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Ketogenic diet treatment in recurrent diffuse intrinsic pontine glioma in children: A safety and feasibility study

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Abstract

Background: The mean overall survival rate of children with diffuse intrinsic pontine glioma (DIPG) is 9–11 months, with current standard treatment with fractionated radiotherapy and adjuvant chemotherapy. So far, novel therapeutic strategies have not yet resulted in significantly better survival. The main source of energy for glioblastoma cells is glucose. Therefore, metabolic alterations induced by the use of the extremely carbohydrate-restricted ketogenic diet (KD) as adjuvant therapy are subject of interest in cancer research.

Procedure: This study explores the safety and feasibility of the KD in children with recurrent DIPG and no remaining treatment options. Safety was defined as the number of adverse effects. Feasibility was defined as the number of patients who were able to use the KD for three months. Coping of patients and parents was measured with questionnaires.

Results: Three of 14 children referred to our hospital between 2010 and 2015 were included. Two patients completed the study, and one died before the end of the study. Hospitalizations were needed for placing a nasogastric tube ($n = 1$) and epileptic seizures ($n = 1$). Adverse effects related to the diet were mild and transient. Parents were highly motivated during the study.

Conclusion: Use of KD is safe and feasible, but the effect on survival has to be proven in a larger cohort of children who start the KD earlier after diagnosis, preferably as adjuvant therapy to fractionated radiotherapy.

KEYWORDS

brain tumor, coping, metabolic alteration, side effects

1 | INTRODUCTION

The prognosis of children with diffuse intrinsic pontine glioma (DIPG) is extremely poor. Fractionated radiotherapy (RT) is the treatment of first choice, with a reported mean overall survival duration of 9–11 months. Only 10% of patients survive longer than two years.[1,2] Adding temozolomide (TMZ) to RT has not yielded any significant improvement in survival.[3] Chemotherapeutic strategies have been tested, but it proves to be difficult to get therapeutic agents across the blood–brain barrier (BBB) without major toxic side effects.[4] Moreover, even after trespassing the BBB, the level of drug delivery may vary greatly due to inconsistent interstitial fluid pressure within the tumor.[5,6]

Glioblastoma cells use glucose as their main source of energy, which is derived from the anaerobic glycolytic pathway.[7] In contrast to normal brain cells, glioblastoma cells cannot compensate for glucose restriction by metabolizing ketone bodies.[8,9] In light of this, metabolic alteration may be an alternative adjuvant treatment therapy. The ketogenic diet (KD)—an extremely carbohydrate-restricted diet—may be an option because it mimics the metabolic response to starvation when ketones become the main fuel for the brain instead of carbohydrates.

In mice with glioblastoma, the KD induced a significant reduction of tumor size compared with a standard diet. The reduction was even more profound when the KD was combined with radiotherapy,

Abbreviations: CT, chemotherapy; DIPG, diffuse intrinsic pontine glioma; GI, gastrointestinal; GMFCS, gross motor functioning classification system; KD, ketogenic diet; LQ, liquid formula; MCT, medium chain triglycerides; OSR, overall survival rate; RT, fractionated radiotherapy; TMZ, temozolomide; VOOK, Ouders van een Overleden Kind

suggesting that KD potentiates the effect of radiotherapy.[10–12] Studies in humans with different types of brain tumors—one case report in adults, one in children,[13,14] and a clinical study in adults[15]—indicate that a KD is well tolerated without severe side effects.

The KD is a well-established treatment option in children with drug-refractory epilepsy. So far, it has not been studied in children with DIPG, and thus we do not know whether children with this rapidly progressive disease are able to use and tolerate such a compliance-demanding and strict diet.

We report a study exploring the feasibility and safety of the KD in children with DIPG who show tumor progression and have no remaining treatment options. The children initially used a full liquid KD version to induce rapidly ketosis, which then was modified to a more liberal KD with medium chain triglyceride (MCT) emulsion.

2 | MATERIALS AND METHODS

In the period 2010–2015, we performed a prospective study in children up to 18 years with recurrent DIPG with no remaining therapeutic options. The setting was the department of pediatric neurology in the Erasmus MC-Sophia Children's Hospital University Medical Centre Rotterdam.

Exclusion criteria were inability of parents to handle the diet and language barrier to understand instructions.

This study was approved by the local Medical Ethical Committee (NL2856807809). In addition, we received a positive response from the Ouders van een Overleden Kind (VOOK) on the ethical issue of prescribing a KD in the palliative phase of DIPG.

The study protocol started after parents had provided informed consent. Children older than 12 years also provided informed consent themselves. To rapidly induce ketosis, the KD was initiated as a full liquid (LQ) KD formula with a 4:1 diet ratio (4 g fat opposite to 1 g protein plus carbohydrates) and used for maximal two weeks. The KD LQ was offered in different recipes of 100 mL and 200 calories with similar nutritional composition, which could be used exchangeable. When ketone levels of 3 mmol/L were reached, the KD LQ formula was stepwise modified into a KD (range diet ratio 1.5:1–2.0:1) with strictly calculated and prepared meals. MCT emulsion mixed with low fat milk was used several times a day in addition to the meals.

The study duration was three months. Patients and parents regularly visited the outpatient clinic or were visited at home by the dietician for monitoring. Any required additional support (by phone and/or email) during the study was provided on an individual basis. Figure 1 demonstrates a flow chart of the study protocol.

Feasibility was defined as the number of patients able to use the KD for three months.

Safety was defined as the occurrence of adverse effects ≥2 grade based on common terminology criteria of adverse events (CTCAE).[16] Adverse effects (e.g., gastrointestinal complaints, fatigue) were all noted in a study diary and evaluated weekly by the dietician. Ketone and glucose levels, growth parameters, and the incidence of side effects were recorded in a study diary following the national and international KD guidelines for children with refractory epilepsy.[17,18] Hyperketosis was defined as >6 mmol/L and hypoglycemia was defined as <2.5 mmol/L.

During neurological examination at baseline and at the end of the study, the patients gross motor functioning was scored using the Gross Motor Functioning Classification System (GMFCS).[19]

By means of a self-designed, not validated, questionnaire of 15 questions administered at baseline and at the end of the study period, we explored if and how parents and patients were able to cope with the KD. The item scores could range from 1 to 5 and indicated the level of difficulty (1 not difficult, 5 very difficult) experienced when applying the KD in daily practice and coping with it. Other items reflecting the level of received information and support could range from 1 to 5, being not enough (1) or enough (5), or motivation to start the study could range from 1 to 5, having no doubts (1) or many doubts (5). The coping questionnaire is shown in Supporting Information data.

2.1 | Patients

During the study period March 2010–March 2015, ten children were treated for DIPG in our center. Four children with DIPG treated in other centers were referred to our center. During a visit, parents and children were extensively informed about the study and study procedures by the neurologist and dietician.

Of the 10 children treated for DIPG in our center, two patients died in the second week of RT due to severe acute edema of the brainstem and had such severe neurological symptoms that further treatment was not meaningful. Parents of six patients were very interested in the KD at disease onset but decided against participation of their child after recurrence of the tumor with severe and highly progressive neurological deterioration. Due to a language barrier, parents of one patient could not be appropriately instructed and the child was therefore excluded. Thus, only one of the 10 children treated for DIPG in our center could be included (case 1).

Of the four patients referred from other centers, two could be included (cases 2 and 3). Parents of one of the other two decided against participation after being informed, and the other family lived in Spain and could not be properly guided there.

Because of the limited number of included patients, data of this study are presented as case descriptions.

2.2 | Case descriptions

Case 1: A male diagnosed with DIPG at the age of 4.4 years started RT within 3 weeks after diagnosis and received a dose of 44.8 Gy in 16 fractions. Progressive neurological symptoms were noted after six stable months. Subsequently, he received three 5-day courses of TMZ 100 mg/m^2/day each month. After initial stabilization, the neurological abnormalities deteriorated again after five cycles of TMZ, and tumor progression was confirmed on MRI. At this point, he was included in our study at 5.3 years of age. His SD score for weight for height was +0.05 and his height for age was +2.00.

The KD LQ formula was stepwise introduced to a maximum of seven exchanges of 100 mL Ketocal LQ 4:1 ratio and 200 kcal. On day 3, he showed hypoglycemia (glucose level, 2.4 mmol/L) combined

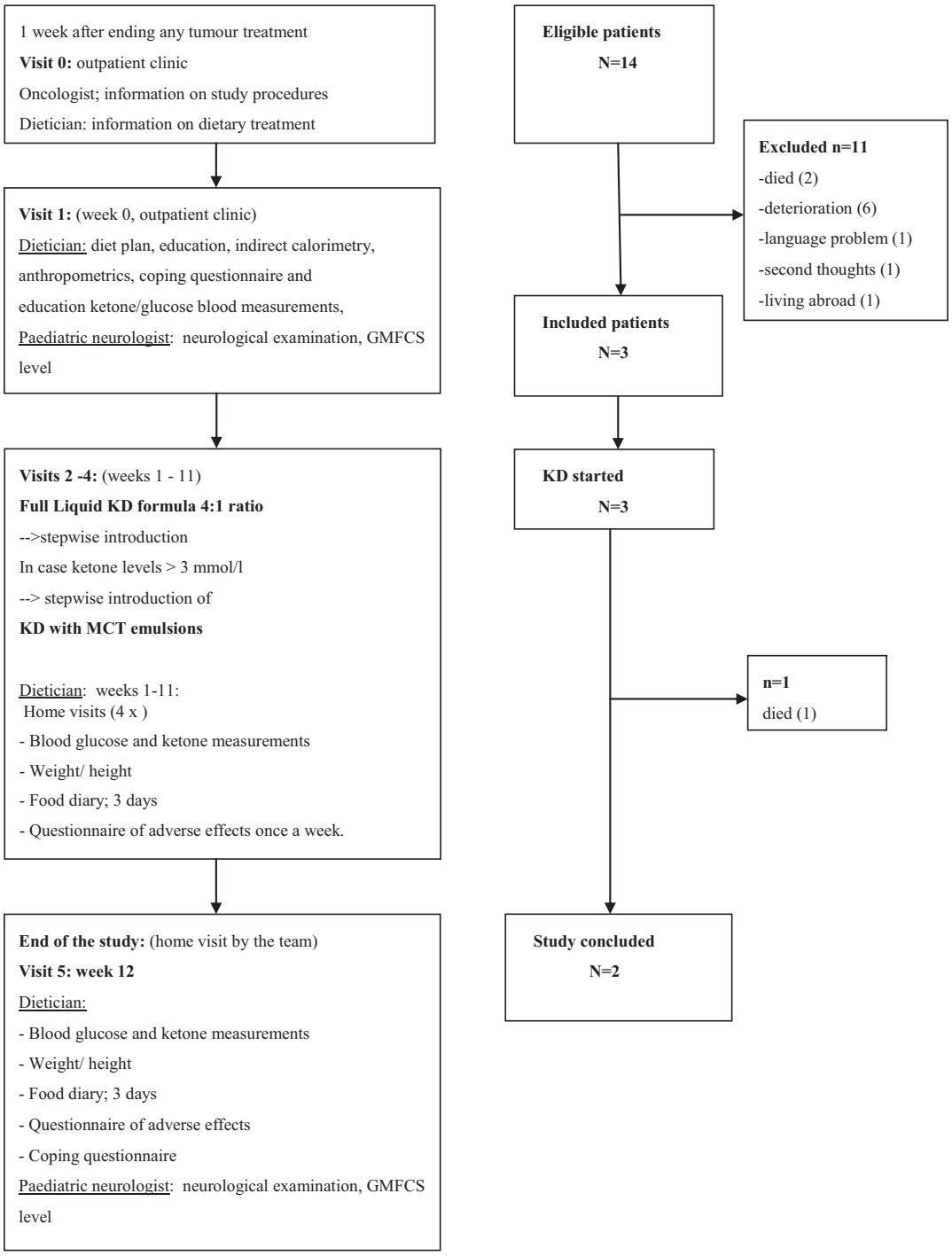

FIGURE 1 Study flowchart
KD, ketogenic diet; MCT, medium triglycerides; GMFCS, gross motor function classification system

with hyperketosis (ketone level, 7.2 mmol/L). Because he vomited and refused the LQ formula, the diet was stepwise changed into a KD of 1.6:1 diet ratio with solid food consisting of 48 grams of carbohydrates and MCT (using total of 100 mL MCT fat emulsion/day), which eliminated these symptoms. Hyperketosis (without hypoglycemia) irregularly occurred, which could be treated by dietary alterations. The KD with MCT was well tolerated without side effects. He showed no significant change in SD scores for weight for height (−0.35) or height for age (+1.83) at the end of the study.

Items of coping questionnaire concerning diet application and daily monitoring scored 2 at both time moments, and use of LQ formula was difficult (score 4). Parents stayed motivated during the study (score 2, no doubts at both time moments).

At the start of the KD, neurological examination showed a bilateral abducens paresis, reduced hearing on the right side and a right pyramidal paresis. The GMFCS was level 3. Rapid neurological deterioration was noted at the end of the study period, and at 3 months follow-up he had bilateral abducens, facial and glossopharyngeal paresis, as well as

a tetraparesis grade 2 on the right side and grade 1 on the left side. The GMFCS level at 3 months was 5.

Parents decided not to continue the diet after the study period. The patient died 3.5 months after end of the KD study, 7 months after end of regular therapy (OSR of 16.5 months).

Case 2: A male diagnosed with DIPG at 11.1 years of age was treated with RT combined with gemcitabine according to the protocol of his local hospital. Four months after diagnosis, progression of neurological symptoms was noted, and progression of the tumor was visible on MRI, as well as an ependymal metastasis in the right ventricle. Parents and patient refused further chemo- or radiotherapeutic options.

He was included into the KD study at the age of 11.6 years. At the start of the study, his SD score for weight for height had declined to −3.09 due to limited food intake and persistent vomiting despite medical treatment.

The KD LQ formula was carefully introduced with a maximum of four exchanges of 100 mL Ketocal LQ 4:1 ratio and 200 kcal and some snacks (i.e., ketomuffin, slices of fish or egg with mayonnaise) with total diet ratio 3.5:1. When adequate ketosis was reached, the diet was stepwise modified into a KD of 1.75:1 diet ratio with solid foods and 35 g of carbohydrates and MCT. The MCT emulsion (at study termination 75% of calculated goal of 100 mL/day had been achieved) was well tolerated and he stopped vomiting.

Ketone and glucose levels were within normal range. Weight gain was not achieved; the SD score for weight for height remained at −3.0.

Parents expected no difficulties applying the diet in daily practice (score 1) but expected it would be difficult for (score 5) them and for their son to cope with the high level of monitoring and the use of LQ formula (score 4) due to his medical situation. Nevertheless, parents were motivated to start the study (score 2).

At start of the study, neurological examination showed dysfunction of the left trigeminal, abducens and facial nerves, a mild ataxia on the left side, right hyperreflexia, and a pathological plantar reflex on the right side. The GMFCS level was level 2.

Three weeks after the start of the KD study, he was admitted to the hospital with a generalized tonic–clonic seizure that easily responded to antiepileptic treatment. MRI now also showed extensive leptomeningeal metastases but no hydrocephalus. Within 24 hours, the level of consciousness severely decreased and he did not regain consciousness. His parents decided to a nonintervention policy, and two days later the patient died (OSR of 6.4 months).

Case 3: A male diagnosed with DIPG at the age of 14.5 years was treated with RT up to 54 Gy in 30 fractions. Three months later, neurological symptoms progressed, and tumor progression was evident on MRI. He was subsequently included in the DIPG-01 phase B treatment study of the VU University Medical Center, Amsterdam. Treatment consisted of two weekly infusions of bevacizumab and irinotecan and daily oral erlotinib. A smaller tumor mass was seen on MRI two months after the start of this therapy. However, MRI scans four months after the start of this study showed tumor progression and, for this reason, treatment was stopped.

He was included into the KD study one month later at the age of 15.5 years. He showed borderline overweight: SD score for weight for height was +2.16 and height for age was −0.31 SD.

The KD LQ formula was stepwise introduced to a maximum of 8.5 exchanges of 100 mL Ketocal LQ 4:1 ratio and 200 kcal and a little snack with an overall diet ratio of 3.8:1. When adequate ketosis was reached, the diet was stepwise modified into a KD of 2.1:1 diet ratio with solid food consisting of 38 g of carbohydrates and MCT (using total of 110 mL MCT fat emulsion/day). As neurological symptoms relentlessly progressed and MRI showed increase of tumor size and enhancement with gadolinium with stable ventricle size, he was offered a short course of irradiation in week 6 of the study initiated by the oncologist of the referring center. He received five fractions of 4 Gy on the tumor. On explicit request of the patient and parents, the KD was continued.

During the period of reirradiation combined with steroids, the ketone levels two times decreased below the adequate range, 2.3 mmol/L and 1.8 mmol/L, respectively, but normalized again after steroid use was stopped. Ketogenic nasogastric tube feeding was started in week 8 because of swallowing difficulty. At the end of the study, the SD score for weight for height stabilized at +2 and height for age was −0.41.

Items of coping questionnaire concerning diet application and daily monitoring scored 1 at both time moments. Parents stayed motivated during the study (score 1 at both time moments).

Neurological examination at the start of the study did not show aphasia or dysarthria. However, a right lateral gaze palsy and a central facial paresis with no other abnormalities of the cranial nerves was present, as well as a left pyramidal paresis grade 3 at the arm and grade 4 at the leg with left hyperreflexia and left pathological plantar reflex. The GMFCS grade was level 3.

After three months of KD, at the end of the study, the patient had a good language comprehension but could neither speak nor swallow and had a complete ocular paresis. He had a left limb paralysis and limited use of the right hand, but just enough to use a communication device. At this time, the GMFCS grade was level 5.

This situation initially stabilized for some weeks, after which it slowly progressed for the worse. The patient died 3.5 months after the end of the study (OSR of 18.7 months).

Patient characteristic are given in Table 1 and treatment characteristics in Table 2.

2.3 | Safety parameters

In all three cases, laboratory tests in blood and urine showed no abnormalities. One patient (case 1) experienced hyperketosis several times during KD use despite dietary adjustments and showed borderline hypoglycemia once during diet initiation. Hospitalizations were needed for placing a nasogastric tube (case 2) and epilepsy management (case 3) and was in both cases not related to the diet.

2.4 | Coping

Parents were highly motivated to start the diet and continued being so. In daily practice, they had no problems with calculating and preparing the KD liquid exchanges or meals of solid food. The children themselves liked the KD with MCT better than the LQ formula, and it was

TABLE 1 Patient characteristics

Patient	Gender	Age at diagnosis (years)	Age at start ketogenic diet (years)	Treatment characteristics	GMFCS		Growth-Weight/height-Height/age(SD)		Overall survival rate (months)
					Start of study (level)	End of study (level)	Start	End	
1	M	4.4	5.3	- TMZ (tablets) - RT	3	5	W + 0.05 H + 2.00	– 0.35 + 1.83	16.5
2	M	11.0	11.6	- GCB - (iv and tablets) - RT	2	–	W – 3.09 H – 0.71	– –	6.4
3	M	14.4	15.5	- TMZ (tablets) - RT - Prednisolone	3	5	W + 2.16 H – 0.31	+ 2.10 – 0.41	18.7

Abbreviations: GCB, gemcitabine; GMFCS, gross motor function classification system; H, height; iv, intravenous; M, male; RT, fractionated radiotherapy; SD, standard deviation score; TMZ, temozolomide; W, weight.

better tolerated. The required daily checking of ketone and glucose levels could be achieved without problems. Overall, parents were able to cope with the situation and were convinced they did the right thing for their child.

Parents were satisfied with the high level of support and information they received from the research team.

3 | DISCUSSION

This study explored feasibility and safety of the KD in three children with recurrent DIPG and without other treatment options. Feasibility could not be properly assessed, however, because only two of the three patients survived the three-month study period. Both showed deterioration of neurological functioning in the final weeks of the study period, suggesting that KD does not impressively reduce tumor growth in the palliative phase. Interestingly, both patients had a relatively prolonged survival of 16.5 and 18.7 months, respectively, after diagnosis. Yet, it is not clear whether the prolonged survival can be ascribed to a particular component or combination of the therapies applied.

As mentioned earlier, studies in mice suggest that KD helps the host to fight against high-grade glioma when ketones instead of glucose become the main fuel for the brain. The underlying mechanism is as yet not clarified nor is the best timing to start the KD or the optimal level of ketosis. Mouse models suggest a more profound effect of KD when combined with RT because sensitization of the tumor cells by the KD.[20] This suggests that in patients with high-grade glioma (both children and adults), the start of KD as adjuvant therapy to RT would be more efficient for reduction of tumor load and lengthening of survival. In addition to this, the ketone levels measured in the mouse study (>2 mmol/L) were lower than the levels (>2.5 mmol/L) we achieved in the three children. Even though ketone levels are not to be 1:1 extrapolated from rodents to humans, the question remains which level of ketosis should be aimed for. However, the strict regimen needed for a substantial level of ketosis puts great demands on the patient and family with risk of noncompliance (i.e., effect on palatability and quality of life). This may be more intense during the period of intensive standard treatment. The prognosis of patients with high-grade glioma is grim, while alternative and effective treatment options are lacking. In this line, metabolic alteration by the use of a KD as adjuvant to standard treatment may be justified.

Severe side effects were not reported. Some mild and transient side effects, such as gastrointestinal complaints, occurred mainly during the diet initiation period and could be resolved medically or by diet modification. The reported fatigue and headache may also have been related to the underlying disease.

After recurrence of DIPG, limited duration of survival can be expected. This is why a full liquid KD was used, which rapidly induces ketosis. Adequate ketosis was indeed reached within a very short period of a week (range, 2–7 days) in all three patients. It cannot be excluded that this strategy was the cause of the reported gastrointestinal complaints during the initiation period. The introduction of some ketogenic snacks (such as the ketomuffins with same 4:1 diet ratio) during this period may have improved the tolerance and compliance of the KD while an adequate ketosis was reached. During the next period, the more liberal KD diet with MCT was well tolerated.

Our study has some limitations that need to be assessed. First, by the absence of questionnaires for evaluation of dietary application, we used a self-designed, not validated, one. Second, an important limitation of our study was the small sample size. Between March 2010 and May 2015, we could include no more than three patients. A possible reason is the timing of recruitment. The parents who consulted us ($N = 14$) were highly motivated to have their child included in a dietary treatment study when the diagnosis of DIPG had been recently made—arguing that they at least could personally contribute to the child's treatment. For children in the palliative stage of disease, however, most parents lost interest when the child started to irreversibly lose neurological functions. They concluded that the KD was not compatible with the best quality of life they wanted for the child.

In summary, we showed that the KD might be a safe intervention in children with end-stage recurrent DIPG. All parents ($n = 3$) included in our study commented that the KD treatment allowed them to participate more intensively in their child's treatment, which was highly important to them. Although the small sample size did not allow

TABLE 2 Treatment characteristics

Patient	Ketogenic diet LQ	Ketogenic diet MCT	Time to adequate ketosis (days)	Complications at start of study	Complications during study	Complications at end of study	Hyperketosis (>6.5 mmol/L)	Hypoglycaemia (<2.5 mmol/L)	After study
1	- Kcal 1400 - Protein 21 g - Diet ratio 4.0:1	- Kcal 1450 - Protein 21 g - Diet ratio 1.6:1	2	- Fatigue	- Fatigue - Vomiting[a] - Food refusal[a]	- Fatigue	- 7.2 mmol/L (day 3) - 6.7 mmol/L (days 18, 27, 57) - 7.2 mmol/L (day 26)	2.4 mmol/L (day 3, in the morning)	Normal diet orally. After 6 weeks: by nasogastric tube
2	- Kcal 1100 - Protein 22 g - Diet ratio 3.5:1	- Kcal 1170 - Protein 25 g - Diet ratio 1.75:1	6	- Fatigue - Headache - Vomiting	- Fatigue - Vomiting[a] - Food refusal[a]	-	-	-	-
3	- Kcal 1770 - Protein 30 g - Diet ratio 3.8:1	- Kcal 1500 - Protein 31 g - Diet ratio 2.1:1	7	-	- Constipation[b] - Inability to swallow[c] - Fatigue[d]	- Fatigue - Inability to swallow	-	-	Continued ketogenic tube feeding

Abbreviations: Kcal, calories; LQ, all liquid; MCT, medium chain triglycerides.
[a]Related to liquid formula.
[b]Treated with medication.
[c]Start of ketogenic tube feeding.
[d]During reirradiation total 20 Gy and steroid use.

addressing the efficacy of KD, it was proven feasible, and therefore our experiences may help design a prospective study. Future studies should focus on the use of modified versions of the KD with a nutritional composition that induces at least a moderate level of ketosis and is started earlier after diagnosis, preferably as adjuvant to RT.[20] A less strict diet might be crucial to recruit a large enough cohort to explore if survival in DIPG benefits from metabolic alteration when it is combined with other treatment modalities.

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CONFLICTS OF INTEREST

All authors declare to have no conflict of (financial) interests or relationships/affiliations relevant to the subject of their manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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