Original Article

Application of a Ketogenic Diet in Children With Autistic Behavior: Pilot Study

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ABSTRACT

A pilot prospective follow-up study of the role of the ketogenic diet was carried out on 30 children, aged between 4 and 10 years, with autistic behavior. The diet was applied for 6 months, with continuous administration for 4 weeks, interrupted by 2-week diet-free intervals. Seven patients could not tolerate the diet, whereas five other patients adhered to the diet for 1 to 2 months and then discontinued it. Of the remaining group who adhered to the diet, 18 of 30 children (60%), improvement was recorded in several parameters and in accordance with the Childhood Autism Rating Scale. Significant improvement (> 12 units of the Childhood Autism Rating Scale) was recorded in two patients (pre-Scale: 35.00 ± 1.41[mean ± SD]), average improvement (> 8–12 units) in eight patients (pre-Scale: 41.88 ± 3.14[mean ± SD]), and minor improvement (2–8 units) in eight patients (pre-Scale: 45.25 ± 2.76 [mean ± SD]). Although these data are very preliminary, there is some evidence that the ketogenic diet may be used in autistic behavior as an additional or alternative therapy. (*J Child Neurol* 2003;18:113–118).

Wilder first introduced the ketogenic diet as a therapeutic method for epileptic seizures in 1921. The implementation of the ketogenic diet was based on clinical observation that fasting had beneficial effects in the control of epileptic seizures.[1] With the widespread use of modern antiepilepsy drugs, the ketogenic diet was not applied until the end of the 1970s, when interest in its use for the treatment of childhood epilepsy was rekindled. Further progress in the basic sciences has established a clear understanding of the ways in which ketone bodies affect the central nervous system, and, as a result, the ketogenic diet is being used as one of a number of therapeutic means for epilepsy in all major epilepsy centers.[2–4]

There have also been reports of application of a ketogenic diet for patients with Rett syndrome. Ketogenic diets were used for these patients primarily for the control of seizures, but it has been found that, in addition, the Ketogenic diet is beneficial for mental behavior and hyperactivity.[5,6]

Apart from epilepsy, ketogenic diets have been used in cancer patients, in whom this diet seems to have a retarding effect on tumor progress by affecting glucose metabolism at the tumor site,[7,8] and has also been applied in the treatment of patients with pyruvate dehydrogenase deficiency.[9]

On Crete, an island of Greece, with a relatively secluded and isolated population, there is a significant number of patients with autistic behavior.[10] Furthermore, as part of metabolic testing, we recorded high levels of blood ketone bodies following glucose loading tests in some of the patients we studied. It is possible that these patients harbor a disturbance somewhere in mitochondrial energy production, leading to an excess of reduced nicotinamide adenine

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Table 1. Classification of Autism Scale

1.	Disorder in human relationship (No appreciation by the individual of the interest that other people show for him/her)
2.	Mimicking (the extent to which the patient mimics)
3.	Improper emotions (eg, the unsuitable timing of emotions such as laughing and crying)
4.	Bizarre use of bodily movements and persistence to stereotypy
5.	Peculiar relations with objects (eg, correct use of objects)
6.	Resistance to changes in the environment
7.	Idiosyncratic optic reactions (eg, avoidance of eye contact)
8.	Idiosyncratic acoustic reactions (avoidance of or exaggerated reaction to noise)
9.	Putting objects in mouth, licking, smelling, and rubbing
10.	Stress reactions (eg, intensity of repression)
11.	Verbal communication (eg, lack of speech, echolalia, replacement of personal pronouns)
12.	Nonverbal communication (eg, use of or response to gestures)
13.	Extreme levels of activity (eg, apathy or hyperactivity)
14.	Mental function (lack of homogeneity of cognitive characteristics)
15.	General impressions (eg, general ranking)

Ranking of symptoms: 1 = normal for age; 2 = mild disorder; 3 = moderate disorder; 4 = serious disorder.

dinucleotide (NADH) or a lack of nicotinamide adenine dinucleotide (NAD). This is particularly true in the post-absorptive period, when more NAD is required to adequately oxidize glycolytic substrate (eg, if the citric acid cycle is hampered, ketone body synthesis increases after meals owing to channeling of acetyl coenyzme A toward ketogenesis).[11,12]

Thus, for the children of our study, we hypothesize that the application of a ketogenic diet should produce an improved mitochondrial function by sparing NAD, which will be consumed in the oxidation of glycolytic substrates. On the basis of these observations and also from other research on disturbed glucose metabolism in autism, we proceeded to administer a ketogenic diet to children with autistic behavior.[13,14]

MATERIALS AND METHOD

Thirty children with autistic behavior (16 boys and 14 girls, between 4 and 10 years of age; median age 7 years) participated in a 1-year prospective study of the role of a ketogenic diet in autistic behavior. The children were admitted to the Pediatric Clinic of the University Hospital of Heraklion, Crete, during the period from May 1999 to May 2000. All patients were concurrently treated with haloperidol. The children of this study were treated with haloperidol at least 6 months before the initiation of a ketogenic diet without having any changes in the Childhood Autism Rating Scale. During and 6 months before and after the diet, no behavioral treatments were given. The haloperidol treatment was continued after the diet was completed, but no increased dosage was needed for the children who, during the diet, diminished or stopped the medication.

Before admission to the hospital, all subjects were referred to a child psychiatrist for a general psychiatric evaluation according to the Childhood Autism Rating Scale as this was adapted by Schopler et al in 1980.[15] According to this scale, scores between 30 and 36 indicate mild to moderate cases, whereas scores of 37 and over indicate severe cases (Table 1). Although the child psychiatrist was aware of the current study, he evaluated and followed up all of the enrolled autistic children, who were among others with autistic behavior, without knowledge of which of the children were included in the study.

At the time of admission, all of the children had to undergo a detailed clinical pediatric and psychiatric examination, somatometric data collection, hearing examination with audiogram and auditory evoked potentials, ophthalmologic examination with funduscopy, and optical acuity testing. Following these, a detailed laboratory investigation was performed, including the following: complete blood count, biochemical tests (electrolytes, blood glucose, transaminases, cholesterol, triglycerides, thyroid hormones), electrocardiogram, and alert-phase electroencephalogram (EEG). Finally, more specific examinations were performed, such as determination of amino acid carnitine, serum purine and pyrimidine, urine amino acids, organic acids, and glucose challenge.[14] Specifically, following 8 hours of fasting, blood was drawn for the determination of lactic acid, pyruvate, and β-hydroxybutyric acid, which was followed by the administration of a dose of a 10% glucose solution (2 g/kg of body weight; maximum dose 50 g). Following the glucose loading, blood was drawn at 60 minutes for the assessment of the same parameters.

Following this detailed investigation, the parents' consent was obtained to have the children placed on a ketogenic diet. The recommended diet was the John Radcliffe diet, which distributes daily energy intake as follows: 30% of energy as medium-chain triglyceride oil, 30% as fresh cream, 11% as saturated fat, 19% as carbohydrates, and 10% as protein. Patients also received vitamin and mineral supplements according to the recommended daily allowances for age.[16,17] In this diet, 30% of total energy is derived from medium-chain triglycerides. The John Radcliffe diet is a variation of the medium-chain triglyceride diet and is easy to manage practically. 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. The diet was executed for 6 months with continuous administration for 4 weeks at a time, interrupted by 2-week intervals that were diet free. Laboratory examinations, including a complete blood count and the assessment of serum electrolytes, carnitine, and β-hydroxybutyric acid, were performed at the end of each 4-week diet phase and at the end of each 2-week interval diet-free phase. Family urine ketones were estimated every afternoon using ketone urine strips (Ketostix, Firma Bayer). The readings were kept and referred to the dietitian with the diet records (including fluid intake). If the child was not toilet trained, the strips were used on his/her wet diaper at the same time every day.

Table 2. Patients With Pathologic Increased β-Hydroxybutyrate After GLT Values in mmol/L

Patient	*β-Hydroxybutyrate Before GLT*	*β-Hydroxybutyrate After GLT*
1	1.45	1.82
2	1.05	1.49
3	1.23	1.65
4	1.45	1.88
5	1.30	1.45
6	1.15	1.34

GLT = glucose loading test.

Following the completion of the diet, children were followed up for 6 months and were submitted to a monthly psychiatric examination. As an assessment criterion, we set an optimistic target of 50% diet tolerance, that is, continuation of the diet beyond 4 weeks. In every psychiatric examination, the children were evaluated according to the Childhood Autism Rating Scale. The difference between the baseline and follow-up Childhood Autism Rating Scale was assessed by the *t*-test for paired comparisons.[18]

RESULTS

At the beginning of the study, the pediatric psychiatric evaluation according to the Childhood Autism Rating Scale yielded 2 patients with scores of 34 and 36, or mild to moderate autistic condition, whereas the remaining patients (28 cases) had scores between 37 and 54, that is, more severe cases.

The laboratory and clinical investigations of three children indicated increased levels of 3-hydroxy-isovaleric acid; however, no evidence of biotinidase or multiple carboxylase deficiency was established in any of these cases, and none of these patients was under valproate treatment. Pathologic levels of β-hydroxybutyrate were recorded following glucose loading in six children (Table 2). This is indicative of a disorder of oxidative phosphorylation with consequent increase in the concentration of reducing equivalents in both mitochondria and cytoplasm and in the functional impairment of the citric acid cycle, owing to the excess of NADH and the lack of NAD. Therefore, an increase in the ketone body (3-hydroxybutyrate) might be expected in the plasma of affected individuals, especially in the postabsorptive period, when more NAD is required to adequately oxidize glycolytic substrates.[11,12] In these particular circumstances, the ketogenic diet would assist an improved mitochondrial function by reducing the flow of glycolytic substrates in the Krebs cycle.[11,12] There were no abnormal findings in the remaining 21 children.

Twenty-three patients (76.6%) tolerated the diet beyond 4 weeks, whereas the remaining seven patients (23.3%) could not. Thus, the diet tolerance was 76.6%, significantly higher than the set target of 50% ($Z = 3.759$; $P < .001$). Of these 23 patients, 5 discontinued application after 4 to 10 weeks owing to lack of improvement. The remaining 18 patients (60%), who concluded the diet for a 6-month period, presented with improvements in their social behavior and interactions, speech, cooperation, stereotypy, and, principally, hyperactivity, which contributed significantly to their improvement in learning.

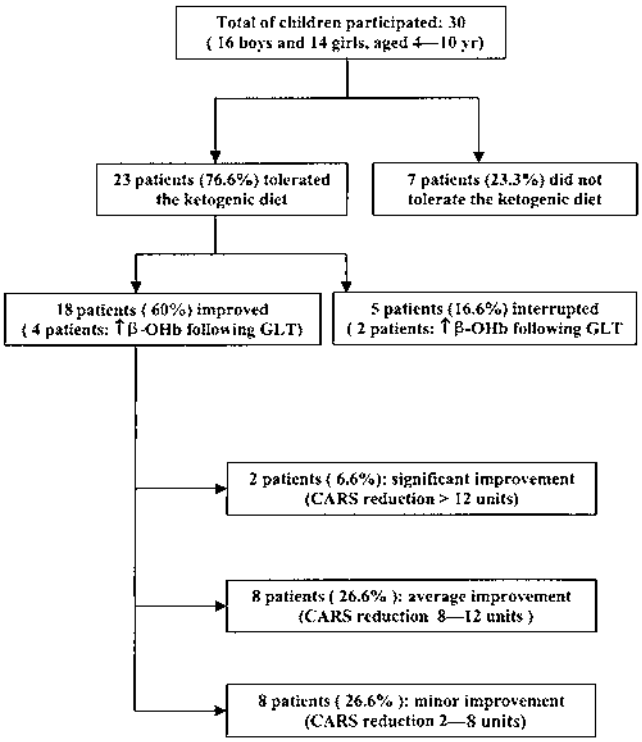

Figure 1. Thirty children participated in the study. From the 23 children who tolerated the diet, 18 (60%) improved according to the Childhood Autism Rating Scale (CARS). β-OHb = β-hydroxybutyrate; GLT = glucose loading test.

Specifically, of the 18 patients who tolerated a ketogenic diet for the entire recommended duration, 2 boys experienced the most significant improvement, with a reduction of more than 12 units on the Childhood Autism Rating Scale. This improvement was so significant that the children could attend a school for non–mentally handicapped children. Eight patients (six boys and two girls) experienced average improvement (8–12 units on the Childhood Autism Rating Scale) and eight (four boys and four girls) displayed minor improvement (2–8 units on the Childhood Autism Rating Scale) (Figure 1). Interestingly patients who did not tolerate or had their diet interrupted early belonged to the category of severe cases with Childhood Autism Rating Scale scores above 50.

It is also noted that the two patients displaying the greatest improvement were the patients with mild autistic behavior (16 and 13 units on the Childhood Autism Rating Scale, respectively). In contrast, the 16 patients with severe autistic behavior who completed the diet displayed moderate or minor improvement (average 7.1 units) (Table 3). These latter patients, although belonging to the severe autism group, had lower initial Childhood Autism Rating Scale scores compared with those who did not tolerate or interrupted their diet (43.6 and 52.7 average units,

Table 3. Patients With Improvement After a Ketogenic Diet

Significant improvement	(CARS: > 12 units)	2: Pre-CARS: 35.00 ± 1.41 (mean ± SD)
Average improvement	(CARS: > 8–12 units)	8: Pre-CARS: 41.88 ± 3.14(mean ± SD)
Minor improvement	(CARS: 2–8 units)	8: Pre-CARS: 45.25 ± 2.76(mean ± SD)

CARS = Childhood Autism Rating Scale.

respectively). The overall average improvement (based on all 30 patients) in terms of the Childhood Autism Rating Scale, was 4.77 (standard error = 0.89); the result is higly significant ($t = 5.347$; df = 29; $P < .001$).

Regarding the six children with a pathologic increase of β-hydroxybutyrate after glucose challenge, one was the one with the most significant improvement in the study. This child underwent muscle biopsy for identification of possible mitochondrial disorder, which was negative. In another two patients, average improvement was observed, whereas one child showed minor improvement. The last two patients of this group were part of the five patients who discontinued the ketogenic diet owing to lack of improvement. Regarding the three children with increased levels of 3-hydroxy-isovaleric acid, two of them with Childhood Autism Rating Scale scores over 40 were among the patients who did not tolerate the diet at all, and one was among the children without improvement who interrupted the diet after 1 month.

The values of β-hydroxybutyrate in serum were maintained at 1.8 to 2.2 mmol/L during the ketogenic diet phase and 0.8 to 1.5 mmol/L during the diet-free phase. From all ketones, β-hydroxybutyrate is largely metabolized in the body, is easy to assess in the blood, and is excreted in the urine, giving also the positive ketone urine strips test. So β-hydroxybutyrate readings in serum reflect the ketosis levels we reached. Low readings of β-hydroxybutyrate (< 1.7 mmol/L) indicate that we have not reached the ketosis levels we require to achieve therapeutic results. None of the adverse effects reported in patients following a ketogenic diet were observed during the study period.

Also, no pathologic EEGs were recorded in our patients, before, during, and 6 months after the diet was discontinued. Following termination of the study, all of the children had regular follow-up care at a special outpatient child psychiatry clinic for 6 months. Monthly follow-up with the Childhood Autism Rating Scale was repeated at the end of the diet and every month after discontinuation of the diet and for 6 months. No significant changes in the Childhood Autism Rating Scale were recorded.

DISCUSSION

Observations that certain foods may have an effect on the behavior in some patients with autism have been made on many occasions. These observations led to the development of a variety of dietetic protocols, with the gluten- and casein-free diets being the most promising.[19,20] Many other dietary interventions have been used, such as the use of vitamin B_6 and secretin.[21–23] However, in all of these trials, only a small percentage of parents reported marked changes in their child's behavior after the diet application.

The application of a ketogenic diet for children with autistic behavior constitutes an attempt to find an additional or alternative treatment for children who show minimal or no improvement with the conventional methods of treatment.

In this study, the application of a ketogenic diet was highly successful for the two patients with mild autistic behavior, whereas minor or moderate improvement was established in patients with severe autistic behavior. We note that higher improvement was seen in children with lower initial Childhood Autism Rating Scale scores, although they belonged to the severe autism group.

The patients in this study received the John Radcliffe ketogenic diet. This particular diet is considered the most acceptable by children and most easy to use at home while simultaneously achieving very satisfactory levels of ketosis. The John Radcliffe diet is a variation of the medium-chain triglyceride diet and is easy to manage practically. 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 for children with mental retardation.[24] Nevertheless, the John Radcliffe diet is still a restrictive and arduous diet when adhered to with absolute precision. The detailed and continuous education of parents, as well as their multifaceted support, was necessary for them to cope with the extremely high demands placed on them by their child's nutrition. The percentage (76.6%) of children who tolerated and adhered to the dietetic guidelines is very satisfactory, indeed very optimistic, keeping in mind the above-mentioned difficulties. The parents invested in this diet for their child's improvement, and their positive attitude acted as a strong motivation for the adherence to the diet. Moreover, the administration of the diet (4-week intervals followed by 2 weeks without the diet) resulted in no complications, usually described in children on a ketogenic diet. In addition, no other changes were observed in the Childhood Autism Rating Scale during the diet-free period. Two of the 30 patients in this study presented with high improvement, whereas 6 presented with average improvement, indicating that 26.66% of the patients benefited significantly from the diet. The overall reduction of the total Childhood Autism Rating Scale, about 5 units, was also a significant improvement. The diet proved to be effective in diminishing various generalized behaviors as it allowed the patients to concentrate better and increase their learning abilities.

The children with the most significant improvement interrupted the pharmacologic treatment, and two of them were able to attend mainstream school. In those with minor to moderate improvement, a reduction of haloperidol dosage was feasible without aggravation of behavior. An interesting observation was that the beneficial effects of the ketogenic diet persisted during the diet-free intervals. Even after termination of the ketogenic diet, its beneficial actions were maintained for a relatively long duration. We cannot formulate any reasonable hypothesis for this. The question of how the diet works remains to be answered. A similar effect of the ketogenic diet has been observed in children treated for the control of resistant epileptic incidents, who had behavioral problems.[25] A logical explanation is difficult to establish because the mechanisms of action of the ketogenic diet are still not well comprehended. The hypothesis that individuals with autistic behavior may have deficient glucose oxidation and therefore use ketone bodies as an alternative energy fuel in the brain is interesting. This hypothesis could be supported by the fact that four of the patients studied showed abnormal increase of ketone bodies after a glucose loading test, an indication of mitochondrial deficiency. No evidence was found, however, of pyruvate dehydrogenase deficiency, other enzyme deficiency (respiratory chain deficiency), or disorder of glucose metabolism in these children. What makes things more complicated is the fact that the ketogenic diet had beneficial effects in patients who had normal biochemical parameters after the glucose loading test. It should be kept in mind, however, that normal loading with glucose does not necessarily mean normal glucose oxidation in the brain or absence of mitochondrial deficiencies. There is the possibility of normal excretion of lactic acid and other toxic metabolites in cases of mutations that affect the brain and not the liver.

Studies that have been performed with positron emission tomographic scans and [^{18}F]fluorodeoxyglucose have shown a deficient glucose oxidation and reduction of the frontal singulate helix volume in individuals with autistic behavior.[13,14] Similar findings and similar effects of the ketogenic diet have been recorded in the brains of patients with epilepsy, Rett syndrome, and fragile chromosome X.[2,5,26,27] It seems that the ketogenic diet has a similar action mechanism in all of these conditions, which indicates possible abnormal glucose metabolism.

Nevertheless, our opinion is that scientific interest should not be focused only on this fact. It is certain that a ketogenic diet affects other essential biochemical pathways that influence the function of the central nervous system. Experimental studies in animals have shown that a ketogenic diet increases ketone bodies. The increase of ketone bodies maintains the synaptosomal content of γ-aminobutyric acid (GABA) at a higher level, a phenomenon that may contribute to the beneficial effect of a ketogenic diet in children with epilepsy and perhaps children with autistic behavior.[28] Other researchers, in an attempt to clarify the manner in which ketone bodies increase the synaptosomal content of GABA, showed that the metabolism of ketone bodies to acetyl coenyzme A results in a decrease of the pool of brain oxaloacetate, which is consumed in the citrate synthetase reaction. As less oxaloacetate is available for the aspartate aminotransferase reaction, thereby lowering the rate of glutamate transamination, more glutamate becomes accessible to the glutamate decarboxylase pathway, thus favoring the synthesis of GABA.[29] Changes in behavior have also been observed with individuals who have developed ketosis during diet for weight reduction.[30] Similar observations have been made in laboratory animals on a ketogenic diet.[31]

Our experience provides significant evidence that a ketogenic diet may have its own place in our reserve for the treatment of autism, in particular for less severe cases. There is no doubt that this subject needs further investigation. Although the number of patients in this study was small, more than one subgroup was included (increased levels of 3-hydroxyisovaleric acid, increased levels of β-hydroxybutyrate after glucose loading). This heterogeneity diminishes the ability of this pilot study to generate more focused hypotheses. The problem is further compounded by including some children with severe autistic behavior, as measured by the Childhood Autism Rating Scale. Compliance versus poor response to the treatment seems to make this group less suitable to be studied further. Further questions arise concerning the optimal duration and manner of diet application. Despite these concerns, we believe that it is necessary to expand our treatment options for autistic behaviors and that a ketogenic diet may hold some promise.

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Correction

Interleukin-1β, Tumor Necrosis Factor-α, and Nitrite Levels in Febrile Seizures

In *Journal of Child Neurology* Volume 17, Number 10, October 2002 "Interleukin-1β, Tumor Necrosis Factor-α, and Nitrite Levels in Febrile Seizures" page 749, one of the author names was incorrectly printed as Özbenm. Unfortunately, this error was carried through to the author names index in Volume 17, Number 12, December 2002 on page 926. The correct spelling of the name is Ozben; please note these corrections in your copies. The corrected information appears below for clarity.

Author names on page 749:

Şenay Haspolat, MD; Ercan Mihçi, MD; Mesut Coşkun, PhD; Saadet Gümüslü, MD; Tomris Ozben, MD; Olcay Yeğin, MD

Author name entry on page 926:

Ozben T, 749