, C-reactive protein; TC, total cholesterol; LDL-c, low-density lipoprotein; HDL-c, high-density lipoprotein; TG, triglyceride; HbA1c, glycosylated hemoglobin; AUC, area under curve; LEV, levetiracetam; OXC, oxcarbazepine; VPA, valproate; ROC, receiver operating characteristic curve.

Ethical Conduct of Research

The study procedure was approved by the ethics committee of the Affiliated ZhongDa Hospital, and informed consent was obtained from each participant. And the study was complied with the Declaration of Helsinki.

Disclosure

The authors declare no competing interests in this work.

References

1. Annegers JF, Dubinsky S, Coan SP et al. The incidence of epilepsy and unprovoked seizures in multiethnic, urban health maintenance organizations. Epilepsia 1999; 40: 502–506. doi:10.1111/j.1528-1157.1999.tb00748.x
2. Hussain SA, Haut SR, Lipton RB, et al. Incidence of epilepsy in a racially diverse, community-dwelling, elderly cohort: results from the Einstein aging study. *Epilepsy Res*. 2006;71:195–205. doi:10.1016/j.eplepsyres.2006.06.018
3. Hermann BP, Dabbs K, Becker T, et al. Brain development in children with new onset epilepsy: a prospective controlled cohort investigation. *Epilepsia*. 2010;51:2038–2046. doi:10.1111/j.1528-1167.2010.02563.x
4. Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: current concepts and future perspectives. *Lancet Neurol*. 2016;15:106–115. doi:10.1016/S1474-4422(15)00225-2
5. Ravizza T, Onat FY, Brooks-Kayal AR, et al. WONOEP appraisal: biomarkers of epilepsy-associated comorbidities. *Epilepsia*. 2017;58:331–342. doi:10.1111/epi.13652
6. Sen A, Capelli V, Husain M. Cognition and dementia in older patients with epilepsy. *Brain*. 2018;141:1592–1608. doi:10.1093/brain/awy022
7. Sen A, Jette N, Husain M, et al. Epilepsy in older people. *Lancet*. 2020;395:735–748. doi:10.1016/S0140-6736(19)33064-8
8. Witt JA, Werhahn KJ, Kramer G, et al. Cognitive-behavioral screening in elderly patients with new-onset epilepsy before treatment. *Acta Neurol Scand*. 2014;130:172–177. doi:10.1111/ane.12260
9. Breteler MM, de Groot RR, van Romunde LK, et al. Risk of dementia in patients with Parkinson's disease, epilepsy, and severe head trauma: a register-based follow-up study. *Am J Epidemiol*. 1995;142:1300–1305. doi:10.1093/oxfordjournals.aje.a117597
10. Sen A, Thom M, Nikolic M et al. The potential role of cyclin-dependent kinase 5 in focal cortical dysplasia. Dev Neurosci 2008; 30: 96–104. doi:10.1159/000109855

11. Scharfman HE. Alzheimer's disease and epilepsy: insight from animal models. *Future Neurol*. 2012;7:177–192. doi:10.2217/fnl.12.8
12. Shi JQ, Wang BR, Tian YY, et al. Antiepileptics topiramate and levetiracetam alleviate behavioral deficits and reduce neuropathology in APPswe/PS1dE9 transgenic mice. *CNS Neurosci Ther*. 2013;19:871–881. doi:10.1111/cns.12144
13. Vezzani A, French J, Bartfai T, et al. The role of inflammation in epilepsy. *Nat Rev Neurol*. 2011;7:31–40. doi:10.1038/nrneurol.2010.178
14. Choi DW. Glutamate neurotoxicity and diseases of the nervous system. *Neuron*. 1988;1:623–634. doi:10.1016/0896-6273(88)90162-6
15. Alapirtti T, Waris M, Fallah M, et al. C-reactive protein and seizures in focal epilepsy: a video-electroencephalographic study. *Epilepsia*. 2012;53:790–796. doi:10.1111/j.1528-1167.2012.03449.x
16. Hermann BP, Sager MA, Koscik RL, et al. Vascular, inflammatory, and metabolic factors associated with cognition in aging persons with chronic epilepsy. *Epilepsia*. 2017;58:e152–e156. doi:10.1111/epi.13891
17. Mintzer S. Metabolic consequences of antiepileptic drugs. *Curr Opin Neurol*. 2010;23:164–169. doi:10.1097/WCO.0b013e32833735e7
18. Rogawski MA, Loscher W. The neurobiology of antiepileptic drugs. *Nat Rev Neurosci*. 2004;5:553–564. doi:10.1038/nrn1430
19. Pitkanen A, Sutula TP. Is epilepsy a progressive disorder? Prospects for new therapeutic approaches in temporal-lobe epilepsy. *Lancet Neurol*. 2002;1:173–181. doi:10.1016/s1474-4422(02)00073-x
20. Hermann B, Seidenberg M, Sager M, et al. Growing old with epilepsy: the neglected issue of cognitive and brain health in aging and elder persons with chronic epilepsy. *Epilepsia*. 2008;49:731–740. doi:10.1111/j.1528-1167.2007.01435.x
21. Norton S, Matthews FE, Barnes DE, et al. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol*. 2014;13:788–794. doi:10.1016/S1474-4422(14)70136-X
22. Yuen AW, Bell GS, Peacock JL, et al. Effects of AEDs on biomarkers in people with epilepsy: CRP, HbA1c and eGFR. *Epilepsy Res*. 2010;91:187–192. doi:10.1016/j.eplepsyres.2010.07.011
23. Pylvanen V, Pakarinen A, Knip M, et al. Insulin-related metabolic changes during treatment with valproate in patients with epilepsy. *Epilepsy Behav*. 2006;8:643–648. doi:10.1016/j.yebeh.2006.02.008
24. Lopinto-Khoury C, Mintzer S. Antiepileptic drugs and markers of vascular risk. *Curr Treat Options Neurol*. 2010;12:300–308. doi:10.1007/s11940-010-0080-y
25. Eiris JM, Lojo S, Del Rio MC, et al. Effects of long-term treatment with antiepileptic drugs on serum lipid levels in children with epilepsy. *Neurology*. 1995;45:1155–1157. doi:10.1212/wnl.45.6.1155
26. Hamed SA, Hamed EA, Kandil MR, et al. Serum thyroid hormone balance and lipid profile in patients with epilepsy. *Epilepsy Res*. 2005;66:173–183. doi:10.1016/j.eplepsyres.2005.08.004