KETOGENIC DIET TREATMENT FOR *STATUS EPILEPTICUS*

CARMEN SANDU^{1,2*}, SANDA ADRIANA MAGUREANU¹, CATRINEL ILIESCU^{1,2}, CRISTINA POMERAN^{1,2}, DANA CRISTINA CRAIU^{1,2}

¹*Pediatric Neurology II Discipline, Clinical Neurosciences Department, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

²*Pediatric Neurology Clinic, "Prof. Dr. Alexandru Obregia" Clinical Hospital, 10, Berceni Avenue, 4th District, 041914, Bucharest, Romania*

*corresponding author: carmensandu_u6@yahoo.com

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Abstract

The ketogenic diet (KD) is a high fat normoproteic, low carbohydrate diet considered in recent years as an alternative treatment option for patients with refractory *status epilepticus* (RSE) or super-refractory *status epilepticus* (SRSE), both, in children and adults. The aim of current research is to review and compare the efficacy of KD in children and adults with RSE and SRSE regardless of underlying aetiology. We performed a retrospective PubMed search between June 1997 until 30th of October 2017 and selected all articles in which KD was used for the treatment of children and adults with *status epilepticus* refractory to standard therapy. 120 patients (adults and children) with RSE and SRSE were identified. An important proportion of patients (92/120 ~ 77%, 64 children and 28 adults) responded to KD therapy. In conclusion, KD is proving to be a valuable therapeutic option in the intensive care units for the treatment of RSE and SRSE in children and adults, available data showing efficacy mostly but not limited to (febrile infection related to encephalopathy in school aged children) FIRES in children and encephalitis in adults. Specific protocols and training should be made available in intensive care units in order to implement and manage KD in children and adults with *status epilepticus* who do not respond to standard therapeutic approaches.

Rezumat

Dieta cetogenă (DC) este o dietă bogată în grăsimi, normoproteică și cu un conținut sărac de carbohidrați, considerată în ultimii ani drept o opțiune de tratament pentru pacienții cu *status epilepticus* refractar (RSE) sau super-refractar (SRSE), atât la copii, cât și la adulți. Scopul cercetării actuale este de a analiza datele existente în literatură și de a compara eficiența DC la copii și adulți cu RSE și SRSE, indiferent de etiologie. S-a efectuat o cercetare retrospectivă a bazei de date PubMed din iunie 1997 până la 30 octombrie 2017, fiind selectate toate articolele în care DC a fost utilizată pentru tratamentul copiilor și adulților cu *status epilepticus* refractar la terapia standard. Au fost identificați 120 de pacienți (adulți și copii) cu RSE și SRSE. O proporție importantă de pacienți (92/120 ~ 77%, 64 copii și 28 adulți) au răspuns la terapia cu DC. În concluzie, DC se dovedește a fi o opțiune terapeutică valoroasă în unitățile de terapie intensivă pentru tratamentul statusului epileptic refractar și superrefractar la copii și adulți, datele existente demonstrând eficiența mai ales, dar nu exclusiv, în FIRES (*febrile infection related encephalopathy in school-age children*) la copii și encefalită la adulți. Protocoale specifice și instruire adecvată ar trebui să fie puse la dispoziție în unitățile de terapie intensivă pentru a implementa și administra DC la copiii și adulții cu *status epilepticus* care nu răspund la abordările terapeutice standard.

Keywords: ketogenic diet, refractory status epilepticus, FIRES, encephalitis

Introduction

The ketogenic diet (KD) is a high fat, normoproteic, low carbohydrate diet used for many years, in various protocols, for the treatment of drug-resistant epilepsy [40]. A high number of publications prove its efficacy, both in children [25, 28], and adults [27], when standard therapy is inefficient.

A guide for implementing and managing the KD in children was published in 2008 by an international group of KD experts, clinicians and dieticians, offering guidance for the main indications of the diet. Among these, specific epileptic syndromes, such as epileptic spasms, Dravet syndrome, tuberous sclerosis complex, Rett or Doose syndrome have

particular benefit from the use of ketogenic diet. KD is the only treatment for special genetic syndromes such as Glut 1 deficiency syndrome or pyruvate dehydrogenase (PDH) deficiency syndrome [18, 13].

Meanwhile, cases of (refractory or super refractory) *status epilepticus* with favourable response to the ketogenic diet have also been reported [41].

According to International League Against Epilepsy (ILAE) - 1981, *status epilepticus* (SE) has been conceptually defined as a seizure "sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition" [12].

The new definition of *status epilepticus* proposed by ILAE Task Force combines the operational and, respectively, the physiopathological definitions of SE as: “a condition resulting either from the failure of mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally prolonged seizures (after time point t1) and can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type of seizures” [36].

Refractory *status epilepticus* (RSE) is defined as the status continuing for more than 2 hours, despite benzodiazepines and other anticonvulsant medication (first- and second-line medication) and requiring general anaesthesia.

Super refractory *status epilepticus* (SRSE) is the last stage of the condition when the status continues or recurs for more than 24 hours, despite general anaesthesia [30]. Both conditions carry high rates of morbidity and mortality, compelling additional interventions. Ketogenic diet (KD) is considered as a “needed adjunct strategy for the management of *status epilepticus*” [29].

Materials and Methods

Search criteria

A systematic search of electronic medical database PubMed from June 1997 to the end of October 2017 has been performed using the following key words „ketogenic diet, *status epilepticus*” „ketogenic diet, FIRES” (febrile infection related encephalopathy in school-age children). The reference list with retrieved articles has been studied. Available abstracts or full texts, have been searched for clinical cases using ketogenic diet as treatment for *status epilepticus*.

Eligibility criteria

We included articles presenting clinical cases of *status epilepticus* regardless of age or aetiology but using ketogenic diet in the therapeutic management that were all reported in the literature by 31st of October 2017. All study types, retrospective and prospective, in English, French and Spanish have been considered. Review articles have also been included.

Results and Discussion

Analysed data

The search for „ketogenic diet and *status epilepticus*” returned 122 articles. An additional search using the keywords „ketogenic diet and FIRES” resulted in other 57 articles. Out of 29 articles in total, 10 referred to adults, 17 to children and 2 for both, adults and children. They have been analysed and 120 patients have been identified as using ketogenic diet in the management of *status epilepticus*. Only one article had a prospective design with a

standardized protocol including 15 adults with super refractory *status epilepticus* [8]. Adults and children were analysed as independent categories and compared.

Adults

36 adults have been identified in 12 articles, listed in chronological order (Table I). In adults, the age varied between 18 - 82 years, with 2 patients of 18 years old reported by Villeneuve in 2009 and Cervenka in 2017 [8, 39]. The average age of the 35 patients was 40.3 years, one patient did not have the age mentioned (“middle-aged”) [4]. Out of the total number of adult patients 22 were females and 14 males.

There were 2 types of *status epilepticus* reported, generalised and focal motor, with 2 exception, one case of myoclonic *status epilepticus* and one case of nonconvulsive *status epilepticus* (NCSE) [4, 21]. Regarding the underlying aetiology, 5 out of 36 cases (~14%) were encephalitis of unknown aetiology or NORSE (new onset refractory *status epilepticus*), 4 out of 36 (11%) anti NMDA-R encephalitis or anoxic ischemic aetiology, 3 out of 36 (~8%) were intracranial haemorrhage, 2 out of 36 (~6%) viral encephalitis. There was also one case of each of the following: focal cortical dysplasia, *glioblastoma multiforma*, Rasmussen encephalitis, Ito syndrome or mitochondrial aetiology. The majority of cases (35 patients) used the classical KD, most of them (33/35, ~94%) with a ratio of 4:1, in only one patient was administered the low glycaemic index diet (LGIT) [21]. The interval between the onset of *status epilepticus* and initiation of ketogenic diet varied between 2 and 101 days, with an average of 23 days for 34 patients. Positive results were achieved in 31 patients, with 28 of 31 (~90%) patients achieving status remission and 3 patients (~10%) a decrease of seizure frequency (improvement). Side effects have been reported in 13 of 26 (~50%) patients, most of them developing various complications like metabolic acidosis (5/14), constipation (2/14), increased lipid profile (3/14), and hyponatremia (1/14). Ketosis has been achieved in 32 patients.

Children

84 children were identified from 19 articles (Table II). Their age varied between 0 and 16 years, with a median age of 7.83 years in 82 patients; in 2 children the age was not mentioned [22]. The youngest patient in which KD was initiated was 9 weeks old [11]. The gender was clearly stated in 82 patients, with 43 males (~52%) and 39 females (~48%).

9 cases with myoclonic *status epilepticus* [7, 5, 10] and 3 cases with NCSE (nonconvulsive *status epilepticus*) have been described [19, 31]. FIRES (febrile-illness related epilepsy syndrome), was the

most common aetiology with 28/84 (~33%) paediatric patients reported, 1 of them with associated PCDH19 and GABRG2 mutation [2]. There are also 4 reported patients with viral encephalitis, 3 patients with anti NMDA-R

encephalitis, 5 patients with unknown aetiology and also isolated cases of variable aetiologies: structural, autoimmune, infectious, genetic or metabolic (Table II).

Table I
Adults

Author, year (reference number)	Number of subjects	Age range (years)/gender	Aetiology/diagnosis	Type of KD, ratio	Ketosis	Day of initiation	Time to suppression/improvement (days)	Clinical outcome	Side effects
Bodenant, 2008 [3]	1	54, M	Pharmacoresistant epilepsy	KD (4:1)	uk	31	7	SE remission (1/1)	uk
Villeneuve, 2009 [39]	1	18, M	Hypomelanosis of ITO syndrome	KD (4:1)	yes	uk	3	SE remission (1/1)	uk
Wusthoff, 2010 [41]	2	29 F, 34 M	Rasmussen, Viral encephalitis	KD (4:1)	yes	18 - 101	8 - 11	SE remission (2/2)	uk
Cervenka, 2011 [9]	1	54, M	Idiopathic (possibly autoimmune)	KD (4:1)	yes	58	uk	SE remission (1/1)	uk
Martikainen, 2011 [21]	1	26, F	Mitochondrial (POLG1)	LGIT	uk	7	4	SE remission (1/1)	uk
Nam, 2011[24]	1	40, F	Viral encephalitis	KD (4:1)	yes	15	30	SE remission (1/1)	none
Strzelczyk, 2013 [33]	1	21, F	Lafora disease	KD iv (4:1)	yes	16	uk	improvement	uk
Thakur, 2014 [35]	10	23 - 51, 6F, 4M	4 Encephalitis of unknown aetiology, 2 NMDA-R encephalitis, LGI1 encephalitis, Cortical dysplasia, Neurocysticercosis, Anoxic ischemic aetiology	KD (4:1-9/10, 3:1)	yes 9/10	2 - 60, median 21.5	1-31, median 3	SE remission (9/10)	2 HTG 1 acidosis
Cash, 2015 [4]	1	middle age, M	Hypoxic ischemic brain injury	KD (4:1)	yes	36	uk	improvement	uk
Amer, 2015 [1]	1	21, F	NMDA-R encephalitis	KD (4:1)	yes	21	na	improvement	uk
Uchida, 2017 [37]	1	20, F	NMDA-R encephalitis	KD	uk	uk	60	SE remission (1/1)	uk
Cervenka, 2017 [8]*	15	18 - 82, 5M, 10F	5 NORSE, 2 Anoxic ischemic injury, 2 LGS, 3 Intracranial haemorrhage, Encephalitis of unknown aetiology, Epilepsy secondary to SBS, GBM	KD (4:1)	yes	2 - 39, median 10	0-10, median 5	SE remission (11/15)	3 metabolic acidosis 2 hypoglycaemia 1 hyponatremia 1 weight loss 1 constipation 1 HLD 1 metabolic acidosis and hypoglycaemia 1 constipation and HLD

Abbreviations: KD = ketogenic diet; M = male; F = female; uk = unknown; na = not applicable; NMDA-R = N-methyl-D-aspartate receptor; NORSE = new-onset refractory *status epilepticus* of unknown aetiology; POLG 1= mitochondrial polymerase c related epilepsy; LGI1 = leucine-rich, glioma-inactivated 1 encephalitis; LGS = Lennox Gastaut Syndrome; GBM = *glioblastoma multiforma*; HTG = high triglycerides; HLD = hyperlipidaemia; SBS = shaken-baby syndrome.

Nearly all patients, 82/84 (~98%) followed the classical KD with variable ratios (1:1 to 6:1), mostly 4:1, 75/82 (~91%) patients. 2 patients have followed the Modified Atkins Diet (MAD) [19]. KD was initiated after an average of 32 days from onset of SE for 58/84 (~69%) patients.

This ranged from day 1 to day 420 [2, 24]. The clinical response, defined as suppression of *status epilepticus* or decrease of frequency and/or duration of seizure was positive in 72/84 (~86%) patients, with 45/72 (~63%) patients achieving suppression of *status epilepticus*, 8/72 (~11%) between 75-99% seizure improvement, 11/72 (~15%) 50 - 74%

seizure improvement and 8/72 (~11%) patients under 50% seizure improvement or shorter seizure duration. Data about side effects related to KD has been reported in 48 patients, with 22 patients reporting adverse effects, mostly constipation 5/21, high

triglycerides 4/21, vomiting 4/21, gastro-esophageal reflux (GER) 2/21, hypoglycaemia 4/21, pancreatitis 3/21 or weight loss 1/21. Data about ketosis has been retrieved in 77 patients, 75/77 achieving ketosis after KD initiation.

Table II
Children

Author, year (reference number)	Number of subjects	Age range (years)/gender	Aetiology/diagnosis	Type of KD, ratio	Ketosis	Day of initiation	Time to suppression/improvement (days)	Clinical outcome	Side effects
Villeneuve, 2009 [39]	4	1 - 10, 1M, 3F	2 Cryptogenic, Sturge-Weber syndrome, Grey matter encephalitis	KD (4:1)	uk	uk	1 - 10, median 3.75	SE remission (3/4)	uk
Kumada, 2010 [19]	2	4 - 5, F	Frontal lobe epilepsy, Subcortical band heterotopia	MAD	yes	uk	5 - 10, median 7.5	SE remission (2/2)	uk
Nabbout, 2010 [23]	9	5 - 8, 5F, 4M	FIRES	KD (4:1)	yes	4 - 55, median 23	4 - 6, median 4.8	SE remission (7/9)	uk
Ismail, 2011 [16]	1	14, F	FIRES	KD (4:1)	uk	120	10	SE remission (1/1)	uk
Nam, 2011 [24]	4	4 - 14, 2F, 2M	Viral encephalitis	KD (4:1)	yes	30 - 420, median 150	3 - 19, median 11	SE remission (1/4) 90% sz reduction (1/4) 75 % sz reduction (2/4)	1 Aspiration pneumonia and constipation 1 Constipation and severe GER 1 HTG, constipation, GER 1 Constipation
Vaccarezza, 2012 [38]	5	1 - 14, 1F, 4M	3 FIRES, Hemimegalencephaly, Chiari syndrome type 2	KD (4:1)	yes	15 - 52, median 32	1 - 3, median 2	SE remission (4/4)	uk
Sort, 2013 [32]	3	3 - 11, 2M, 1F	HHES, Mitochondrial respiratory chain enzyme defect, FIRES	KD (4:1)	yes	6 - 48, median A*	1 - 13, median 7	SE remission (2/3) No response (1/3)	1 Weight loss, HTG
Caraballo, 2014 [6]	10	0 - 16, 6M, 4F	NMDA-R encephalitis, Hemimegalencephaly, 2 FCD, 4 Refractory focal seizures associated with febrile illness, 2 Unknown	KD (4:1)	yes	uk	median 5	75-90% sz reduction (2/10) 50-75% sz reduction (5/10) <50% sz reduction (3/10)	1 Vomiting and hypoglycaemia 2 Pancreatitis
O'Connor, 2014 [26]	5	0 - 10, 3M, 2F	Alpers Huttenlocher syndrome, Mitochondrial defect and influenza A, 2 Symptomatic generalized epilepsy, Unknown	KD (4:1)	yes	4 - 22, median 12.8	2 - 8, median 4.6	SE remission (5/5)	none
Singh, 2014 [31]	2	7 - 10, 1M, 1F	FIRES	KD (4:1, 6:1)	yes	3 - 13, median 8	2 - 20, median 10	SE remission (2/2)	uk
Caraballo, 2015 [7]	2	1 - 2, M	Progressive encephalopathy, Unknown	KD (4:1)	yes	30, uk	7	75-90% sz reduction (1/2) 50% sz reduction (1/2)	none
Cobo, 2015 [11]	4	0 - 13, 1F, 3M	MMPSI, TSC, 2 Cryptogenic	KD (2:1, 3:2:1, 4:1 - 2/4)	yes	19 - 67, median 35	2 - 8, median 5.3	50% sz reduction (1/3) Shorter seizures (2/4) No improvement (1/4)	1 Nephrolithiasis 1 Asymptomatic hypoglycaemia 1 Constipation, GER

Author, year (reference number)	Number of subjects	Age range (years)/gender	Aetiology/diagnosis	Type of KD, ratio	Ketosis	Day of initiation	Time to suppression/improvement (days)	Clinical outcome	Side effects
Fung, 2015 [15]	4	6 - 16, 2M, 2F	NORSE, VGKC encephalitis, FIRES, Encephalitis of possible autoimmune origin	KD (4:1)	yes 3/4	12 - 18, median 17.5	5	SE remission (1/4) No response (3/4)	1 Falling plasma proteins 1 Vomiting 1 increase seizure
Lin, 2015 [20]	1	6, M	NORSE	KD (4:1)	yes	1.5	1	SE remission (1/1)	uk
Millichap, 2015 [22]	2	uk	FIRES	KD (4:1)	uk	uk	uk	SE remission (2/2)	uk
Appavu, 2016 [2]	10	2 - 16, 4F, 6M	Rasmussen encephalitis Generalized epilepsy, intractable LGS Non-ketotic hyperglycaemia Mycoplasma post-infectious encephalitis NORSE FIRES FIRES and PCDH19, GABRG2 mutation 2 NMDA-R encephalitis	KD (4:1 - 9/10, 5:1)	yes 9/10	1 - 45, median 20	1 - 19, median 7	SE remission (9/10) No response (1/10)	uk
Chiusolo, 2016 [10]	1	8, M	Unknown	KD (3:1)	yes	uk	na	No response (1/1)	1 high liver enzymes
Caraballo, 2017 [5]	6	2, 5 - 9, 4F, 2M	CDKL5, SCN8A, 2 Angelman, Rett, Unknown	KD (4:1)	yes	uk	uk	75-99% sz reduction (2/6) 50-74% sz reduction (3/6) <50% sz reduction (1/6)	2 Vomiting
Farias-Moeller, 2017 [14]	9	2 - 8, 6F, 3M	5 Encephalitis/FIRES, 2 FIRES, Epileptic encephalopathy, CNS-HLF	KD (1:1, 3:1, 4:1 - 7/9)	yes	10 - 16, median 13	7	SE remission (5/9) 50% sz reduction (1/9) 10% sz reduction (2/9) Unknown (1/9)	1 HTG 1 HTG and pancreatitis *VPA

Abbreviations: KD = ketogenic diet; MAD = modified Atkins diet, M = male; F = female; uk = unknown; na = not applicable; sz = seizure; FIRES = febrile infection related encephalopathy in school-age children, HHES = heiconvulsion hemiplegia epilepsy syndrome, NMDA-R = N-methyl-D-aspartate receptor; FCD = frontal cortical dysplasia, MMPSI = malignant migrating partial seizures of infancy, TSC = tuberous sclerosis complex, NORSE = new-onset refractory *status epilepticus* of unknown aetiology, VGKC = voltage gated potassium channel, LGS = Lennox Gastaut syndrome, PCDH 19 = Protocadherin 19, GABRG2 = gamma-aminobutyric acid type A receptor gamma 2, CDKL5 = cyclin-dependent kinase-like 5, SCN8A = Sodium channel, voltage gated, type VIII, alpha subunit, CNS-HLF = central nervous system- hemophagocytic lymphohistiocytosis, GER = gastroesophageal reflux, HTG = high triglycerides, HLD = hyperlipidaemia, *VPA = on valproic acid; A* KD tried twice (day 8, day 83).

In the last few years, KD gained more and more interest as a therapeutic option for emergency situations like refractory or super refractory *status epilepticus*. In a retrospective review of 10 publications from 2013, the authors reported a total of 32 children and adults receiving dietary treatment for *status epilepticus*, of which 78 % (25/32) of patients achieved complete control of SE [17]. During our investigation, we found comparable results, with 73/120 (~61%) patients reported to achieve complete control of SE and 92/120 (~77%)

more than 50% improvement, 17/120 (~23%) patients have shown no improvement at all.

Regarding FIRES and febrile illness related epilepsy, Nabout and Kossoff considered that these entities should be added to the list of indications in the next KD Expert Consensus Statement and that was recently updated with the new recommendations of the International Ketogenic Diet Study Group published in 2018 [13, 17].

FIRES was the most common aetiology found in children also, with 28/84 patients reported, 21 of

them (~75%) achieving complete remission of *status epilepticus*.

Apart from the beneficial role in the acute management of FIRES, there are authors outlining the importance of KD for the cognitive outcome, for the short, as well as for the long term one [16, 22, 31, 41].

Although comparing results of using of KD in adults *versus* children is difficult due to the heterogeneous cohorts, the variable ways of initiation and associated treatments, it can be concluded that in adults, encephalitis, mostly autoimmune and viral, is the most reported entity (14/34) ~39%, with high rates of response, 12/14 with complete status remission. The average interval from the onset of SE until the initiation of KD was 23 days in adults and 32 days in children, and still with good results. There are studies suggesting the initiation of KD, earlier in the management of SE [2]. Refractory myoclonic SE is also considered an entity in which the KD should be commenced earlier in the course of the treatment. Cognitive deterioration may be avoided if seizures are well controlled [7].

In a recent prospective study of 15 adult patients treated with KD, a high number of patients, 11/14 patients (79%) completing the therapy, achieved remission of *status epilepticus* [8].

Compliance in patients with *status epilepticus* is not an issue, due to their critical condition. The majority of children but adult patients too, followed classical KD, ratio 4:1, administered via gastrostomy or nasogastric tube. Some authors consider that children with seizures may benefit from IV (parenteral) KD due to enteral feeding intolerance [10].

A metanalysis of Ye and collaborators in 2015 showed that in adults with intractable epilepsy classical KD may be more effective but adult patients are less compliant with it than with a modified Atkins diet [42]. In our cohort, one adult patient followed LGIT with good seizure outcome [21] and 2 children followed MAD with similar results [19].

External factors, like „concurrent therapies” may contribute to remission of *status epilepticus*. The authors recognise the need for prospective trials, difficult to achieve for those patients in critical condition [2].

Specific recommendation (guidelines) with clear key points regarding when to consider starting KD for *status epilepticus* are made available by different authors [13, 18, 26, 34].

Conclusions

Our current research shows that KD can work in refractory and super-refractory *status epilepticus*. More than 60 % of monitored patients responded

by suppression of *status epilepticus*. Other retrospective studies with series of cases using KD as a treatment for SE and SRSE have been published, in adults [34], children [10] or both [17, 32]. At the time of publication there were few retrospective studies about using KD as a treatment method for SE and SRSE in adults, children or both but this is, by our knowledge, the largest study to gather children and adults. Specific protocols and training should be made available in intensive care units in order to implement and manage KD in children and adults with *status epilepticus* and no response to standard approaches.

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