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Efficacy of the ketogenic diet in Chinese children with Dravet syndrome: A focus on neuropsychological development

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ABSTRACT

Objectives: In this retrospective study, we evaluated the efficacy of the ketogenic diet (KD) treatment in Chinese children with Dravet syndrome (DS) as well as its effect on neuropsychological development.
Methods: Twenty-six children (14 male) living with DS and being treated with KD at our department between July 2014 and December 2017 were enrolled in the study. The efficacy of KD was measured by seizure frequency before and after the diet. Additionally, children's neuropsychological development, as evaluated by the Gesell developmental schedule, was compared between the KD and a non-KD group.
Results: After 3, 6, 12, 18, 24, and 30 months, 92.3%, 84.6%, 46.2%, 30.8%, 19.2%, and 19.2% remained on the KD, while 38.4%, 34.6%, 38.4%, 23.0%, 15.4%, and 15.4% showed >50% reduction in seizure. The development age (DA) subscores of 12 children, as measured by the Gesell developmental schedule, increased after commencement of KD. However, children's development quotient (DQ) subscores (age-adjusted) decreased after KD. In the non-KD group (40 participants), an increase of DA subscores and decrease of DQ subscores were also observed. Results found no difference in changes of DQ subscores over time between the two groups. The DQ subscores after the diet in the KD group (20 participants) did not differ significantly when compared to the DQ subscores at same age in the non-KD group (20 patients) (*t*-test).
Conclusions: The DA subscores of 12 children in KD group increased after KD; when compared with that of the non-KD group, no significant difference was observed in respect to the changes of DQ subscore over time. Effects on cognitive and other neuropsychological development outcomes of KD for children living with DS require further study.

1. Introduction

Dravet syndrome (DS) is an infantile onset malignant epilepsy, which was first described by Dravet [1]. It is characterized by seizures occurring during the first year of life, which are often prolonged and associated with fever. Progressive developmental delay occurs later [2]. Despite the development of anticonvulsants, seizures in children with DS are difficult to treat with medicine.

The ketogenic diet (KD) has been used as a therapy for childhood epilepsy since the 1920s. The efficacy of the KD for childhood epilepsy has been reported in randomized clinical trials [3,4], and neuroprotective effects have also been found [5,6]. A randomized control trial found that people living with refractory epilepsy showed improvements in cognition following the KD [7]. The majority of previous studies on the efficacy of the KD for those with DS have typically contained small numbers of patients with DS. Evaluation of the KD's impact on neuropsychological development for those living with DS is descriptive and has not yet been compared with that of a control group [8–10]. This report analyzed three years' worth of clinical data to assess the efficacy of the KD for Chinese children, as well as their neuropsychological development, as evaluated by Gesell developmental schedules.

2. Patients and methods

Twenty-six children (14 male) with DS were treated with KD at our department between July 2014 and December 2017. Clinical data (sex, date of birth, age of onset, antiepileptic drug (AED) history, family febrile seizure history, KD duration, seizure types, seizure frequency, and gene testing results) were collected from medical records and caregivers' diet diaries as well as telephone and outpatient follow-up. Physical examinations were performed by our pediatric neurologist.

Seizures in all patients had shown resistance to at least two types of AEDs and had been on the KD for at least two months. The KD was in addition to AEDs. Patients were started gradually on the classic 4:1 ketogenic ratio. Children were admitted to our hospital as they embarked on the KD in order to learn how to follow the diet correctly and teach their parents how to follow it at home. While on the KD, protocols were adjusted according to patients' blood test results, including ketone concentration and manifestations.

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Efficacy was measured mainly by changes in seizure frequency as assessed by seizure diaries and parental report. As most participants were on the KD for at least three months, the frequency of seizures from three months before initiation of the KD was defined as 'baseline' and used to evaluate treatment outcome. Efficacy was categorized into the following categories: (1) Aggravation: ≥50% increase in frequency; (2) nonresponder: <50% reduction; (3) responder: ≥50% reduction; (4) significant responder: 75%–99% reduction; (5) seizure-free.

Neuropsychological development was evaluated using Gesell developmental schedules. In total, Gesell developmental schedules outcomes following KD were available for 20 participants. Of those, 12 participants were evaluated with Gesell developmental schedules before and after the KD, and 8 children were only evaluated after the KD. In order to better evaluate the effects of KD on patients' neuropsychological development, a non-KD group was enrolled. We performed a total of 48 neuropsychological evaluations with Gesell Scales, including 40 patients with DS who were not being treated with the KD. Furthermore, 20 of these patients whose ages of assessment were similar to that of the 20 patients with DS were used to compare neuropsychological development outcomes after the KD. The clinical data collection for the non-KD group followed the same pattern as the KD group.

We used the statistical software package SPSS 20.0 to analyze our descriptive data. Paired *t*-tests and Student's *t*-tests were performed to compare neuropsychological development outcomes. A P-value of <0.05 was considered statistically significant.

The research protocol has been approved by the ethics committee of Xiangya Hospital of Central South University. An informed consent for collecting clinical data and the publication of the results of each patient was signed by the parents, on accordance with the Declaration of Helsinki.

3. Results

3.1. Patients' characteristics

Characteristics of participants in the KD group can be seen in Table 1. The average age of seizure onset was 6.1 months, with a range of three to 11 months. Febrile seizures were observed in all children, and 20 patients experienced at least one episode of status epilepticus (SE). Twenty-four children had genetic testing. *SCN1A* gene mutations were identified in 23 children, and a *PCDH19* gene mutation was found in the remaining child. Eleven of the children who had an *SCN1A* mutation (48%) had a missense mutation. There was a pair of heterozygotic twins in the study, whose genetic results were the same; these were cases 13 and 14. All children had previously been exposed to a median of three (minimum one, maximum seven) different AEDs.

For the non-KD group, the average age of onset was 6.2 months, ranging from one to 11 months. All patients experienced multiple seizure types. Febrile seizures were observed in 40 patients, and 27 patients experienced at least one episode of SE. Twenty-nine patients had undergone genetic testing. Twenty-four of them carried pathogenic mutations in the *SCN1A* gene, including twelve missense mutations. One participant had a missense mutation in *SCN2A* gene. These children had been exposed to a median of two (minimum one, maximum three) different types of AEDs.

3.2. Efficacy of KD for DS

All 26 children being treated at our department were placed on the KD. The mean KD duration for these 26 children was 15.4 months (SD 11.9, minimum 2, maximum 40). Age at initiation of KD ranged from 0.83 to 8.08 years (mean 3.27 ± 1.76). The treatment lag from seizure onset to KD initiation differed, with a minimum of 0.33 years and a maximum of 7.42 years (mean 2.76 ± 1.75).

Efficacy of the KD can be seen in Table 2. No aggravation was recorded during follow-up. Status epilepticus was present in 20 of the 26 children before initiation of the KD, and occurred in 4 of the 26 patients during KD ($P < 0.001$). After 3, 6, 12, 18, 24, and 30 months, 92.3%, 84.6%, 46.2%, 30.8%, 19.2%, and 19.2% remained on the KD, while 38.4%, 34.6%, 38.4%, 23.0%, 15.4%, and 15.4% showed >50% reduction in seizure. In total, nine of the 26 children were still on the diet in December 2017, including five who had stayed on the diet for more than 30 months.

Table 1
Patients' characteristics.

Patients	Gender	Age at onset (months)	Age at initiation of KD (years)	KD duration (months)	Gene	Nucleotide change	Mutation types	Seizure types	AEDs before KD
1	M	3	1.75	9	*SCN1A*	c.4573C>T	Nonsense	SE,GTCS	VPA,LEV
2	F	6	0.83	6	*SCN1A*	c.4352C>T	Missense	SE,CS,PS,SGTCS	OXC,LEV,VPA
3	M	8	2.75	14	*SCN1A*	c.2792G>A	Missense	PS,MS,AS	LEV,VPA
4	F	7	2.75	5	*SCN1A*	c.5666T>G	Missense	SE,PS,SGTCS	LEV,VPA,NZP
5	M	5	4.00	>32	*SCN1A*	c.2732T>C	Missense	SE,SGTCS,PS,MS	LTG,LEV,VPA
6	F	7	2.83	>36	*SCN1A*	c.5246G>A	Missense	SE,TS,GTCS,PS,SGTCS	LEV,VPA,NZP
7	M	3	2.83	18	*SCN1A*	c.5270G>A	Missense	SE,SGTCS	VPA,OXC,LTG,TPM,LEV
8	M	7	1.67	>40	*SCN1A*	c.1624C>T	Nonsense	SE,SGTCS	OXC,VPA,LEV
9	M	6	3.00	3	*SCN1A*	c.4261A>G	Missense	SE,CS,MPS,TS	PB,LEV,OXC,LEV,TPM,NZP
10	M	8	1.67	>28	*SCN1A*	IVS6ds + 1G>C	Splicing	SE,TS,PS	VPA
11	F	5	2.92	15	*SCN1A*	c.1129C>T	Nonsense	PS,TS	VPA,LEV,TPM,LTG
12	F	7	4.08	15	*SCN1A*	c.2134C>T	Nonsense	SE,GTCS,SGTCS	OXC,LEV,VPA,TPM
13	F	4	3.33	>37	*SCN1A*	IVS19-1G>A	Splicing	SE,TS,PS	VPA,LEV,NZP
14	F	9	3.33	>37	*SCN1A*	IVS19-1G>A	Splicing	TS,PS,AS	VPA,LEV,NZP
15	M	3	1.00	9	*SCN1A*	c.5344A>C	Missense	SE,SGTCS	OXC,LEV,VPA
16	M	3	4.58	9	*SCN1A*	c.3402_3403del	Frameshift	SE,GTCS,SGTCS	VPA,LEV
17	F	7	1.00	8	*SCN1A*	c.602 + 1G>A	Splicing	SE,PS,SGTCS	VPA,LEV
18	M	6	3.50	>13	*SCN1A*	c.4353G>T	Nonsense	GTCS,AS	PB,VPA
19	M	6	2.83	>8	*SCN1A*	c.3182delG	Frameshift	SE,PS,SGTCS	LEV,VPA,NZP
20	F	3	3.33	>9	*SCN1A*	c.4769T>C	Missense	SE,PS,SGTCS,AS	PHB,LEV,OXC,VPA,NZP,LTG,TPM
21	M	7	5.25	>9	*SCN1A*	c.4261G>C	Missense	SE,PS,SGTCS	VPA,OXC,LEV,TPM
22	M	5	5.67	7	*SCN1A*	IVS4ds + 1G>A	Splicing	TS	VPA,LEV,NZP
23	F	11	4.00	20	*SCN1A*	c.2849G>C	Missense	SE,PS,GTCS	PB,LEV,VPA,OXC
24	F	9	1.33	6	*PCDH19*	c.746A>G	Missense	SE,GTCS	PB,VPA
25	M	6	6.75	>9	NA	NA	NA	SE,MPS,SGTCS	VPA,TPM,LEV
26	F	8	8.08	2	NA	NA	NA	GTCS	VPA,LEV,PB,NZP

(F — female, M — male, SCN1A — sodium channel, GTCS — generalized tonic–clonic seizures, SE — status epilepticus, MS — myoclonic seizures, MYO — myoclonias, AS — absence seizures, PS — partial seizures, ATS — atonic seizures, KD — ketogenic diet, AED — antiepileptic drug, VPA — Valproic Acid, CLB — Clobazam, LEV — Levetiracetam, TPM — Topiramate, CNZ — Clonazepam, NZP — Nitrazepam, OXC — Oxcarbazepine, LTG — Lamotrigine, PB — Phenobarbitone.)

Table 2
Seizure outcomes after initiation of the KD.

	Patients off the diet	SE	No response	Reduction 50%–74%	Reduction 75%–99%	Seizure-free	Retention
3 months	2	1	14	4	3	3	24(92.3%)
6 months	4	2	13	4	2	3	22(84.6%)
12 months	10	0	2	3	7	0	12(46.1%)
18 months	13	0	2	2	4	0	8(30.8%)
24 months	15	1	1	2	2	0	5(19.2%)
30 months	15	0	1	3	1	0	5(19.2%)

3.3. Results of assessment with Gesell developmental schedules

Twelve of the participants were assessed according to Gesell developmental schedules before and after starting the KD. The mean age at KD initiation was 34.58 ± 17.75 months, minimum 12 and maximum 68 months. The KD duration ranged from 3 to 24 months, mean 12.41 ± 6.32 months. Mean age at assessment before and after the KD was 26.67 ± 11.77 months (minimum 10, maximum 48 months) and 55.17 ± 16.47 months (minimum 25, maximum 83 months).

The development quotient (DQ = DA/age) at the first evaluation was significantly higher than at the second evaluation in all five fields: gross motor, fine motor, adaptive behavior, language, and personal-social ability (paired *t*-test, see Table 4). Fine motor DQ subscores dropped mostly, according to the quotients. While DQ scores decreased after the KD, children continuously acquired new abilities, as DA subscores increased over the KD duration. This slow progress was also noted by the children's parents.

3.4. Comparison with non-KD group

Fig. 1 shows changes of DQ subscores over time in non-KD group and 12 of KD group. Forty-eight reports were collected from non-KD group. The DQ subscores in non-KD group dropped overtime, as DQ subscores of the 12 patients with DS in the KD group also decreased after the KD. No significant differences of DQ changes over time were observed between the two groups.

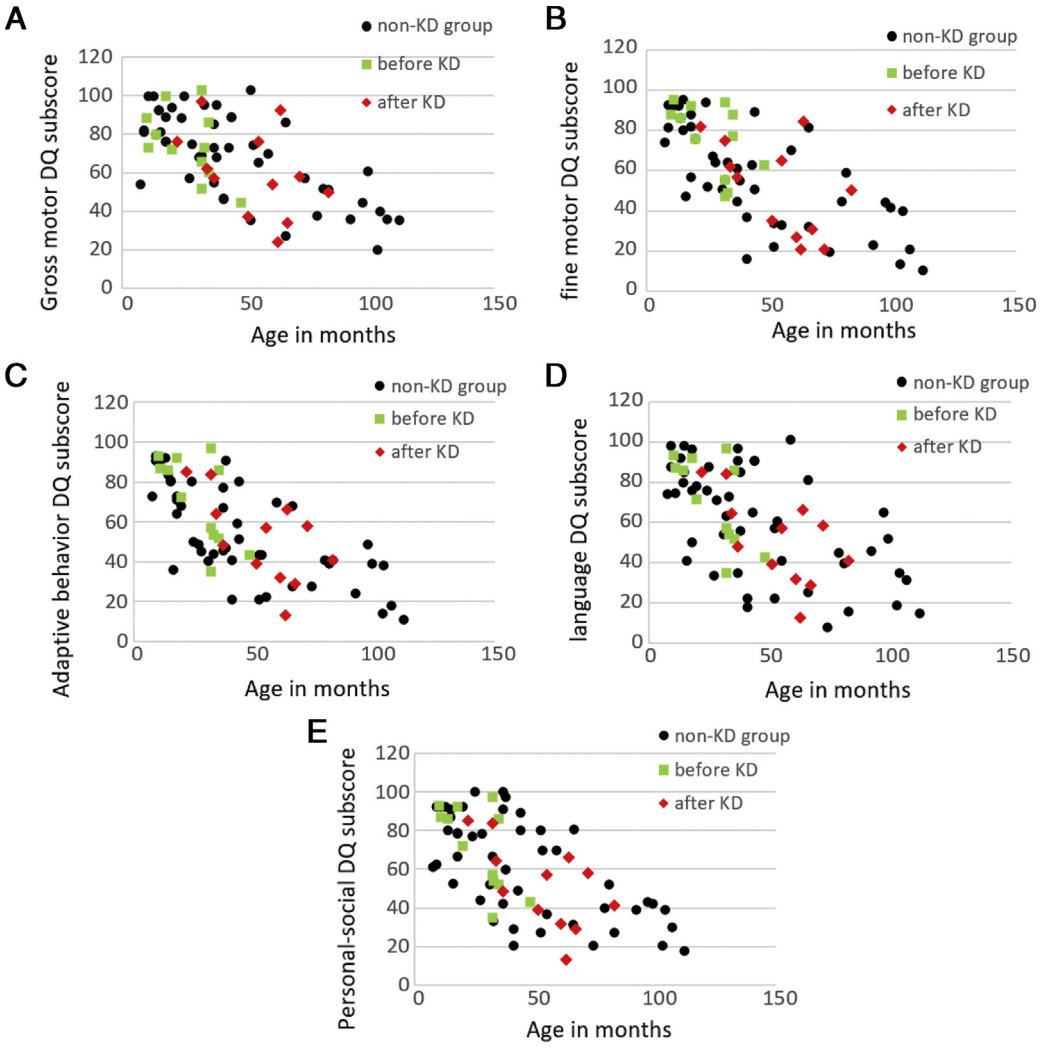

Fig. 1. Trends of DQ subscores over time in both KD and non-KD group. In non-KD group (40 patients), 48 reports of Gesell Scale were available. The DQ subscores tended to drop over time. Twelve patients in the KD group got two reports before and after the diet in which the DQ subscores also decreased.

Table 3
Comparison of DQ between KD and non-KD groups at similar age. There was no significant difference in DQ between two groups (Student's *t*-test).

DQ subfields	Group	Mean	SD	*t*	P-value
Gross motor	KD	61.6	20.3	−1.143	0.26
	non-KD	69.0	20.6		
Fine motor	KD	55.1	21.9	0.234	0.816
	Non-KD	53.5	19.6		
Adaptive behavior	KD	51.5	20.1	0.149	0.882
	Non-KD	50.6	18.0		
Language	KD	55.1	22.0	−0.117	0.907
	Non-KD	56.1	27.6		
Personal-social ability	KD	60	24.2	0.572	0.571
	Non-KD	55.6	24.5		

KD = Ketogenic Diets, DQ = Development Quotient, SD = Standard Deviation.

At least one Gesell report was available for 20 patients following the KD. The KD duration of these children was 14.9 ± 9.7 months. Twenty patients with DS in the non-KD group whose age of neuropsychological development were similar to that of the 20 patients with DS in the KD groups were selected as control group. Age of assessment in KD group was 51.5 ± 19 months and 48.7 ± 18.9 months in the non-KD group. A paired *t*-test found no significant difference in DQ subscores between the two groups (Table 3, Student's *t*-test).

4. Discussion

Patients with DS typically experience a slowing of cognitive achievements that becomes evident after the first year of life, and reach a low DQ/IQ level by five years of age. In several studies, patients with DS who had not been exposed to KD therapy were found to have progressive retardation in cognitive and behavioral profiles [2,11]. However, regression in cognitive or neuropsychological development may not be common. In a study by Nabbout and colleagues, DQ/IQ significantly decreased with age in 15 patients with DS, while raw (not age-adjusted) DQ subscores increased during the first decade [12]. A slow progress in cognition or neuropsychological development was also clinically obvious.

It has previously been observed that the KD may be effective for improving cognition and behavior. Korff and colleagues reported that one in six of the patients with DS who were exposed to KD showed a positive cognitive improvement [11]. In a retrospective study by Laux and Blackford, 15 of 20 children with DS showed improvements in cognitive and behavior after six months of KD therapy [9]. In 2018, Yan and colleagues found that 16 of 20 (80%) patients with DS improved in cognition after six months of KD therapy [10]. However, these results were based on observations by caregivers or pediatricians and did not include a comparison. While a randomized controlled trial has previously demonstrated improvement of cognitions following drug-resistant epilepsy after KD [7], the results for those living with DS may be different. Therefore, whether the KD facilitates progress in cognition and other neuropsychological developmental aspects remained open to debate.

In our study, we measured neuropsychological development with a Gesell developmental schedule. According to the Gesell developmental schedule, the DA subscores of 12 children increased after the diet, which indicates a progress in cognition and other neuropsychological developmental aspects following the KD. Despite ketogenic treatment, DQ subscores significantly reduced with age, especially in the fine motor field. Therefore, it appears that DQ subscores were relative to age. We found a decline of DQ subscores following KD, which suggests that neuropsychological developmental delay worsens progressively with age when compared with typical children at the same age, despite the addition of the KD.

As a control group, 40 patients with DS not being treated by the KD were enrolled. The data exhibited decrease of DQ subscores in non-KD group, which was also observed in KD group. No significant difference of the trends of DQ was found between two groups. We compared DQ subscores after KD in a KD group with an age-controlled non-KD group, and found no significant difference. The results suggested that KD may not fascinate progress in cognition and other neuropsychological developmental aspects obviously as reported by others, considering clinical course of DS.

As KD is a second-line therapy for DS, seizures in the KD group were more severe than that in the non-KD group. In particular, SE was presented in 20/26(77%) patients in the KD group and in 27/40(68%) patients in the non-KD group. Further to this, sampling errors cannot be avoided because of limited numbers of available neuropsychological development outcomes for non-KD groups. Even so, our study suggests that there KD may not have profound effect on cognitive and other neuropsychological developmental outcomes in patients with DS, and so suggests the need for a well-designed prospective study. Other scales of measurement should also be introduced.

5. Conclusions

In conclusion, we can see that cognitive and other neuropsychological developmental aspects improved after KD, but that no significant difference was observed when compared to a non-KD group with DS. The effect of KD on neuropsychological development of DS patients is therefore worthy of further investigation.

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Table 4
Paired *t*-test of outcomes with Gesell developmental schedules in 12 children.

Subfields	KD	DQ				DA			
		Mean	SD.	*t*	P-value	Mean	SD	*t*	P-value
Gross motor	Before	74.75	17.92	3.896	0.002	18.92	7.79	3.662	0.004
	After	59.83	22.61			30.35	13.56		
Fine motor	Before	75.91	17.75	4.724	0.001	19.17	8.07	1.638	0.130
	After	50.83	23.37			24.87	12.34		
Adaptive behavior	Before	68.33	19.38	5.958	<0.001	16.91	6.93	2.652	0.022
	After	46.33	17.01			23.58	11.81		
Language	Before	67.33	21.73	3.492	0.005	16.82	8.02	3.129	0.010
	After	50.00	22.66			24.10	9.15		
Personal-social ability	Before	71.16	21.81	5.162	<0.001	17.44	7.15	3.774	0.003
	After	51.36	21.89			25.99	10.43		

KD = Ketogenic Diets, DQ = Development Quotient, DA = Development Age, SD = Standard Deviation.

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References

[1] Dravet C. Les épilepsies graves de l'enfant. Vie Med 1978;8:543–8.
[2] Ragona F, Granata T, Bernardina BD, Offredi F, Darra F, Battaglia D, et al. Cognitive development in Dravet syndrome: a retrospective, multicenter study of 26 patients. Epilepsia 2011;52:386–92.
[3] Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol 2008;7:500–6.
[4] Lambrechts DAJE, de Kinderen RJA, Vles JSH, de Louw AJA, Aldenkamp AP, Majoie HJM. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. Acta Neurol Scand 2017;135:231–9.
[5] Dutton SBB, Sawyer NT, Kalume F, Jumbo-Lucioni P, Borges K, Catterall WA, et al. Protective effect of the ketogenic diet in Scn1a mutant mice. Epilepsia 2011;52:2050–6.
[6] Luan G, Zhao Y, Zhai F, Chen Y, Li T. Ketogenic diet reduces Smac/Diablo and cytochrome c release and attenuates neuronal death in a mouse model of limbic epilepsy. Brain Res Bull 2012;89:79–85.
[7] IJff DM, Postulart D, Lambrechts DAJE, Majoie MHJM, de Kinderen RJA, Hendriksen JGM, et al. Cognitive and behavioral impact of the ketogenic diet in children and adolescents with refractory epilepsy: a randomized controlled trial. Epilepsy Behav 2016;60:153–7.
[8] Korff C, Laux L, Kelley K, Goldstein J, Koh S, Nordli Jr D. Dravet syndrome (severe myoclonic epilepsy in infancy): a retrospective study of 16 patients. J Child Neurol 2007;22:185–94.
[9] Laux L, Blackford R. The ketogenic diet in Dravet syndrome. J Child Neurol 2013;28:1041–4.
[10] Yan N, Xin-Hua W, Lin-Mei Z, Yi-Ming C, Wen-Hui L, Yuan-Feng Z, et al. Prospective study of the efficacy of a ketogenic diet in 20 patients with Dravet syndrome. Seizure 2018;60:144–8.
[11] Olivieri G, Battaglia D, Chieffo D, Rubbino R, Ranalli D, Contaldo I, et al. Cognitive-behavioral profiles in teenagers with Dravet syndrome. Brain Dev 2016;38:554–62.
[12] Nabbout R, Chemaly N, Chipaux M, Barcia G, Bouis C, Dubouch C, et al. Encephalopathy in children with Dravet syndrome is not a pure consequence of epilepsy. Orphanet J Rare Dis 2013;8:176.