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KETOGENICS

KETOGENIC DIET THERAPY FOR THE MANAGEMENT OF INFANTILE SPASMS

An introduction for healthcare professionals

ISs booklet is reviewed and endorsed by
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INTRODUCTION

Infantile Spasms (ISs) belong to the group of early epileptic encephalopathies associated with difficult to control seizures and often persistent electroencephalographic (EEG) abnormalities. Long-term changes in psychomotor development as well as high mortality rates during early childhood are linked with ISs.

Notwithstanding, pharmacological treatment options are often scarce resulting in difficult to control epilepsy and relapse rates remain high, leaving a significant number of children suffering from ISs without successful management.

Evidence for the effectiveness and safety of ketogenic dietary therapy (KDT) has grown substantially in the last decade demonstrating impressive reductions in seizures:

- Seizure reduction of more than 50% in 48-80% of infants[1]
- Complete seizure freedom in 14-54%[1]
- Responder rate of 60-70% percent[21]

Although adverse effects are reported these are largely transient and resolvable[1].

Given the impact on children's lives of treatment failure and with the mounting evidence to support its use, it is imperative that after failure of standard treatment KDT be initiated promptly in line with the latest evidence. Delays should be avoided as swift action is necessary to deliver the best possible short- and long-term outcomes for infants with ISs.

This booklet is designed to provide insights into the management of ISs with KDT in young children.

INTRODUCTION TO INFANTILE SPASMS

Background

ISs belong to severe and rare epilepsy syndromes in infants and young children being affected by seizures (fits) in clusters or as single convulsions. The term infantile spasms is used for describing the clinical seizures (epileptic spasms), but also for the syndrome itself.

ISs occur most frequently within the first year of life with a peak of onset between three to seven months and an incidence of 2 - 3.5 per 10,000 live births[3]. Whilst the disorder resolves in some children, the majority will have varying degrees of long-term developmental delays and cognitive problems as well as an increased risk of premature death, which is not limited to early age but continues into adulthood[4].

ISs are the most common infantile onset epileptic encephalopathies or severe infant brain disorders as a result of the most likely progression to cognitive deterioration and persistence of epilepsy in later life[5,6]. West syndrome named after Dr William West, who first described the syndrome in his four month old son in a letter to *The Lancet* in 1841, is the most frequent subtype of ISs, including epileptic spasms, a characteristic EEG pattern (called hypsarrhythmia), and (not mandatory) developmental regression before epilepsy onset[7].

Approximately two thirds (60-70%) of infants with ISs have an identifiable cause for the seizures[3] which can result from a wide range of issues. The most frequent are changes to the brain structure, often due to a prior injury either focal or multi focal, or a lack of oxygen to the brain. Other known causes include cortical malformations, genetic mutations or metabolic disorders. In 10 to 40 percent of the infants the underlying cause is unknown and epilepsy onset is not always associated with atypical development[3,7].

Seizure Presentation

Seizures associated with ISs (epileptic spasms) may be subtle and are frequently mistaken by other conditions, such as baby colic, because of the pattern of attacks and the cry that a child gives during or after a seizure. Epileptic spasms can present in different ways, are usually infrequent at first and often occur in clusters. These combined factors may lead to late diagnosis.

Typically features of epileptic spasms are:

- They present as flexor, extensor, and mixed flexor–extensor spasms[3]
- They involve brief symmetrical contractions of musculature of the neck, trunk, and extremities, lasting up to five seconds[3]
- Infants may cry during or after the seizure[8]
- They may appear close together in clusters which distinguishes them from baby colic where the attacks do not occur in a cluster[8]
- They usually occur just before falling asleep or on awakening and rarely occur during sleep itsself[6]

Diagnosis

Diagnosis of ISs can often be challenging but early diagnosis is essential to allow prompt treatment as scientific evidence confirms early treatment as a positive predictive factor not only for seizure freedom but also for psychomotor development. It has been shown that the shorter the time between diagnosis and treatment, the more favourable developmental and seizure outcomes. It is therefore critical to identify ISs patients early and initiate prompt and effective treatment[9,10,11,12].

Treatment goals

The main aim of treatment is to improve children's short and long-term quality of life. Short-term goals focus on achieving freedom from both epileptic spasms and abnormalities in the EEG (hypsarrhythmia). Long-term goals are to maintain seizure freedom and to minimise the impact on development and intellectual performance in later childhood and adulthood[9].

Although for many children epileptic spasms and hypsarrhythmia resolve with time, others develop other forms of therapy-resistant epilepsy syndromes and about 70% of infants show severe psychomotor delay[11].

Pharmacological treatment for Infantile Spasms

Only a few randomised controlled trials have been performed in the treatment of ISs, and the best evidence for effectiveness has been shown for:

- Adrenocorticotropic hormone (ACTH),
- Vigabatrin (VGB) and
- Oral corticosteroids[3]

These are the recommended standard therapies (first line treatments), showing higher effectiveness when combined (hormonal therapy combined with VGB)[13].

However, lack of response to or relapse after first line therapy is frequent[14,15] and medical treatment options remain limited and unsatisfactory with respect to seizure control and developmental outcomes[11] leaving a large percentage of children without successful treatment[14].

Frequent severe adverse effects have been observed for hormonal treatments (including a higher mortality rate) as well as VBG, which has been associated with irreversible visual field defects after long-term use[16].
The need for effective and safe treatment options is extremely high[9], leading to an increased interest and to further studies of other therapies, such as non-pharmacological options[17], including KDT.

The National Institute for Health and Care Excellence (NICE) recommends that children who have not responded to treatment with anti-seizure medication are considered for KDT[18]. This approach is also recommended by Kossoff et al. in the International KDT Study Group consensus guideline, highlighting the particular effectiveness of KDT in early infancy epilepsy syndromes[2,19].

Given the significant implications and need for early effective treatments, we look at the growing body of evidence for the safety and effectiveness of KDT in ISs and provide guidance for its successful implementation to improve outcomes and hence quality of life.

EVIDENCE TO SUPPORT THE KDT FOR INFANTILE SPASMS

About KDT

KDT is a well-established, non-pharmacological intervention, which has been successfully used in children and adults with medication resistant epilepsy since the 1920s[2]. It is a high-fat, adequate protein and carbohydrate restricted diet. For infants a 3:1 ratio is recommended in order to provide adequate protein intake to support optimal growth[19]. The diet is thought to work by mimicking the effects of starvation, targeting the most fundamental aspects of cell function – cell energy[17], thereby enhancing gamma-Aminobutyric acid (GABA) synthesis and improving energy utilisation in the brain[3].

With the increased use in infants, data have shown that KDT is effective and safe in infants[19,20]. Greater success in achieving seizure freedom has been shown when KDT was used in time, particularly in epilepsy syndromes of early infancy such as ISs[1,20]. Current guidelines[2] therefore specify conditions, including ISs, where KDT should be introduced early. These recommendations are based on the growing evidence that KDT is more successful at achieving seizure freedom when initiated at a younger age, particularly in epilepsy syndromes emerging during early infancy such as ISs[1].

Effectiveness and safety of the KDT in ISs

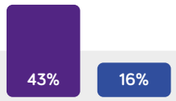
Knowledge and understanding of KDT is gaining momentum as an increasing number of clinical studies and reviews, as well as clinical practice, clearly demonstrate the effectiveness of KDT in ISs. Recently published data and reviews advocate the initiation of KDT as the next-line preferred therapy should standard treatment fail:

- A retrospective study by Kossoff et al. on the KDT versus ACTH for new-onset ISs showed that KDT stopped spasm in almost two thirds (62%) of cases and had fewer side effects and relapses than ACTH[21].
- A systematic review examining the effectiveness of KDT in ISs showed that about a third (35%) of patients were spasm free and two thirds (65%) had a greater than 50% reduction in spasms by six months. Seizure freedom was more often achieved in infants without a clear cause[22].

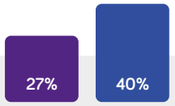
Randomised controlled trials (RCTs) are scarce as a result of the small numbers of infants affected by ISs. To date only one head-to-head comparison of KDT versus standard-of-care high dose ACTH for the treatment of ISs has been performed[17]. This single-centre parallel-cohort, randomised controlled trial showed that KDT is as effective as ACTH for the treatment of ISs in the long-term but better tolerated[17]. Following graphs show the main results:

In the combined group of 101 infants, there was no difference in spasm freedom by 28 days for KDT versus ACTH 47% vs. 48%, respectively).

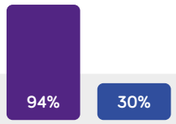
The time to respond with seizure freedom and cessation of hypsarrhythmia (i.e. electroclinical remission) was similar for both treatments (16 vs. 14 days, KDT vs. ACTH, respectively).



Spasm relapse rates were significantly higher for ACTH (43%) compared to KDT (16%).



Seizure freedom at last follow-up was 27% ACTH and 40% for KDT



Adverse effects were much higher with ACTH (94%) than KDT (30%).

A recent pooled analysis of cohort studies and case series in infants below 12 months showed that KDT reduced seizures by more than 50% in 48-80% of patients and achieved seizure freedom in 14-5%. The review concluded that KDT is effective and safe to use in infants and should be used early in specific epilepsy syndromes and genetic aetiologies including ISs[1]. Adverse effects were largely transient and resolvable by dietary adjustments, most frequently occurring as gastrointestinal symptoms as emesis, hypoglycaemia, food and liquid refusal and constipation[1].

A current meta-analysis in infants below 24 months[23] showed seizure reduction ≥ 50% in 59 percent at a 3- to 12 month follow-up and seizure freedom in 33 percent including 33 studies. Adverse effects were comparable to older children and adults showing frequently dyslipidaemia, vomiting, constipation, gastroesophageal reflux and diarrhoea. The authors concluded that high-quality studies are urgently needed for the use of KDT in infancy.

In another recent review[24] infants ranging from 0-23 months were studied in 52 studies published between the years 2015 to 2018. The authors concluded that the classic KDT remains the first choice in infancy and in Glucose-1 transporter deficiency with an earlier start promising a better seizure and developmental outcome.

EVIDENCE SUMMARY

KDT is an effective and safe management option for infants, reducing seizures by more than 50% in 48-80% of patients and achieving seizure freedom in 14-54 percent supporting its early use in specific epilepsy syndromes like ISs[1] and Glut-1 deficiency[24] However, large-scale studies of high quality are needed[23].

Support for KDT as an early intervention in ISs in the epilepsy care pathway in ISs

The majority of research evaluating the effectiveness of KDT in ISs has been carried out in pre-treated infants, after the failure of a number of pharmacological interventions. Given the lack of evidence to support first-line use, the focus for the KDT has tended to be on second-line use, where a high response rate has been achieved, following first-line treatment failure with hormonal treatment (ACTH or oral corticosteroids) and/or VGB[3].

However, research has explored the merits of KDT earlier in the epilepsy care pathway in ISs:

- Kossoff's retrospective study suggested that the high response to KDT warranted exploring it as a first-line therapy in infants who experienced spasms for less than two-weeks in order to allow for a maximum potential total spasm time of no more than four weeks prior to hormonal therapy[20].
- In a prospective single-centre experience of ISs managed with KDT by the same working group, including infants from the first study, infants with new onset spasms were offered a 2-week trial of KDT as an alternative to pharmacological treatments. Fifty-six% of infants became spasm-free within two weeks of starting therapy and had a normal EEG within two months[25].
- Dressler's recent head-to-head study on KDT versus standard therapy showed that for those infants without prior VGB treatment, ACTH remains the first choice to achieve short term remission. However, in those with prior VGB, KDT was at least as effective as ACTH in the short term and was associated with lower relapse rates in the long-term representing an appropriate second line treatment after VGB. Infants with prior VGB treatment had a longer duration of prior epilepsy, indicating epilepsy that was difficult to treat. As KDT is highly effective in medication resistant epilepsy, the authors concluded that this would also be the case in ISs pre-treated with VGB[17].

EVIDENCE SUMMARY

Extended research in the last decade on KDT and a greater understanding of the mode of action through clinical studies and clinical practice has led to a key guideline update in 2018. *Optimal clinical management of children receiving dietary therapies for epilepsy; updated recommendations of the international Ketogenic Study Group*[2].

The mode of action is an effective and safe therapy for ISs and should be strongly considered very early in the course of treatment particularly in those infants who are refractory to standard therapies such as corticosteroids and vigabatrin[2].

MANAGEMENT OF THE KETOGENIC DIET THERAPY IN INFANTILE SPASMS

Use of KDT in infants

KDT is an established, valuable non-pharmacological management option for medication resistant epilepsy with proven effectiveness and safety in early childhood. This evidence has resulted into specific infant guidelines on the use of KDT in infancy[19]:

- Urgent need for standardised protocols and recommendations for clinical use in infancy.
- A project group of 5 experts developed a consensus statement on the clinical management of KDT in infants which was then revised by a larger group of 10 international experts.
- Consensus was achieved on how to manage KDT in infants.
- The KDT in infants is gradually introduced with a classic KDT (fixed fat/ non-fat ratio) of 3: 1 to meet protein requirements of infants.
- The ratio can be modified, if necessary, based on the level of ketosis and/or tolerance to the ratio, without fasting and fluid restriction[1,19].
- Neither fluid restriction nor fasting is recommended in infants.
- Preparation for treatment is in line with the clinical consensus guideline for children receiving the KDT[2].
- Close monitoring during inpatient initiation by a multidisciplinary team and regular follow-up are required[2,19].

EVIDENCE SUMMARY

With the growing evidence that children younger than two years of age may be an ideal age population in which to start KDT, recommendations for the management in infancy include:

- An inpatient stay with a gradual introduction of a classic KDT with a lower fat/ non-fat ratio to meet protein requirements in infants is needed
- No fluid restriction or fasting.
- Dietary adjustments according to the individual clinical situation.
- Close inpatient and outpatient monitoring by a multidisciplinary team[19].

Goals and considerations of KDT for Infantile Spasms:

Primary goal [26]

Like other treatments the primary goals of KDT are:

- Seizure freedom.
- Resolution of hypsarrhythmia (EEG verified).

Secondary goals[18]

For those infants receiving KDT:

- Prescribe an age-appropriate energy intake and prevent deficiencies of macro-and micronutrients with an individual and age-adjusted dietary prescription.
- Attain adequate growth, based on an individual growth curve.
- Limit/prevent adverse effects and complications due to KDT.
- Achieve an age-dependent feeding pattern and development.

KetoCal is a Food for Special Medical Purposes for the dietary management of drug resistant epilepsy or other conditions where the ketogenic diet is indicated and must be used under medical supervision.

EVIDENCE SUMMARY

Overall the risk of serious adverse events is low; KDT does not need to be discontinued for most adverse effects. Gastrointestinal complaints are often common but can be easily remedied[1,2].

KDT and breastfeeding

Previous recommendations suggesting that infants must be weaned before starting on the KDT resulted in reservations about its use in infants. More recently, this view has changed with studies demonstrating the benefits of the early introduction of KDT together with the feasibility, effectiveness and safety of simultaneously continuing to breastfeed[1,27]. Direct breastfeeding is possible by either calculating the amount of breastmilk into a 3:1 formula or potentially allowing it for a limited amount of time on demand after a ketogenic formula with a fixed fat/ non-fat ratio[1,2,27].

Duration of the KDT for Infantile Spasms

Infants started on a KDT usually respond within 14 days of therapy initiation and improvements most frequently experienced within one month and at most three months[26]. As a minimum however, duration of KDT should be no less than 14 weeks (3.2 months) to fully allow for potential improvement to be experienced[2]. After such time consideration should be given to discontinuing KDT if unsuccessful. Where benefit has been experienced the recommendation is for therapy to continue for two years, although a shorter duration may be appropriate for infants with ISs[2]. When appropriate, discontinuation should happen gradually over several months[2].

The benefits of KDT can be seen long-term, even in those who stopped it years earlier[2].

EVIDENCE SUMMARY

KDT should be provided for at least three months before considering the therapy non-effective and discontinuing[2].

Ketogenic formulas to support KDT

The development of readily available, specific ketogenic formulas has facilitated the increased use of KDT in young infants[1]. KDT formulas such as Nutricia's KetoCal® 3:1 - an infant feed for special medical purposes, indicated from birth, specifically developed to meet the nutritional requirements of very young epilepsy patients and can be used in combination with breastmilk and breastfeeding - has simplified and aided initiation of KDT in infants. Multiple studies have shown KetoCal® to be safe, effective and well tolerated by this age group[21,22,23,27,28,29,30].

FURTHER INFORMATION

For further information on KDT management including pre-counselling, adverse effects, monitoring etc please consult the full guidance:

www.ilae.org/patient-care/ketogenic-diet-therapies
www.nice.org.uk/guidance/cg137
www.epilepsy.com/learn/treating-seizures-and-epilepsy/dietary-therapies/ketogenic-diet

www.matthewsfriends.org/
www.thedaisygarland.org.uk
www.youngepilepsy.org.uk
www.charliefoundation.org

Optimal clinical management of children receiving dietary therapies for epilepsy; updated recommendations of the international Ketogenic Study Group: https://onlinelibrary.wiley.com/doi/full/10.1002/epi4.12225

Ketogenic diet guidelines for infants refractory epilepsy: https://pubmed.ncbi.nlm.nih.gov/27470655/
www.nice.org.uk/guidance/cg137

INFANTILE SPASMS (ISs)

An overview

Severe infant brain disorder with poor outcomes

- Regular epileptic spasms[1]
- Characteristic EEG pattern (hypsarrhythmia)[1]
- Long-term developmental delays and cognitive problems[2]
- Increased risk of developmental regression and premature death[2,3]

Most common infantile onset epileptic encephalopathy

- Peak age of onset 3-7 months[1]
- Incidence 2-3.5 per 10,000 live births[1]

Typical features of ISs

- Seizures
  - present as flexor, extensor and mixed flexor-extensor spasms, typical for ISs[1]
  - involve symmetrical contractions of musculature of neck, trunk and extremities[1]
  - lasting up to 5 seconds[1]
- Infant may cry during or after seizure[5]
- May appear close together in clusters[5]
- Usually occur just before falling asleep or on awakening[5]

Treatment goals

- Improve short and long-term quality of life[6]
- Short-term: freedom from epileptic spasms and hypsarrhythmia[6]
- Long-term: maintain seizure freedom and minimise impact on longer-term development and intellect[6]

First-line treatment

- Standard treatment option: ACTH, Vigabatrin and oral corticosteroids[1]
- These drugs are associated with significant side effects and high relapse rates[6]
- Some show considerable risks with long-term use[8]
- Demand for safer and more effective treatment options is extremely high[6]

Guidelines recommend ketogenic diet therapy (KDT) for drug resistant epilepsies and infancy epilepsy syndromes such as ISs[8,9]

- Following first-line pharmacological treatment failure[8]

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KETOGENIC DIET THERAPY (KDT)

As an effective management option for IS's

About KDT

- Well established nutritional intervention
- High-fat, carbohydrate restricted diet[8]
- Fat to carbohydrate and protein ratio of 3:1 favoured for infants to meet their protein requirements[10]

KDT in Infants

- KDT is effective and safe in infants[12]
- Reducing seizures by more than 50% in 48-80 per cent of patients[13]
- Achieving seizure freedom in 14-54 percent supporting its early use in specific epilepsy syndromes like ISs[13]

KDT is an effective evidence-based second-line treatment in ISs

- Greater success in achieving seizure freedom when used early in epilepsy syndromes emerging in early life[1]
- Systematic review showed: 35% spasms free and 65% had a greater than 50% seizure reduction by 6 months on KDT[11]
- Seizure freedom more often achieved in infants without clear cause[11]

Easy to initiate

- Children under two years of age ideal population in which to start KDT[8]
- Safe and effective to continue to simultaneously breastfeed[14]
- Readily available KDT formulas have facilitated use of KDT in young infants[14]

...and with good safety

- Largely transient and resolvable adverse events[14]
- Discontinuation rare and gastrointestinal complaints easily remedied[8]
- Readily available KDT formulas have facilitated use of KDT in young infants[1]

Response to KDT can be seen reasonably quickly[8]

14 DAYS	Usual response within 14 days
1-3 MONTHS	Improvements typically experienced within 1-3 months
14 WEEKS	Minimum duration 14 weeks
2 YEARS	KDT should typically be implemented for 2 years

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