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Short communication

Concomitant lamotrigine use is associated with decreased efficacy of the ketogenic diet in childhood refractory epilepsy

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ABSTRACT

Purpose: Anti-epileptic drugs (AEDs) and the ketogenic diet (KD) are often used concomitantly in children with refractory epilepsy. It has been hypothesised that certain AEDs may interfere with KD. The purpose of this study was to elucidate relationships between efficacy of KD and use of specific AEDs.
Methods: A retrospective study was performed in 71 children with refractory epilepsy starting the KD between 2008 and 2014 in Erasmus University Hospital Sophia Children's Hospital. Efficacy of the KD (defined as 50% seizure reduction) was evaluated after three months of treatment and related to the AEDs used.
Results: The KD was successful after three months in 61% of the children ($N = 71$). Efficacy was significantly reduced if children ($n = 16$) used lamotrigine (31%) at diet initiation or in the course of the diet, compared to other antiepileptic drugs (69%) ($p = 0.006$). In comparison to children using other antiepileptic drugs, the percentage of children that had adequate ketosis was significantly reduced in case of lamotrigine use ($p = 0.049$).
Conclusion: Lamotrigine treatment during KD is associated with a decreased efficacy of the KD.

1. Introduction

In 20–30% of epileptic children the epilepsy becomes refractory. This is defined as inadequate control of seizures despite optimal treatment with two well-chosen and well-dosed antiepileptic drugs (AEDs) [1]. Because adding more AEDs rarely yields important seizure reduction, other treatment options like the ketogenic diet (KD) are often prescribed in an attempt to obtain seizure control [2].

KD is compliance demanding and requires a high degree of medical and dietetic monitoring because of its side effects and restrictiveness [3]. As its underlying working mechanism is not fully understood yet, it is not clear which patients benefit most [4].

After careful implementation and monitoring, some children still show insufficient seizure reduction after three months of KD treatment. It is hypothesised that specific AEDs may interfere with the rate of success of the KD [5].

The aim of this study is to identify AEDs, that influence the efficacy of KD treatment in children with refractory epilepsy.

2. Methods

All children aged 0–18 years starting KD treatment between 2008 and 2014 for refractory epilepsy in our tertiary care paediatric hospital were included in this retrospective cohort study. Additional inclusion criteria were the concomitant use of AEDs, use of the KD for at least 3 months and complete medical and dietary records, according to the routine systematic workup in our multidisciplinary KD outpatient clinic [3]. Medical and dietary records were reviewed with respect to seizure control, epilepsy syndrome, age at onset of seizures, duration of the KD, type of AED, number of AEDs at start and during the KD, adequate ketosis, type of KD used and possible switches between types of diets. Because AEDs could be added or stopped during the three month period, we also noted switches in AEDs.

All ketone values were acquired by serum tests with Precision Xceed (ABBOTT). Adequate ketosis was defined as blood ketone level above 2.5 mmol/l.

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Epilepsy was classified by using the International League Against Epilepsy (ILAE) Proposal for Revised Terminology of Organization of Seizures and Epilepsies 2010 [6]. Success was defined as >50% seizure reduction at three months after start of the diet compared to baseline. Data on the three months period of KD use were collected using standardised scoring forms.

We only analysed data of those AEDs used in more than 10 patients. The efficacy of KD at three months was evaluated for each of these AEDs (data shown in Fig. 1).

Data were analysed using SPSS Statistics 21.0. The Pearson Chi-square test, the Fisher's exact test, the Fisher–Freeman–Halton test, and Mann–Whitney U test were used when appropriate. A p-value below 0.05 was considered significant.

3. Results

3.1. Demographics and clinical data

Seventy-one of 83 children that started the KD could be included in our study. Three had no measurable type of seizures, three children did not use AEDs at KD start, four children discontinued the KD within three months, and two children died of non-dietary related reasons. Patient characteristics are presented in Table 1.

3.2. Efficacy of ketogenic diet treatment

In our cohort 61% ($n = 43$) of the 71 children achieved >50% seizure reduction within three months and in 39% ($n = 28$) the KD was not efficious.

Comparing covariates in combination with success on the KD yielded no significant differences except for ketosis. Nine of 11 children with inadequate ketosis failed to reach adequate seizure control ($p = 0.005$) (Table 1). The chance to reach adequate ketosis was significantly reduced in case of concomitant lamotrigine use ($p = 0.049$). Five out of 16 children (31%) on lamotrigine at diet start did not reach adequate ketosis. All five patients on lamotrigine at diet initiation that did not reach adequate ketosis failed to reach adequate seizure control at three months.

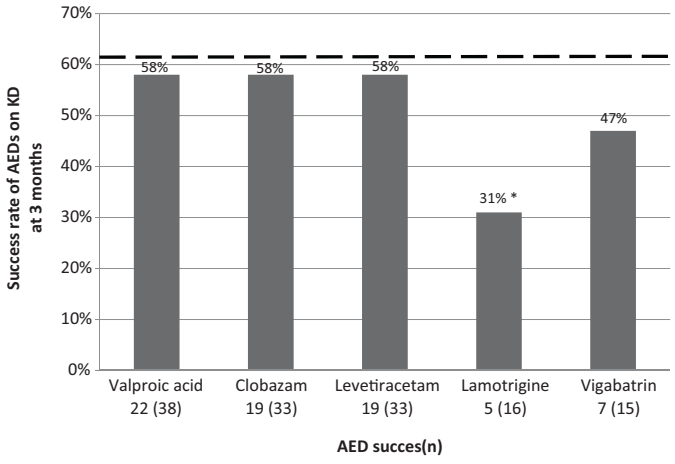

Fig. 1. Effects of concomitantly used AEDs on the success rate of the KD at three months.
Shows the differences in success rate of the KD for several concomitantly used AED's. The dashed line indicates the success rate in the total group ($n = 71$, 61%). In case of lamotrigine use the success rate was significantly reduced, $^{*}p = 0.006$. AEDs = antiepileptic drugs. KD = ketogenic diet.

Table 1
Comparison of covariates and seizure reduction.

Child and diet characteristics ($N = 71$)		Success at 3 months	No success at 3 months	p-value
Gender				
Female	$n = 26$	14(54%)	12(46%)	$p = 0.379$
Male	$n = 45$	29(64%)	16(36%)	
Age at onset epilepsy				
<1 year	$n = 48$	30(63%)	18(37%)	$p = 0.630$
>1year	$n = 23$	13(57%)	10(43%)	
Age at diet initiation				
<2 year	$n = 25$	14(56%)	11(44%)	$p = 0.836$
2–5 year	$n = 25$	16(64%)	9(36%)	
>5 year	$n = 21$	13(62%)	8(38%)	
Time elapsed between start epilepsy and diet initiation				
<1 year	$n = 20$	14(70%)	6(30%)	$p = 0.050$
1–2 years	$n = 17$	6(35%)	11(65%)	
>2 years	$n = 34$	23(68%)	11(32%)	
Number of AEDs used at diet initiation				
1	$n = 8$	7(88%)	1(22%)	$p = 0.066$
2	$n = 21$	16(76%)	5(24%)	
3	$n = 27$	14(52%)	13(48%)	
4	$n = 14$	6(43%)	8(57%)	
5	$n = 1$	0(0%)	1(100%)	
Seizure type				
One	$n = 14$	8(57%)	6(43%)	$p = 0.770$
Multiple	$n = 57$	35(61%)	22(39%)	
Seizure type				
Generalised seizures	$n = 60$	34(57%)	26(43%)	$p = 0.181$
Focal seizures	$n = 20$	10(50%)	10(50%)	$p = 0.254$
Unknown	$n = 17$	10(59%)	7(41%)	$p = 0.866$
Epilepsy classification				
Electroclinical syndrome	$n = 43$	27(63%)	16(37%)	$p = 0.602$
No electroclinical syndrome	$n = 28$	16 (57%)	12(43%)	
Etiology				
Structural/metabolic epilepsy	$n = 16$	10(62%)	6 (38%)	$p = 0.921$
Genetic epilepsy	$n = 16$	10(62%)	6 (38%)	
Epilepsy of unknown cause	$n = 39$	24(61%)	15(39%)	
Diet type at initiation				
Classic	$n = 25$	15(60%)	10(40%)	$p = 0.798$
MCT	$n = 10$	7(70%)	3(30%)	
Combination	$n = 36$	21(58%)	15(42%)	
Ketosis				
<2.5 mmol	$n = 11$	2(18%)	9(82%)	$p = 0.005^{*}$
>2.5 mmol	$n = 59$	40(68%)	19(32%)	

Table 1 shows correlation of covariates on efficacy of the ketogenic diet at 3 months.
AEDs = antiepileptic drugs; MCT = medium chain triglycerides.
* Statistical significant.

3.3. Anti-epileptic drugs

In our group of children, 16 different AEDs were used. The most commonly used AEDs at diet initiation were valproic acid ($n = 39$), levetiracetam ($n = 35$), clobazam ($n = 34$), lamotrigine ($n = 16$), vigabatrin ($n = 15$). Other antiepileptic drugs were only used by nine children or less.

3.4. Seizure reduction and AED use

Children using lamotrigine alone or in polytherapy at diet initiation were significantly less likely (5/16 = 31%, Fig. 1) to have successful seizure reduction of >50% after three months on the KD ($p = 0.006$), compared to children that did not use lamotrigine (38/55 = 69%). The average dose of lamotrigine in these children at diet start was 5.3 mg/kg (SD 4.79). Three children started using

lamotrigine during KD treatment. Two of them started using lamotrigine the same time as they started the KD using a very low dose at 3 months of around 1 mg/kg. The third child started using lamotrigine on a low dose but used 4.6 mg/kg at 3 months. Analysis of lamotrigine use (average dose 5.0 mg/kg) at 3 months of KD in 17 children with (sub)normal dose efficacy of the KD remained significantly reduced ($p = 0.032$). Comparisons of covariates in case of lamotrigine use are presented in supplementary data (Table 2).

Valproic acid, levetiracetam, clobazam or vigabatrin use did not yield any significant negative results on the efficacy of the KD.

Age, type of epilepsy, age at onset of epilepsy, epilepsy syndrome, type of KD received, duration of the KD, number of AEDs at start KD and number of AEDs during the KD did not differ between the children treated with lamotrigine and those who were not.

3.5. Ketosis and AED use

Data on blood ketones were available in 70 patients. Adequate ketosis was achieved in 84% ($n = 59$) of children at three months. Nine of 11 children (82%) with inadequate ketosis failed to reach adequate seizure control ($p = 0.005$) (Table 1). Five out of 16 children (31%) on lamotrigine at diet initiation did not reach adequate ketosis and all failed to reach adequate seizure control within three months.

4. Discussion

Our results show that in children using lamotrigine at diet initiation, the effect of the KD (>50% seizure reduction) is significantly reduced after three months. This lower efficacy of the KD with concomitant use of lamotrigine was also observed in one previous study of Morrison et al., although this lower efficacy did not reach significance. They however found that a combination of the KD with phenobarbital was significantly associated with a lower efficacy [7]. We could not reproduce the latter finding, because the number of children that used phenobarbital in our cohort is very low.

A possible explanation of this decreased efficacy of KD in children with concomitant lamotrigine use may be that lamotrigine inhibits glutamate release and is metabolised for 65% by glucuronyltransferase in the liver to inactive metabolites. The ketogenic diet results in induction of UGT1A6 enzymatic activity, which increases the glucuronidation of lamotrigine to inactive metabolites [8]. This may result in sub therapeutic lamotrigine levels. A sub therapeutic lamotrigine level can be overlooked, if an immunochemical assay is used that measures both lamotrigine and its glucuronide. However, Dahlin et al. did not find a decline in lamotrigine levels in children on KD, using a HPLC-method that differentiates between lamotrigine and its inactive metabolites [9].

One of the possible working mechanisms of the KD is inhibition of glutamatergic excitatory synaptic transmission [10]. Ketones block glutamate transport into synaptic vesicles, and lamotrigine inhibits glutamate release from these vesicles. Although it remains unclear if and how ketones and lamotrigine interact on glutamate release, an antagonistic action may be plausible as almost all AEDs, except for lamotrigine do not have working mechanisms including the neurotransmitter glutamate. An alternative explanation, and not reported in the literature yet, could be sought in the reduction of ketone formation by lamotrigine, because in our study lamotrigine users reached adequate ketosis less often than patients on other AEDs.

Our study has several limitations. Although the data are collected in a routine and systematic clinical work up, this study is still based on retrospective analysis of these data with relatively small subgroups for analysis. Children used several AEDs prior to diet initiation and most children keep using a cocktail of AEDs when using the diet. Because of small numbers we could not analyse the effects of specific combinations of AEDs on the efficacy of the KD. For this goal larger multicenter studies are needed.

Our study results may have implications on the use of lamotrigine when starting KD treatment. The next step would be to measure serum levels of lamotrigine and its glucuronides and adjust lamotrigine doses in children with poor efficacy of KD treatment or discontinuing lamotrigine if ketone levels remain inadequate. Future studies should focus on the extent of ketosis and seizure reduction in lamotrigine users on KD. Although the efficacy of the KD in our cohort is in accordance of other studies, this study may help to improve success rates of this non pharmacological treatment of refractory epilepsy in children [11,12].

Conflict of interest

There are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2015.09.007.

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