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Safety and tolerance of the ketogenic diet in patients with Zellweger Syndrome

Borst Stephanie [a,*], Ciliberto Michael [b], Thati Ganganna Sreenath [b]

[a] The University of Iowa, 225 S Grand Ave Iowa City, Iowa 52242, United States
[b] The University of Iowa Stead Family Children's Hospital, 200 Hawkins Drive Iowa City, Iowa 52242, United States

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ABSTRACT

Zellweger Syndrome is a peroxisomal disorder that can lead to elevation of long chain fatty acids and epilepsy, which can be drug resistant. The treatment of drug resistant epilepsy can include the ketogenic diet in appropriately chosen patients. Typically, the ketogenic diet is contraindicated in individuals with defects in fatty acid metabolism because of the diet's reliance on medium and long chain fatty acids. To our knowledge this is the first publication outlining the use of the ketogenic diet in patients with defects in beta oxidation of very long chain fatty acids. We present two patients with Zellweger Syndrome who were placed on a ketogenic diet for drug resistant epilepsy.

Safety and tolerance of the ketogenic diet in patients with Zellweger Syndrome.

Introduction

Zellweger Syndrome is a peroxisome biosynthesis disorder affecting peroxisome function including but not limited to alpha oxidation of phytanic acid and beta oxidation of very long chain fatty acids (VLCFA) and branched-chain fatty acids (pristanic acid). Patients with peroxisomal fatty acid beta oxidation defects present with elevations of C26:0 and C26:1 fatty acids and ratios of C24:0/C22:0 and C26:0/C22:0 [1]. Peroxisome dysfunction can lead to elevations in phytanic acid, however, patients with Zellweger Syndrome may present with normal phytanic acid levels [1,2]. Symptoms have been reported from phytanic acid accumulation in patients with another peroxisome disorder, Refsum's Disease. These symptoms include neuropathy, ichthyosis, kidney damage, and arrythmias [3]. Clinical features of Zellweger Syndrome can include hypotonia, poor feeding, impaired hearing and vision, adrenal insufficiency, liver dysfunction, renal insufficiency, and seizures [1,4]. Seizures in these patients can be difficult to control and can be quite severe [5].

The ketogenic diet (KD) is a well-established treatment used in children and adults with drug resistant epilepsy (DRE) [6]. Ketosis is achieved by eating a high fat, low carbohydrate, moderate protein diet, primarily high in long chain and potentially medium chain fatty acids. With elevated fat intake, in the presence of carbohydrate restriction, fatty acids (FA) undergo beta oxidation after which acetyl-coA is used as a substrate to produce the ketone bodies, acetoacetate and beta hydroxybutyrate [7]. While the exact mechanism by which dietary therapy improves seizure frequency in epilepsy is unclear, multiple studies have shown the safety and effectiveness of the KD under medical supervision [6,7,8].

Because of the reliance of fats for energy in the KD, patients with dysfunction in fatty acid metabolism may be at risk for complications [10]. There are no specific diet recommendations for patients diagnosed with Zellweger Syndrome [1]. To our knowledge, there have been no published studies on initiating the KD for patients with Zellweger Syndrome. We present two cases indicating that the KD is a safe treatment option for Zellweger Syndrome despite elevations in phytanic acid levels.

Case 1

A 2-year-old with Zellweger Syndrome (PEX 1 pathogenic variant) and epileptic spasms started on the KD with cautious ratio advancement while monitoring VLCFA levels. Due to limited information on how VLCFA levels would change for patients with Zellweger Syndrome on the KD, ratio adjustments were made after obtaining these levels, resulting in a slower than typical transition to goal ratio. The diet was initiated and advanced in the outpatient setting, starting at a 1:1 ratio and increased to a 3:1 ratio over the course of 4 months. At the time of

* Corresponding author.
E-mail address: stephanie-borst@uiowa.edu (B. Stephanie).

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diet start her diet consisted of mostly formula with a small amount of food by mouth. Her ketogenic formula was whey-based with a blend of saturated, polyunsaturated, monounsaturated fats, and medium chain triglyceride oil and was combined with breast milk for the desired ratio. Higher ratios were achieved over time by adding MCT oil to the ketogenic formula and breast milk mixture.

Routine monitoring of VLCFA levels revealed a steady increase in phytanic acid levels within the first 7.5 months on diet. Her phytanic acid level peaked at 7.5 months at > 40 μg/ml (normal values < 3.00 μg/ml). Following this result, diet ratio (3:1) and formula components were unchanged, but cheese, which is a phytanic acid source was removed from her diet [10]. Phytanic acid levels were rechecked 3.5 months later and had declined and then remained stable for an additional 11 months (22.60–26.54 μg/ml) even with ratio increases during this time.

Between 11 and 24 months on the diet, ratio changed 4 times and ranged from 3:1–4:1. Ratio decreases occurred during times of illness where it was unclear if illness was masking symptoms of excess ketosis. In this time, phytanic acid levels were checked 4 times at ratios of 3:1, 3.5:1, 3.67:1, 3.25:1 and were 24.68 μg/ml, 26.54 μg/ml, 22.60 μg/ml, and 13.61 μg/ml respectively. A phytanic acid sample was not obtained during the 1 month she was at a 4:1 ratio. At the start of diet, the patient was not on any anti seizures medications as Prednisolone and Vigabatrin treatment were recently completed. While seizure activity was unchanged in the first 6 months after starting diet, diet was continued due to good tolerance and reports of improved vocalization and social interaction since starting KD. An additional medication was added, followed by a second until seizure freedom was achieved while on combination therapy of KD and two other anti-seizure medications, Zonisamide and Clobazam.

Acidosis, constipation, iron deficiency anemia, zinc deficiency, and vitamin D insufficiency occurred while on the diet. Constipation initially improved with increases of MCT oil and then managed with laxative medication. Acidosis was treated with potassium bicarbonate. Vitamin deficiencies were found with routine ketogenic monitoring, treated with additional supplementation, and resolved. A gastrostomy tube was placed after diet initiation, although this was not thought to be due to KD but rather progression of feeding difficulties that are described with Zellweger Syndrome.

Case 2

An 11-year-old with Zellweger Syndrome (PEX1 pathogenic variant) and drug resistant epilepsy was started on the KD while on Levetiracetam, Felbamate, Topiramate, and Epidiolex. He is fed primarily by gastrostomy tube with some pureed food intake by mouth. Prior to starting the diet, food intake excluded any beef or milk products as the family preferred to limit food sources of phytanic acid. The diet was initiated and advanced in the outpatient setting and ratio changed weekly for 4 weeks until the goal ratio of 3:1 was achieved. A 4:1 whey-based formula with a blend of saturated, polyunsaturated, monounsaturated fats, and medium chain triglyceride oil was combined with an additional protein powder for a 3:1 ratio. Phytanic acid levels were elevated after 2 weeks on a 3:1 ketogenic ratio without any reported side effects. The diet ratio increased twice within the first 6 months and then was maintained at a 3.5:1 ratio for one year. Phytanic acid levels were checked again after 1 year on diet and increased to 22.98 μg/ml without any reported side effects. Phytanic acid levels declined but remained above pre diet levels after 17.5 months on the diet. Prior to starting the KD, he had a history of constipation. Constipation continued to be managed with additional medications. Cytra K solution was added while on KD due to risk of kidney stones. After two weeks on KD the family reported an approximately 50 % decrease in seizure activity.

Discussion

Zellweger Syndrome is a complex multi-organ disease with a heterogeneous phenotype and alterations in very long chain fatty acids. Patients with defects in FA metabolism are often not considered to be candidates for KD treatment. These cases demonstrate the safety and tolerance of KD in Zellweger Syndrome. Due to the risk of drug resistant epilepsy in these patients, treatment with KD may be considered.

Very long chain fatty acid alterations have been reported in patients on the KD without defects of peroxisomal function, including elevations of C22:0 and C24:0, with normal levels of C26:0, C24:0/C22:0 and C26:0/C22:0 ratios [11]. Both of our patients were noted to have elevations in phytanic acids after initiation of the KD. There are no studies outlining effects of elevated phytanic acid levels for patients with Zellweger Syndrome [1]. Accumulation of phytanic acid levels can be seen in other peroxisome disorders such as Refsum's Disease and can lead to neuropathy, ichthyosis, kidney damage, and arrythmias. However, symptomatic levels have been reported of 700–8000 μmol/L [3]. These two cases had a range of 13.61 μg/mL to >40 μg/mL and 13.45 μg/mL to 22.98 μg/mL, respectively throughout their time on diet without any clinical symptoms.

Common side effects of the KD include constipation, emesis, abdominal pain, hyperlipidemia, renal calculi, cardiac abnormalities, decreased growth, acidosis, vitamin deficiencies, and risk for bone fractures [9]. Constipation was present for both patients and treated with laxative medications. Routine laboratory monitoring was completed while on the KD and revealed acidosis and vitamin and mineral deficiencies for one patient which were treated and continued to be monitored while on the diet. No patient experienced side effects that resulted in a discontinuation of the diet but rather continued to report good tolerance while on diet.

Conclusion

Although phytanic acid levels increased on the KD clinically, the patients tolerated the therapy without adverse side effects and remained on diet due to improved seizure control. More research is needed on long term side effects of elevated phytanic acid levels in patients with Zellweger Syndrome. The KD may be a safe therapeutic option for patients with Zellweger Syndrome despite the intrinsic metabolic problems present in this disease.

CRediT authorship contribution statement

Borst Stephanie: Writing, Review, Editing, Visualization, Investigation, Validation. **Ciliberto Michael:** Reviewing, Editing, Validation. **Thati Ganganna Sreenath:** Reviewing, Editing, Validation.

Ethical Statement

This report was determined not human subject research. Written permission was obtained although no protected health information or images were presented in this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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