[Original article: 2 tables, 2 online figures]

Antiseizure medication reduction and withdrawal in children with drug-resistant epilepsy after starting theketogenic diet

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ABBREVIATION

ASM antiseizure medication

[abstract]

AIMTo investigate the rate of successful withdrawal of antiseizure medication (ASM) after starting the ketogenic diet in children and identify predictive factors.

METHOD We retrospectively reviewed data of children with epilepsy who were treated with the ketogenic dietfor 6 months or longer at our institution over a 5-year period. We defined successful withdrawal of oneor more medications as a time period of 3 months or more off this medication without restarting it or startinga new one. Predictive clinical factors were investigated using binary multivariable logistic regression.

RESULTSSeventy-one children were included (28 females, 43 males; median age atseizure onset 5 months, median age at diet initiation 58.5 months, median duration of ketogenic diet 27.7 months). Reduction of oneor more ASMs was attempted in 54 out of 71 (76%) children and successful in 34 out of 54 (63%), including discontinuation of all ASMs in 14.Younger age at the start of theketogenic diet was associated with higher odds of successful ASM withdrawal.ASM withdrawal was successful in 11 out of 19 children with less than 50% seizure reduction at 3 months.

INTERPRETATION Reduction of ASM was achieved in two-thirds of patients after the start of the ketogenic diet, where attempted, and can be successful even with little or unchanged seizure frequency while on the diet.

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What this paper adds

- Withdrawal of oneor more antiseizure medicationswas achieved in two-thirds of ourcohort.
- Younger age at the start of the ketogenic dietwas a significant predictive factor.
- Non-significantimprovement in seizure frequency did not preclude successful withdrawal.

[main text]

Epilepsy is a chronic medical condition associated with neurodevelopmental, cognitive, and behavioural impairments. Consideration and management of such comorbidities is important because their detrimental impact on quality of life is as significant or in some cases even greater than that of seizures.[1] According to the literature, among children with epilepsy, those with early-onset epilepsy, epilepsy of known or presumed aetiology (previously described as symptomaticor cryptogenic),and those treated with several antiseizure medications (ASMs) (polypharmacy) are most at risk of neurodevelopmental impairment.[2] Of those factors, only polypharmacy is a potentially modifiable risk factor. Indeed, a wide range of adverse events affecting daily functioning (e.g. performing everyday activities, social interactions, achieving independent living skills, controlling impulsive behaviours)have been described with a significant number of ASMs.[3–6]Therefore, it is important to minimize ASMs and the side effect burden, especially when considering alternative therapeutic options, such as aketogenic diet.

One century after the first use of the ketogenic diet by Wilder for patients with epilepsy, ketogenic diet treatments have been shown to be effective in treating children, adolescents, and adults with drug-resistantepilepsy.[7–9] The efficacy of the diet has been documented in severalrandomized controlled trials, although the overall evidence is limited by the quality of studies and small number of individualsenrolled in the trials.[9–12] Uncontrolled open studies also suggest efficacy of the diet in infancy, while seizure freedom is often achieved and maintained in this age group.[12]

A wide range of molecular, biochemical, cellular, and anti-epileptogenic actions have been proposed. In contrast to many conventional ASMs, whichtarget ion channels or act as modulators of the presynaptic release machinery,[13] there is emerging evidence that the ketogenic diet (including ketone bodies, such as beta-hydroxybutyrate, and medium-chain triglyceride fatty acids, such as decanoic acid) impacts on multiple processes and targets involved in epileptogenesis.[14] Beyond the well-described reduction in glucose supply to neurons, ketone bodies can serve as precursors of γ-aminobutyric acid, thereby regulating excitatory and inhibitory receptors at the synapse.[14] Decanoic acid induces mitochondrial biogenesis and function through the interaction with peroxisome proliferator-activated receptor gamma and also blocks the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.[15,16]In addition, the ketogenic dietaffectsdownregulation ofthe mammalian target of rapamycinpathway,[15] enhances removal of reactive oxygen species by increasing levels of glutathione in mitochondria,[15,16] inhibitscellular inflammation (i.e. reducing cytokine processing and release, inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells inflammatory signalling),[17] influences gene transcription with antiepileptic effect through the alteration of DNA methylation profiles (as shown recently in animal rodent models), and altersthe gut microbiota synthesis associated with seizure reduction.[7,8,14]

Although the efficacy of an antiseizure treatment is most commonly assessed using seizure frequency as the outcome measure, the efficacy assessment of ketogenic dietdata from adult populations showed that additional outcome measures are also important(e.g. concentration, alertness, energy, more interest in life, oral food intake).[18] The decrease in the total number of ASMs could theoretically also have an impact on the aforementioned aspects. Therefore, it is important to investigate which factors previously shown to be related to seizure outcome on ketogenic diettreatment (e.g. age, sex, aetiology of epilepsy, seizure types)could also predict the successful withdrawal of one or more ASMs.[18–23]This has only been previously explored to a limited degree.[24,25]Their identification and information about the chance of potentially successful ASM reduction is important for patients and families when they decide to consider the ketogenic dietas a treatment option.

The aim of this study was to investigate the rate of successful withdrawal of ASM after commencing the ketogenic dietin children and adolescents and identify potential predictive factors. We also compared the clinical characteristics of patients treated with the ketogenic dietin whom ASM withdrawal was attempted to those in whomASM withdrawal was not attempted.

METHOD

Study population

All patients who started the ketogenic diet from January 2013 to June 2018 and remained on this treatment for at least 6 months at our institution providing specialist epilepsy and neurology services were considered. Their medical records were reviewedretrospectively. Children were excluded if they were started on the ketogenic dietwithout receiving any ASM or without having any seizures (i.e. glucose transporter 1 deficiency without concurrent epilepsy), and if the length of treatment with the ketogenic dietwas less than 6 months since in our centre reduction of ASMs is typically attempted after a period of 3 months after the

startand establishment of the diet, although no official institutional guideline about this exists (Figure S1).

Study type

This was a retrospective study. Demographic data, including information about aetiology, seizure frequency, and ASM changes were obtained by reviewing electronic patient records. More specifically, information about seizure outcomes was extracted from interviews with parents and patient diaries reviewed during clinical visits.The visits took place every 3 to 4 months and we used time points that hadadequate clinical data (3, 6, 9, and 12 months).The duration of follow-up was 24 months after ketogenic diet initiation or until the diet was discontinued, whichever occurred first(Figure S1).

Definitions

The primary outcome of the study was the proportion of patients in whom a successful withdrawal of at least oneASM was possible. A successful withdrawal of an ASM was defined as a period of 3 months or more off this particular drug (over the total follow-up period) without restarting or starting any new ASM.

Seizure outcome after the start of the ketogenic dietwas categorized as follows: non-responders if the reduction inseizure frequency from baseline was less than 50%; responders if the reduction was 50% or more from baseline (seizure frequency as recorded in the patient's records before starting on the ketogenic diet). This was assessed at 3 and 6 months after the start of the ketogenicdiet and at the following time points if the patient was still continuing on the diet: 12 and 24 months.

Statistical analysis

Results are expressed as frequencies and percentages for categorical variables, as the mean plus or minus the SD, or median with interquartile range for continuous variables. Differences between groups were analysed using non-parametric tests (Mann–Whitney

*U*testfor continuous variables) or χ^2/Fisher'sexact test for categorical variables. Statistical significance was set at 0.05.

To investigate predictors of 'successful withdrawalof oneor more ASMs' for all children enrolled in our cohort, the following factorswere first investigated with univariable logistic regression and subsequently entered into a multivariable logistic regression: age atseizure onset; age at the start of the ketogenic diet; number of ASMs at the start of the ketogenic diet; seizure type pattern: multiple seizure types versussingle seizure type;seizure outcome at 3 months;andaetiology known versus unknown.To select the variables entered in the final model, backwardsstepwise eliminationusing a likelihood ratio with probability threshold for removal of 0.1 was applied.

Ethical approval

The study was approved by the ethics committee of Great Ormond Street Hospital for Children as a project for service evaluation (registration no. 3209).

RESULTS

Study population

From January 2013 to June 2018, a total of 104 children and adolescents were started on the ketogenic dietat our institution. Of those patients, 71 (39.4% female, 60.6% male) fulfilled the inclusion criteria and were included in the study. The baseline demographic data and clinical details of our cohort arelisted in Table 1. The average follow-up period for the total cohort was 18.8 plus or minus 6.6 months.

An underlying genetic aetiology was identified in 32 (45.1%). Details of the distribution across the threeaetiological categories (genetic, structural, unknown)are detailed in Table 1.In the category 'genetic', mutations in the genes coding for sodium and potassium voltage-gated channel alpha subunits represented the most frequent causes identified in nine children

(*SCN1A* gene in four, *SCN8A* gene in two, *SCN4A* gene in one, *KCNQ2* gene in one, *KCNT1* gene in one), while hypoxic ischaemic encephalopathy accounted for most cases of the structural aetiology category (8 out of 24).

Adverse effects potentially attributed to ASMs were documented in 9 out of 71 patients (12.7%), while side effects related to the ketogenic dietwere recorded in 41 out of 71 patients (57.7%). The latter were mild to moderate and mainly included gastrointestinal symptoms (i.e. constipation, abdominal distension). In total, 66 patients were on a classical diet, 14 on a modified diet, and eight on a medium-chain triglyceride diet. The levels of macronutrients varied with 60% to 90% fat of varying sources but diets were adjusted to induce ketosis between 2mmol/land6mmol/l.

The ketogenic diet responder rates (≥50 seizure reduction) were40 out of 71 (56.3%) after 3 months;34 out of 71(47.9%)after 6 months; 35 out of 51 (68.6%; attrition rate 28.1%) after 12 months; and 22 out of 29 (75.9%; attrition rate 59.1%)after 24 months. The attrition rate was due to diet discontinuation (12 and 24 months). Reasons for diet discontinuation (before 24 months) included: no improvement inseizure control (34 patients);adverse events (four patients); anddeath (one patient, death not related to the ketogenic diet).Reasonswere unspecified in threepatients.

ASM withdrawal

In general, withdrawal of at least one ASM was attempted 3 to 6 months after starting the ketogenic dietin 54 out of 71 patients (76%) and was successful in 34 children (62.9%). In the group of patients in whom withdrawal was attempted, the follow-up period was 19.9 plus or minus6 months (in nine patients, the follow-up period was <12 months). The responder rate (assessed at 3 months on the diet) was significantly higher among patients in whom weaning was attempted (35 out of 54, 89.7% vs19 out of 54, 25%, $p = 0.009$), while there was no significant difference in the number of ASMs at the startof the ketogenic dietbetween those

groups (Table 1). In the responder group, ASM withdrawal was successful in 23 of 35 patients in whom it was attempted.When withdrawal was attempted in the ketogenic dietnon-responder group, it was successful in 11 out of 19.

In the group achieving successful ASM withdrawal(n = 34), one ASM was discontinued in 20 children, two ASMs in 10 children, and three ASMs in four children. The ASMs withdrawn were not restarted in any of those casesduring the follow-up period. Thirteen children in this subgroup were weaned off all regular ASMs during treatment with the ketogenic diet.In most children (52 out of 54, 96.3%) attempts were made to withdraw ASMs of the regular regime; in only two cases, ASMs were started as the intervention for acute seizure worsening (i.e. phenytoin, clobazam). In those twopatients, ASM withdrawal was not successful.

Seizure recurrence during ASM withdrawal occurred in 26 of 54 children (48.1%). However, in most cases the seizure burden did not result fromrestarting the medication or becausea new ASM was introduced (Figure S2). Out of 34 patients in whom ASM was successful, a new ASM was started in only onecase more than3 months after successful withdrawal (i.e. cannabidiol was started in a child with Lennox–Gastaut syndrome after successful withdrawal of all other ASMs to further improve seizure control [Figure S2]).

Factors predicting successful ASM withdrawal

The data for the entire cohorts were entered in these analyses. Applying the cross-tableχ^2statistics showed that there was no significant association between successfulwithdrawal of oneor more ASMs and the genetic, structural, and unknown aetiological categories (Pearson'sχ^2 = 1.64, p = 0.4). In the subsequent analyses, aetiology was therefore coded as known or unknown.

Table 2 shows the results of the univariable analyses. Older age at the start of the ketogenic dietand presence of multiple seizure types were associated with a significantly

lower chance ofsuccessfulwithdrawal of oneor more ASMs, while there was a non-significant trend for ketogenic dietresponders at 3 months, that is, those with 50% or more seizure reduction, towards a higher chance of successful ASM withdrawal.

Entering all variables in a stepwise backwards multivariable logistic regression model retained age andstart of ketogenic dietas significant predictors of successful withdrawal of oneor more ASMs (Table 2).

DISCUSSION

In our study,ASM withdrawal was attempted in most of our cohort(76%) and successful (withdrawal of one or more ASMs) in almost two-thirds of children (34 out of 54, 62.9%), who were on the ketogenic dietfor at least 6 months. Age at the start of the diet was independently and significantly associated with successful ASM withdrawal.

Published data about ASM withdrawal in children started on the ketogenic diet are limited but generally encouraging.[24–26] According to previous studies, approximately 19% of children on the ketogenic dietachieve complete ASM withdrawal during dietary treatment, similar to the observation in our cohort (complete ASM withdrawal in 13 out of 71, 18.3%).Gilbert et al.[26] looked at 150 children with epilepsy startedon the ketogenic dietand found that at the 12-month follow-up, 74% (63 out of 85) of children who remained on the diet had their number of medications reduced.However, no further analysis was performed because this study mainly focused on the costs of medication.Regarding the time of starting to reduce ASMs, data were only available in onestudy in the literature, ranging from immediately after the startof the diet to 6 months after starting it.[24] In previous studies, however, combined information about the proportion of patients in whom ASM withdrawal was attempted and the proportion of patients achieving ASM reduction rather than complete withdrawal wasnot

always provided. Furthermore, factors relating to successful ASM withdrawal were not investigatedexhaustively.[24–26]

Our group comparison showed that the rate of ketogenic dietresponders after the diet was startedwas significantly higher among children in whom withdrawal was attempted. This finding may be explained by physicians' clinical practice and parental/caregiverpreference, whereby ASM reduction is more likely to be attempted in circumstances of changed (reduced) seizure frequency. However, when withdrawal was attempted in the ketogenic dietnon-responder group (19 out of 54), it was successful in 11 out of 19.No significant differences in aetiological categories and other clinical epilepsy-related variables at baseline were identified between the group with ASM withdrawal attempted compared to children in whom no attempt was made. This raises the question as to what guides the clinical decision to withdraw ASMs and why clinicians and parents/caregiversmay be hesitant to reduce ASMs thatwere not effective. It is interesting that, in the literature, data from adult patients show that discontinuation of ASM treatment is not systematically discussed, even in patients with long-term good seizure control; subsequently, many patients may be living with an unnecessary drug burden.[27]

In our cohort of patients on the ketogenic diet,younger age at the start of the ketogenic dietwas a significant independent predictor of successful ASM withdrawal. In the study by Shah et al.[25] younger age was also a factor significantly associated with ASM-free status.In general, age (mainly age atseizure onset and age at the startof the ketogenic diet)was previously separately studied as a potential predictor of the efficacy of the ketogenic dietin children. Agarwal et al.[19] showed that later age atseizure onset is positively correlated with response to the diet but the literature to date about the effect of age at the start of the diet does not show any significant relationship.[19,20,22,23] Seizure onset in infants and young children is often a feature of epilepsy type/syndromes associated with a more severe course and

drugresistance (e.g. developmental epileptic encephalopathies) compared to onset in later childhood.[19] On the other hand, younger children and infants often comply better with the dietary restrictions of the ketogenic diet. A shorter duration of epilepsy has also been associated with more favourable seizure outcomes with other therapeutic interventions, such as surgery.[28] Furthermore, as mentioned earlier, the ketogenic dietand diet-related substrates exert and influence multiple molecular and cellular processes shown to be relevant for epileptogenesis; therefore, especially if started earlier, the diet may offer a greater chance of disease modification affecting network plasticity and recovery processes in the young brain.[14]The relationship between age atstarting the diet and seizure outcome, which was not the primary focus of the current study, as well as the long-term impact on cognition/behaviour requires further investigation in the future.

Regarding the underlying aetiology, in our cohort we didnot identifya significant impact on successful ASM withdrawal. However, this finding is limited by the relatively small number of children in our cohort and especially in the aetiological subcategories that did not permit statistical analysis.For the same reason, we were not able toinclude subgroupswith specificseizure typesand all specific electroclinical syndromes in the statistical analysis of factors associated with successful ASM withdrawal. We only investigated the effect of history or presence of epileptic spasms at the time of the ketogenic diet in the univariate model (as a factor related to successful ASM withdrawal) but no significant difference was found; therefore, it was not included in the multivariate model. Shah et al.[25]showed that glucose transporter 1 deficiency and epilepsy with myoclonic-atonic seizures were significant predictors of ASM-free status after the start of the ketogenic diet, whereas Lennox–Gastaut syndrome was associated with unsuccessful withdrawal of all ASMs. The latter is relevant to our findings since multiple seizure types were associated with a lower chance of successful withdrawal of oneor more ASMs.

Thammongkol et al.[21] found that patients with an underlying known or presumed genetic defect (e.g.Dravet syndrome, childhood absence epilepsy, epilepsy with myoclonic and atonic seizures) and patients with lissencephaly are good responders to the ketogenic diet.Furthermore, Villaluz et al.[29]showed that the ketogenic dietwas significantly effective in patients with a developmental and epileptic encephalopathy due to an acquired structural aetiology. Although these results suggest that earlier ASM reductionin the aforementioned patient groups would be possible and desirable, given the epileptogenicity associated with some structural lesions such as lissencephaly, the issue of safety inrelation to complete ASM withdrawal on the ketogenic dietrequires consideration. This issue needs careful clinical assessment and judgement on an individual basis considering the drug burden, partial response to specific ASMpreviously commenced,and ensuringthat appropriate emergency seizure medication regimes are in place. Medication reduction to a minimum (if monotherapy is possible), especially by discontinuing medications that were or have become ineffective over time,ratherthan complete withdrawal, may well be the goal for individual patients. In this context, we showed that being a good responder is not equivalent to successful withdrawal.

Indeed, in the final multivariable regression analysis seizure outcome was not significantly associated with successful ASM withdrawal. Althoughwith a larger sample this association might have reached statistical significance, this findingcould also suggest that the responder rate seizure frequency reduction threshold of 50% or more from baseline may not be a factor relating to successful ASM withdrawal. We also observed in our cohort that although seizures may recur or increase afterASM withdrawal, this does not require ASM to be restarted or new medication to be added(Figure S2). Kossoff et al.[24] reported a similar observation with transient seizure worsening during medication tapering, without affecting the final outcome of ASM discontinuation. Furthermore, fluctuations in seizure frequency are commonly seen

in patients with pharmacoresistant epilepsy considered for the ketogenic diet.[30] Therefore, review of additional outcomes, apart from seizure frequency (e.g. seizure duration, seizure intensity, quality of life), is of paramount importance.

Limitations of our study include itsretrospective design and variability in the documentation of information. The relatively small number of patients enrolled may have affected the statistical power of the analyses. Data about the impact of the ketogenic diet on additional seizure aspects (e.g. duration, severity) were not systematically recorded. Although the total follow-up period was reasonable, in a few patients it was less than12 months and this might have affected a small part of the resultsslightly. The data for this study were obtained from a single centre and therefore might have been influenced by the local ASM withdrawal practice. However, several senior clinicians who are mainlyinvolved with working withepilepsy, are working in our ketogenic dietservice.

Future multicentre and prospectively designed studies are required to investigate factors influencing the decision-making of clinicians about ASM withdrawal and identify new clinically essential outcomes.

All theaforementioned findings highlight the need to broaden our understanding of treatment outcomes and consider aspects of daily functioning (e.g. decrease in ASM burden and associated adverse events). From this point of view, discussion of therapeutic priorities and goals with patients and families before diet implementation is essential.

Conclusion

Medication management is an important part of ketogenic diet care.Our study shows that weaning of one or more ASMs is possible in a large proportion of children with epilepsy after the start of theketogenic diet, especially for those of younger age at the start of the diet. Although withdrawal is more likely attempted in those patients who have responded to the diet, ASM reduction in those who are categorized as non-responders after starting the

ketogenic dietshould be considered, especially inchildren who are on multiple ASMs, those with significant side effects, those on medications that have no apparent effect, and those of younger age at the start of the diet, always with guidance froma paediatric neurologist/epileptologist. Therapeutic priorities in children with epilepsy need to be reconsidered and, apart from seizure frequency, additional clinically meaningful aspects of patients' lives should be included.

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Supporting information

The following additional material may be found online:

Figure S1: A total of 71 patients with epilepsy who were started on the ketogenic diet between January 2013 and June 2018 were analysed.

Figure S2: ASM withdrawal was attempted in 54 out of 71 children in our cohort and was successful in 34.

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Table 1: Demographic and clinical traits of the total cohort and comparisons between groups (withdrawal attempted vs withdrawal not attempted)

Baseline patient demographics and clinical traits	**Weaning attempted (*n* = 54)**	**Weaning not attempted (*n* = 17)**	***p***	**Total cohort (*n* = 71)**
Sex: female	22 (78.5)	6 (60.7)	0.160	28 (39.4)
Median age at seizure onset, months (IQR)	5 (153)	10 (59)	0.142	5 (16)
Aetiology				
Genetic	25 (78.1)	7(21.9)	0.819	32 (45.1)
Structural	17 (70.8)	7 (29.2)		24 (33.8)
Unknown	12 (80)	3 (20)		15 (21.1)
Single seizure type	24 (70.6)	10 (29.4)	0.406	34 (47.9)
History or presence of epileptic spasms at the time of theketogenic diet	30 (55.5)	9 (52.9)	0.850	39 (54.9)
Baseline seizure frequency				
Daily	47 (77)	14 (23)	0.830	61 (85.9)
Weekly	3 (60)	2 (40)		5 (7.05)
Monthly	4 (80)	1 (20)		5 (7.05)
Median number of ASM at the start of ketogenic diet (IQR)	2 (3)	3 (3)	0.285	2 (1)
Median age at the start ofketogenic diet, months (IQR)	54.1 (84.5)	95 (127.3)	0.142	58.5 (97.4)
Seizure outcome (responders) 3 months after the start of the ketogenic diet[a]	35 (89.7)	5 (10.3)	0.009	40 (54.9)

Data are *n* (%) unless otherwise stated.[a]See text for seizure outcomes at 6, 9, and 12 months. Abbreviations: ASM, antiseizure medication; IQR, interquartile range.

Table 2: Predictors of successful withdrawal of oneor more ASMs on univariate univariable analysis and multivariable logistic regression (*n* = 70)

Univariable analysis		
Clinical variable	**OR (95%CI)**	***p***
Age at seizure onset	0.67 (0.98–1.01)	0.67
Age at the start of the ketogenic diet	0.98 (0.97–0.99)	0.002
Number of ASMs at the start of the ketogenic diet	0.72 (0.41–1.28)	0.27
Multiple vssingle seizure types	0.29 (0.11–0.77)	0.017
Aetiology (known vs unknown)	1.50 (0.47–4.78)	0.57
Seizure outcome after 3 months on theketogenic diet(responders vs non-responders)	2.62 (0.99–6.91)	0.059
Multivariable backwards logistic regression		
Variables retained in the model	**OR (95%CI)**	***p***
Age at seizure onset	1.02 (0.99–1.05)	0.1
Age at the start of the ketogenic diet	0.98 (0.96–0.99)	<0.001
Seizure outcome after 3 months on the ketogenic diet(responders vs non-responders)	2.86 (0.962–8.51)	0.59

Seizure outcome: responders 50% or greater seizure reduction. Abbreviations: ASM,antiseizure medication; CI, confidence interval; OR, odds ratio.