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Autism and Dietary Therapy: Case Report and Review of the Literature

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Abstract

We report the history of a child with autism and epilepsy who, after limited response to other interventions following her regression into autism, was placed on a gluten-free, casein-free diet, after which she showed marked improvement in autistic and medical symptoms. Subsequently, following pubertal onset of seizures and after failing to achieve full seizure control pharmacologically she was advanced to a ketogenic diet that was customized to continue the gluten-free, casein-free regimen. On this diet, while still continuing on anticonvulsants, she showed significant improvement in seizure activity. This gluten-free casein-free ketogenic diet used medium-chain triglycerides rather than butter and cream as its primary source of fat. Medium-chain triglycerides are known to be highly ketogenic, and this allowed the use of a lower ratio (1.5:1) leaving more calories available for consumption of vegetables with their associated health benefits. Secondary benefits included resolution of morbid obesity and improvement of cognitive and behavioral features. Over the course of several years following her initial diagnosis, the child's Childhood Autism Rating Scale score decreased from 49 to 17, representing a change from severe autism to nonautistic, and her intelligence quotient increased 70 points. The initial electroencephalogram after seizure onset showed lengthy 3 Hz spike-wave activity; 14 months after the initiation of the diet the child was essentially seizure free and the electroencephalogram showed only occasional 1-1.5 second spike-wave activity without clinical accompaniments.

Keywords

autism, dietary therapy, ketogenic diet

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The ketogenic diet is by now well-studied for refractory epilepsy,[1,2] but there is only limited assessment of its efficacy for seizures in the setting of autism spectrum conditions. At the same time seizures and epileptiform activity are common in autism spectrum conditions, with seizure prevalence estimates varying from 5% to 46%, and the prevalence of epileptiform electroencephalogram discharges as high as 60%.[3,4] Autism commonly accompanies epilepsy-associated syndromes such as Landau-Kleffner syndrome, Dravet Syndrome, and tuberous sclerosis complex.[5,6] Seizure onset in autism spectrum conditions most commonly occurs in early childhood and in puberty and adolescence.[7] Treatment of epilepsy in autism spectrum conditions may be complicated by atypicality of seizure presentation, as well as atypical and sometimes paradoxical response to anticonvulsants.[8]

Dietary therapies, particularly elimination diets, are commonly used in autism spectrum conditions, but at present are considered "alternative." A recent meta-analysis evaluated the level of evidence for elimination diets as Grade C.[9] Evidence supporting physiological pertinence of diet includes documentation of a higher rate of production of or reaction to antibodies to milk, gluten, and casein (a milk protein). In some studies this is associated with autoantibody formation or proinflammatory cytokines.[10-13] Conversely a different study found that children with autism spectrum conditions on a gluten-free casein-free diet had fewer tumor necrosis factor-α producing cells in their colonic mucosa when compared with children whose diet involved no exclusions.[14] Celiac disease was found to be 3-fold higher in prevalence in children with autism spectrum conditions than in the general population.[15] Children with autism spectrum conditions and gastrointestinal symptoms such as diarrhea and constipation have had an increased rate of immune abnormalities in response to food.[14,16-18] Several case reports and open-labeled trials as well as one study have documented improvement of behaviors with food elimination and worsening of behaviors with reintroduction.[19-26] Several large surveys have reported that a substantial number of children undergoing gluten-free casein-

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free diet experienced behavioral improvements.[27,28] Although many of these studies have methodological flaws,[29] and a number of studies have reported no impact on behavior of the gluten-free casein-free diet in autism spectrum conditions,[30] a Cochrane review of the gluten-free casein-free diet in autism spectrum conditions calculated from pooled data showed that there was significant improvement compared to autism spectrum conditions in children on a control diet in overall autistic traits ($P = .001$), social isolation ($P = .002$), and overall communication and interaction ($P = .006$). This report noted no harmful outcomes and recommended larger controlled trials.[31] In one such trial published subsequently, the ScanBrit trial, which had a large sample size and a long duration of dietary treatment, significant improvement was noted on subdomains of Autism Diagnostic Observation Scale, the Gilliam Autism Rating Scale, and ADHD-IV Rating Scale. Children in the control group were later reassigned to the diet treatment group.[32] According to a recent review by the ScanBrit study's lead author, while much remains to be done to characterize responders versus nonresponders and to elucidate modes of action, debate on practical guidelines for dietary intervention in the autism spectrum is warranted.[33]

A ketogenic diet utilizing medium-chain triglycerides was tried in 30 children with autism spectrum conditions but without epilepsy; of the 18 who tolerated the diet, 10 demonstrated moderate or significant behavioral improvement.[20] There was no control diet utilized, and this study, to date the only published series using a ketogenic diet for autism, has yet to be formally replicated. A survey of parents of children with autism revealed that parents perceived a ketogenic diet to contribute to improvement of both seizures and other clinical factors.[8] In addition, adenosine, an endogenous neuromodulator and anticonvulsant, has been reported to ameliorate autistic disorders and is also associated with mechanisms involved in the ketogenic diet.[34,35]

The following case report reviews the history of a child with autism and epilepsy who after limited response to other interventions following her regression was placed on a gluten-free casein-free diet with marked improvement in autistic and medical symptoms; subsequently following pubertal onset of seizures she was placed on a gluten-free casein-free ketogenic diet after failing to achieve seizure control pharmacologically, and on this regimen showed significant improvement in seizure activity.

Case History

A previously neurologically normal girl experienced sudden social, behavioral and language deterioration consistent with severe regressive autism over the course of a week, at the age of 4 years. She was the product of a full-term pregnancy, delivered via normal spontaneous vaginal delivery at 38 weeks, Apgar scores of 9/9. Pregnancy was complicated by maternal hyperemesis, 30-pound weight loss, colitis necessitating colonoscopies, and preterm contractions requiring bed rest. Family history included maternal adult onset asthma, paternal metabolic syndrome and kidney stones, and asthma in an older brother. Early development included severe asthma, recurrent otitis media and sinusitis, with pressure equalization tympanostomy tube placement at 6 months, tonsillectomy and adenoidectomy at 2 years, and functional endoscopic sinus surgery at 3 years. Developmentally she was on target, with borderline delay in motor skills and advanced and cognitive and verbal skills. Immediately after her 4-year-old well child visit her language regressed to the 18 month level. Concomitantly her behavior deteriorated, with unexplained escalating tantrums and "meltdowns." She stopped making eye contact, stopped manifesting social awareness or interest, and manifested sensory hypersensitivity, hypotonia, and stereotypies. Bowel movements were consistently foul smelling orange diarrhea, which she sometimes smeared on the walls; she had a distended abdomen, moaned every morning as she awakened, and was continuously ill. Her Childhood Autism Rating Scale score was 49 (this scale rates symptoms of autism with scores from 15 to 60; a score between 30 and 37 reflects mild autism, and scores between 38 and 60 represent severe autism). Although physical therapy and speech therapy led to modest gains, behaviors were better only if no limits or challenges were present.

During her fifth year, approximately 15 months after her regression, the family initiated a gluten-free, casein-free diet using increasingly organic and largely unprocessed foods. Dramatic improvements in language were observed almost immediately, including resumption of speaking in simple needs-based sentences and answering concrete questions. Auditory sensitivity improved in that she no longer ran from the sound of a vacuum cleaner and was able to tolerate the sound of fireworks. Temper tantrums improved but were not resolved; she awakened without moaning in the mornings but was still dysphoric most days. In addition, abdominal distension improved but did not resolve; her bowel movements continued to have a foul odor and orange color with undigested food, but were better formed and were consistently passed in the toilet without fecal smearing on the household walls.

She continued to be frequently ill with recurrent use of antibiotics, and was found with laboratory evaluation to have low normal levels of Immunoglobulin G and Immunoglobulin G subclasses. Intravenous immunoglobulin was begun for her immune dysregulation. Illnesses rapidly resolved and the frequency of antibiotic use decreased. Three weeks after initiating intravenous immunoglobulin, she began verbalizing some emotions, stating, "Mommy I love you." Interest in social interaction began a slow increase, temper tantrums were less frequent and severe, and language continued to become more complex and age appropriate.

In the setting of refractory asthma, and after laboratory studies revealed the presence of a methionine synthase single nucleotide polymorphism (methionine synthase reductase) as well as low levels of glutathione and cysteine consistent with oxidative stress, supplementation with a multivitamin high in B-vitamins, injectable methylcobalamin, nebulized glutathione, and methionine were initiated. Over the course of a year there was near resolution of the asthma. Peroxisome proliferator activated receptor modulator Isoprinosine and low

dose naltrexone were also introduced over several months, as was mesalamine for the significant inflammatory bowel disease found on endoscopy. These interventions were all were well tolerated; the family noted steady improvement in behavior, reduction in stereotypies, significant improvement in language, and improvement in cognitive function. Later, vitamin D3, 5-Hydroxytryptophan and methylfolate were introduced to address residual anxiety,[36-42] after which clinical observations included reductions in rigidity, resistance to change and to transition, obsessive thinking, and social anxiety

In the sixth year of life she began mainstreaming in school. Cognitive testing showed a 50-point improvement in intelligence quotient 24 months after her regression, 18 months after her initial comprehensive psychoeducational evaluation, and 11 months after beginning the medical interventions described above. Her individualized education program was modified to include a dual diagnosis of both autism and gifted for the purposes of appropriate enrichment of her education. Her challenging behaviors resolved, and she was able to tell jokes and demonstrate a sense of humor, but she was still struggling socially.

Although a gluten-free casein-free diet was continued, from age 7 she self-limited her food selection to mostly carbohydrates with increasing intensity, and gained approximately 60 pounds. Her body mass index increased from 24.1 (the first documented measure of body mass index as weight began to climb) to 33.6 by the age of 11, by which time she was also undergoing pubertal changes. Another assessment showed a 70-point intelligence quotient increase since the time of autism spectrum conditions, diagnosis, and a reduction of her Childhood Autism Rating Scale rating to 17, which put her in the nonautistic range.

At age 11.5 years, along with her pubertal changes she began to have seizures. These were atypical in presentation clinically as well as difficult to control. Initially she was thought to have classic grand mal seizures (although these have never been captured on electroencephalogram) as well as absence seizures (which were typical on initial electroencephalogram prior to medication and induced with hyperventilation). Later, when her family reported episodes that started with the appearance of grand mal seizure but continued with prolonged fasciculation of muscles all over her body for as long as 50 minutes, seizures were felt to be more complex partial in nature. Staring spells occurred several times weekly, whereas the longer seizures were initially associated with early menstrual cycles, occurring approximately every 6 weeks. It was difficult to assess the success of medical management given the infrequency with which the complex partial seizures occurred, and this was further complicated by a past history of prolonged paradoxical screaming associated with benzodiazepine use at 2 years of age, making the use of rectal valium untenable. The medical team initiated therapy with lamotrigine, and therapeutic levels were obtained; doses were increased when seizures were not controlled without seizure resolution. Levetiracetam was added as a second drug several months later, but this did not lead to clinical seizure control, and moreover led to exceptional irritability and worsening of the electroencephalogram. At this juncture, taurine and vitamin B6 at high dosage were added, along with oral γ-aminobutyric acid (GABA),[43-47] and these interventions were followed by clinical reduction in frequency and duration of complex seizures, but not resolution. Methylfolate dosages were increased to counter the observed increased anxiety and subtle decrease in cognitive function that was thought probably to be a consequence of impact on folate metabolism associated with some antiepileptic drugs.[48-51] Her medications were switched to lamotrigine and ethosuximide. Therapeutic drug levels were obtained, and staring spells improved clinically and were no longer inducible with hyperventilation; however, electroencephalogram tracings while asleep continued to be abnormal.

Rather than add a third medication to her regimen of lamotrigine and ethosuximide, and in an effort to control the complex partial seizures, the family elected to start a ketogenic diet. To avoid compromising the significant and sustained positive clinical response since the removal of casein and gluten several years previously, the family committed to continuing casein and gluten elimination while initiating ketogenesis, and continued to use largely organic and completely unprocessed foods. With the assistance of an experienced nutritionist, a ketogenic diet at a 1.5:1 ratio was implemented, using primarily medium-chain triglycerides as the fat source. Moderate to large ketosis was obtained without hospitalization within one week, and is maintained currently.

The initial electroencephalogram, performed after her first seizure at 10 years 7 months of age, was wakeful only and showed 3 Hz spike and wave activity both spontaneously and with hyperventilation (Figure 1, left). During a second wakeful electroencephalogram 5 months later, on lamotrigine as the single medication, two 2.5 Hz spike and wave discharges were produced during hyperventilation, with 1 event originating in the left hemisphere and the second being more generalized in onset; but the electroencephalogram was otherwise spike-free. An electroencephalogram performed approximately 4 months after adding levetiracetam showed frequent diffuse spike and wave activity of up to 15 seconds duration while awake without outward clinical change on video. While asleep, these spike and wave events were increased in frequency and voltage, and polyspike in morphology. In addition, there was a 7 second episode of "different appearing repetitive fast activity associated with subtle clinical change."

After a gluten-free casein-free ketogenic 1.5:1 ratio diet was started at age 12 years, seizures were significantly clinically improved within several weeks of achieving ketosis. An electroencephalogram performed while on lamotrigine and several weeks after changing from levetiracetam to ethosuximide and implementing the ketogenic diet showed modest improvement. Background was reported as good, with rare generalized spike and wave discharges while asleep. No events were triggered by hyperventilation. An electroencephalogram performed 14 months after starting diet and continuing on lamotrigine and ethosuximide showed only sporadic generalized spike and wave activity lasting 1 to 1.5 seconds (Figure 1, right) with no clinical accompaniments. The background was good, and again there were no events triggered with hyperventilation.

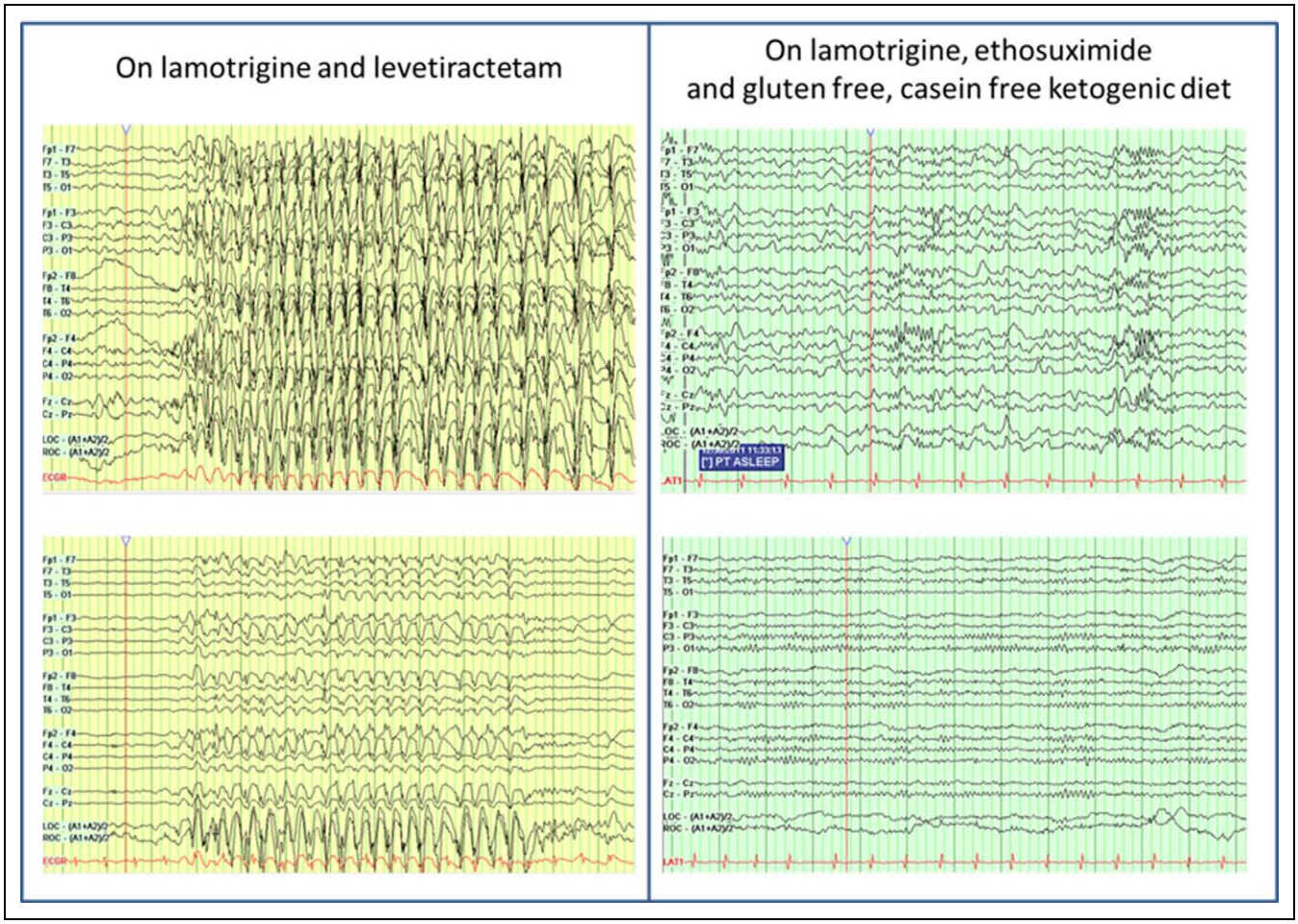

Figure 1. Electroencephalogram studies were obtained before and after initiating the gluten-free casein-free ketogenic diet, as described in text.

In addition to improvement in seizures, there was a 60-pound weight loss subsequent to initiation of the gluten-free casein-free ketogenic diet, as well as improved cognitive and language function, marked improvement in social skills, increased calmness, and complete resolution of stereotypies. Intravenous immunoglobulin treatments continued, since delays in delivery of immunoglobulin G were associated with illness accompanied by convulsion. Based on the clinical improvement, the electroencephalogram improvement, and development of a side effect involving extreme medication associated somnolence, anticonvulsant medication doses were reduced (first lamotrigine by 50%, and then ethosuximide by 25%) without worsening of seizures. Cholesterol was 152 mg/dl before starting diet, and was 160 mg/dl after more than a year on the diet.

Discussion

This case report reviews the emergence in a preschool child of regressive autism, followed by development of carbohydrate craving and obesity in grade school and then seizure onset in puberty, where the autism was ameliorated while on a gluten-free casein-free diet and seizures were substantially ameliorated on a gluten-free casein-free ketogenic diet. This child had substantial medical comorbidities and had a strong family history of medical problems known to be associated with metabolic and immune disturbances. Immune and gastrointestinal vulnerability were particularly prominent for the child and the immune issues were not overcome by the therapeutic regimen.

This child's ketogenic diet was centered around medium-chain triglycerides but also provided polyunsaturated fats for essential fatty acids. The transport of medium-chain triglycerides into mitochondria is not carnitine dependent, and whose metabolism bypasses complex I, thus avoiding the rise in cholesterol often seen with use of a traditional ketogenic diet.[52] Seizures can be associated with mitochondrial abnormalities, and conversely seizure activity is harmful to mitochondria.[53-56] While about 7% of children with autism could have mitochondrial disease,[57] a much larger proportion have laboratory indications of mitochondrial dysfunction without identifiable mutations in pertinent genes in the mitochondria or the cell nucleus; such abnormalities are most commonly associated with complex I deficiencies.[58,59] Thus while the use of medium-chain triglycerides allows compliance with a gluten-free casein-free regimen while also following a ketogenic regimen, it may also concurrently offer a workaround to a metabolic barrier at

complex I that affects a substantial number individuals with autism spectrum conditions.

Oxidative stress is also a significant problem in many individuals with autism spectrum conditions,[60-66] and it is also both a cause and a consequence of seizures; both oxidative stress and seizures deplete glutathione and increase oxidative stress,[67-71] and together they can lead to a vicious cycle, with each worsening the other as noted above for mitochondrial dysfunction.[56] Vulnerability to oxidative stress is exacerbated by various common genetic polymorphisms, particularly a number associated with folate, methylation, and glutathione metabolism.[72] These polymorphisms can worsen oxidative stress, and can do so to a greater extent when anticonvulsants are at the same time interfering with folate metabolism, specifically by impairing the functional efficacy of the methylenetetrahydrofolate reductase enzyme.[50,73] In the presence of the methylenetetrahydrofolate reductase mutations, one finds decreased methylfolate, methylcobalamin, and reduced glutathione synthesis. These mutations contribute to risk for autism spectrum conditions,[74] and may also increase risk for bearing an autistic child when present in mothers who do not take folate-containing preconception vitamins.[75]

The family's choice to significantly increase her methylfolate supplementation dose was based on concern about the potential mutually exacerbating effects of autism, seizures, and many of the commonly used antiepileptic medications on impairing folate metabolism and increasing oxidative stress.[51] This decision was also influenced by anecdotal reports that methylfolate, which is "downstream" from methylenetetrahydrofolate reductase in the methylation chemistry pathway, showed more efficacy in the setting of autism spectrum conditions plus seizures than folic acid, which may fail to be appropriately metabolized in the setting of a methylenetetrahydrofolate reductase mutation. It is conceivable that methylfolate supplementation may have contributed to the improvements seen in this case alongside of the gluten-free casein-free ketogenic diet and the antiepileptic medications.

A further rationale for a casein-free, medium-chain-triglyceride-predominant ketogenic diet in the setting of autism spectrum conditions and seizures is that some children with autism produce cerebral folate antibodies, whereas this process is downregulated with a dairy-free diet.[76] Careful study would be necessary to determine whether ghee (derived from butter), sometimes used as a fat source in the ketogenic diet, is sufficiently casein-free to be safe for individuals with autism spectrum conditions. Ghee, which is a short chain rather than medium-chain fatty acid, also may not be so ketogenic and may not bypass mitochondrial complex I.

Our understanding of the relationship of gluten sensitivity and celiac disease is evolving, with heterogeneity, prevalence and the contribution of environmental and lifestyle influences all greater than previously appreciated.[77] Related considerations may contribute to the non-homogeneous distribution of the prevalence of celiac disease among patients with epilepsy.[78] Gluten sensitivity and celiac disease appear to have increased prevalence in endocrine diseases of autoimmune origin.[79] Loss of intestinal barrier function has been hypothesized as being contributory.[80] In the case presently being reviewed, while stool character improved after dietary intervention and may have been accompanied by a recovery of compromised intestinal villi, it did not reduce the child's dependence on regular intravenous immunoglobulin treatment.

This child's foul-smelling orange-colored, and abnormally textured stool may be an indication of abnormalities in the gut microbiome. The gut microbiome is an emergent area of research in autism spectrum conditions as well as in celiac disease[81] and in neuropsychiatric disorders and medicine more generally.[82] The high carbohydrate consumption that led to the development of morbid obesity could have been associated with shifts in the gut microbiome, as it is known that obesity involves a shift in the ecology of intestinal microbial ecology.[83-86] At present there is little known about the impact of the ketogenic diet on the intestinal microbiome, or the impact of microbiome abnormalities on seizure risk. The relationship between gluten sensitivity enteropathy and the intestinal microbiome is also poorly understood.

Of note, the decision to use medium-chain triglyceride oils almost exclusively to avoid casein allowed for achieving ketosis with a much lower ratio than is typically needed. Medium-chain triglycerides, because of the length of their carbon chain, are metabolized differently and are therefore known to be more ketogenic.[87] This lower ratio allows for better nutrition overall as more calories are available for vegetable consumption. The use of medium-chain triglycerides, because of their metabolic advantages, also avoids the typical rise in cholesterol associated with traditional ketogenic diet. In conclusion, this case report suggests that a gluten-free, casein-free medium-chain-triglyceride-rich ketogenic diet may be a better option than a traditional ketogenic diet for children with autism spectrum conditions, particularly those on a gluten-free casein-free diet. In addition, the implementation of a gluten-free casein-free ketogenic diet in autism spectrum conditions children with seizures may be more effective than pharmacological agents alone, and may ameliorate some of the undesirable and atypical responses to antiepileptic drugs commonly seen in autism spectrum conditions in children.[8] Moreover, the addition of medium-chain triglycerides to a healthy gluten-free casein-free diet may significantly improve symptoms of autism spectrum disorders, and may be an alternative worth investigating for others as well. A secondary benefit of a gluten-free casein-free medium-chain-triglyceride-rich ketogenic diet in addition to seizure and behavioral symptom amelioration may be decreased morbidity and potential improved health outcomes.

Author Contributions

MRH and JAB contributed equally to this work.

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