



Keto-Sleuths – An Unusual Cause of Loss of Ketosis?

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Abstract

Ketogenic diets provide a non-pharmaceutical alternative for treatment of refractory epilepsy. When successful in reducing or eliminating seizures, medication numbers or doses may be reduced. Unexpected loss of ketosis is a common problem in management of patients on ketogenic diets and, especially when the diet is an effective treatment, loss of ketosis may be associated with an exacerbation in seizures. Identification of the cause of loss of ketosis is critical to allow rapid resumption of seizure control, and prevention of unnecessarily increased diet restriction or increased medication doses. Here an unusual environmental cause of loss of ketosis is described (contamination with starch-containing drywall dust), illustrating the extent of investigation sometimes necessary to understand the clinical scenario.

Keywords

ketogenic diet, ketosis, epilepsy

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Despite the availability of new anti-seizure drugs and the ever-increasing new information about the genetic underpinnings of epilepsy, there remains a substantial proportion of children whose epilepsy is refractory to available medications or whose epilepsy is not readily amenable to surgical approaches.¹ Diet therapies, including ketogenic diets and non-ketogenic diets (Low Glycemic Index Diet Therapy) can provide an effective therapy for some of these children. These diets can now be provided using a number of different protocols which can facilitate integration of the diet in different lifestyles and at different ages.²⁻⁴ Ketogenic diet initiation leads to the development of ketosis – an increase in plasma ketone bodies and free fatty acids, which provides an alternative to glucose-based cellular energy metabolism. In a substantial proportion of patients, this results in a worthwhile reduction in seizures, sometimes seizure-freedom.⁵ While the anti-seizure and/or anti-epileptic mechanisms are not fully understood, breach of ketosis by dietary indiscretion or other means may be associated with recurrence of seizures in some but not all cases. Ketosis or ketonuria is monitored on a more or less regular basis in patients on ketogenic diets. When there is an unexpected recurrence of seizures in a patient on a ketogenic diet, one of the first goals is to establish if ketosis has been compromised. If so,

investigation into the source of the breach is undertaken. Ketosis can usually be re-established over hours to days.

This report describes an unusual cause of loss of ketosis which we had not encountered (or recognized) in >15 years of providing diet therapy for epilepsy at a quaternary level epilepsy center. It illustrates the need for sometimes wide-ranging investigation in cases of loss of ketosis, in order to re-establish and maintain ketosis in these medically fragile patients.

Case

A 7-week-old male infant, born at 37 weeks after an uncomplicated pregnancy presented with focal seizures (eyes deviated to the right, right-sided twitching and sialorrhea) and was found to have right hemimegalencephaly. Initial electroencephalogram

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(EEG) revealed seizures from the right hemisphere evolving bilaterally, and resulting in non-convulsive status epilepticus despite treatment with intravenous (IV) lorazepam and an IV levetiracetam loading dose. Additional loading doses of phenobarbital and fosphenytoin, and treatment with clobazam and valproic acid were ineffective. (The patient does not have a POLG1 mutation). He was intubated and transferred to our center for further care. Addition of midazolam infusion and IV lacosamide decreased seizure frequency from 5-8 seizures/hour to 2-3 seizures/hour. He was successfully extubated and medication administration was transitioned to the enteral route via NG tube. Pending surgical planning for his hemimegalencephaly, the ketogenic diet was initiated, using a combination of a high-fat, soy-protein-based ketogenic formula combined with other fat and carbohydrate modular products, initially at a 1:1 ratio, and with escalation in the ratio over an 8-day period to a 4:1 ratio. Acidosis developed at a 2.5:1 ratio and was treated without recurrence. Plasma beta hydroxybutyrate levels rose steadily and stabilized at 3.07-3.25 mmol/L by discharge 2 weeks following diet initiation. He was discharged on diet and a combination of medications including levetiracetam 92 mg/kg/day, lacosamide 5.25 mg/kg/day, clobazam ~2 mg/kg/day and valproic acid 52 mg/kg/day. EEG prior to discharge continued to show 3-10 seizures/hour some of which were subclinical.

Following discharge, the clinical seizure frequency reduced from ~50 per day to ~20 per day with stable high urine ketones (>50% reduction in clinical seizures). He slowly developed a social smile, improved head control and auditory tracking of family members.

One month following discharge, seizures increased to ~50 per day and ketonuria decreased (from large to small) over a 2-day period. Initial assessment excluded intercurrent infection, break in diet, missed medications or new formulations and yielded no other apparent cause for loss of ketosis. During discussion, the family volunteered that there was construction work being done in the home with thick accumulation of dust in the main living areas. They additionally reported that a family member with celiac disease had previously developed recurrent GI symptoms in the setting of construction, which had been attributed to exposure to the gluten-containing starch content in drywall dust. They questioned whether similar environmental contamination could result in loss of ketosis in their son. Construction and work with drywall were ongoing adjacent to where they prepared and administered the diet formula, and there was significant environmental contamination with dust during the 2-day time frame of seizure recurrence and reduction of ketosis.

Following discussion, the family removed the infant from the home while the work was completed, the home ventilated and the area decontaminated. The infant's seizure frequency quickly returned to previous baseline (50 back to 20 per day) and "large" ketonuria was re-established without other change in his diet. Subsequently, ketonuria was well maintained up to and following a right functional hemispherectomy.

Discussion

During diet treatment of epilepsy, unexpected seizure recurrence or escalation is a source of distress for patients and families and concern for their healthcare providers. This is especially the case when diet treatment has been successful and medications have been tapered and/or withdrawn, the diet then being the patient's sole anti-seizure treatment. In these settings, identifying loss or diminution of ketosis provides a potential explanation for the clinical change, as well as an opportunity for rapid resolution of the problem and return to better seizure control. Also, failure to identify the cause of reduced ketosis may lead to loss of confidence in diet, unnecessary increase in diet ratio, and/or an unnecessary increase in anti-seizure medication dose.

There are many factors to investigate when loss or reduction in ketosis has occurred.⁵ Patient-related changes, such as illness, break/error in diet compliance, administration of non-compliant medications (often carbohydrate rich liquid antibiotic formulations) are common but may not be the only factors involved. Equipment failure (expired ketone strips), diurnal variation in ketone levels, and other systemic issues must also be considered. Acceptance of diet restriction as a therapy may be challenging for cultural reasons and may lead to unexpected breach of the diet protocol by family members or caregivers. Also, orally fed children often struggle with compliance especially if preferred, non-compliant foods are within reach.

The case described here indicates a new avenue of investigation when the usual causes of loss of ketosis are excluded. In this case environmental exposure to significant amounts of starch-containing drywall dust⁶ was temporally associated with reduced ketosis and seizure exacerbation. Drywall, also known as plasterboard, contains mostly gypsum (calcium sulfate) along with other components to affect its durability, fire-resistance and soundproofing. Starch, typically comprising up to 5% by weight, is gelatinized to produce adherence of the outer paper layers to the gypsum core. Chelating property of starch decreases mold and mildew.⁷ In US manufacturing, cornstarch is used, while in Europe starch content is from corn, wheat, potato and other sources.⁷ In our patient immediate removal from the source and decontamination of the environment resulted in a rapid improvement in ketosis and seizure control. Escalation of medication doses or diet ratio were avoided.

We have found no other reports of environmental starch contamination resulting in loss of ketosis, or other reports implicating other physical environmental factors. While such exposures may have been underappreciated as factors in loss of ketosis, they are easily remediated if identified. Also, starch content may vary among drywall products offering an opportunity for prevention in appropriate circumstances.

In summary, we recommend adding questions regarding potential exposure to environmental contaminants in the home environment, particularly regarding construction and home renovations before initiation and during the diet maintenance period, especially when an otherwise unaccountable loss of ketosis occurs.

ADDENDUM: Information regarding the content of specific products can be found by searching online for the material safety data sheets (MSDS) for various products (search “MSDS: product X”)

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