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Experience in diagnostics and treatment of milk allergy in children in the city of Padua (Italy)

Key words: *food allergy, oral provocation test, specific immunotherapy, children.*

Currently, the medical science has accepted specific standardized medical protocols for diagnosis and treatment of various diseases. Unfortunately, they can not always cover all possible options for the course of the disease, as well as develop comprehensive tactics of prognosis of the treatment outcome. It largely concerns the oral provocation test (OPT) and specific immunotherapy.

The European Academy of Allergy and Clinical Immunology has recently published a new Guideline for Allergen Immunotherapy for IgE-mediated food allergy [3]. At the same time, specific clinical recommendations regarding the OPT have been developed and could be applied to the process of sampling patients, creating an algorithm of research on different groups of allergens, and in defining the scope of medical assistance in cases when a patient develops a reaction during the treatment process. [4]. However, there is still no universal source of knowledge and every rule has an exception. Working experience is an essential component of memorizing details while being a treating physician. The learning path can often be walked differently – through reading and implementation, through observance and repetition, and through learning in the best experts and utilization of one's knowledge in one's practice.

The art of OPT and appropriate application of SIT could be learned from the world leaders in this field of science, especially in the Veneto Region Referral Centre for Food Allergy Diagnosis and Treatment in Padua General University Hospital (Padua, Italy), supervised by Professor Antonella Muraro.

The best way to learn medicine is through clinical cases, as only the complex analysis of the particular case allows to track the development of symptoms, create a diagnostic algorithm, and define the approach to treatment.

Here are the two cases with the confirmation of the IgE-mediated and non-IgE-mediated types of allergic reactions in patients that were seen at the Center for Food Allergy from an early age and currently reached 9 and 10 years, having reached positive outcomes in the treatment process.

Clinical case № 1

Boy, 10 years old.

From the day he was born until the age of 3 months the boy was being fed with breast milk. In the age of 3 months, the child began to eat an adapted milk formula. The mother noticed that in 1-2 hours after feeding the child became restless and 2-3 hours later he experienced the urge to vomit. At the same time, with the increased volume of the formula, the vomiting began to appear more frequently. With this concern, the parents of the child referred to a physician for further consultancy.

Visit 1 (child's age – 4 months)

At the moment of examination – within the normal ranges.

Lab Tests

Total IgE – 2 kU/L (Norm 0 – 30).

Specific IgE to milk, eggs, wheat, and soy – negative.

Gastrointestinal symptoms that were present in the infant may be due to two main reasons – the development of an allergic reaction to proteins of cow's milk (IgE-dependent or IgE-independent allergy) or lactose intolerance (the dysfunction of lactose digestion due to the lack or absence of a specific enzyme). For this reason, OPT was

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conducted using an adapted lactose-free formula to give a clear answer about the nature of the allergy (table 1). Before performing the procedure a venous catheter was placed in the child's peripheral vein.

The complaints began to arise in 1,5 hours after the end of the provocation test. First, the child began to vomit (with the functional indexes being within the ranges of the established norms, the child did not experience skin rashes or swelling, auscultation of the lungs did not show any specific symptoms.

The boy was transferred to the intensive care unit and remained under careful observation.

The child began to vomit again after 20 and 35 minutes. Soon the child experienced a plaque rash on his skin (10 elements at the back and abdomen), the boy became pale and began to cry heavily (he also flexed his legs to his body).

All of the symptoms are signs of an anaphylactic reaction.

Treatment tactics (body mass – 4 kg):

• Adrenalin (0,1 mg/ml) – 0,4 ml, intra/musculus in the lateral surface of the thigh;

• Chlorphenamine (0.2 mg/kg) – 0.8 ml intravenous in physiological saline;

• Hydrocortisone (10 mg/kg) – 40 mg intravenous in physiological saline;

• Physiological Saline – 40 ml;

• Free flow of oxygen through a mask.

The symptoms disappeared in 2 hours from the moment of administration of medical assistance.

Recommendations:

1. Use an adapted formula with complete protein hydrolysis.
2. Elimination of milk and its derivatives from the daily diet up to 12 months followed by a correction after a visit to the doctor.
3. Short course of antihistamines.
4. Constantly carry around an EpiPen in case of acute reactions.

Visit 2 (child's age – 1 year 4 months)

At the moment of examination – within the normal ranges.

Lab Tests

Total IgE – 21 kU/L (Norm 0 – 30).

Skin prick allergy tests – negative (alpha-lactalbumin, beta-lactalbumin, casein, ovalbumin, D. Pterontssinus, D. Farinae).

Specific IgE to milk – 0,27 kUa/L (sensibilization).

Specific IgE to eggs, wheat, soy – negative.

Recommendations:

1. It is recommended to completely exclude milk and its derivatives for 1 year followed by further administration of OPT.
2. Constantly carry around an EpiPen in case of acute reactions.

Visit 3 (child's age – 3 years old)

At the moment of examination – within the normal ranges.

Lab Tests

Total IgE – 17,3 kU/L (norm 0 – 30).

Specific IgE to milk – 0,13 kUa/L (sensibilization).

Specific IgE to eggs, wheat, soy – negative.

Oral provocation test with the lactose-free formula was done (table 2). Before performing the procedure a venous catheter was placed in the child's peripheral vein.

After 50 minutes after consumption of milk – nausea. After 3 hours – vomiting (3 episodes), abdominal pain. Respiratory rate, heart rate and saturation were normal. There were no skin reactions in the form of rashes or swelling, lung auscultation – normal.

Tactics of medical assistance (body mass 13 kg):

• Hydrocortisone (10 mg/kg) – 130 mg/in physiological saline;

• Physiological saline – 200 ml.

The symptoms dissapeared in 1.5 hours after medical assistance.

Recommendations:

1. Elimination of milk and its derivatives from the daily diet.
2. Constantly carry around an EpiPen or adrenaline in case of acute reactions.

Visit 4 (age of the child – 9 years old)

At the moment of examination – within the normal ranges.

Lab Tests

Total IgE – 74,9 kU/L (norm 0 –148).

Oral provocation test with the lactose-free formula was done (table 3). Before performing the procedure a venous catheter was placed in the child's peripheral vein.

Table 1

Oral provocation test with an adapted dairy-free formula on visit 1

Step	Volume of the lactose-free formula, ml	Amount of protein	Overall child's condition
100 ml of the lactose-free formula has 1,7 g of protein			
1	1	0,017	–
2	6	0,102	–
3	10	0,17	–
4	40	0,68	–
5	100	1,7	–
Total volume – 157 ml		**Total amount of protein – 2,669 g**	

Table 2

Oral provocation test with the lactose-free formula on visit 3

Step	Volume of the lactose-free formula, ml	Amount of protein	Overall child's condition
100 ml of milk – 3,3 g of protein			
1	1	0,033	–
2	9	0,297	–
Total volume – 10 ml		**Total amount of protein – 0,33 g**	

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Table 3
Oral provocation test with the lactose-free milk on visit 4

tep	Volume of the lactose-free milk, ml	Amount of protein	Overall child's condition
100 ml of milk – 3,3 g of protein			
1	0,5	0,0165	–
2	1,0	0,033	–
3	2,0	0,066	
4	2,5	0,0825	
Total volume – 6 ml		**Total amount of protein – 0,198 g**	

After 40 minutes after consumption of milk – nausea. After 1,5 hours – vomiting. Functional indicators – within the normal ranges. There were no skin reactions in the form of rashes or swelling, lung auscultation – normal.

The symptoms disappeared in 1,5 hours, no medical assistance was administered.

Recommendations:

1. Use of lactose-free milk in 1.0 ml daily – 3 months.
2. The gradual increase of the dose of milk per 1.0 ml for every 3 months.
3. Control OPT control in 1 year.
4. Constantly carry around an EpiPen or adrenaline in case of acute reactions.

Visit 5 (child's age – 10 years old)

At the moment of examination – within the normal ranges.

The patient gets 6 ml lactose-free milk daily.

Oral provocation test with the lactose-free formula was done (table 4). Before performing the procedure a venous catheter was placed in the child's peripheral vein.

The general condition of the child after administering OPT was satisfactory, the patient did not experience any complaints.

Recommendations:

1. Usage of lactose-free milk 20 ml daily – 20 days.
2. Then gradually add another 20 ml of milk during each subsequent week to achieve 150 ml.
3. With good endurance of 150 ml of milk its derivatives could be added into the daily diet.
4. Constantly carry around an EpiPen in case of acute reactions.

Table 4
Oral provocation test with the lactose-free milk on visit 5

Step	Volume of the lactose-free milk, ml	Amount of protein	Overall child's condition
100 ml of milk – 3,3 g of protein			
1	6,0	0,00225	–
2	50,0	0,0045	–
Total volume – 56 ml		**Total amount of protein – 0,198 g**	

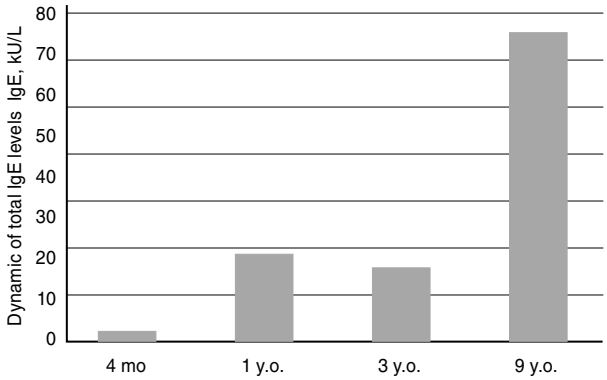

Figure 1. Age dynamic of total IgE levels in child

During a telephone call with the patient, it was specified that he is in satisfactory condition and is capable of tolerating 60 ml of lactose-free milk and is constantly increasing the dose.

Thus, the presented case showed that the non-IgE-medaiated type of allergic reactions could be seen in the form enterocolitis, that was caused by the proteins of cow's milk. The disease may be accompanied by diarrhea and/or vomiting, abdominal pain, pallor, weakness. The occurrence of the symptoms may vary – from 1-2 to 10 hours, and even later after consumption of dairy products. The development of symptoms may be of varying intensity depending on the child's age, the amount of food consumed, and the presence of additional triggers. Severe symptoms of dehydration are dangerous due to the development of a hypovolemic shock.

It should be remembered that when suspecting IgE-independent type of allergic reactions, the OPT should be conducted with an elongated interval between doses up to 30-45 minutes. Accordingly, the patients are under the supervision of a medical facility for a longer period of time – 4-8 hours after the last dose and the telephone contact should be made after 24 and 48 hours [2].

Clinical Case № 2

Boy, 9 years old.

Since the age of 4 months the child is suffering from severe atopic dermatitis and food allergies to milk and eggs. He is supervised by an allergologist. Dermatitis has manifested more severely during the early age of the childhood, however the overall conditions stabilized after the patient reached the age of 3.

Visit 1 (child's age – 8 months)

At the moment of examination – generalized maculopapular rash all over the body.

Recommendations:

1. Implementation of an adapted formula with complete protein hydrolysis in the child's daily diet.
2. Elimination of milk, eggs and their derivatives in the child's daily diet during the next 12 months.
3. Antihistamines according to the prescribed scheme.
4. Topical care.
5. Constantly carry around an EpiPen in case of acute reactions.

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Visit 2 (child's age – 4 years old)

At the moment of examination – severe dryness of the skin, single elements of excoriation.

Oral provocation test with the biscuit containing milk was done (table 5). Before performing the procedure a venous catheter was placed in the child's peripheral vein.

Complaints on solitary spotty and itchy elements on the body appeared immediately after the child ate 2g of biscuits.

The boy was transferred to the intensive care unit for further observation.

20 minutes later the child developed generalized urticaria (with functional indexes within the normal ranges, auscultation of the lungs – within the normal ranges).

Medical assistance tactics (body mass – 18 kg):

• Chlorphenamine (0.2 mg/kg) – 3.6 mg intravenous, in physiological saline;

• Hydrocortisone (10 mg/kg) – 180 mg intravenous, in physiological saline;

• Physiological saline – 250 ml.

The symptoms began to regress in 2 hours after administering the named drugs and procedures. The patient received a prescription of antihistamines when he was discharged from the institution.

Recomendations:

1. Elimination of milk, eggs and their derivatives in the child's daily diet.
2. Short course of antihistamines.
3. Constantly carry around an EpiPen in case of acute reactions.

Visit 3 (child's age – 5 years old)

At the moment of examination – severe dryness of the skin.

Oral provocation test with the biscuit containing eggs was done (table 6). Before performing the procedure a venous catheter was placed in the child's peripheral vein.

Complaints regarding a dry cough appeared immediately after the child ate 0,4 g of biscuits.

The boy was transferred to the intensive care unit for further observation.

The cough increased and became more severe and the child experienced the occurrence of bronchospasm 15 minutes later (dry wheezing and prolonged exhalation).

Table 5

Oral provocation test with the biscuit on visit 2

Step	Weight of the biscuit, g	Amount of protein	Overall child's condition during the test
100 g of biscuits– 0,078 g of milk protein			
1	0,5	0,00039	–
2	1,0	0,00078	–
3	2,0	0,00156	Solitary spotty and itchy elements all over the body
Total amount – 3,5 g		**Total amount of milk protein – 0,00273 g**	

Table 6

Oral provocation test with buscuits that contain eggs (Savoiardi) on visit 3

Step	Weight of the biscuit, g	Amount of protein	Overall child's condition during the test
100 g of biscuits– 3,14 g of egg protein			
1	0,1	0,0031	–
2	0,2	0,0063	–
3	0,4	0,0126	Dry cough
Total amount – 0,7 g		**Total amount of egg protein – 0,022 g**	

Medical assistance tactics (body mass – 19 kg):

• Nebulization with salbutamol and beclomethasone (twice with an 1 hour interval).

The symptoms stabilized and the patient was discharged home with prescribed antihistamines.

Recommendations:

1. Elimination of milk, eggs and their derivatives in the child's daily diet.
2. Short course of antihistamines.
3. Constantly carry around an EpiPen in case of acute reactions.

Visit 4 (child's age – 6 years old)

At the moment of examination – severe dryness of the skin.

Oral provocation test with the biscuit cantaining eggs was done (table 7). Before performing the procedure a venous catheter was placed in the child's peripheral vein.

As the patient, after consuming products that contained approximately 5,83 g of protein in total, did not experience any reactions, it could be stated that eggs and their derivatives could be actively introduced to the patient's diet.

Recommendations:

1. Elimination of milk in the patient's diet.
2. Control OPT in 1 year.
3. Free consumption of eggs in the daily diet.
4. Constantly carry around an EpiPen in case of acute reactions.

Visit 6 (child's age – 8 years old)

At the moment of examination – severe dryness of the skin.

Oral provocation test with the biscuit cantaining milk was done (table 9). Before performing the procedure a venous catheter was placed in the child's peripheral vein.

After consuming 0,74 g of milk protein in total products, the patient experienced stomach pain that did not require any medical assistance and regressed in 40 minutes.

Recommendations:

1. Include lactose-free milk in diet in the amount of 3 ml daily (0,01 g of protein).
2. Control OPT with milk in 1 year.
3. Free consumption of eggs in the daily diet.
4. Constantly carry around an EpiPen in case of acute reactions.

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Table 7

Oral provocation test with products that contain eggs on visit 4

Step	Weight of the biscuit, g	Amount of protein	Overall child's condition during the test
100 g of biscuits (savoiardi) – 3,14 g of egg protein			
1	0,1	0,0031	–
2	0,2	0,0063	–
3	0,4	0,0126	–
4	0,8	0,0252	–
5	2,0	0,063	–
6	4,0	0,126	–
7	8,0	0,252	–
Total amount of biscuits – 15,5 g		**Total amount of egg protein – 0,4882 g**	
100 g of sponge cake – 4,8 g of egg protein			
8	3,0	0,144	–
9	6,0	0,288	–
10	12,0	0,576	–
Total amount of sponge cake – 21 g		**Total amount of egg protein – 1,008 g**	
100 g of boiled eggs – 12 g of egg protein			
11	1 г	0,12	–
12	3 г	0,36	–
13	10 г	1,2	–
14	10 г	1,2	Vomiting
Total egg weight – 24 g		**Total amount of egg protein – 2,88 g**	
Total amount of test products – 60,5 g		**Total amount of egg protein in the test products – 4,3762 g**	

Table 8

Oral provocation test with eggs on visit 5

Step	Weight of the product, g	Amount of protein	Overall child's condition during the test
100 g of boiled eggs – 12 g of egg protein			
1	0,3 г	0,036	–
2	1 г	0,12	–
3	3 г	0,36	–
4	10 г	1,2	–
5	30 г	3,6	–
Total amount of eggs – 44,3 g (one egg)		**Total amount of egg protein – 5,316 g**	
100 ml of a raw egg – 11,86 г of egg protein			
6	0,3 мл	0,03558	–
7	1 мл	0,1186	–
8	3 мл	0,3558	–
Total amount of eggs – 4,3 ml		**Total amount of egg protein – 0,50998 g**	
Total amount of test products – 60,5 g and 4,3 ml		**Total amount of egg protein in test products – 5,82598 g**	

Table 9

Oral provocation test with biscuits cantaining milk on visit 6

Step	Weight of the product, g	Amount of protein	Overall child's condition during the test
100 g of biscuits – 0,078 g of milk protein			
1	1 г	0,00078	–
2	10 г	0,0078	–
Total amount of biscuits – 11 g		**Total amount of milk protein – 0,00858 g**	
100 ml of milk in 20% dilution – 0,66 g of milk protein			
3	1 мл	0,066	–
4	3 мл	0,0198	–
5	10 мл	0,066	–
6	30 мл	0,198	
Total amount – 44,0 ml		**Total amount of milk protein – 0,3498 g**	
100 ml of pudding – 2,657 g of milk protein			
7	0,3	0,00797	–
8	1,0	0,02657	–
9	3,0	0,0797	–
10	10,0	0,2657	Stomach pain
Total amount – 14,3 ml		**Total amount of milk protein – 0,37994 g**	
Total amount of test products – 11 g and 58,3 ml		**Total amount of egg protein in the test products – 0,73832 g**	

Visit 7 (child's age – 9 years old)

At the moment – within the age norms.

Oral provocation test with milk was done (table 10). Before performing the procedure a venous catheter was placed in the child's peripheral vein.

After consuming 5,11 g of milk protein in the form of milk the patient did not experience any symptoms and expressed no complaints.

Recommendations:

1. It is recommended that lactose-free milk becomes a part of the daily diet in the dose of 50 ml daily with a gradual increase in 10 ml every month.
2. Constantly carry around an EpiPen in case of acute reactions.

Visit 8 (child's age – 10 years old)

The boy expressed feeling well and is freely drinking milk and eating its derivatives, not experiencing any symptoms of discomfort. He always carries around an EpiPen in cases of acute reactions.

Summing up the case, we have noticed that the IgE-mediated type of allergy is linked to the development of symptoms mainly in 30 minutes after consumption of the product. Skin reactions tend to appear more frequently, especially in children. With the help of the administration of specific immunotherapy the boy began to tolerate milk, eggs, and their derivatives. The child can freely consume

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Table 10

Oral provocation test with milk on visit 7

Step	Weight of product, ml	Amount of protein	Overall child's condition during the test
100 ml of milk – 3,3 g of milk protein			
1	0,3 мл	0,0099	–
2	0,5 мл	0,0165	–
3	1,0 мл	0,033	–
4	3,0 мл	0,099	–
5	10,0 мл	0,33	–
6	20,0 мл	0,66	–
7	40,0 мл	1,32	–
8	40,0 мл	1,32	–
9	40,0 мл	1,32	–
Total amount of milk – 154,8 ml		**Total amount of milk protein – 5,1084 g**	

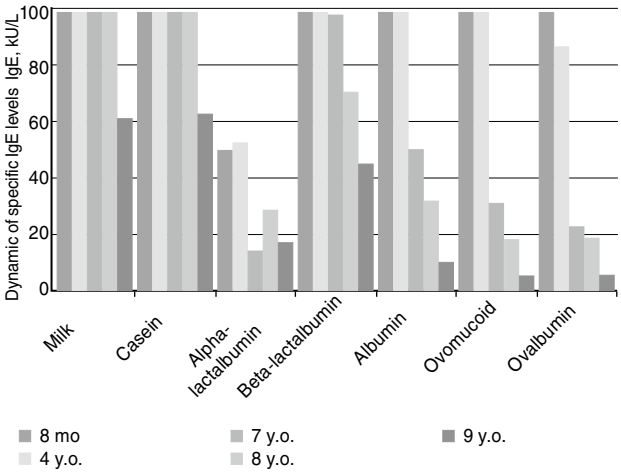

Figure 2. Age dynamic of specific IgE levels in child

the same products as his family and peers, which directly affects the quality of life of each patient [2, 6].

Oral provocation test is a great opportunity in the hands of an experienced allergologist. It is an effective tool which can help to give answers on a number of questions, including whether the patient has an allergy or is actually tolerant [1, 5]. The achieved results allow to determine the patient's diet and define the treatment strategies. Moreover, it is always difficult to interpret mild, subjective or atypical symptoms. They could be present as an emotional compound, as well as may be the first signs of serious reactions [2, 4]. That is why the OPT has to be conducted with the assistance of an experienced team of medical personnel, who can control the course of the events and provide the appropriate amount of care.

Список літератури

1. Berin MC, Mayer L. Can we produce true tolerance in patients with food allergy? J Allergy Clin Immunol. 2013;131:14-22.

2. Food allergy. John M. James, Wesley Burks, Philippe Eigenmann. Elsevier Inc; 2012. P. 113-127, 143-204.

3. The European Academy of Allergy and Clinical Immunology is in the process of developing the EAACI Guidelines for Allergen Immunotherapy for IgE-mediated food allergy. Clinical and Translational Allergy. 2016;6:24.

4. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy. 2014;69:1008-25.

5. Nurmatov U, Devereux G, Worth A, Healy L, Sheikh A. Effectiveness and safety of orally administered immunotherapy for food allergies: a systematic review and meta-analysis. Br J Nutr. 2014;111:12-22.

6. Salvilla SA, Dubois AE, Flokstra-de Blok BM, Panesar SS, Worth A, Patel S, et al. Disease-specific health-related quality of life instruments for IgE-mediated food allergy. Allergy. 2014;69:834-44.

References

1. Berin MC, Mayer L. Can we produce true tolerance in patients with food allergy? J Allergy Clin Immunol. 2013;131:14-22.

2. Food allergy. John M. James, Wesley Burks, Philippe Eigenmann. Elsevier Inc; 2012. P. 113-127, 143-204.

3. The European Academy of Allergy and Clinical Immunology is in the process of developing the EAACI Guidelines for Allergen Immunotherapy for IgE-mediated food allergy. Clinical and Translational Allergy. 2016;6:24.

4. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy. 2014;69:1008-25.

5. Nurmatov U, Devereux G, Worth A, Healy L, Sheikh A. Effectiveness and safety of orally administered immunotherapy for food allergies: a systematic review and meta-analysis. Br J Nutr. 2014;111:12-22.

6. Salvilla SA, Dubois AE, Flokstra-de Blok BM, Panesar SS, Worth A, Patel S, et al. Disease-specific health-related quality of life instruments for IgE-mediated food allergy. Allergy. 2014;69:834-44.

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