Clinical Neurology and Neurosurgery 184 (2019) 105402

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Prognostic utility of hypsarrhythmia scoring in children with West syndrome after ketogenic diet

Yunjian Zhang[1], Lifei Yu[1], Yuanfeng Zhou, Linmei Zhang, Yi Wang, Shuizhen Zhou*

Department of Pediatric Neurology, Children's Hospital of Fudan University, China

ARTICLE INFO

Keywords:
West syndrome
Ketogenic diet
EEG
Hypsarrhythmia

ABSTRACT

Objective: The aim of this study was to evaluate the clinical efficacy and electroencephalographic (EEG) changes of West syndrome after ketogenic diet (KD) therapy and to explore the correlation of EEG features and clinical efficacy.

Patients and methods: We retrospectively studied 39 patients with West syndrome who accepted KD therapy from May 2011 to October 2017. Outcomes including clinical efficacy and EEG features with hypsarrhythmia severity scores were analyzed.

Results: After 3 months of treatment, 20 patients (51.3%) had ≥50% seizure reduction, including 4 patients (10.3%) who became seizure-free. After 6 months of treatment, 4 patients remained seizure free, 12 (30.8%) had 90–99% seizure reduction, 8 (20.5%) had a reduction of 50–89%, and 15 (38.5%) had < 50% reduction. Hypsarrhythmia scores were significantly decreased at 3 months of KD. They were associated with seizure outcomes at 6 months independent of gender, the course of disease and etiologies. Patients with a hypsarrhythmia score ≥8 at 3 months of therapy may not be benefited from KD.

Conclusion: Our findings suggest a potential benefit of KD for patients with drug-resistant West syndrome. Early change of EEG after KD may be a predictor of a patient's response to the therapy.

1. Introduction

West syndrome is an age-related, specific epileptic encephalopathy that begins during early infancy. It is characterized by a unique type of seizure called infantile spasms and gross EEG abnormalities of hypsarrhythmia [1]. It is a rare disease, with an estimated incidence of 2–3.5 per 10,000 live births [1], and the etiologies of it are extensive and diverse [2]. Recent guidelines recommend the use of adrenocorticotropic hormone steroids, or vigabatrin, as the first-line treatment for West syndrome [3,4]. However, it remains one of the most challenging epilepsies to treat. An alternative therapeutic option is the ketogenic diet (KD), which may be useful and, according to some authors, should be used as early as possible [5–7].

The KD, with a high-fat and low-carbohydrate content, has been used in children with refractory epilepsy since the 1920s and has been shown to be beneficial for the treatment of drug-resistant epilepsy. It has been reported that a median rate of 64.7% of patients experienced a spasm reduction > 50% after KD, and the median spasm-free rate was 34.6% [6]. However, little attention has been paid to identify predictors of the response to the KD.

There is a paucity of published data on the EEG features of patients with West syndrome after KD therapy. It has been reported that a classification of pre-hypsarrhythmic EEGs could enable an early treatment option for West syndrome [8]. It has been observed that the lower IQ of patients with tuberous sclerosis complex was significantly associated with higher hypsarrhythmia severity scores on EEG [9]. However, the relationship between EEG features, especially hypsarrhythmia severity scores, and the clinical efficacy of the KD is unknown in patients with West syndrome. Therefore, the purpose of this study was to examine the effects of the KD on clinical and EEG features in children with drug-resistant West syndrome and to evaluate whether EEG features predict KD response.

2. Patients and methods

2.1. Patients

In our center, patients with West syndrome were treated with adrenocorticotropic hormone (ACTH), or oral corticosteroids as the first-line therapy. Patients who failed to first-line therapy or whose

* Corresponding author at: 399 Wanyuan Road, Minhang District, Shanghai, China.
E-mail address: szzhou@shmu.edu.cn (S. Zhou).
[1] Co-first author.

https://doi.org/10.1016/j.clineuro.2019.105402
Received 27 November 2018; Received in revised form 4 May 2019; Accepted 25 June 2019
Available online 26 June 2019
0303-8467/

parents refused to use corticosteroids were treated with antiepileptic drugs (AEDs). Those who still experienced epileptic spasms despite the therapy with at least 2 appropriate AEDs were advised to receive KD. Patients diagnosed with drug refractory West syndrome, characterized by epileptic spasms, hypsarrhythmia on the EEG, and psychomotor retardation were included in our study. All information was obtained retrospectively. Patients were started on the diet after conventional pharmacologic therapy failed. Informed parental consent was obtained before the start of the diet. Patients were excluded if their parents did not adhere to providing the diet or they were not suitable for the KD—for example, those who had any deficiencies of the transportation or oxidation of fatty acids, or had deficiency of pyruvate carboxylase.

Patients were admitted to our hospital for diet initiation. The classic 4:1 ratio KD (fat:protein plus carbohydrate) without fasting was used, and KD therapy was given for at least 6 months. Plant fat such as olive oil and coconut oil accounted for about 70% of the amount of fat. At least 1 g of protein per kg body weight from animal sources were included in the diet. Carbohydrate-containing foods such as fruits and vegetables were added. Patients continued to receive AEDs treatment during the KD. Seizure frequency was documented daily, using seizure diaries kept by the families, which were reviewed at each clinic visit.

2.2. MRI and EEG

We retrospectively investigated the abnormalities revealed by magnetic resonance imaging (MRI) and electrographic patterns of patients. Abnormalities depicted by MRI were classified as lesional (e.g., tuberous sclerosis, cortical dysplasia, gray matter heterotopia, cerebral softening) or developmental (e.g., mild dilatation of the ventricles or subarachnoid spaces).

Electrographic patterns were measured through video-EEG monitoring prior to KD therapy and 3 months after KD therapy. EEGs were recorded by the international 10–20 system of electrode placement and performed when patients were both awake and asleep. Severity shown by EEG was quantified by the criteria proposed by Kramer et al [10]. Scoring for each patient was reviewed by two of the authors; if no consensus was reached, disagreements were resolved by mutual discussion in the 3-member team. All EEG reviewers were blinded to treatment status and epilepsy outcome.

According to the hypsarrhythmia scoring system described by Kramer [10], a single, relatively uniform 10-second segment that contained the most representative and severe hypsarrhythmic part of the tracing was chosen for scoring. Items such as disorganization of background, percentage of delta activity, amplitude of slow waves, and frequency of spikes and sharp waves were scored, each on a scale from 0 to 3, according to their severity. The items, namely electrodecremental discharges, burst suppression in sleep, absence of normal sleep pattern, and relative normalization, were scored as present (score of 1) or absent (score of 0).

2.3. Seizure frequency

Seizure reduction, which included all types of seizures, was obtained by comparing seizure frequency after treatment with the baseline level. The outcome was classified as $< 50\%$, 50–89%, 90–99%, or seizure-free. Treatment response was defined as $\geq 50\%$ reduction in seizure frequency. Patients who had a $< 50\%$ seizure frequency reduction were defined as non-responders.

2.4. Statistical analysis

The statistical analysis was carried out with SPSS software version 22 for Windows (IBM Corp., Armonk, NY, USA). General characteristics of patients were represented as mean ± standard deviation (SD) or median with range (minimum to maximum) for continuous data and n (%) for categorical data. The continuous data were compared by applying Student's *t*-test or Mann-Whitney test if required. Chi-square test or Fisher's exact test wherever necessary was applied to compare categorical data. P value < 0.05 was considered significant. Multiple logistic regression was done to find significant predictor variables. Diagnostic accuracy of hypsarrhythmia severity scores to predict epilepsy outcome was assessed using receiver operating characteristic (ROC) curves and determining the area under ROC curves (AUC). The cut-point for dichotomizing the scores was defined using the Youden index.

3. Results

3.1. General characteristics of patients

A total of 39 patients (21 males, 18 females) who met the inclusion criteria were included between May 2011 and October 2017 at the Children's Hospital of Fudan University. The median ages at seizure onset and initiation of the KD were 6.0 months (range: 3–13 months) and 18.0 months (range: 6–36 months), respectively. The course of disease ranged from 3 to 30 months.

All children had epileptic spasms as their predominant seizure type at the onset of seizures. Twenty-three percent (9/39) had other seizure types (myoclonic, focal, generalized tonic–clonic) at the time of KD initiation, but epileptic spasms were clearly predominant.

All patients underwent magnetic resonance imaging (MRI). Eighteen patients (46.2%) had abnormalities noted on MRI scans; 13 had lesional and 5 had developmental abnormalities. Metabolic screening in the form of blood ammonia, lactate, tandem mass spectrometry (TMS), and urinary gas chromatography mass spectroscopy (GCMS) were negative in all patients. In our study, fourteen of thirty-nine (35.9%) patients received hormonal therapy before KD. Five patients received ACTH, while other nine received oral corticosteroids. Two patients with TSC received vigabatrin. All patients had received at least two types of antiepileptic drugs (AEDs) before being given the KD. The baseline characteristics of the study group are presented in Table 1.

Table 1
Patients' demographics and baseline characteristics.

Characteristics	(n = 39)
Median age at seizure onset, months	6.0 (3 to 13)
Median age at initiation of KD, months	18.0 (6 to 36)
Course of disease, months	12.0 (3 to 30)
Gender, Male (%)	21 (53.8)
Etiology	
Genetic	6 (15.4)
Structural	10 (25.6)
Unknown	23 (59.0)
Seizure types	
Epileptic spasms only	30 (76.9)
Spasm with other types	9 (23.1)
Number of AEDs used at the initiation of diet	
Two	21 (53.9)
Three	16 (41.0)
Four	2 (5.1)
AEDs used at the initiation of diet (only top five listed)	
Valproate	35 (89.7)
Topiramate	24 (61.5)
Levetiracetam	24 (61.5)
Clonazepam	9 (23.1)
Lamotrigine	3 (7.7)
MRI abnormality	
Lesional	13 (33.3)
Developmental	5 (12.8)
Normal	21 (53.8)

Data are represented as median (range: min. to max.) for continuous data and n (%) for categorical data.

The side effects noted in this study included hyperlipidemia (n = 12), vomit at start (n = 6), drowsiness (n = 6), fatigue (n = 5), constipation (n = 4), and diarrhea (n = 2). There were no dropouts during this study.

3.2. Efficacy of the diet

Three months after initiation of KD, 20 (51.3%) showed a reduction in seizure frequency of more than 50%, including 13 (33.3%) with a reduction of 50–89%, 3 (7.69%) with 90–99% seizure reduction and 4 (10.3%) with seizure-free. After 6 months of treatment, 4 (10.3%) patients remained seizure-free, 12 (30.8%) had 90–99% seizure reduction, 8 (20.5%) had a reduction of 50–89%, and 15 (38.5%) had < 50% reduction.

3.3. Evaluation of early EEG changes

Hypsarrhythmia scores before KD ranged from 8 to 14 with a mean ± standard deviation of 10.05 ± 1.36. There was no significant difference in hypsarrhythmia scores before KD among children with different efficacy at 6 months of therapy. However, in the present study, the mean score significantly decreased after 3 months of KD, with 7.62 ± 2.36. Mean score for patients with good efficacy was 6.29 ± 1.90, which was significantly lower than the invalid cases whose mean score was 9.73 ± 1.16. After 3 months of treatment, 19 patients had < 50% seizure reduction. Among these patients, 15 were still non-responders, while other 4 patients achieved ≥50% seizure reduction after 6 months of KD. The EEGs of the fifteen non-responders showed hypsarrhythmia score ≥8 after 3 months of treatment, and eight of them did not achieve any reduction of hypsarrhythmia score. Fig. 1 shows the EEG examples before and after the KD.

3.4. Factors related to clinical efficacy

Several factors were analyzed for potential value in predicting response to the KD. No obvious correlation was seen between improvement in seizure control and gender, ages at seizure onset or initiation of the KD, underlying causes, and numbers of AEDs received at the initiation of KD therapy. There was no significant difference between patients with or without structural abnormalities on KD efficiency. There was also no significant difference between mean ketone levels among responders whose level was 2.98 ± 0.38 mmol/L and non-responders with a mean level of 2.86 ± 0.23 mmol/L.

Table 2
Factors associated with clinical efficacy at 6 months of KD.

Factors	OR value	95% CI	*P* value
Gender	0.794	0.061–10.404	0.861
Course of disease	0.967	0.819–1.141	0.689
Etiologies			
Unknown	1.000		
Genetic	0.619	0.016–24.146	0.798
Structural	0.120	0.005–3.105	0.201
Hypsarrhythmia scores at 3 months of KD	0.136	0.035–0.530	0.004*

The variables assignment: Gender (male = 1, female = 2), Efficacy (invalid = 0, valid = 1). Etiologies were converted to dummy variables with "unknown" as reference.

* Significant values ($P < 0.05$).

After multivariate regression to adjust for potentially predictive factors, only hypsarrhythmia scores at 3 months of KD remained statistically significant. Hypsarrhythmia scores at 3 months of KD were associated with seizure outcomes at 6 months independent of gender, the course of disease and etiologies. Factors associated with clinical efficacy at 6 months of KD were shown in Table 2.

The diagnostic accuracy of hypsarrhythmia scores at 3 months of KD to predict epilepsy outcome was further assessed using ROC curve analysis. The area under the ROC curve was 0.960 (95% CI: 0.901–1.000). Fig. 2 shows that the hypsarrhythmia score had AUC ≥ 0.95 for discrimination of responders and non-responders after

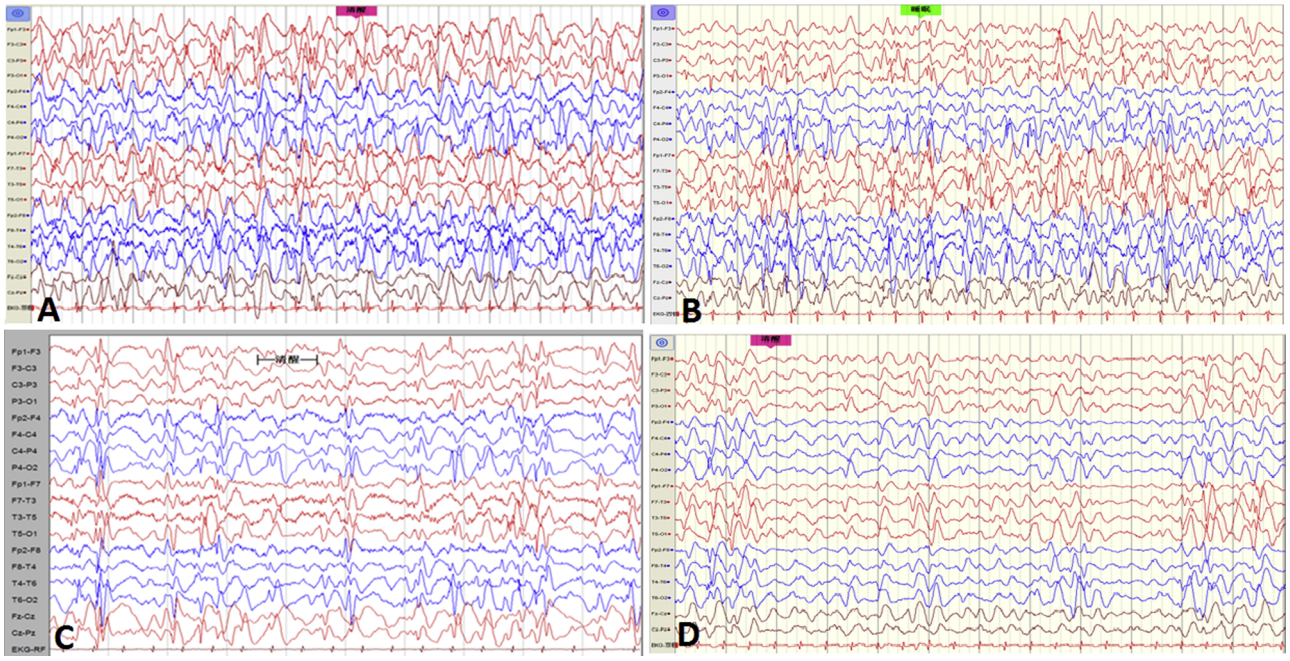

Fig. 1. EEG examples before and after the KD with different hypsarrhythmia scores.
(A) A pre-treatment hypsarrhythmia score of 12. It was a chaos of background without synchrony or gradient. Diffuse delta activity was 100% and its voltage was > 500 u V. Spikes at a frequency of ≥1/s. (B) A post-treatment hypsarrhythmia score of 10. It was also a chaos of background. Diffuse delta activity was ≥75% but < 100% and its voltage was 200–500 u V. Spikes at a frequency of ≥1/s. (C) A pre-treatment hypsarrhythmia score of 8. Partially formed gradient with some synchrony. Diffuse delta activity was ≥75% but < 100% and its voltage was 200–500 u V. Spikes at a frequency of ≥1/s. (D) A post-treatment hypsarrhythmia score of 5. Good gradient and synchrony. Diffuse delta activity was ≥50% but < 75% and its voltage was 200–500 u V. Spikes at a frequency of 1/5s – 1/s.

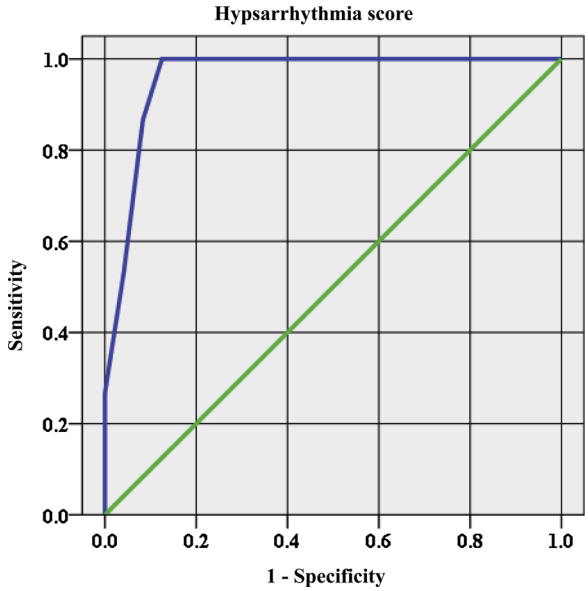

Fig. 2. Receiver operating characteristic (ROC) plots for diagnostic accuracy of hypsarrhythmia scores for epilepsy outcome.
The area under the curve was 0.960 (95% CI: 0.901–1.000). The best cut-off point was hypsarrhythmia score ≥8 with Youden index of 0.875.

6 months of KD therapy. Based on the ROC curve, patients with hypsarrhythmia score ≥8 had unfavorable epilepsy outcomes, and it was defined as the cut-point, with sensitivity and specificity of 100% and 87.5%, respectively.

4. Discussion

Our results suggest that the KD may be effective for treatment of drug-refractory West syndrome. We found that 61.5% of the patients achieved ≥50% seizure reduction 6 months after KD therapy, and 4 children were seizure-free. Our efficacy parallels that reported in previous studies and contributes to further support of the effectiveness of KD in the treatment of refractory epilepsy [6]. We also found that early improvement of EEG results after KD may help to predict a patient's response to the therapy.

It was observed that West syndrome was one of the epileptic encephalopathies in which the KD produced the best results [11–14]. Recently, the varying efficacy of KD therapy on individual patients has led to the search for predictors that might indicate positive or negative response to the therapy. It has been reported that the treatment delay in responders was significantly shorter than in non-responders [15]. You et al. reported that earlier use of the KD in patients with West syndrome may play a key role in preventing the evolution of West syndrome to Lennox-Gastaut syndrome (LGS) [16]. However, in our study, we found no significant difference between outcome groups in relation to gender, age at seizure onset or initiation of the KD. In our samples, differences in etiologies between responders and non-responders were not statistically significant. There was also no difference in ketone levels between different outcome groups.

Currently, few studies are examining the relationship between EEG characteristics and seizure reduction during KD treatment. A study of 37 patients undergoing KD therapy showed that patients with ≥10% improvement in spikes frequency of routine EEGs at 1 month were more than six times as likely to be KD responders [17]. Walker et al. reported that patients with the lowest encephalopathy scores on last EEG strongly correlated with > 95% seizure reduction after KD [18]. Ebus et al. described a correlation between nocturnal reduction of interictal epileptic discharge index (IED-index) at 6 weeks and seizure reduction in the follow-up period [19]. Zhang et al. retrospectively studied 47 patients with LGS who accepted KD therapy and found that patients with early improved EEG background and reduced IEDs achieved more seizure reduction than those without early EEG improvement [20]. However, the results obtained from these previously published studies may not be specific to West syndrome. To our knowledge, the data herein are the examination of hypsarrhythmia scores in responders versus non-responders in patients with drug-refractory West syndrome on the KD.

The hypsarrhythmia score criteria applied in our study were a widely used traditional method of EEG analysis that was first devised by Kramer et al [10]. Although other abbreviated scales to ascertain hypsarrhythmia have been reported by Muzykewicz et al and Mytinger et al [9,21], they are simplified and may not have investigated potential significance of the various hypsarrhythmic variant patterns. The hypsarrhythmia scoring system we used in this study includes more items. Although this may add to the complexity of application, all the items are relevant to the severity of hypsarrhythmia. This may be useful in the clinical evaluations and prognostication of patients with West syndrome. Muzykewicz et al. found that lower follow-up IQs in patients were significantly associated with higher hypsarrhythmia severity scores, the presence of background disorganization, the absence of normal sleep patterns, and a lower degree of treatment success [9]. All patients in our study had hypsarrhythmia and were refractory to medications. The results showed a higher score of 10.05 ± 1.36 prior to KD. In this study, we have showed that there was no significant difference in hypsarrhythmia scores before KD among children with different efficacy. So baseline EEG features should not necessarily be used to encourage or discourage the use of the KD in a particular patient. However, we found that hypsarrhythmia scores at 3 months of KD were associated with different epilepsy outcomes. It was shown that unfavorable epilepsy outcome could be predicted with high sensitivity and specificity with a quantitative cut-off of hypsarrhythmia score that was calculated to be ≥8. Therefore, for patients who had no improvement clinically or showed hypsarrhythmia score ≥8 after KD, the long-term efficacy would be predicted to be not good, and other therapies should be recommended. This might be a critical step to achieve personalized therapeutic strategies.

There were some limitations in this study. It was a retrospective study, and the data on seizure frequency were based on unblinded records of parental seizure diaries. This study was also limited by relatively small sample size. A mixture of etiologies was represented in the study. Of course, the validity of these observations needs to be further confirmed. More prospective studies, especially multicenter studies, are needed on larger populations to confirm our findings and explore other potential significance of prognostic predictors.

5. Conclusion

The KD is an effective treatment for children with drug-refractory West syndrome. It can not only effectively control clinical seizures, but it can also improve EEG abnormalities. The hypsarrhythmia score by Kramer's method significantly decreased at 3 months after KD therapy, and it may help to indicate prognostic marker associated with efficacy.

Funding

This work was supported by Research Project of Shanghai Municipal Commission of Health and Family Planning (Grant No: 201640065); Key Research Project of the Ministry of Science and Technology of China (Grant No: 2016YFC0904400); and Shanghai Hospital Development Center (SHDC12015113).

References

[1] J.M. Pellock, R. Hrachovy, S. Shinnar, et al., Infantile spasms: a U.S. consensus report, Epilepsia 51 (2010) 2175–2189.

[2] E.C. Wirrell, R.A. Shellhaas, C. Joshi, C. Keator, S. Kumar, W.G. Mitchell, How should children with West syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium, Epilepsia 56 (2015) 617–625.
[3] G.R. Nelson, Management of infantile spasms, Transl. Pediatr. 4 (2015) 260–270.
[4] J.M. Wilmshurst, W.D. Gaillard, K.P. Vinayan, et al., Summary of recommendations for the management of infantile seizures: task force report for the ILAE commission of pediatrics, Epilepsia 56 (2015) 1185–1197.
[5] E.H. Kossoff, P.L. Pyzik, J.R. McGrogan, E.P. Vining, J.M. Freeman, Efficacy of the ketogenic diet for infantile spasms, Pediatrics 109 (2002) 780–783.
[6] G. Prezioso, G. Carlone, G. Zaccara, A. Verrotti, Efficacy of ketogenic diet for infantile spasms: a systematic review, Acta Neurol. Scand. 137 (2018) 4–11.
[7] A. Dressler, P. Trimmel-Schwahofer, E. Reithofer, et al., The ketogenic diet in infants–advantages of early use, Epilepsy Res. 116 (2015) 53–58.
[8] H. Philippi, G. Wohlrab, U. Bettendorf, et al., Electroencephalographic evolution of hypsarrhythmia: toward an early treatment option, Epilepsia 49 (2008) 1859–1864.
[9] D.A. Muzykewicz, D.J. Costello, E.F. Halpern, E.A. Thiele, Infantile spasms in tuberous sclerosis complex: prognostic utility of EEG, Epilepsia 50 (2009) 290–296.
[10] U. Kramer, W.C. Sue, M.A. Mikati, Hypsarrhythmia: frequency of variant patterns and correlation with etiology and outcome, Neurology 48 (1997) 197–203.
[11] S.H. Eun, H.C. Kang, D.W. Kim, H.D. Kim, Ketogenic diet for treatment of infantile spasms, Brain Dev. 28 (2006) 566–571.
[12] H.R. Kayyali, M. Gustafson, T. Myers, L. Thompson, M. Williams, A. Abdelmoity, Ketogenic diet efficacy in the treatment of intractable epileptic spasms, Pediatr. Neurol. 50 (2014) 224–227.
[13] M.E. Pires, A. Ilea, E. Bourel, et al., Ketogenic diet for infantile spasms refractory to first-line treatments: an open prospective study, Epilepsy Res. 105 (2013) 189–194.
[14] Y. Hirano, H. Oguni, M. Shiota, A. Nishikawa, M. Osawa, Ketogenic diet therapy can improve ACTH-resistant West syndrome in Japan, Brain Dev. 37 (2015) 18–22.
[15] A. Dressler, B. Stöcklin, E. Reithofer, et al., Long-term outcome and tolerability of the ketogenic diet in drug-resistant childhood epilepsy–the Austrian experience, Seizure 19 (2010) 404–408.
[16] S.J. You, H.D. Kim, H.C. Kang, Factors influencing the evolution of West syndrome to Lennox-Gastaut syndrome, Pediatr. Neurol. 41 (2009) 111–113.
[17] S.K. Kessler, P.R. Gallagher, R.A. Shellhaas, R.R. Clancy, A.G. Bergqvist, Early EEG improvement after ketogenic diet initiation, Epilepsy Res. 94 (2011) 94–101.
[18] I. Walker, R.R. Said, Predictors of ketogenic diet efficacy in children based on the electroencephalogram (EEG), J. Child Neurol. 30 (2015) 1270–1274.
[19] S.C. Ebus, D.A. Lambrechts, I.J. Herraets, et al., Can an early 24-hour EEG predict the response to the ketogenic diet? A prospective study in 34 children and adults with refractory epilepsy treated with the ketogenic diet, Seizure 23 (2014) 468–474.
[20] Y.J. Zhang, Y. Wang, Y.F. Zhou, L.M. Zhang, L.F. Yu, S.Z. Zhou, Therapeutic effects of the ketogenic diet in children with Lennox-Gastaut syndrome, Epilepsy Res. 128 (2016) 176–180.
[21] J.R. Mytinger, S.A. Hussain, M.P. Islam, et al., Improving the inter-rater agreement of hypsarrhythmia using a simplified EEG grading scale for children with infantile spasms, Epilepsy Res. 116 (2015) 93–98.