







Oral tolerance induction protocol to egg white – A report of three pediatric cases

Protocolo de indução de tolerância oral à clara de ovo – Um relato de três casos pediátricos

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ABSTRACT

Food allergies are the main cause of anaphylaxis in children. Cow's milk and egg white are the most common agents and elimination diets are considered the current strategy for their management. Many children can tolerate increasing amounts of the known allergen, and thus, oral tolerance induction protocols seem to be a promising approach. The authors present a protocol drawn up in a pediatric allergic diseases' outpatient clinic, at a level II hospital, with the aim of egg white oral tolerance induction. During the protocol there is an increase in the amount of egg white offered to children, at the end, tolerance is tested with the ingestion of an entire egg. The protocol was performed in three children with anaphylaxis to egg white. Two children completed the protocol successfully. Oral tolerance to egg white allows a less restrictive diet and improves the quality of life of the patients and their caregivers.

Keywords: Egg hypersensitivity, food hypersensitivity, immunotherapy, oral tolerance induction.

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RESUMO

A alergia alimentar é a principal causa de anafilaxia nas crianças. Os principais alimentos responsáveis são o leite e a clara de ovo, e as dietas de evicção são a principal abordagem terapêutica. Muitas crianças conseguem tolerar quantidades progressivamente maiores do alérgeno em causa, o que torna os protocolos de indução de tolerância oral uma abordagem promissora. Apresentamos um protocolo, elaborado na consulta de pediatria de doenças alérgicas num hospital nível II, cujo objetivo é a indução de tolerância oral à clara de ovo. Durante o protocolo há um aumento progressivo da quantidade de clara de ovo oferecida às crianças e no fim a tolerância é testada com a ingestão de um ovo inteiro. O protocolo foi iniciado em três crianças com anafilaxia à clara de ovo. Duas conseguiram concluí-lo com sucesso. A tolerância à clara de ovo permite uma dieta menos restritiva melhorando a qualidade de vida dos doentes e seus cuidadores.

Palavras-chave: Alergia alimentar, alergia ao ovo, imunoterapia, indução de tolerância oral.

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INTRODUCTION

Food allergies are the main cause of anaphylaxis in children^(1,2). Cow's milk is the main trigger, followed by egg⁽³⁾, which affects 1-2% of children⁽⁴⁾.

The current strategy regarding immunoglobulin E (IgE) mediated food allergies is allergen avoidance, symptom recognition in case of allergic reaction, and the administration of injectable adrenaline when needed^(1,3-8).

Oral immunotherapy (OIT) has shown promising results. This involves the regular administration of small amounts of the allergen that are progressively increased to a maximum tolerated dose. The aim is to desensitize patients, i.e., to achieve a state of food tolerance while the allergen is administered on a regular basis and, if possible, to achieve a state of sustained food tolerance after the end of immunotherapy⁽⁶⁻⁸⁾. Since young children have a high likelihood of developing spontaneous tolerance^(2,5-7) the right time to start OIT may be around 4-5 years of age⁽⁷⁾.

So far, there are no standardized OIT protocols for allergy to egg white. Therefore, after reviewing the recent advances on OIT, the authors decided to create an orig-

inal and careful protocol to apply to their patients. Its aim was to achieve the ingestion of an entire egg, without adverse reaction, with the use of pasteurized egg white (PEW) (allergenicity equivalent to a natural raw egg)⁽⁸⁾ over eight medical visits, which took place two weeks apart and were carried out in the outpatient department (Table I). During each visit there was a progressive increase in the amount of PEW offered to the children, and between visits a daily maintenance dose was administered at home. In the last visit, the children ingested a total amount of PEW that roughly corresponds to the amount of egg white of an entire egg (15ml + 15ml of PEW = 40g of egg white). Finally, the next day, desensitization was confirmed with the ingestion of an entire boiled egg under medical supervision. Upon conclusion of the protocol, children may ingest egg *ad libitum* but must keep the ingestion of an entire egg (cooked or raw) on alternate days.

The procedure was approved by the hospital ethics committee. An informed consent was obtained from the children's parents. Parents and their children were taught to recognize any symptoms of an allergic reaction and to administer adrenaline immediately, if needed.

Table 1. Egg white oral tolerance induction protocol. Each visit takes place two weeks apart with the exception of visit 9 that happens the next day after visit number 8.

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
1 drop	1 drop	2 drops	8 drops	14 drops	2 ml	8 ml	15 ml	Ingestion of an entire boiled egg under medical supervision
–	2 drops	4 drops	10 drops	20 drops (=1 ml)	4 ml	15 ml	15ml	
	–	6 drops	12 drops	2 ml	6 ml	–	–	
		8 drops	14 drops	–	8 ml			
	30 minutes between doses	30 minutes between doses	30 minutes between doses	30 minutes between doses	30 minutes between doses	30 minutes between doses	30 minutes between doses	
Maintenance dose at home: 1 drop/day	Maintenance dose at home: 2 drops/day	Maintenance dose at home: 8 drops/day	Maintenance dose at home: 14 drops/day	Maintenance dose at home: 2 ml/day	Maintenance dose at home: 8 ml/day	Maintenance dose at home: 15 ml/day		Maintenance dose at home: 1 egg on alternate days*

*At home children must eat an egg on alternate days; if more than 48 hours pass between egg ingestions, children must go to the day hospital to ingest an egg under medical supervision.

CLINICAL CASES

Three children with persistent IgE mediated egg white allergy, with history of anaphylaxis, were submitted to the protocol (patients' characterization is summarized in Table 2). All tolerated egg yolk. If present, asthma was well controlled.

Their food allergy diagnosis was based on clinical history, skin prick tests (SPT), serum specific IgE levels and oral food challenges (with boiled egg). SPT were performed according to the European Academy of Allergy and Clinical Immunology recommendations, on the forearm with commercial extracts and a synthetic lancet. A negative (saline 0,9%) and a positive (histamine 10mg/mL) control tests were used. SPT were considered positive if a ≥ 3 mm wheal diameter was reported after 15 minutes. Serum specific IgE levels to egg white were determined by an immunoenzymatic assay (UniCAP-FEIA), and results were expressed in KU/L, positive cut-off $\geq 0,35$ KU/L.

Two children completed the protocol with success (results are described in Table 2).

The first child who initiated the protocol was an eight-year-old male. He had an anaphylactic reaction at home, 45 minutes after 15 ml of PEW five days after visit number seven, and adrenaline was administered. No triggering factor such as exercise, non-steroidal anti-inflammatory drugs intake or infection was identified. At this point, the protocol was readjusted. The maintenance dose of the PEW he was ingesting at home was reduced to 10 ml. On his eighth visit, he ingested 10 ml, followed by 15 ml with tolerance, so he kept 15 ml at home. At the ninth visit he ingested 15 ml plus 15 ml, 30 minutes apart, without eliciting symptoms and so, the next day, he ingested a boiled egg under medical supervision, without any complication.

The second child was a five-year-old male but, unfortunately, the protocol had to be stopped following two anaphylactic reactions. The first one occurred on the fourth visit, after the administration of 12 drops of PEW. The protocol was adapted and he kept a daily dose of 10 drops per day at home. On his adapted fifth visit, he started with the 10 drops that he was tolerating at home, followed by 12 drops that he also ingested with-

Table 2. Patients' characterization (age of egg allergy diagnosis, clinical presentation, allergological assessment and accidental exposures) and oral tolerance induction protocol to egg white results.

Cases	Sex	Age of egg white allergy presentation	Clinical signs and symptoms at presentation	Co-morbidities	Skin prick tests	IgE levels to egg white	Oral food challenges	Accidental exposures	Age of OTIP	Result of OTIP	Adverse reactions during OTIP
1	♂	15 months	Rash, cough, and respiratory distress	Asthma and allergic rhinitis	8 years-old Positive (histamine 5 mm, egg white 3 mm, OVM 3mm, OVA 4mm)	2 years-old 75,5 KU/L	3y → urticaria with the ingestion of 10g of egg white. 4y → urticaria with the ingestion of 10g of egg white. 8y → vomiting with the ingestion of 10g of egg white	5y → turkey mortadella ingestion resulting in facial rash and sleepiness 7y → pizza ingestion resulting in abdominal pain, vomiting, cough, and rash.	8 years-old	Tolerance achieved	• Rash, swelling and pruritus of the lips and tongue, cough and abdominal pain five days after visit number seven, 45 minutes after the ingestion of 15 ml of egg white
2	♂	13 months	Egg allergy diagnosed during atopic dermatitis follow-up	Atopic dermatitis and cow's milk allergy (resolved)	2 years-old Positive (histamine 4 mm, egg white 5 mm, OVM 5mm OVA 5mm)	2 years-old >100 KU/L	3y → rash with the ingestion of 10g of egg white 5y → rash + cough + abdominal pain with the ingestion of 10g of egg white	None	5 years-old	Tolerance not achieved	• Cough and generalized pruritus after the administration of 12 drops pasteurized of egg white during visit number four • Generalized rash and cough after the administration of 14 drops of pasteurized egg white during visit number five
3	♂	21 months	Perianal erythema	Asthma and allergic rhinitis	2 years-old Positive (histamine 3 mm, egg white 4 mm, OVM 4 mm, OVA 4 mm)	2 years-old 13,9 KU/L	6y → rash + cough + abdominal pain with the ingestion of 10g of egg white	22 months → accidental egg at kindergarten resulting in urticaria, cough, and diarrhea 5y → cake ingestion resulting in urticaria and facial and oral pruritus	6 years-old	Tolerance achieved	• Rash, nasal congestion and abdominal pain after two drops of pasteurized egg white during visit number two

OTIP – oral tolerance induction protocol; OVA – ovalbumin; OVM – ovomucoid

out any symptoms. However, on this same medical visit, he had another anaphylactic reaction with the administration of 14 drops of PEW, so the protocol was interrupted.

The third child was a six-year-old male. He had an anaphylactic reaction during his second visit, after two drops of PEW, and adrenaline was used. The protocol was adapted, and the child went home with a maintenance dose of one drop of PEW per day. On his third visit, the administered doses were as referred in Table 1 for visit number 2. Since there were no more symptoms, the protocol followed as planned from that point forward and tolerance to egg was successfully achieved.

The two children that completed the protocol with success currently maintain egg ingestion as pleased, with the mandatory ingestion of an entire egg (either cooked

or raw) on alternate days, without any other complications so far. They both concluded the protocol three years ago.

The protocol had to be extended by two weeks for the two children that completed it.

All children had at least one anaphylactic reaction during the protocol.

DISCUSSION

So far, avoidance diets are the only approved therapeutic option for food allergies⁽⁶⁾. Although apparently simple, these diets may have various implications for the quality of life of patients. There is therefore interest in novel strategies that allow the possibility of food toler-

ance⁽⁷⁾. OIT, although logistically demanding and time-consuming, has been tested and satisfactory results have been reported^(1,3-6,9).

According to the Cochrane review on OIT for egg white, that included 10 studies, 45% of the children receiving OIT were able to tolerate a full serving of egg compared to 10% of the control group⁽⁶⁾. However, the existing studies involve small sample sizes, adverse allergic reactions occur in virtually all participants treated, and the evidence quality is low⁽⁶⁾. The egg OIT protocols differ in several aspects: egg preparation; place where the amount of egg preparation is increased (home versus day unit); dose escalation and duration of OIT to achieve desensitization (2.5 to 22 months)⁽⁶⁾. More recently, Martin-Muñoz *et al.*⁽⁹⁾ desensitized 81% of the patients submitted to their OIT protocol⁽⁹⁾.

In the protocol we present, the amount of PEW was always increased in the outpatient department, which, in the authors' opinion, confers greater safety to the procedure. However, it is not risk-free. All children experienced anaphylaxis, one of them even experienced an anaphylactic reaction with the maintenance dose at home. The authors could not identify any potential triggering factor to explain this reaction. Adverse reactions in children undergoing food specific immunotherapy are not rare⁽⁶⁻⁸⁾. Most of them are mild and self-limited, however, more serious adverse reactions may occur^(7,8). It is extremely important that parents understand the risks of the protocol and are taught to recognize any symptoms suggestive of an anaphylactic reaction so that they can act quickly and accordingly.

This protocol was expected to last 105 days, but it was prolonged due to adverse reactions. The optimal duration of immunotherapy to achieve desensitization has not been established^(6,7). Faster protocols have been associated with more frequent and severe adverse reactions, while slower protocols could reduce treatment adherence^(1,9). The fact that all of the children submitted to our protocol presented anaphylaxis, leads us to question whether further adjustments to the protocol should be made, including more gradual increases in the doses of PEW offered to children.

Although sustained tolerance has not been assessed, the fact that these children were desensitized to egg white, even if it involves its regular intake is, in itself, beneficial for patients and their caregivers.

It is not clear whether the results are due to a desensitization state, or to a sustained tolerance state⁽³⁾. Some studies seeking to assess the induction of a sustained tolerance through OIT have shown that its effects may persist over time^(3,5,10). Martin-Muñoz *et al.*⁽¹⁰⁾ observed that one year of OIT with at least 6 months maintenance and dose equivalent to one pasteurized egg white improved the effectiveness of the egg OIT and allowed *ad libitum* egg consumption. They also concluded that two egg serving per week ensures the persistence of total desensitization in most patients 6 months after ending a year of OIT⁽¹⁰⁾.

This study has some limitations, namely its small sample, which makes it difficult to generalize the results and no control group was included.

Although questions concerning its safety and its potential for developing long-term immunological tolerance remain, OIT is a promising therapy for food allergies. The induction of oral tolerance to egg white allows a less restrictive diet and greater safety preventing anaphylaxis, improving the quality of life of patients and their caregivers. The development of standardized protocols would help to incorporate desensitization into general clinical practice.

Conflicts of interest

The authors have no conflict of interest to declare.

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