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Case Study

Unrestricted Ketogenic Diet In A Child With Medulloblastoma

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ABSTRACT

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Brain tumors are the most frequent malignancies in children. Despite modern treatment, many children still have a dismal prognosis and survivors have to face treatment toxicity.

Ketogenic diet (KD) has recently been proposed as a complementary approach in the treatment of brain tumors. Limited clinical experience exists and large case series are lacking. There is even less experience in children. We describe a child with medulloblastoma that received KD during craniospinal radiation for his disease. No steroids were necessary and good tolerability was observed. No clear oncological effect was documented.

INTRODUCTION:

Despite recent advances in conventional treatment strategies, the prognosis for many childhood brain tumors remains poor. Moreover, most current treatments are burdened by heavy toxicity profiles. Recently, a great interest has risen for complementary approaches aiming at enhancing tumor response rate while reducing toxicity. Numerous dietary components and supplements have been evaluated as possible anti-cancer additional agents¹⁻². The ketogenic diet (KD) has been proposed to be a potential adjuvant approach, as a dietary regimen selectively enhancing metabolic oxidative stress in cancer cells³.

Basics of biochemistry in normal brain tissue

In physiologic conditions, neurons use glucose, lactate and ketone bodies (aceto-acetate and β -hydroxybutyrate) as substrates for their energetic needs¹. Whenever blood glucose levels fall, neurons have the capacity to completely shift to different energy sources, mostly KBs derived from liver^[1]. Metabolism of glucose and lactate happens through the oxidation to pyruvate and its further processing in the mitochondria where the tricarboxylic acid cycle (TCA) takes place. Resulting NADH and FADH₂ reduction potential is used in the mitochondrial respiratory chain where oxidative phosphorylation takes place generating many more ATP molecules and reactive oxygen species (ROS) are neutralized². In fact, a metabolic balance exists between energy production by oxidation and anaplerosis for cell proliferation and tissue growth³. The latter is enhanced in astrocytic networks⁴ to support neuronal metabolic demands and to provide neurons with lactate for energetic needs⁵.

Basics of biochemistry in neoplastic brain tissue

Brain tumor cells electively use glucose as substrate for energy and have low capacities to adapt to use ketones. Even under aerobic conditions, oxidative phosphorylation is inhibited in brain tumor cells. This phenomenon, named aerobic fermentation², has been extensively described since Warburg times in virtually any cancer tissue, and recent work has contributed to clarify many of the molecular mechanisms involved. Possible explanations

include regulation of biochemical pathways by oxygen availability but observation of peculiar molecular profile in cancer cells suggests a change in the cell metabolic program might be key towards an anabolic state³.

Principles of Ketogenic diet

KD consists of a strict alimentary regimen with high fat, moderate/low protein content and very low carbohydrates. The ratio by weight is 3:1 or 4:1 fat to carbohydrate + protein, with an energy distribution of about 8% protein, 2% carbohydrate and 90% fat. KD meals² consist of food rich in fat such as butter, oils, cheese, meat, fish, eggs in order to ensure an adequate protein supply, associated with very small portions of vegetables to minimize carbohydrate intake. Ketogenic formulations are also commercially available as dietary supplements to maintain appropriate serum KB levels.

The aim of this regimen is to force the body to burn fat instead of glucose for ATP synthesis. The low carbohydrate content of the ketogenic diet also induces a reduction of blood glucose with improved glycemic control². Short-term metabolic effects of the diet have been described in animal models and human healthy volunteers. Timing and extent of metabolic shift depends on the specific diet but invariably results in increase of circulating KBs and reduced glycemia. When associated to a restricted calorie regimen, even higher levels of circulating KBs and lower glucose levels have been obtained.

The promising rationale of the anti-cancer properties of the KD is based on the metabolic alterations seen in cancer cells, such as an increase in the rate of glycolytic metabolism even in presence of oxygen, as well as alterations in mitochondrial oxidative metabolism, that result in chronic metabolic oxidative stress²⁻⁴. Few papers have focused on the safety and efficacy of KD as an adjuvant approach in childhood brain tumors. We describe a single case of medulloblastoma, in which the KD was used during conventional treatment due to parental request. We also review current literature on the topic, providing

a critical overview with particular attention to the pediatric population.

CASE PRESENTATION AND METHODS

A 7 years old boy presented to our Center after subtotal resection of a vermian anaplastic medulloblastoma. After four chemotherapy cycles progression of residual disease was documented and craniospinal radiation performed.

Following parental request, KD was used for 8 weeks before and during radiation. Institutional review board approval and informed consent were obtained. Dietary guidelines were prescribed and strictly supervised by a nutritionist. KD consisted of a ratio of 2:1 obtained through the combination of a modified Atkins diet (1:1) and Ketocal® (4:1) flavoured formula. The diet scheme provided a daily intake of 1000 calories, corresponding to the energy intake that the child was able to assume spontaneously, divided in 3 main meals with 20g of Ketocal® to be taken after every meal. B-complex vitamins, vitamin D, calcium and iron were supplemented according to age requirements. A dietary manual containing recipes and a food exchange list was developed for the parents to assist the compliance.

After five daily outpatient evaluations weekly home care assessments followed. In addition, the nutritionist was available 24/7 for specific advice. Anthropometric parameters (weight, height, body surface area) and nutritional intake were registered at the beginning of KD and twice a week thereafter for early detection and correction of weight loss. Metabolism was monitored by blood and urine tests during the whole duration of the diet (blood counts, liver and renal function tests, blood lipidic assessment, acid-base balance, circulating and urinary ketones).

No pathologic modification of parameters was observed. Ketonuria was stably 2-3+ and ketonaemia was between 2.0 and 3.6 mmol/l. Toxicity was assessed by the Common Terminology Criteria (CTC) for Adverse Events version 4.

No steroids were necessary during radiation therapy. Stable disease was confirmed after

radiation and gross total surgical resection performed with confirmation of histology.

Two courses of high-dose chemotherapy with autologous rescue followed. Due to dismal prognosis in case of further recurrence parents refused further follow-up imaging and the child remained clinically stable for 10 months after which neurological deterioration prompted neuroimaging demonstrating recurrence of disease with craniospinal dissemination.

DISCUSSION

Treatment of pediatric brain tumors represent a tremendous challenge for the scientific community².

KD has recently been attracting attention as a complementary approach in the treatment of cancer, including brain tumors. Moving from the experience of its efficacy and tolerability in epilepsy²⁻⁷ and Warburg's observation of aerobic glycolysis in cancer cells, a fair amount of pre-clinical data has cumulated so far⁸⁻⁹.

Proposed mechanisms of action deriving from *in vitro* evidence extend from inhibition of glycolytic metabolic flux to conditioning of cellular response to oxidative stress ^{[iii][iii]}. KD seems to have two main targets: reduction of the glucose energy source for cancer cells and activation of neuro-protective genetic programs by calorie restriction. In fact, KD and other complementary metabolic approaches to brain tumors might act both on metabolism and cell fate program, as detailed *in vitro* evidence suggest⁴.

To our knowledge, this is the first report of KD during treatment for a pediatric medulloblastoma. Diet was used during radiation therapy with clinical confirmation of adequate ketosis and good clinical compliance. Direct supervision by a nutritionist and strict follow-up visits were provided to ensure accurate monitoring and to encourage acceptance. No major discomfort or toxicity was observed. Despite bad prognostic factors present at the time of diagnosis, no assumptions can be made on anti-neoplastic effects for obvious reasons. In fact, a recent report has shown no effect on tumor growth in a medulloblastoma murine model^[28].

KD has been demonstrated to be effective in inducing ketosis and reducing glycemia. Effects are significantly enhanced if concomitant calorie restriction (CR) is applied. Notably, many CR/KD regimens include a fasting period at the beginning of the diet.

We were able to reach and maintain therapeutic levels of ketosis without recurring to fasting or voluntary CR. In fact, in our unpublished experience KD itself generally induces a reduction of overall introduced calories with no need for fasting with beneficial effects on quality of life. Use of pre-confectioned ketogenic products might further increase compliance to the diet, particularly in children. Clinical experience with KD for central nervous system malignancies is limited^{4,8} and there is no evidence to support its clinical use. Even more uncertainty exists for the pediatric population with only two reported cases in the literature⁸. Stabilization of disease has been described but there is no way to ascribe it to KD rather than to natural history of disease after conventional treatment.

Differential mitochondrial functional reserve in normal brain cells and tumor cells would suggest selective accumulation of reactive oxygen species (ROS) in tumor cells, especially during radiation. Both direct and indirect lowering of blood glucose levels by KD regimen and steroid reduction might share a role in boosting neuro-protective anti-oxidant effects in normal tissues. Our patient did not need steroids during radiotherapy, suggesting possible anti-edema properties of KD, however steroids are not mandatory in modern radiation approaches.

Moreover, ethical issues related to the introduction of this complementary strategy in childhood have to be considered as KD is in no way a benign therapy. Short- and long-term side effects have extensively been reported⁴. Our experience suggests that KD is feasible in children with highly motivated parents if a comprehensive monitoring program is offered. We believe that available data are insufficient to support KD as complementary therapeutic approach for central nervous system

malignancies, especially in children. Randomized trials would be necessary to test its benefits. Areas of particular interest for KD in children should include: role of concomitant calorie restriction, monitoring of side effects, timing and duration of treatment, role in side effects reduction.

CONCLUSIONS

KD has been proposed as a potential adjuvant approach in the treatment of brain tumors in childhood. Both practical and ethical issues limit the application of KD in childhood. We described the first case of medulloblastoma treated with KD during radiotherapy. Therapy was well tolerated but no oncological effect can be inferred. Large clinical series are needed to test efficacy of KD in association to standard treatment for brain tumors.

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