

Ketogenic dietary therapy for neurometabolic disease

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Ketogenic dietary therapy is a high fat, restricted carbohydrate regime that can be delivered by the traditional classical or medium chain triglyceride (MCT) ketogenic diets (KD), or by modified and more liberal dietary protocols such as the modified Atkins diet (MAD) and low glycaemic index treatment (LGIT). KDs are designed to induce a similar metabolic response to starvation, with the ketone bodies acetoacetate and β -hydroxybutyrate becoming the primary brain energy source in absence of adequate glucose supply. The KD has been used as a successful treatment for epilepsy since the 1920s and is also treatment of choice in two rare neurometabolic diseases which affect energy metabolism of the brain, glucose transporter type 1 deficiency syndrome (GLUT1DS) and pyruvate dehydrogenase (PDH) deficiency.

GLUT1DS is caused by a defect in the transporter protein responsible for moving glucose across the blood-brain barrier into the brain. It usually presents with seizures early in life; brain growth may be impaired with developmental delay and other neurological problems including a complex movement disorder. It is characterized by a low glucose concentration in the cerebrospinal fluid in the absence of hypoglycaemia, in combination with a low to normal lactate in the cerebrospinal fluid (1). Ketogenic dietary therapy is the recommended first-line treatment as ketones can be used as an alternative brain energy source (2). The classical KD will significantly reduce seizure frequency in most patients and improvements in movement disorders, neurological function and cognition have also been reported (3-9) with no significant adverse effects on short term inflammatory and metabolic profiles (10) or longer-term body composition or bone mineralization (11). There have been case reports (12-16) and a retrospective study (17) on successful use of MAD in GLUT1DS, and LGIT combined with modified high amylopectin corn starch has also been tried (18). Two GLUT1DS surveys have highlighted use of the different dietary protocols in GLUT1DS. Japanese physicians provided positive efficacy data on 34 GLUT1DS patients: 5 on classical KD, 9 on MCT KD, 18 on MAD, one LGIT (and one unspecified) (19). A survey of 90 parents of diet-treated GLUT1DS children attending a GLUT1DS Foundation meeting in USA found no significant seizure outcome differences between the different diet variants (59 classical KD, 29 MAD, 4 MCT KD and 2 LGIT) with many switching between the types of diet (20). However, international GLUT1DS consensus recommendations suggest the stricter classical KD may be preferable for young children as typically yields higher ketone levels, with MAD more feasible for quality of life and compliance in adolescents and adults, but LGIT not recommended as has no evidence of benefit in GLUT1DS and provides very low ketones (2).

PDH deficiency is a severe mitochondrial disorder caused by deficiency in one of the enzymes involved in glucose metabolism (21). It can present with lactic acidosis and variable degrees of neurological

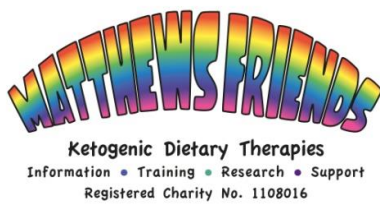
degeneration during infancy and childhood including seizures; prognosis is poor. First-line therapy is KD which will bypass the metabolic block by providing ketones as an alternative fuel to glucose. Although it will not fully reverse clinical symptoms, the progressive loss of neurological function can be slowed, especially if the diet is initiated early in life (21, 22, 23). A classical KD is usually recommended as stricter carbohydrate restriction has been associated with greater improvement in clinical outcome (22) although one case report suggests a modified diet may also be helpful (24). A study of 19 diet-treated PDH children included 7 on classical KD and 12 on modified KD. Median diet duration was 2.9 years, during which time the ketogenic ratio was increased in most patients, with an effective ketosis important in maintaining the benefits of the diet on motor and neurocognitive development (25).

As advised by international consensus recommendations (2, 26), the KD should be used as first line therapy for these neurometabolic diseases, and in GLUT1DS will usually need to be continued well beyond childhood, with benefits thought to extend to adults (2). A long-term follow up study of 10 GLUT1DS patients did not identify any cardiovascular risk factors after 10 years on KD (27), however on-going regular monitoring and support from a ketogenic team will be essential to ensure the most appropriate dietary prescription with minimal risk of side-effects.

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