

Ketogenic Dietary Therapy for Dravet syndrome

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Dravet syndrome (DS), originally termed severe myoclonic epilepsy of infancy, was first described in 1978 (1). It is characterised by onset of prolonged seizures in the first year of life, often triggered by fever, then development of different seizure types over time (2); *SCN1A* gene mutation being responsible in over 85% of typical DS (3). Anti-epileptic drugs (AEDs) are used as first line therapy but seizures are particularly resistant to medication with high likelihood of recurrent status epilepticus and need for further treatments; options include other AEDs or ketogenic dietary therapy (KDT) (2, 4, 5). Future treatments may involve repurposing new medications and gene therapy (6). DS co-morbidities include intellectual disability and behavioural, motor and sleep problems (2), with considerable NHS and social care cost implications for supporting medical and educational needs.

KDT is a high fat, restricted carbohydrate regime that has been used to treat epilepsy since the 1920s, and includes the traditional Classical and Medium Chain Triglyceride diets and less restrictive Modified Atkins diet and Low Glycaemic Index Treatment (LGIT). Randomised trials have reported efficacy of all types of KDT (7, 8, 9, 10), which has a 'relative risk' of 3.16 of achieving seizure freedom, and 5.80 of over 50% seizure reduction, compared to the usual care of children with drug-resistant epilepsy (11).

There are many positive reports of the benefits of KDT on seizure control in DS, including smaller retrospective studies from Argentina and USA (12, 13, 14) and a review from China which found KDT to be effective in over half of the 60 DS children at 12, 24 and 48 weeks of diet (15). An analysis of 32 Austrian children reported over 50% seizure reduction in 70% after 3 months and 60% after 12 months on KDT; these results were not significantly inferior to those in patients on the recommended DS first line AED combination so the authors concluded that the diet should be considered as an early treatment for this syndrome (16). A further retrospective multi-centre cohort study of 114 DS patients from 14 centres in China reported rates of seizure freedom to be 32.5%, 30.7% and 19.3% after 3, 6 and 12 months of KDT; with over 50% seizure reduction rates of 76.3%, 59.6%, and 43% at 3, 6 and 12 months respectively (17). Similar positive results were seen in two prospective trials of KDT in drug-resistant DS: 10 of 15 French children achieved over 75% seizure reduction after one month on diet (18); and 17 of 20 Chinese children achieved over 50% seizure reduction after 3 months on diet including 6 who were seizure-free, increasing to 10 after 6 months (19). Children in these studies all followed a Classical KDT protocol, however the possibility of LGIT as an alternative was explored in 36 children and adolescents from South Korea with drug-resistant epilepsy; two became seizure free after 3 months on LGIT, both of whom had DS (20). A meta-analysis of KDT efficacy in DS included seven studies involving 167 patients on Classical diet and found 63%, 60% and 47% of responder patients achieved over 50% seizure reduction after 3, 6 and 12 months respectively, concluding KDT to be a safe treatment option for DS with mostly acceptable adverse effects, although further larger studies were recommended (21).

Additional positive benefits of KDT on behaviour disturbances and questionnaire-assessed cognition in DS children have been reported (14, 15, 18, 19) but the benefit on neuropsychological development is less conclusive and needs further study. A small retrospective Chinese study found developmental age subscores of 12 children increased after commencing KDT, but there was no significant difference between diet and non-diet groups in developmental quotient at the same age (22).

International consensus recommendations suggest that KDT should be strongly considered early in the course of epilepsy management in children with certain specific conditions, including DS (23). 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 DS ([nice.org.uk:ng217](http://nice.org.uk/ng217)). We therefore propose that DS children who have failed appropriate AED therapy are funded for an initial assessment of KDT suitability, with diet ideally followed for a minimum of 3 months to allow adequate assessment of benefit and appropriate fine-tuning of the dietary prescription to a child's individual needs. If seizure control is improved, it is likely that AEDs would be reduced or discontinued after that time. KDT is usually continued for least two years if successful.

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