



International ward rounds

The modified Atkins diet for intractable epilepsy may be associated with late-onset egg-induced anaphylactic reaction: A case report

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ARTICLE INFO

Article history:

Received 2 July 2010

Accepted 23 November 2010

Keywords:

Epilepsy

Egg

Anaphylaxis

Modified Atkins diet

ABSTRACT

The modified Atkins diet is a therapeutic option for children with intractable epilepsy. It is less restrictive than the traditional ketogenic diet, with ~60% of calories from fat sources. We describe a 6-y-old boy with intractable epilepsy treated with the modified Atkins diet who presented to the emergency department with first-time anaphylactic reaction to egg. Symptoms of urticaria and angioedema, shortness of breath, wheezing, and cyanosis developed several minutes after he ate a hard-boiled egg. His history was remarkable for asthma, but no food allergies were documented. The anaphylactic reaction appeared after 6 mo of treatment with the modified Atkins diet (including 10–15 eggs daily), which ameliorated his seizures, and was preceded by streptococcal pharyngitis. Laboratory workup revealed specific immunoglobulin E antibodies to egg. This is the first report of new-onset egg allergy in a child, probably triggered by the high egg content of the modified Atkins diet. The risk of egg allergy should be kept in mind when treating epileptic children with the modified Atkins diet, especially those with comorbid asthma.

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Introduction

Apart from migraine, epilepsy is the most common neurologic disorder, with a prevalence of 5 to 10 cases per 1000 [1]. The treatment of choice is antiepileptic drugs. Other treatment options, such as surgery and diet (mainly in children), are reserved for patients with drug-resistant (intractable) epilepsy [2].

Fasting has long been recognized as a means to improve seizure control [3]. During prolonged fasting, the metabolic pathways use body fat for energy to spare protein breakdown. β -Oxidation of free fatty acids instead of glucose use leads to the formation of acetyl coenzyme A, which is converted to ketone bodies in the liver mitochondria. Ketone bodies are able to cross the blood–brain barrier [2] and are converted back to acetyl coenzyme A, which then enters the tricarboxylic acid cycle.

Wilkins [4], in 1937, was the first to suggest that a high-fat, low-carbohydrate diet may mimic the beneficial effect of starving in epilepsy. Since then several studies have reported a decrease of at least 50% in seizure activity in epileptic patients

treated with a ketogenic diet [2]. According to Bough and Rho [5], the clinical efficacy of this approach is apparently related to the effect of sustained ketosis rather than a direct anticonvulsant activity of ketone bodies (such as β -hydroxybutyrate, acetoacetate). Possible underlying mechanisms include glucose-restriction-mediated activation of adenosine triphosphate-sensitive potassium channels, which regulate seizure activity, and the decrease or limitation of neuronal excitability due to elevation of polyunsaturated fatty acids such as docosahexaenoic acid and eicosapentaenoic acid. In addition, ketosis induces a decrease in aspartate relative to glutamate, which is the precursor of γ -aminobutyric acid synthesis. γ -Aminobutyric acid is the major inhibitory neurotransmitter in the brain.

The classic ketogenic diet provides 90% of calories from fat (long-chain fatty acids) and 10% from protein and carbohydrates, with a 3:1 to 4:1 ratio of fat to protein plus carbohydrate [2]. The modified Atkins diet (MAD) is similar to the ketogenic diet in composition, but without caloric, protein, or fluid restrictions; ~60% of the calories are derived from fat sources [6,7], with 1:1 ratio of fat to protein plus carbohydrate. Recent studies have shown that the MAD is an effective and well-tolerated therapeutic option for children with intractable epilepsy [7,8].

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Egg is a common allergenic food in infants, especially those with atopic dermatitis [9]. Egg allergy usually develops in the first year of life and only rarely after 2 y of age [9]. The reported prevalence of oral challenge-confirmed egg allergy in children to 1 y of age is as high as 1.7% [10]. The typical clinical presentation is an immediate hypersensitivity reaction involving the skin and mucous membranes (urticaria and angioedema) and the gastrointestinal tract (abdominal pain, vomiting). More severe anaphylactic reactions involving also the respiratory system have been reported in children with asthma [9]. Egg allergy may present even after the first known exposure to egg [9].

We describe a 6-y-old boy with asthma and epilepsy who presented with a first-time severe allergic reaction to egg. The boy was being treated with the MAD, and the role of this diet in the late-onset presentation of the egg allergy is discussed.

Case report

A 6-y-old boy presented to the emergency department because of throat pruritus that began immediately after he ate a hard-boiled egg. Urticaria and angioedema, shortness of breath, and cyanosis developed after a few minutes. The patient had known asthma and epilepsy.

The patient's history revealed that he was born after an uneventful pregnancy and delivery, without perinatal complications. Recurrent episodes of wheezing started at 3 y of age and were treated with inhaled corticosteroids and bronchodilators; the patient had been hospitalized several times for asthma exacerbations. He did not undergo allergic tests at this time. There was no history of eczema or food allergies, and the parents reported no exposure to birds.

Family history was negative for epilepsy, and the patient's medical history was negative for febrile seizures.

At 3.5 y of age, the patient started having seizures, characterized clinically by eye deviation to the left and hand posturing, with no generalized tonic-clonic component. Electroencephalogram showed bifrontal spike waves with occasional secondary generalization. Findings on magnetic resonance imaging raised a suspicion of right cortical frontal dysplasia, and interictal single-photon emission computed tomogram showed decreased perfusion in the right hemisphere. The seizures were controlled for the first 2 y with carbamazepine but then reappeared and failed to respond to various antiepileptic drugs (sulthiame, valproic acid, lamotrigine, topiramate, phenobarbital, phenytoin, idantoin, clobazam, and levetiracetam). The parents refused to consider surgery, so the child was started on a ketogenic diet with a fat-to-protein plus carbohydrate ratio of 4:1. When he failed to comply, he was switched to the MAD in which carbohydrates are restricted to 10 g/d and consumption of high-fat foods is encouraged [7]. On this diet, the patient ate 10 to 15 eggs per day. He had remained seizure-free up to the time of the present acute anaphylactic reaction, which occurred 6 mo after the MAD was started.

Physical examination in the emergency department revealed swelling of the lips, tongue, and pharynx, generalized urticaria, and wheezing. Treatment with intramuscular epinephrine, intravenous corticosteroids, and inhaled bronchodilators alleviated the symptoms. The patient was hospitalized for 2 d for further observation. In the department, the parents reported that 2 d before the episode, the child had had an elevated temperature and a sore throat. Culture of a throat swab taken at admission yielded group A β -hemolytic *Streptococcus*. Appropriate antibiotic treatment was instituted, and the patient was referred for the evaluation of allergy.

A prick skin test (ALK, Abello, Port Washington, NY, USA) revealed a positive reaction to egg white and egg yolk. The serum level of egg-white-specific immunoglobulin E (IgE) was 7.9 kU/L, and the egg-yolk-specific IgE was 3.78 kU/L (normal <0.1 kU/L; Immulite 2000, Siemens, Medical Solutions Diagnostics, Tarrytown, NY, USA). No IgE antibodies specific to other foods (milk, soy, peanuts, nuts, sesame, wheat, or fish) were found.

A diagnosis of egg allergy was made based on the clinical presentation, skin prick test results, and serum-specific IgE findings. Because of the severity of the anaphylactic reaction, we did not attempt a supervised oral egg challenge. The family refused to continue with the MAD. Currently, the patient's epilepsy is being treated with a combination of carbamazepine and levetiracetam. He has occasional brief seizures.

Discussion

We describe a 6-y-old boy with asthma and intractable epilepsy who had a first-time anaphylactic reaction to egg. The epilepsy was most probably due to focal cortical maldevelopment. When medical treatment failed, surgery was recommended, as accepted [11], but the parents refused. Therefore, the child was started on the ketogenic diet. Studies have shown that the ketogenic diet is a good alternative in young children with medically intractable epilepsy, and it yielded a good response in patients with an immature cerebral cortex due to developmental malformation. Jung-Eun et al. [12] reported a greater than 50% decrease in seizure frequency with the ketogenic diet in 29 of 47 patients (61.7%); 21 (44.7%) became seizure-free 3 mo after starting treatment. However, the ketogenic diet is known to be difficult to introduce to older children, and, indeed, compliance in our patient was poor. Therefore, we switched to the MAD, which is less restrictive and more tolerable. In a study by Weber et al. [6], 6 of 15 children with intractable epilepsy (40%) had a greater than 50% seizure decrease after 3 mo of treatment with the MAD. After 12 mo, 20% were still on the diet.

Treatment with the MAD was successful in our patient, who remained seizure-free for 6 mo. However, at that time, he had a severe anaphylactic reaction to egg and had to stop the diet.

Reported side effects of the MAD include increased serum cholesterol and serum urea nitrogen levels [7]. To our knowledge, this is the first report of new-onset egg allergy at the age of 6 y in a patient treated with the MAD. Egg allergy usually develops during the first year of life [9]. Sensitization to egg and the presence of egg-specific IgE antibodies have also been demonstrated in infants with atopic dermatitis not previously exposed to egg, presumably induced by the transfer of egg allergens through the placenta or in breast milk [9]. In the infrequent cases of egg allergy in adults, it was almost always found to have started in early childhood [13]. New-onset egg allergy in adults is caused by bird-egg syndrome in which sensitization to inhaled bird-feather allergens results in the production of cross-reactive IgE antibodies against the egg yolk protein before the manifestation of symptoms [13,14]. In children, bird-egg syndrome is very rare [15]. Our patient had no history of exposure to birds, and he had previously eaten egg and other foods containing egg without any adverse effects. We attributed the new-onset egg allergy to the large consumption of eggs on the MAD.

Oral tolerance refers to a state of active inhibition of immune responses to an antigen after exposure to that antigen through the oral route [16]. Food allergy is caused by a breakdown in oral tolerance. The factors involved in oral tolerance are dose of the antigen, form of the antigen, genetics, the normal flora of the

host, and age of the host (neonates are more prone to breakdown of oral tolerance) [16]. Tolerance appears to be driven by regular exposure to small amounts of allergens during a “critical early window” of development, resulting in the activation of regulatory T cells [16,17]. Although the timing of this window in humans is not clear, current evidence suggests that the most likely age is 4 to 6 mo [17].

In the present case, the new-onset egg allergy at the age of 6 y and the absence of a history of exposure to birds may suggest that the patient's oral tolerance to egg was disrupted, most probably owing to the high egg content of the MAD. However, the streptococcal pharyngitis that preceded the anaphylactic episode may also have played a role. Studies in murine models have reported that bacterial products and superantigens and products of complement activation can induce the secretion of mast-cell mediators [18,19]. These findings have recently been confirmed in an experimental study showing that the streptococcal toxin streptolysin O induces degranulation of rat peritoneal and connective tissue type mast cells in vitro and in vivo [20].

In conclusion, we present a patient with asthma and epilepsy who had a first acute anaphylactic reaction to egg at the age of 6 y. The development of egg allergy was probably attributable to the high egg content of the MAD, which had been instituted 6 mo previously to treat the epilepsy. The anaphylactic reaction may have been hastened by a precedent streptococcal infection. Pediatric neurologists and dietitians should bear the risk of new-onset egg allergy in mind when treating epileptic patients with the MAD, particularly those with comorbid asthma.

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