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Case Report

Dose Positive CHD8 have a Role in Ketogenic Diet Response in Autism: A Case Report

Amal AlQassmi[1*], Maha AlOtiabi[2] and Fahad AlRabeeah[3]

[1]*Department of Pediatric Neurology and Epilepsy, King Saud Medical City, Riyadh, Saudi Arabia*

[2]*King Saud Medical City, Riyadh, Saudi Arabia*

[3]*Pediatric Endocrinology, King Saud Medical City, Riyadh, Saudi Arabia*

Abstract

Autism is a brain disorder that limits a person's ability to communicate and relate to other people. The symptoms of autism spectrum disorder are poorly treated with current medications. Symptoms of autism spectrum disorder are frequently co-morbid with a diagnosis of epilepsy. Ketogenic diets are remarkably effective in treatments for epilepsy in children in the same time there are several studies showed the effectiveness of ketogenic in Autism and behavior associated with it.

This study tests the effects of ketogenic diet feeding in Autism and their behavior, a child with autism spectrum disorder. The child was started on ketogenic diet formulas starting at 5 years of age, diet protocols continued and performance of tests of sociability and repetitive behavior was assessed. A ketogenic diet improved behavioral characteristics of autism spectrum disorder. Ketogenic diet feeding improved multiple measures of sociability and reduced repetitive behavior in autism child. Positive gene mutation of autism may be an important factors in showing the response of high lipid diet in those children.

Keywords: Autism; Behavior; Gene; Lipid diet; Sociability

***Corresponding author:** Amal AlQassmi, Department of Pediatric Neurology and Epilepsy, King Saud Medical City, Riyadh, Saudi Arabia, Tel: +966 570006241; E-mail: dr_alqasmi@yahoo.com

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Introduction

Autism is a brain disorder that limits a person's ability to communicate and relate to other people. It first appears in young children, who fall along a spectrum from mild to severe. Some people can navigate their world, some have exceptional abilities, while others struggle to speak [1,2]. Autism Spectrum Disorders (ASDs) affect about one child in 68, striking nearly five times as many boys as girls.

Before a child turns three, careful observers can see signs of autism [1]. Some children develop normally until 18-24 months old and then stop or lose skills. Signs of an ASD can include: Repeated motions (rocking or spinning), avoiding eye contact or physical touch, delays in learning to talk, repeating words or phrases (echolalia), getting upset by minor changes. It's important to note that these signs can occur in children without ASDs, too [3].

The signs of autism are more noticeable in a child's second year. While other children are forming their first words and pointing to things they want, a child with autism remains detached. Signs of autism include: No single words by 16 months, no pretend games by 18 months, no two-word phrases by age 2, loss of language skills, no interest when adults point out objects, such as a plane flying overhead.

ASD has been associated to metabolic dysfunction [4,5] and autism is a common trait of epilepsy-associated diseases [6], and syndromes like Landau-Kleffner, Dravet [7], and Rett [8]. Thus, given the beneficial effects of KGD on epilepsy and increased mitochondrial function, its use has the potential to ameliorate some of the ASD-associated symptoms.

How we diagnosed Autism, by early assessment and evaluation by phycology and neurology [9]. There no specific management for autism, although there is now a trial of stem cell therapy that show some improvement in reported cases, but dose natural diet is more effective and is that related genetic type that had been describe in many cases of autism [4].

The use of the ketogenic diet to treat epilepsy dates as far back as Hippocrates time. The major way to induce ketosis at that time was using fasting or starvation. Since then, modern reports put the use of the KD in treating childhood epilepsy starting in the 1920's [10].

It was within this time that discoveries were made to show that the same level of ketosis could be induced with carbohydrate restriction and higher levels of fat intake.

Although the KD is an established treatment option in the major epilepsy centres around the world, the exact mechanism of its action is still not fully understood.

Over the past 2 decades, the understanding into the mechanism has begun to grow. Proposed mechanisms of action for the anticonvulsant effects of the ketogenic diet are believed to be due to:

The state of ketosis, a reduction in glucose levels, a rise in fatty acids and enhanced bioenergetic reserves.

It is believed that the ketone bodies produced with the ketogenic diet provide the anticonvulsant effects as well as reducing neuronal excitability in the brain [11]. However, the exact link between ketone bodies and the anticonvulsant efficacy of the ketogenic diet is not fully understood.

The mechanism by which KD acts is not clearly understood. However, among the many hypotheses advanced, elevation of brain acetone may account for the efficacy of the diet in epilepsy as it has proven anticonvulsant effects [12].

Ketogenic diet had been tried in treating Autism, but no clear hypothesis or mechanism of the Diet in Autistic spectrum. The suggested mechanisms of action of KD in ASD include that it may reduce pain sensitivity through the reduction of glucose and may have anti-inflammatory properties as it reduces swelling and plasma extravasation [13].

Case Report

We present a case of 7 and 6 months old Saudi boy who presented to neurology with history of speech delayed and behavior issue that had been concern by parents since age of 2 years they did seek medical advice, but no clear or major help was provided by general physician till age of 4 years where he had been referred to neurology for assessment.

This child was born healthy with no risk of asphyxia or neonatal intensive care admission, normal motor developmental apart from social skills and behavior problem, delayed speech till age 4 years, still not able to form a sentence or connect 2 words together unable to express himself, no eye to eye contact, scream a lot, had difficulty to engaged with other kids, walking in circle, enjoy cars, he keep a small fork that he attached to since age of 2 years and 8 months.

After we did full history and examination which was normal apart from social developmental, speech delayed. Blood work up (CBC and chemistry) was normal, bone profile and renal function was normal. Metabolic screening (serum amino acid, urine organic acid, quantitative amino acid, CDT) all was normal. MRI (Magnatic Resonance Imaging) brain normal, EEG (Electro Encephalogram) was normal, BEAR (Hearing Test) was done normal, patient seen by psychiatry and the Autism Rating Scale score assessment was diagnosed as autism scored 49, IQ assessment was 85%, SNP array was not significant, patient was diagnosed with Autism.

As there was a few reports diagnosed gene mutation in Autism, we did send whole exome to see any positive gene will be found and would that be useful for parents if they will consider to have another baby, the result came positive for CHD8:NM_001170629:exon26:c.4984C>T:p.R1662X heterozygous (autosomal dominant). Family segregation done was negative for both parents.

This patient was started on Risperdal but no much improvement in his behavior. Then shifted to Methylphenidate no much change, parents decide to stop it by their own.

Parents tried to keep him in special diet (their own effort) as they read about avoiding carbohydrate in Autism, so they kept him on regular food with less amount of carbohydrate and milk content, and they notice change in his behavior and his sleep pattern change. So, that raise the point of ketogenic diet if that similar to what they are doing or different. There is no enough data about the use of ketogenic diet in Autism but was worth to try and see if that will support the previous report had been published.

Following this detailed investigation, the parent's consent was obtained to have the children placed on a ketogenic diet. The recommended diet was Consists of 71-7% energy from fat, of which 30-40% energy is from MCT and 11-25% energy is from LCT 20% as fresh cream. This version of the KD provides more protein (10% energy) and carbohydrates (15-19% energy).

Patients also received vitamin and mineral supplements according to the recommended daily allowances for age. In this diet, 30% of total energy is derived from medium-chain triglycerides. The classic ketogenic diet is very restrictive and requires a large amount of dietetic involvement in terms of calculations, monitoring, patient support, and motivation from the family to adhere to the diet; consequently it is difficult to adapt the diet for children with mental retardation.

Patient started on ketogenic diet 1.5:1 then 2:1 lipid : non lipid food. Diet was continue for 6 months with a period of break for 6 weeks.

Over the course of 18 months following his initial diagnosis, during that period diet introductions, he was seen and follow by psychiatry, the child's Childhood Autism Rating Scale score decreased from 49 to 17, representing a change from severe autism to non-autistic, and her intelligence quotient increased 60 points.

The result was so impressive and parents did notice the difference in their child behavior response, his ability to understand and communicate is improved and his repetitive behavior (walking in circle and repeat words) improved and school performance, he was in grade 1 school, doing great. He was still in ketogenic diet with a period of rest for 2-3 months in between then back to same keto-diet again. No side effect was reported in our patient during his treatment over 2 years period now. Interestingly that we stopped keto-diet as is not easy to follow even with close monitoring from parents which was a huge effort from them, but parents continue on sugar free and dairy product free with a break of 1 week, which really shows a good result and progress in his developmental and communications skills.

Discussion

Autism Spectrum Disorders (ASD) include a complex neuro developmental condition characterized by abnormal social interaction, verbal and non-verbal communication [1]. Limited scientific advances have been made regarding the causes of ASD, with general agreement that both genetic and environmental factors contribute to this disorder [14]. ASD has been associated to metabolic dysfunction [5].

Changes in over 1,000 genes have been reported to be associated with ASD, but a large number of these associations have not been confirmed. Many common gene variations, most of which have not been identified, are thought to affect the risk of developing ASD, but not all people with the gene variation will be affected. Most of the gene variations have only a small effect, and variations in many genes can combine with environmental risk factors, such as parental age, birth complications, and others that have not been identified, to determine an individual's risk of developing this complex condition. Non-genetic factors may contribute up to about 40 percent of ASD risk.

By contrast, in about 2 to 4 percent of people with ASD, rare gene mutations or chromosome abnormalities are thought to be the cause of the condition, often as a feature of syndromes that also involve additional signs and symptoms affecting various parts of the body. For example, mutations in the ADNP gene cause a disorder called ADNP syndrome. In addition to ASD and intellectual disability, this condition involves distinctive facial features and a wide variety of other signs and symptoms. Some of the other genes in which rare mutations are associated with ASD, often with other signs and symptoms, are ARID1B [15], CHD2, CHD8 [16], DYRK1A, SHANK3 and SYNGAP1. In most individuals with ASD caused by rare gene mutations, the mutations occur in only a single gene.

In our patient, it had CHD8 gene mutation, in spite different gene mutations had been discovered in Autism but none of them had different presentation or describe the severity of behavior changes in Autistic child and non-had addressed the use of ketogenic diet in this different type of mutations.

Beneficial effects of KGD in children with ASD symptoms have been reported in two independent studies [17,18]. The first study evaluated the role of KGD on 30 ASD children [17]. The John Radcliffe diet (a modified medium-chain triglyceride diet with a caloric distribution of 30% in medium-chain triglyceride oil, 30% fresh cream, 11% saturated fat, 19% carbohydrates, and 10% proteins) was administered for 6 months, with intervals of 4 weeks interrupted by two diet-free weeks. Of the 30 children, 40% did not comply or did not tolerate the diet. From the rest, the two children with the milder autistic behaviors showed the most improvement (as judged by total Childhood Autism Rating Scale score, concentration and learning abilities, and social behavior and interactions), while the rest displayed mild to moderate improvements. Interestingly, the beneficial effects of KGD persisted even after termination of the trial. Six of the children enrolled in this study had a higher baseline ketonemia with no apparent PDH and/or RC deficiencies; but it is not clear if any of the other patients underwent this screening, before and/or after the administration of the diet in addition to the lack of the inclusion of a control diet before administering the KGD to the ASD group or during the trial.

The other study [18] reports the administration of a gluten-free casein-free modified KGD (1.5:1 lipid : non-lipid ratio; medium-chain and polyunsaturated FA) for 14-months to a 12-year-old child with ASD and seizures with substantial medical comorbidities associated with a family history of metabolic and immune disturbances. Due to the improvements in seizure activity, improved electroencephalogram, cognitive and social skills, language function, and complete resolution of stereotypies, anticonvulsant medication doses were reduced without worsening of seizures. Of note, the administration of the diet was accompanied by a wealth of medications, a significant weight loss, and transitioning to puberty, so it is difficult to assess the sole role of the diet with this clinical background.

A ketogenic diet would extremely limit the sweet and starchy processed foods. This deprives certain gut bacteria of the food they need and may be a way to help restore balance in the microbiome. To further the argument of the role that the gut microbiota play on autism [19].

In mouse models of ASD Rett syndrome [20], and Succinate Semialdehyde Dehydrogenase (SSADH) deficiency [21], the use of the KGD has improved behavioral abnormalities (increased sociability and decreased self-directed repetitive behavior) and/or decreased the number of seizures, normalized ataxia, and increased lifespan of mutant mice. However, while the KGD was originally designed to be administered under controlled caloric intake. Most of the mouse studies have been performed under ad libitum conditions and/or for a relatively short period [18]. Moreover, a ketogenic low-carbohydrate diet does not have a significant metabolic advantage over a non-ketogenic low-carbohydrate diet as judged by equal effects in body weight reduction and decreased insulin resistance; however, the former one was associated with higher inflammatory risk and increased perception of fatigue.

In a case study of a child with autism and epilepsy, following standard treatment non-response, the individual was placed on KD (1.5:1 lipid : non-lipid ratio) with adjunct anticonvulsant therapy [22]. The patient was in ketosis. After initiation of the diet several benefits ensued including the resolution of morbid obesity and the improvement of cognitive and behavioural features of the disorder. After several years on the diet, the patient's score on the Childhood Autism Rating Scale decreased from 49 to 17, a change from a rating of severe autism to non-autistic, and IQ increased by 70 points. Fourteen months following the initiation of the diet the patient was also seizure free.

Although the exact molecular mechanisms underlying the effect of the KGD are still under investigation, several scenarios are reported below to explore the potential therapeutic effects of the KGD in ASD.

Would the effect of ketogenic diet related to the different gene mutation that is associated with Autism not clear, this need more study and research.

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