

Ketogenic Dietary Therapy for Infantile Spasms



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Infantile spasms (IS), first reported in 1841, and newly classified as Infantile Epileptic Spasm Syndrome (1), typically presents within the first year of life as spasm-type seizures. It is often associated with an EEG abnormality known as hypsarrhythmia and developmental regression; this triad of symptoms being termed West Syndrome (2). First-line treatment options for IS include adrenocorticotropin hormone (ACTH), oral prednisolone or vigabatrin; the latter being medication of choice for spasms associated with tuberous sclerosis (3). These treatments will successfully control seizures in many cases but have significant side effects that limit their duration of use (4). Second line treatments include pyridoxine and ketogenic dietary therapy (KDT), with alternative anti-epileptic drugs (AEDs) also used if first-line treatments are unsuccessful, however with variable success (4). Continued intractable seizure activity in an infant will impact on long-term cognitive and behavioural outcomes, with considerable cost implications for health services due to need for regular clinical reviews, hospital treatment, medications, and support of other therapies. Treatment options for this syndrome should therefore be explored as early as possible.

KDT is a high fat, restricted carbohydrate regime that has been used since the 1920s, and includes the traditional Classical and Medium Chain Triglyceride diets and less restrictive Modified Atkins diet (MAD) and Low Glycaemic Index Treatment. Efficacy of these diets in epilepsy has been demonstrated in many studies including randomised controlled trials in children (5, 6, 7, 8). Reviews support KDT as a safe, tolerable, and effective treatment in infants with drug-resistant epilepsy (9, 10, 11) and a recent randomised open label trial of 136 infants found Classical KDT to be similar in efficacy and tolerability to a further AED and was safe to use in infants with epilepsy (12). Retrospective studies looking specifically at infants with IS have also shown KDT to be effective and well-tolerated (13, 14, 15, 16), with one study reporting significant spasm improvements and less side effects when KDT was used as an alternative first-line therapy to ACTH (17). One study of 119 infants who had genetic sequencing prior to KDT reported a higher response rate to diet in those with CDKL5 mutation (18). Prospective studies also demonstrate KDT efficacy in IS unresponsive to first line treatments. In a study of 104 infants, 64% had over 50% improvement in spasms after 6 months on KD, 29 of whom became seizure free (19). Three smaller studies have also reported positive results (20, 21, 22) although another study of 22 children has questioned whether complete seizure response to KDT can be achieved in highly refractive IS (23). A larger prospective controlled study of KDT efficacy in 227 infants divided outcomes into three grades depending on extent of spasm reduction and hypsarrhythmia remission; for all grades, efficacy in the diet group was superior to that in the control group (AED adjustment only) (24).

A trial comparing efficacy and tolerability of KDT with standard high-dose ACTH treatment for IS followed 101 infants (32 in a randomised trial and 69 in a parallel cohort) including those with and without prior vigabatrin

treatment: results showed similar electroclinical remission in ACTH and diet groups after 28 days but better tolerance in the KDT group. The authors concluded that without prior vigabatrin treatment, ACTH should be first choice to achieve short-term seizure remission, however with prior vigabatrin, KDT was as effective as ACTH with lower long-term relapse rate (25). A systematic review of KDT efficacy in IS included 13 observational studies with results supporting benefit of the diet: of a total 341 patients, a median of 65% experienced over 50% spasm reduction and 35% were spasm-free, although this fell to 10% with longer follow up data (26).

International consensus recommendations suggest that KDT should be strongly considered early in the course of epilepsy management in children with certain specific conditions, including IS (27). UK guidelines on management of epilepsy also suggest KDT should be considered under the guidance of a tertiary epilepsy specialist in certain childhood-onset epilepsy syndromes including IS ([nice.org.uk:ng217](http://nice.org.uk/ng217)). Early KDT use in infants is recommended: a review of outcomes in 115 children with a range of epilepsy syndromes, over half with IS, found significantly more infants under 18 months of age achieved seizure freedom when compared to those over 18 months, this difference was even greater when infants under 9 months of age were examined separately (16). Practical guidelines for KDT use in infants recommend a Classical ketogenic diet (28), although MAD has also been shown to be successful in this group (29, 30, 31), KDT can be initiated in infants maintained on breast milk (32, 33) and, with careful screening, used safely in a neonatal intensive care setting (34). Most common early adverse effects of KDT in infants are hypoglycaemia and vomiting (35, 36), with other common side effects being gastro-intestinal disturbances especially constipation and reflux, altered lipid levels, renal stones, and acidosis; most complications being transient and controlled with diet adjustment and monitoring (28). Although there have been concerns about the effect of KDT on linear growth in infants, this has not been shown to be a problem after either 3 or 12 months on diet (37, 38); initiating a lower ketogenic ratio dietary protocol may also reduce risk (39).

We therefore propose that infants with IS who have failed appropriate first-line treatment options are funded for an initial assessment of suitability for KDT. Evaluation after two or three months on diet is suggested to allow adequate assessment of benefit and appropriate fine-tuning of the dietary prescription to individual needs; earlier assessment after one month may be needed in infants on KDT as first, second- or third-line treatments in view of the risks of uncontrolled seizures (28). Although it is often suggested that children with epilepsy who are benefiting from KDT continue this for at least two years, duration of treatment could be shorter in patients with IS who become seizure-free; one study reported no adverse effect on seizure outcomes and less risk of growth disturbances when diet treatment was tapered down after 8 months (40).

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