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Ketogenic Diet Therapy

Epilepsy and brain tumours

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Introduction

Contrary to improvements in the quality of life and survival for many cancers, the outcome for those with malignant brain tumours has not improved in decades (see **Figure 1**). This is leading to increased interest in an adjunctive treatment that may exploit the metabolic difference between tumour cells and healthy cells. Living with a brain tumour can also mean living with debilitating seizures. This article will discuss ketogenic diet therapy (KD), its use in the management of drug resistant seizures and the emerging evidence that suggests that the impact of this 90 year old treatment may reach beyond the seizures to the tumour itself.

Figure 1: Brain Cancer – The statistics[1]

- 16,000 people each year are diagnosed with a brain tumour
- More children and adults under 40 die of a brain tumour than from any other cancer
- Only 18.8% of those diagnosed with a brain tumour survive beyond five years, compared with a 50% average for all cancers
- Brain cancer incidence is actually rising: 23% higher for men and 25% higher for women in 2012 than in 1970
- Brain cancer deaths are rising, unlike most other cancers – these rose 10% for women and 15% for men from 1970 to 2011

Source: Brain Tumour Research; National Funding Report July 2013

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Ketogenic diet (KD) and epilepsy

The KD evolved from the discovery that fasting could halt seizures and that a similar therapeutic effect could be achieved by altering the ratio of carbohydrate and protein to fat in the diet (see **Figure 2**). Though the KD was effective in both children and adults, the discovery of anticonvulsants eclipsed further interest in the dietary approach for almost 80 years. However, in the last decade, interest in KD therapy has expanded worldwide as more neurology teams and their patients have found it to be effective in cases where many anticonvulsant drugs have failed. Ketogenic therapy can impact on all types of seizures and can be as effective in adults as in children with almost half gaining a 50 per cent or greater reduction in seizures.[2, 3] The 1920s 'Classical' KD and the 1970s medium chain triglyceride (MCT) KD are still the basis of many of today's paediatric treatments for refractory epilepsy and work well.[4, 5] However the advent of more liberal ketogenic regimes, such as the modified Atkins diet (MAD) and the low glycaemic index treatment (LGIT), make dietary treatment a more practical possibility for both adults and children.[6, 7]

How does a KD influence epilepsy symptoms and the quality of life BETWEEN seizures?

It is thought that epilepsy involves disruptions of brain energy channels and this may trigger seizures. When brain tissue is exposed to the shift in fuel availability as a result of the KD, there are adaptive changes in gene expression leading to an up-regulation of transcripts encoding energy metabolism enzymes and an increase in the density of mitochondria in neuronal processes. Overall, the brain tissue becomes more resistant to metabolic stress and less susceptible to seizure triggers. The energy shift is also thought to influence the balance of neurotransmitters and a range of chemical compounds involved in exciting and inhibiting electrical activity within brain tissue.[8]

In addition to improvements in seizure frequency, intensity and the time taken to recover from seizures, responders to the KD 'shift' may report more subjective changes, such as being able to think more clearly, concentrate better, having more energy and generally feeling brighter in mood.[9, 10, 11] A three-month treatment trial is generally sufficient to allow the individual to gauge whether they are evolving sufficiently worthwhile benefits or not.

Living a life with brain cancer and associated seizures

A seizure may be the first indication of a brain tumour with the stage of tumour cell type (WHO Grade 1, 2, 3 or 4) and the location determining the most appropriate medical intervention advised.[12] In cases of relatively slow growing 'low grade' tumours, the time taken for the tumour to progress, if at all, is unknown and intervention may be minimal with a 'watch and wait' approach advised. Those living with drug resistant epilepsy as a result of these tumours cope with the combined psychological and quality of life impacts of two unpredictable and potentially life limiting medical conditions and the side effects associated with the treatments for these conditions. Often in difficult cases, drugs are used in combination to reduce seizure frequency but this requires a careful balance between maximising seizure control on the one hand while minimising drug toxicity on the other. Quality of life may be significantly impaired by drug effects, such as cognitive impairment, sedation and metabolic bone disease.[13]

There is currently no active part that the individual can play in their symptom management: leaving them watching and waiting for illness, rather than focusing on actively pursuing wellness and this can lead to a sense of frustration, helplessness and hopelessness. Two UK cases of astrocytoma (WHO Grade 2) with symptomatic epilepsy impacting adversely on day to day life, have achieved significant improvements as a result of clinically supported KD (see **Figure 3**). Any impact on the tumours is unknown at the present time.

Tumour metabolism: the focus on glucose

In 1924, Otto Warburg first proposed that impaired cellular energy metabolism was a defining characteristic of cancer cells and that the vast energy requirement of tumour growth is readily driven by the fermentation of glucose in the presence of oxygen (aerobic glycolysis) rather than mitochondrial based oxidative phosphorylation, favoured by healthy cells.[14] Known as The Warburg Effect, this metabolic 'difference' is exploited in research, when monitoring tumour progression via PET scans (Positron Emission Tomography). The tumour cells 'light up' due to their abnormally high consumption of the radioactive glucose tracer (fluoro-deoxy-glucose, FDG).

Despite the fact that malignant tumours are now known to be composed of a heterogeneous mix of cell types, are genetically unstable and more metabolically adaptable than Warburg predicted, there is increasing interest in finding a way of turning this underlying fuelling difference into an active component of cancer management.

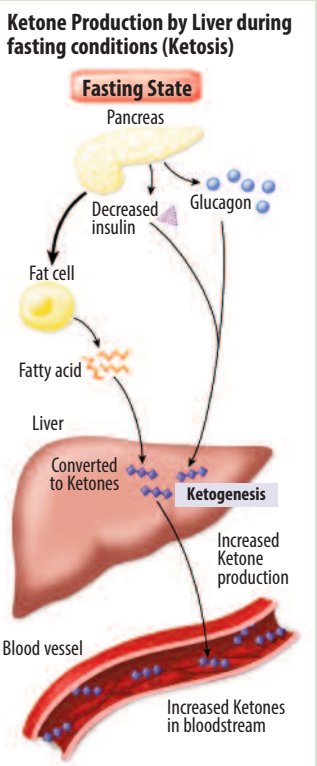
The evidence for the impact of KD on malignant brain tumours

Clinical cases

The use of the MCT version of a KD as an adjunctive component in the management of two paediatric cases of malignant brain cancer was first reported in 1995. They found a 21.8 per cent average decrease in glucose uptake at the tumour sites (as monitored by PET - FDG scans), with one patient exhibiting significant clinical improvements in mood and skill development during the eight-week study and continuing on the regime for 12 months. Both patients were reported to be enjoying a good quality of life four and five years after diagnosis.[15]

Figure 2: Carbohydrate Reduction – The key to the KD fuel switch

- A KD is very low in carbohydrate, provides adequate protein and supplies most of its calories in the form of fats.
- When carbohydrate intake is significantly reduced, circulating glucose and insulin levels are also reduced and this leads to a compensatory shift from fatty acid esterification (insulin stimulated) to fatty acid oxidation (glucagon stimulated) in the liver.
- Increased oxidation of fatty acids leads to an increased production of the ketone bodies, beta-hydroxybutyrate and acetoacetate. These are then available as an oxidative fuel and can be used by all tissues other than those dependent on glycolysis such as erythrocytes and the renal medulla. Healthy brain tissue rapidly adapts to using ketones in preference to glucose. However it is thought that malignant brain tumour tissue may be less able to thrive in this biochemically shifted landscape.
- The KD prescription is based on the nutritional requirements of the individual and provides an appropriate amount of dietary fat to meet the increased oxidation of fatty acids so that changes in body fat stores (i.e. weight loss or weight maintenance) are controlled.



In 2007, the use of a restricted KD (around 600 kcals/day, leading to a 20% loss in body weight) was reported in a 65-year-old woman.[16] Standard therapy was maintained and the progression of the tumour was tracked using PET - FDG scans. After two months treatment, no discernible brain tumour tissue was detected. However, 10 weeks after suspension of the strict dietary therapy, MRI evidence of tumour recurrence was found.[16]

Preclinical studies

In 2010, studies on a mouse model of aggressive malignant tumours (WHO Grade 4) reported that an unrestricted KD can: (a) specifically retard tumour growth; (b) prevent increases in reactive oxygen species associated with tumour growth; and (c) shift overall gene expression in tumour tissue to that seen in the normal brain.[17] In 2012, the same research group reported that a KD significantly enhanced the effect of radiation in the same model.[18]

For over a decade Professor Tom Seyfried and associated researchers have been studying the concept of cancer as a metabolic disease.[19] In 2012 they proposed the restricted KD (combined with drugs to control glucose and glutamine availability) as a viable alternative to the standard of care for managing malignant brain cancer.[20]

Barriers to treatment

There is no randomised controlled trial evidence for the use of the KD for the management of drug resistant epilepsy in adults and so adult dietetic provision in the NHS is negligible.

Healthcare professionals and patients new to KD therapies readily voice their concern about the high fat intake required. However, the low carbohydrate intake produces flatter glucose and insulin profiles and ensures that the fat is metabolised, not stored. The lipid profile is measured at baseline then at three-to-six monthly intervals throughout the treatment, and dietary fat sources can be adjusted to influence lipid fractions if required. Low carbohydrate regimes have been shown to be beneficial for the management of obesity, Type 2 diabetes and metabolic syndrome, in terms of weight loss, increased serum high density lipoprotein cholesterol, increased low density lipoprotein particle size, reduced serum triglyceride levels and improved sensitivity to insulin.[21, 22, 23, 24] Therefore, it is possible that the KD may convey additional metabolic benefits to some adults with refractory epilepsy.

Understanding the mechanisms – the missing key?

With the evidence to date, the option of ketogenic therapy for those living with difficult epilepsy in association with a brain tumour, would seem reasonable. In such cases, changes in seizures and associated symptoms enable the individual to readily feel the benefit day-to-day; providing a positive return for the considerable efforts that are required in the first few months of pursuing a KD. However, for those with a brain tumour but no discernible seizures, tracking and optimising the therapy can be hard as MRI monitoring may not be more frequent than six-monthly and may readily register 'no change'. There is an urgent need to find simple ways of monitoring markers of tumour energy metabolism and for appropriately designed clinical trials to determine the efficacy of KD and, if favourable, the easiest way for patients to manage this. Key UK neuro-oncology research teams are now taking an interest in this area, but it will take time and considerable investment to reach any meaningful conclusions.

For further information please go to:

http://site.matthewsfriends.org

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Figure 3: Case Study

Clinical details:

- A 38 year old mother of two young children.
- A 6 year history of epilepsy as a result of an astrocytoma (WHO Grade 2) diagnosed in 2007.
- Seizures poorly controlled despite concurrent treatment with four anticonvulsant drugs.
- Other health concerns included polycystic ovary syndrome, long standing weight issues and impaired mobility.
- Patient's objectives were to achieve an improvement in seizure symptoms, weight control and the possibility of reducing anticonvulsant drug doses.

Treatment:

- After neurological/biochemical/nutritional screening and training on the diet and blood glucose/ketone monitoring, the patient commenced KD treatment in February 2013:
- The 'Modified' KD prescription of three meals and two snacks was fine-tuned over time to maximise symptom control and provides approximately: 20 g carbohydrate, 130 g fat (including 30 g MCT oil) and moderate portions of protein with each meal.
- A significant level of dietetic support was required in the initial three months of treatment.

Outcome:

- After 9 months treatment, the patient has lost 30 kg (24% of body weight) and seizure frequency/intensity have both been significantly reduced for over 6 months now. Under neurological supervision, the patient is starting to lower the dose of one of her anticonvulsant drugs. The patient plans to continue on KD therapy for the foreseeable future.

  Patient's comments: *"I began to see changes in my seizure symptoms after two weeks. Initially the postictal phase largely disappeared. By about six weeks seizure intensity decreased and by three months frequency had reduced significantly. Now if seizures appear, they merely interrupt my day for a few seconds whereas before ketogenic diet, my whole day was disrupted due to seizure recovery. My energy levels have increased and my family have commented on seeing the 'old me' returning; bright, sharp and quick!"*

  "Emotionally, it's all very empowering. I feel like I am in control of my treatment. I feel like I am nurturing my body and giving it the means to function at its best."

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1) Butler R, Neal E. Efficacy and acceptabillity of a nutritionally complete ketogenic formula used to administer the classical 4:1 ketogenic diet in children with refractory epilepsy. IEC February 2011 Poster.

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