

Levetiracetam administration is correlated with lower mortality in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes: a retrospective study

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Abstract

Background: Studies on the relationship between antiepileptic drug (AED) administration and clinical outcomes in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) remain scarce. Levetiracetam (LEV) is an AED that is neuroprotective in various neurologic disorders. This study aimed to determine the impact of LEV on the outcome of MELAS.

Methods: A retrospective, single-center study was performed based on a large cohort of patients with MELAS with a history of seizures ($n=102$). Decisions on antiepileptic therapies were made empirically. Patients were followed up for 1 to 8 years (median, 4 years) and divided into 2 groups based on whether LEV was administered (LEV or non-LEV). The modified Rankin scale (mRS) scores and mortality risks were analyzed in all patients.

Results: LEV, carbamazepine, benzodiazepines, topiramate, oxcarbazepine, valproate, and lamotrigine were administered in 48, 37, 18, 13, 11, 9, and 9 patients, singly or in combination, respectively. The mean mRS score of the LEV group ($n=48$) was lower than that of the non-LEV group ($n=54$; mean \pm standard deviation, 2.79 ± 1.47 vs. 3.83 ± 1.93 , $P=0.006$) up to the end of the study. Nevertheless, there was no difference in the proportion of subjects without disability (mRS ranging 0–1) between the groups ($P=0.37$). The multivariate regressions revealed that LEV treatment was associated with lower mRS scores (odds ratio 0.32, 95% confidence interval [CI] 0.15–0.68, $P=0.003$) and mortality rates (hazard ratio 0.24, 95% CI 0.08–0.74, $P=0.013$). There was a significant difference in the Kaplan-Meier survival curves between the groups ($\chi^2=4.29$, $P=0.04$).

Conclusions: The LEV administration is associated with lower mortality in patients with MELAS in this retrospective study. Further laboratory research and prospective cohort studies are needed to confirm whether LEV has neuroprotective effects on patients with mitochondrial diseases.

Keywords: Syndrome; Seizures; Epilepsy; Anticonvulsants; Levetiracetam; Survival analysis

Introduction

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS; OMIM 540000) is a mitochondrial syndrome characterized by recurrent stroke-like episodes (SLEs) that are commonly associated with epileptic seizures.^[1,2] In clinical practice, the same treatment is often used for epileptic seizures in MELAS as for those resulting from other causes. However, this management is not evidence-based because few studies

have measured the efficacy of antiepileptic drug (AED) administration on patients with MELAS. Some AEDs, such as valproate (VPA) and carbamazepine (CBZ), are potentially mitochondrion toxic,^[3,4] while some others, such as levetiracetam (LEV), have beneficial effects on mitochondrial function in non-mitochondrial diseases.^[5-7] To examine the impact of LEV on the prognosis of MELAS, we retrospectively analyzed the disability and mortality of a cohort of patients with MELAS in whose clinical course the epileptic seizures were present.

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.1097/CM9.0000000000000061

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Chinese Medical Journal 2019;132(3)

Received: 21-11-2018 Edited by: Li-Shao Guo

Methods

Ethical approval

The study was approved by the local ethics committee. All patients or their guardians by statute provided informed consent prior to their inclusion in this study.

Study design

This is an observational, retrospective, single-center study to determine whether LEV administration is associated with MELAS outcome. The patients with MELAS included in this study cohort visited or were referred to the local hospital from January 2008 to March 2015. Patients were followed up from their 1st visit to March 2016. The median follow-up period was 4 years (range, 1–8 years). Through a face-to-face visit or telephone interview, we obtained the medical history of each patient, including clinical manifestations, and dose and period of AED administration. The patients were divided into the LEV or non-LEV group based on whether they had a prescription for LEV, either alone as a monotherapy or as an adjunctive treatment. The disability of patients was evaluated using the modified Rankin Scale (mRS) with age-specific modification at last follow-up.^[8] A favorable clinical outcome was defined as an mRS score of 0–1. The treatment responses of the AEDs in all survived patients were also assessed. Clinical seizure reduction within the last year of the study was defined as follows: 0, no change or a <50% decrease in epileptic frequency from baseline; 1, a ≥50% decrease in epileptic frequency from baseline; 2, complete seizure freedom.

Patients selection

The patients who were included in this study fulfilled these criteria:

- MELAS diagnosis by meeting criteria that have been previously reported^[9,10]: a definitive mitochondrial gene mutation and/or mitochondrial abnormalities on muscle biopsy, such as ragged-red fibers.
- Manifestation of epileptic seizures and regular administration of oral AEDs from the start of the follow-up period. AED selection decisions were made empirically by patients' physicians based on semiology and electroencephalography (EEG) findings.

The patients were excluded if they met one or more of the following:

- Incomplete antiepileptic therapy data.
- A change in the type of oral AED being administered during follow-up.

Statistical analyses

Statistical analyses were performed using Stata 12.0 SE (Stata Corporation, College Station, TX, USA). Data are reported as mean ± standard deviation (SD). The Wilcoxon rank-sum test was used to detect differences between 2 groups with continuous variables, and the Chi-squared or Fisher's exact tests were used to analyze categorical

variables. Kaplan-Meier curves were drawn to estimate the survival function. The log-rank test was used to determine whether the survival rates between the LEV and the non-LEV groups were significantly different. Univariate and multivariate analyses were performed using logistic regression and Cox proportional-hazards model. Variables that were significantly different between the groups were further included as possible confounding factors in the regression analysis. *P* values <0.05 were considered statistically significant.

Results

AED administration in this cohort

We successfully followed up 121 patients with MELAS. Of these, 102 patients met the appropriate criteria and were included in our analyses. LEV, CBZ, benzodiazepines (BDZ), topiramate (TPM), oxcarbazepine (OXC), VPA, and lamotrigine (LTG) were administered in 48, 37, 18, 13, 11, 9, and 9 subjects, respectively. LEV was the most commonly administered (47.1% [48/102] subjects) in this cohort. Twenty subjects in the LEV group (*n*=48) received combination therapy, with BDZ (*n*=6), CBZ (*n*=3), OXC (*n*=2), TPM (*n*=2), LTG (*n*=1), VPA (*n*=1), CBZ + BDZ (*n*=1), LTG + BDZ (*n*=1), TPM + OXC (*n*=1), TPM + OXC + BDZ (*n*=1), and VPA + LTG (*n*=1). In the non-LEV group (*n*=54), AEDs that were prescribed were as follows: CBZ (*n*=23), OXC (*n*=5), TPM (*n*=4), BDZ (*n*=3), LTG (*n*=2), VPA (*n*=1), CBZ + VPA (*n*=4), CBZ + BDZ (*n*=2), TPM + OXC (*n*=2), CBZ + TPM (*n*=1), CBZ + LTG (*n*=1), TPM + VPA (*n*=1), TPM + LTG (*n*=1), TPM + BDZ (*n*=1), TPM + LTG + BDZ (*n*=2), and CBZ + BDZ + VPA (*n*=1).

The average durations of AED administration of the LEV and non-LEV groups were 4.1 ± 2.6 and 5.5 ± 4.1 years, respectively, which were not significantly different (*Z* = 1.577, *P* = 0.11). Demographic data and the major clinical manifestations of the LEV and non-LEV groups at baseline are listed in Table 1. Differences in the prevalence of deafness and diabetes were significant between the groups ($\chi^2 = 5.4803$ for deafness, both *P* = 0.02).

Comparison of mRS scores between the 2 groups

The mRS scores are illustrated in Figure 1. At the end of the study, the mean mRS score of the LEV group (*n*=48) was lower than that of the non-LEV group (*n*=54; 2.79 ± 1.47 vs. 3.83 ± 1.93, *Z* = 2.746, *P* = 0.006). However, the proportion of patients with a favorable outcome (mRS score of 0–1) was not different between the groups (16.7% vs. 9.3% in the LEV vs. non-LEV groups, respectively; *P* = 0.37). Furthermore, LEV administration was a protective factor that favored lower mRS scores in the multiple variant logistic regression, after adjustments for age of onset, gender, disease duration, prevalence of deafness, and diabetes (odds ratio [OR] 0.32, 95% confidence interval [CI] 0.15–0.68, *P* = 0.003).

Table 1: Demographic characteristics and major clinical manifestations at baseline

Parameters	LEV group (n=48)	Non-LEV group (n=54)	Statistics	P
Male (gender), n (%)	29 (60.4)	28 (51.9)	0.7561*	0.39
Age of onset (years), Median (IQR)	12 (5–18)	14 (8–20)	1.296†	0.20
Age at baseline (years), Median (IQR)	15 (10–20)	20 (11–29)	1.731†	0.08
Disease duration at baseline (years), median (IQR)	3 (1–5)	3 (1–9)	0.875†	0.38
Headache, n (%)	40 (83.3)	40 (74.1)	1.2879*	0.26
Cortical blindness, n (%)	34 (70.8)	38 (70.4)	0.0026*	0.96
Deafness, n (%)	20 (41.7)	35 (64.8)	5.4803*	0.02
Hemiplegia or hemianesthesia, n (%)	27 (56.3)	30 (55.6)	0.0050*	0.94
Aphasia, n (%)	20 (41.7)	28 (51.9)	1.0581*	0.30
Constipation or diarrhea, n (%)	17 (35.4)	22 (40.7)	0.3050*	0.58
Short stature, n (%)	12 (25.0)	23 (42.6)	3.4894*	0.06
Low BMI, n (%)	11 (22.9)	21 (38.9)	3.0110*	0.08
Diabetes, n (%)	6 (12.5)	18 (33.3)	–	0.02

* χ^2 value; †Z value. Short stature and low BMI are defined as less than the third percentile or mean $-2 \times$ SD of age. –: no data; BMI: Body mass index; IQR: Interquartile range; LEV: Levetiracetam.

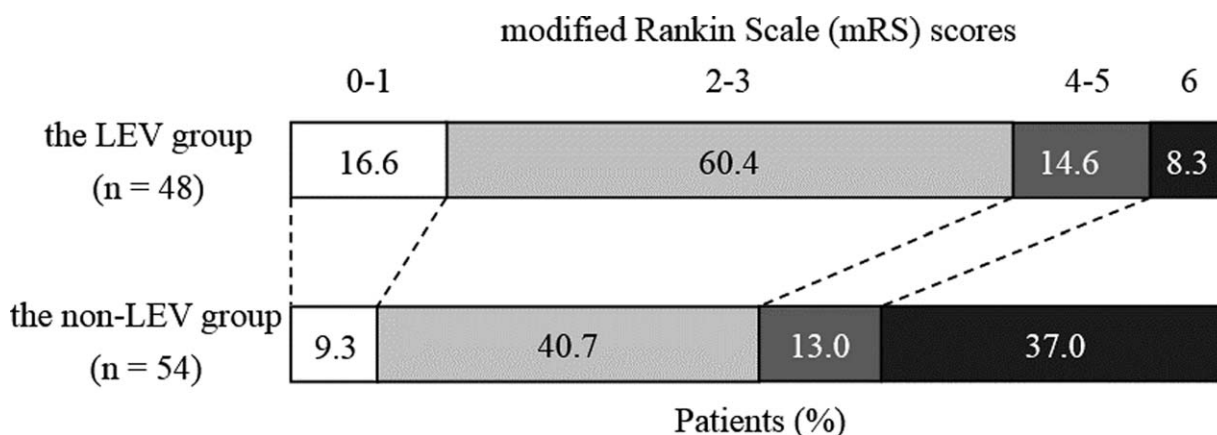


Figure 1: The distribution of mRS scores of the subjects in the LEV and the non-LEV groups. The difference of proportion of subjects with favorable outcome (mRS ranging 0-1) between the two groups was unremarkable ($P=0.37$). LEV: Levetiracetam; mRS: Modified Rankin Scale.

Table 2: Responses to the antiepileptic therapies

Seizure reduction	LEV group (n=48)	Non-LEV group (n=54)	χ^2	P
0*, n (%)	13 (27.1)	33 (61.1)	11.8838	0.001
1†, n (%)	8 (16.7)	3 (5.6)		0.070
2‡, n (%)	27 (56.3)	18 (33.3)	5.4132	0.020

*No change or a decrease of $<50\%$ in the epileptic frequency from baseline. †A decrease of $\geq 50\%$ in the epileptic frequency from baseline. ‡Complete seizure freedom. LEV: Levetiracetam.

Comparison of the response to antiepileptic treatments between the two groups

Treatment response to AEDs was evaluated based on clinical seizure reduction within the last 1 year of follow-up. As listed in Table 2, the results demonstrated a better seizure reduction in the LEV group compared with the non-LEV group. Of the 48 subjects in the LEV group, the average dosage of LEV was 0.029 ± 0.013 g/kg per day in the last year of follow-up. Patients who achieved complete seizure freedom (level 2) used a smaller dose ($0.024 \pm$

0.012 g/kg per day) than those with seizure reduction levels of 0 (0.031 ± 0.010 g/kg per day, $Z=2.140$, $P=0.03$) and 1 (0.040 ± 0.016 g/kg per day, $Z=2.279$, $P=0.02$). The duration of LEV administration was not correlated with seizure reduction ($r=-0.0211$, $P=0.84$).

Survival analysis of LEV and non-LEV groups

Up to the end of the follow-up or death, the average disease duration of this cohort was 8.8 ± 6.1 years. The median age of subjects in the LEV group was 19 years (interquartile

range [IQR] 13–26) and <24 years (IQR 18–32) in the non-LEV group ($Z=2.621, P=0.01$). The median disease duration of subjects in the LEV group was also less than that in the non-LEV group (6 [IQR 4–10] vs. 9 [IQR 5–13], $Z=2.180, P=0.03$). By the end of the last interview, 4 subjects in the LEV group had died, while 20 had died in the non-LEV group, leading to significantly lower mortality rate in the LEV group (8.3%) compared with the non-LEV group (37.0%; $\chi^2=10.2394, P=0.001$).

Of the deceased patients in the LEV group, death was attributed to SLEs with or without seizure ($n=2$), sudden unexpected death (SUD; $n=1$), and pseudo-intestinal obstruction ($n=1$). Of the deceased patients in the non-LEV group, death was attributed to status epilepticus ($n=6$), pseudo-intestinal obstruction ($n=4$), SLEs without seizure ($n=2$), nephropathy with cardiac failure ($n=1$), patent foramen ovale with pneumonia ($n=1$), traumatic brain injury ($n=1$), SUD ($n=1$), and reason unknown ($n=4$).

The Kaplan-Meier curves of the 2 groups are illustrated in Figure 2. There was a significant difference between the curves ($\chi^2=4.29, P=0.04$). Using a Cox proportional-hazards model, after adjusting for age of onset, gender, and prevalence of deafness and diabetes, we found that LEV

administration was significantly associated with survival (hazard ratio [HR] 0.24, 95% CI 0.08–0.74, $P=0.013$) [Table 3].

Discussion

The key findings of this study are that LEV administration was associated with a lower mRS score at follow-up compared with non-LEV-treated patients. However, there was no overall effect of LEV administration on the proportion of patients with a favorable outcome. Nonetheless, LEV administration was associated with lower mortality rates and improved survival, indicating a possible protective effect with this treatment.

Epilepsy is a common manifestation of MELAS, accounting for 56.3% to 90% according to different reports.^[9,11,12] Previous work has shown the prevalence of epilepsy was 94.2% in Chinese patients with MELAS.^[2] Both focal and generalized seizures can occur in patients with MELAS; however, focal seizures are the predominant type, especially when patients had SLEs.^[1,13,14] Based on the current recommendations for AED selection for epilepsy,^[15,16] LEV and CBZ are the most commonly prescribed for patients with MELAS. However, concerns have been raised due to the mitochondrion-toxicity of some AEDs. VPA showed liver toxicity in patients with Alpers-Huttenlocher syndrome due to *POLG* mutations.^[17] Furthermore, AEDs such as phenobarbital, CBZ, phenytoin, OXC, ethosuximide, zonisamide, TPM, gabapentin, and vigabatrin may have potentially harmful effects on mitochondrial function, whereas LEV, LTG, and lacosamide have relatively low mitochondrion toxicity and are recommended treatments.^[3,4]

The MELAS shows high mortality and morbidity with neurologic deterioration over time.^[11,18] The average mRS score is 3.3 (SD 1.8) in Chinese patients with MELAS.^[2] In this study, mRS scores at baseline were not available because not all patients had been suffering from acute SLEs when they were enrolled. A SLE may recover a few weeks later, making it difficult to compare mRS scores at baseline. Gender, age of disease onset, age at baseline, and disease duration were not significantly different between the groups; therefore, we could reasonably speculate that patients showed similar severity at baseline. Up to the end of the study or death, patients in the LEV group had

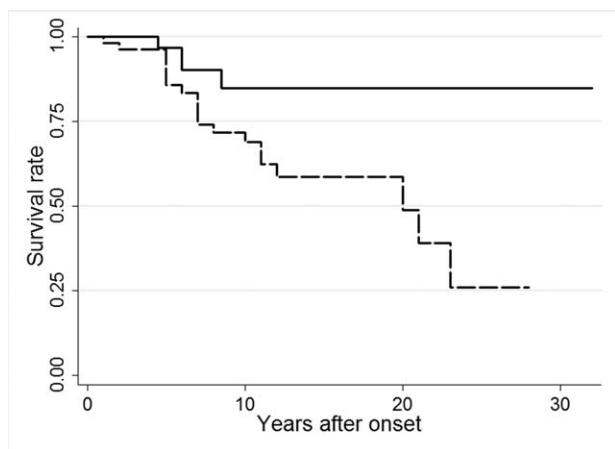


Figure 2: The Kaplan-Meier survival curve of the LEV group was significantly different from that of the non-LEV group ($\chi^2=4.29, P=0.04$), demonstrating patients with LEV administration had a lower risk of mortality than those without. LEV: levetiracetam.

Table 3: Univariate and multivariate analyses using the Cox proportional-hazards model

Risk factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age of onset	1.00	0.96–1.04	0.956	1.01	0.96–1.06	0.705
Male	0.87	0.39–1.95	0.738	1.03	0.42–2.52	0.953
Deafness	0.50	0.21–1.19	0.118	0.30	0.11–0.81	0.018
Diabetes	0.99	0.42–2.32	0.975	1.07	0.42–2.52	0.953
LEV administration	0.34	0.11–0.99	0.048	0.24	0.08–0.74	0.013

CI: Confidential interval; HR: Hazard ratio; LEV: Levetiracetam.

lower mRS scores compared with the non-LEV group; therefore, the protective effect of LEV on mRS score was further confirmed by multivariate logistic regression. Unfortunately, LEV administration did not improve the functional outcome of patients with MELAS, because the incidence of favorable outcomes was not different between the groups. The divergence in mRS scores may originate from different mortality rates, which were further demonstrated by distinct survival curves between groups. Furthermore, multivariate Cox regression analysis showed that LEV administration could extend the lifespan of patients with MELAS. While other factors, including mutation type, mutation loads, involvement of vital organs, complications, and disease severity can also contribute to the clinical outcome.^[19-22]

According to our results, none of the deceased patients in the LEV group suffered status epilepticus at death, and patients who were administered LEV showed a better clinical response to the antiepileptic treatments. These findings suggested that the protective effect of LEV might be due to seizure reduction in patients with MELAS. However, it is notable that the seizures in some patients were controlled more easily with a low LEV dosage, demonstrating that the protective effect of LEV was not dose dependent. In addition, LEV may be protective for mitochondrial function. Synaptic vesicle protein 2A (SV2a) is the molecular target of LEV, which is expressed in mitochondria.^[5] Rogers *et al*^[7] have found that LEV increases the mitochondrial membrane potential in neuronal cells *in vitro*, demonstrating that the antiepileptic action of LEV is associated with mitochondrial energy metabolism regulation. In addition, some reports have indicated that LEV may benefit myoclonus due to mitochondrial dysfunction^[23,24]; however, this is contradicted in a different report.^[25] Gibbs *et al*^[6] have highlighted that LEV injections do not terminate seizure or reduce EEG spike frequency in a rat model of status epilepticus, but improve biochemical parameters, including complex I activity. Moreover, the antiepileptic effects of LEV are time and dose dependent in animal models. Cheng *et al*^[26] have used a rhesus monkey Coriaria lactone-induced status epilepticus model, and concluded that the development of status epilepticus was inhibited when LEV was administered 30 minutes before seizure induction, and its neuroprotective action was dose dependent. Gibbs and Cock^[27] have also shown that LEV does not protect mitochondrial function when administered 5 hours after seizure onset.

Several limitations of this study should be noted. First, the treatment response to AEDs was not evaluated due to our follow-up protocol. Therefore, we could not precisely identify whether an ictal event was an epileptic seizure or a pseudo-seizure during phone interview. Second, this study has a retrospective and observational design and inherent bias was difficult to avoid. For example, LEV and other novel AEDs are more expensive than the traditional AEDs, such as CBZ and BDZ, in China. This indicates that domestic income and family care are possible confounding factors. A prospective study in the future would better address this limitation. Third, our cohort with over 100 patients is large for rare diseases,

such as MELAS; however, it is too small to perform some statistical adjustments for some possible confounding factors. Hence, further research using animal models or cell lines with respiratory chain dysfunction is warranted to confirm whether LEV has mitochondrion-protective effects.

Conclusion

Our retrospective analysis of patients with MELAS and seizures revealed that LEV administration was associated with a lower mortality rate within a median follow-up of 4 years, although there was no effect on functional outcome, as measured by mRS scores of 0–1. Further laboratory research and prospective cohort studies are needed to confirm whether LEV has neuroprotective effects on patients with mitochondrial diseases.

Funding

This work was supported by the grants from the Ministry of Science and Technology of China (No. 2011ZX09307-001-07), the National Natural Science Foundation of China (No. 81571219), and the Beijing Municipal Science and Technology Commission (No. Z151100003915126).

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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How to cite this article: Zhang Z, Zhao DH, Zhao XT, Zhang X, Xiong H, Bao XH, Yuan Y, Wang ZX. Levetiracetam administration is correlated with lower mortality in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes: a retrospective study. *Chin Med J* 2019;132:269–274. doi: 10.1097/CM9.00000000000000061