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 typically characterised by onset of prolonged seizures or status epilepticus, often hemiclonic, in the first year of life, often triggered by fever. In the second year, other seizure types evolve such as generalised tonic clonic seizures (GTCS), myoclonic seizures and there it typically photosensitivity or pattern sensitivity in many. Development is typically normal in the first 18-24 months followed by emerging developmental problems. 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.

Most cases, (89%) are associated with a pathogenic mutation in *SCN1A* gene mutation. (3). Anti-seizure medications (ASMs), often in combinations, are used as first line therapy but seizures are almost always refractory to medications. Further treatment options as second line interventions include other ASMs such as Cannabidiol or Fenfluramine or ketogenic dietary therapy (KDT) (2, 4, 5). Future treatments may involve repurposing new medications and gene therapy (6).

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 medication-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). A review from China found KDT to be effective in over half of the 60 DS children at 12, 24 and 48 weeks of diet (15). Similar findings were noted in a group of 32 with 70% and 60% attaining 50% seizure reduction at 3 months and 12 months on KDT respectively. These results were not significantly inferior to recommended DS first line ASM 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 over 50% seizure reduction rates of 76.3%, 59.6%, and 43% at 3, 6 and 12 months respectively with just under half of these being seizure free (17).

Two prospective trials of classical KDT in medication-resistant DS were similarly positive in short term studies with 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, and a third to half seizure free at 3 and 6 months. (19).

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). We therefore propose that DS children who have failed appropriate ASM 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 ASMs would be reduced or discontinued after that time. KDT is usually continued for least two years if successful.

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