

To provide the patient with an alternative diagnostic option for the monitoring of her pathology, an oral challenge with a single dose with a “macrogol-free” evacuant solution was performed with good tolerance.

Based on the clinical history and in vivo and in vitro positive results, our patient was diagnosed with an anaphylactic reaction to macrogol (PEG). Subsequently, we advised the patient to check the excipients listed for all kinds of drugs, cosmetics, foods, and other pharmaceutical products that could contain macrogol.

Anaphylactic reactions to macrogol have been rarely reported in the scientific literature. Wenande and Garvey² identified 37 case reports of immediate-type hypersensitivity to PEGs from January 1977 until April 2016.² Therefore, PEG is considered safe and well-tolerated, and consequently, its application has been growing exponentially in multiple fields.^{1–3} In most cases, the described reactions fulfill criteria of anaphylaxis. Despite an intestinal absorption lower than 1% for PEG 3350 g/mol, more than half of reported cases have been described after the administration of laxative solutions,² but specific cases were described with intra-articular, intramuscular, and intravenous injection, and even via topical or vaginal mucosa.^{2,4,5}

Some authors account for the greater frequency of the oral route by citing increased absorption of high-molecular-weight PEG in patients with inflammatory bowel disease and damaged gastrointestinal mucosa.^{1,2} In this way, the loss of the structural or functional integrity is considered a predisposing factor for greater PEG absorption and subsequently sensitization.⁶ The diagnostic workup varies according to the route of administration and the clinical history referred, being the clinical history in many cases the unique tool to deduce an IgE-mediated reaction to PEG.

Both Antón Gironés et al⁷ and Antolin-Amerigo et al⁸ published clinical cases after the use of Bohm evacuant solutions. In contrast with our patient, all patients presented negative results in the skin prick test for PEG 4000, whereas the intradermal test was positive in the group of Antón Gironés et al and negative in the patient described by Antolin-Amerigo et al. Antón Gironés et al performed a single-blind placebo oral challenge, with a positive result in both patients.

Cross-reactivity between PEGs of different molecular weights has been studied. Because of the patient's severe disease, we have not investigated possible cross-reactivity, ignoring possible tolerance to PEG of other molecular weights.

Reviewing the published literature, Bommarito et al⁹ reported a positive BAT after the oral intake of nimesulide granules and paracetamol syrup containing macrogol 4000 and 6000, respectively. Also, Jover Cerdá et al¹⁰ obtained positive BAT response to macrogol

4000 1% and PEG derivatives in a patient who experienced reactions with cough syrup drug, skin cream, and antiseptic containing PEG 6000, PEG-9, PEG-6, PEG-75 and PEG-100, respectively.

In conclusion, we reported a case of anaphylactic reaction to Bohm laxative solution containing macrogol 4000, diagnosed by the clinical history, a positive skin prick test, and BAT to macrogol 4000, suggesting an IgE-mediated immunological mechanism. To our knowledge, this is the first case of systemic hypersensitivity reaction to Bohm laxative solution with a positive BAT for macrogol 4000.

Nicola Giangrande, MD*

Jesús Miguel García-Menaya, MD, PhD*

Mariana Marcos-Fernández, MD†

Carmen Cámara-Hijón, MD‡

Pedro Bobadilla-González, MD, PhD*

*Department of Allergy and Clinical Immunology
Badajoz University Hospital
Badajoz, Spain

†Primary Health-Care Center Pueblonuevo del Guadiana
Badajoz, Spain

‡Department of Immunology
Cáceres University Hospital
Cáceres, Spain

jesusmiguelgarciamenaya@gmail.com

References

- Shah S, Prematta T, Adkinson NF, Ishmael FT. Hypersensitivity to polyethylene glycols. *J Clin Pharmacol*. 2013;53:352–355.
- Wenande E, Garvey LH. Immediate-type hypersensitivity to polyethylene glycols: a review. *Clin Exp Allergy*. 2016;46:907–922.
- Lee SH, Cha JM, Lee JI, et al. Anaphylactic shock caused by ingestion of polyethylene glycol. *Intest Res*. 2015;13:90–94.
- Wylon K, Dölle S, Worm M. Polyethylene glycol as a cause of anaphylaxis. *Allergy Asthma Clin Immunol*. 2016;12:67.
- Jakubovic BD, Saperia C, Sussman GL. Anaphylaxis following a transvaginal ultrasound. *Allergy Asthma Clin Immunol*. 2016;12:3.
- Lee SH, Hwang SH, Park JS, et al. Anaphylaxis to polyethylene glycol (Colyte®) in a patient with diverticulitis. *J Korean Med Sci*. 2016;31:1662–1663.
- Antón Gironés M, Roan Roan J, de la Hoz B, Sánchez Cano M. Immediate allergic reactions by polyethylene glycol 4000: two cases. *Allergol Immunopathol*. 2008;36:110–112.
- Antolin-Amerigo D, Sánchez-González MJ, Barbarroja-Escudero J, Rodríguez-Rodríguez M, Álvarez-Perea A, Álvarez-Mon M. Allergic reaction to polyethylene glycol in a painter. *Occup Med*. 2015;65:502–504.
- Bommarito L, Mietta S, Nebiolo F, Geuna M, Rolla G. Macrogol hypersensitivity in multiple drug allergy. *Ann Allergy Asthma Immunol*. 2011;107:542–543.
- Jover Cerdá V, Rodríguez Pacheco R, Doménech Witek J, Marco de la Calle FM, de la Sen Fernández ML. Immediate hypersensitivity to polyethylene glycols in unrelated products: when standardization in the nomenclature of the components of drugs, cosmetics, and food becomes necessary. *Allergy Asthma Clin Immunol*. 2019;15:9.

Immediate vs delayed cow's milk protein allergy in terms of tolerance at year 1

We conducted a trial to compare the rates of positive oral provocation tests (OPTs) and of clinical symptoms present from different systems (gut, skin, respiratory tract) in cases with a positive OPT in a group of immunoglobulin E (IgE) and in 1 of non-IgE cow's milk protein allergy (CMPA) at 1 year of age. Moreover, we tried to identify possible prognostic factors contributing to tolerance at 1 year of age OPT, such as the existence of multiple food allergies, a family history of atopy, the type of milk feeding (breastfeeding vs formula feeding), and the level of antibody concentration against cow's milk protein.

Methods

The study received ethical approval from the Ethics Committee of the Aristotle University of Thessaloniki (Prot. No: 7894). All parents of the participating infants signed written informed consent.

The protocol of the OPT was always starting with a labial challenge followed by gradually increasing doses of 0.1, 0.3, 1, 3, 10, 30, and 100 mL cow's milk (CM) administered with intervals of 20 minutes. In the next day, 3 consecutive doses of 20, 50, and 100 mL CM were administered. Regular assessments were performed to detect symptoms from skin, respiratory, cardiovascular, or gastrointestinal systems. Finally, 100 mL were administered daily from day 3 to day 10 at home.^{1,2}

Disclosures: none.

Funding Sources: none.



Table 1
Prognostic Factors Indicating a High Risk for a Positive Oral Provocation Test (OPT) at 1 Year of Age Were the Type of Cow's Milk Protein Allergy (CMPA) with the IgE Immune Type Causing Significant Burden Even in Breastfed Infants, as Well as a Positive Family History of Atopy

Prognostic factors	Positive OPTs at 1 year of age			
	No (%)	P value	OR (95% CI)	a OR (95% CI)
Type of CMPA		<.001		
IgE CMPA	11/28 (39.3)		8.9 (2.7–29.1)	7.2 (2.5–20.3)
Non-IgE CMPA	5/74 (6.8)		Ref.	Ref.
Family history of atopy		<.001		
Positive	9/15 (60.0)		17.1 (4.7–62.3)	13.2 (3.6–47.6)
Negative	7/87 (8.0)		Ref.	Ref.
Number of food allergies		.154		
Multiple food allergies	4/14 (28.6)		2.5 (0.7–9.4)	1.8 (0.5–7.7)
Sole CMPA	12/88 (13.6)		Ref.	Ref.
Breastfeeding:		.016		
Yes	9/42 (21.4)		Ref.	Ref.
No	6/10 (60.0)		5.5 (1.3–23.8)	2.4 (0.8–7.5)
Type of allergy in breastfed infants		.001		
Breastfed with IgE CMPA	9/20 (45.0)		n.c.	n.c.
Breastfed with non-IgE CMPA	0/22 (0.0)			
ImmunoCAP grade in IgE CMPA		.269		
(Grade 2–3)	8/24 (33.3)		Ref.	Ref.
(Grade 4–6)	3/4 (75.0)		6.0 (0.5–67.3)	4.5 (0.4–49.6)

OPTs, oral provocation tests; CMPA, cow's milk protein allergy; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; n.c., not calculated.

Patients

The participating infants had a mean age of 2.16 ± 1.32 months, and a clinical presentation suggestive of CMPA. Patients with positive specific IgEs, assessed by ImmunoCAP and skin prick tests (SPTs) who had a positive response to a 6-week elimination diet were included in the IgE CMPA group. Patients with negative laboratory tests and a positive response to an elimination diet were included in the non-IgE CMPA group. All of the patients were placed on a CMP elimination diet until the age of 1 year. At a mean age of 12.24 ± 0.96 months, all participating infants were subjected to an OPT for evaluation of tolerance acquisition, and the reaction rates between the 2 groups IgE and non-IgE were compared. The following data were recorded at the end of the 1st year of life in the 2 groups: 1) presenting symptoms of a positive OPT in the 2 groups from the different systems, such as skin, gastrointestinal, respiratory, cardiovascular, and central nervous system; 2) reaction rates; 3) family history of atopy; 4) co-sensitization to other food allergens apart from milk; 5) type of feeding, that is, breastfeeding, or formula feeding after the diagnosis with CMPA; 6) ImmunoCAP test grades.

Infants diagnosed with CMPA that were considered eligible for participating in the study were divided into the following groups:

- Infants with clinical presentation consistent with CMPA in combination with positive IgEs were included in the IgE group.
- Infants with clinical presentation consistent with CMPA with negative sensitivity (specific IgEs or SPTs) plus a positive response to a 6-week elimination diet with a reverse of their symptoms, were included in the non-IgE CMPA group. Those patients had mild or moderate non-IgE CMPA. None of them was diagnosed with eosinophilic esophagitis or food protein–induced enterocolitis syndrome.

Patients whose condition did not respond to the 6-week cow's milk elimination diet or who did not thrive well or in whom another diagnosis was suspected were excluded from the study.

Statistical Analysis

To analyze the qualitative comparative parameters, odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated by means of simple logistic regression analysis, as the measure of the associations between the qualitative parameters. To assess the independent effect of children's characteristics on the presence of

positive OPT multivariate stepwise logistic regression models were constructed. All tests were 2-tailed, and statistical significance was considered for *P* values less than .05.

Results

One hundred two children with CMPA participated in the clinical trial (55 boys and 47 girls). Twenty-eight (27.4%) were diagnosed with IgE-mediated CMPA and 74 (72.5%) with non-IgE CMPA.

Symptoms from the gastrointestinal tract developed 68 of 74 (91.9%) infants diagnosed with non-IgE-mediated CMPA vs 11 of 28 infants with IgE-mediated CMPA ($P < .001$; OR: 26.3; 95% CI: 7.4–92.8; adjusted OR: 8.3; 95% CI: 2.9–23.4). Twenty-two of 28 (78.6%) infants with IgE-mediated CMPA developed skin symptoms, compared with 14 of 74 (18.9%) infants with non-IgE-mediated CMPA ($P < .001$; OR: 15.7; 95% CI: 5.4–46.0; aOR: 10.1; 95% CI: 3.7–27.7). Four of 28 (14.3%) infants with IgE-mediated CMPA developed symptoms from the respiratory tract compared with none from the non-IgE group ($P = .001$). Respiratory symptoms were present only in the IgE group (15%). Anaphylaxis was recorded in 2 infants in the IgE-mediated group at a rate of 0.019% (2/102) of the subjects.

The rates of positive OPTs in relation to various risk factors in the study group infants at the age of 1 year are shown in Table 1.

Discussion

At year 1, there was a higher rate of positive OPTs to CM protein in the IgE group of CM protein–allergic infants compared with the non-IgE group. The risk for a positive reaction to the OPT in the IgE CMPA group of infants was almost 7-fold higher compared with the non-IgE group. A positive family history of atopy increased significantly (13-fold) the risk of failing to acquire tolerance at 1 year of age. Breastfed infants with IgE CMPA had a higher risk for a positive OPT at 1 year of age in comparison with those with non-IgE CMPA. Although breastmilk contains factors that induce tolerance, such as transforming growth factor beta, it could not change the natural course of IgE-CMPA, which is known to be more persistent than the non-IgE type of CMPA. Multiple food allergies and high levels of specific IgEs had a higher risk for a positive OPT, although the differences did not reach statistical significance.^{3–10}

In conclusion, the current study has shown that comparing the IgE CMPA with the non-IgE CMPA, the risk factors for a positive OPT at 1 year of age were: 1) IgE type of CMPA, even in breastfed infants, and 2) a family history of atopy.

Ioannis Xinias, MD, PhD*
 Dimitrios Cassimos, MD, PhD†
 Grigorios Trypsianis, MD, PhD‡
 Maria Nivatsi, MD§
 Antigoni Mavroudi, MD, PhD¶
 *3rd Paediatric Department
 Aristotle University of Thessaloniki
 Greece
 †Department of Pediatrics
 Democritus University of Thrace
 Greece
 ‡Department of Medical Statistics
 Democritus University of Thrace
 Greece
 §1st Paediatric Department
 Aristotle University of Thessaloniki
 Greece
 ¶Allergy Unit
 Aristotle University of Thessaloniki
 Greece
antigonemavroudi@gmail.com

References

1. Sicherer SH. Food allergy: when and how to perform oral food challenges. *Pediatr Allergy Immunol*. 1999;10:226–234.
2. Niggemann B, Wahn U, Sampson HA. Proposals for standardization of oral food challenge tests in infants and children. *Pediatr Allergy Immunol*. 1994;5:11–13.
3. Koletzko S, Niggemann B, Arato A, et al. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. *J Pediatr Gastroenterol Nutr*. 2012;55(2):221–229.
4. Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol*. 2007;120(5):1172–1177.
5. Saarinen KM, Pelkonen AS, Makela MJ, Savilahti E. Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. *J Allergy Clin Immunol*. 2005;116(4):869–875.
6. Vanto T, Hellepila S, Juntunen-Backman K, et al. Prediction of the development of tolerance to milk in children with cow's milk hypersensitivity. *J Pediatr*. 2004;144(2):218–222.
7. Sampaio S, Marinho S, Prates M, Almeida M, Rosado-Pinto J. Transient vs persistent cow's milk allergy and development of other allergic diseases. *Allergy*. 2005;60(3):411–412.
8. Kvenshagen B, Halvorsen R, Jacobsen M. Adverse reactions to milk in infants. *Acta Paediatr*. 2008;97(2):196–200.
9. Shek LP, Soderstrom L, Ahlstedt S, Beyer K, Sampson HA. Determination of food specific IgE levels over time can predict the development of tolerance in cow's milk and hen's egg allergy. *J Allergy Clin Immunol*. 2004;114(2):387–391.
10. Vassilopoulou E, Konstantinou G, Kassimos D, et al. Reintroduction of cow's milk in milk-allergic children: safety and risk factors. *Int Arch Allergy Immunol*. 2008;146:156–161.

Weed pollen season trends in relation to atmospheric CO₂ changes in Indiana and Ohio



Allergic rhinitis (AR) and asthma both lead to significant morbidity and health care usage in the United States.^{1,2} Pollens contribute to increased AR symptoms and asthma exacerbations. Ragweed (*Ambrosia* spp) and other weed pollens have been shown to affect AR and asthma issues in the Midwestern United States, especially in the late summer and early fall seasons. Knowledge about pollen season lengths and patterns can help with management of allergic rhinitis and asthma.^{3–5}

Atmospheric carbon dioxide (CO₂), precipitation, and temperature all impact the length of the weed pollen season.^{4,6} Atmospheric temperature has significantly increased in the past century.⁴ Global atmospheric CO₂ levels, collected at the Mauna Loa observatory in Hawaii, have increased from 312 parts per million (ppm) in 1960 to 415 ppm in May 2019.⁷

Ragweed pollen season has been shown to increase in the presence of increased atmospheric CO₂.⁶ In multiple areas of the central United States, the pollen seasons of ragweed and other weeds have increased in the past 2 decades.^{4,8,9} Weed pollen trends in relation to CO₂ and temperature changes have not previously been studied in the midwestern states of Indiana and Ohio. One hundred twenty miles separate Indianapolis, Indiana, and Dayton, Ohio. Despite their close location and similar latitude of 39.7°FN, significant pollen variation has been demonstrated between these 2 cities.¹⁰ The purposes of this study are to study trends in the lengths of pollen seasons for ragweed and other weeds in Indianapolis and in Dayton, in relation to changes in atmospheric CO₂, temperature, and precipitation, from 2003 to 2018.

The American Academy of Allergy, Asthma and Immunology—National Allergy Bureau (AAAAI-NAB) and the Regional Air Pollution Control Agency (RAPCA) for Dayton provided pollen counts for Indianapolis and Dayton, respectively (Data from AAAAI-NAB, for Indianapolis from 2003–2009, and Communication from RAPCA, Dayton, Ohio, February 6, 2019). RAPCA also posts Dayton pollen

counts to the NAB website. Indianapolis had complete pollen data from 2003 to 2009. Dayton had pollen counts from 2003 to 2006, and 2008 to 2018. In Indianapolis, pollen counts were reported daily, with limited exceptions. In Dayton, pollen counts were mainly reported Monday through Friday. Both sites used Burkard spore traps atop urban buildings, and reported counts in grains/m³ air, per NAB guidelines. Data were analyzed via Statistical Analysis Software v9.4 (SAS Institute Inc, Cary, NC).

No significant differences were found in annual temperature or precipitation between Indianapolis and Dayton from 2003 to 2009 (median, 51.9°F vs 53.7°F; $P = .07$, NS) (median 44.4 in vs 49.0 in; $P = .08$, NS). No significant differences were seen between in Dayton between 2003 to 2009 and 2010 to 2018, regarding precipitation (median, 42.5 in vs 41.4 in, $P = .72$, NS). Temperature did significantly increase from 2003 to 2009, to 2010 to 2018, in Dayton (51.8°F vs 53.2°F; $P = .03$).¹¹ In the past century, average temperature has increased 0.1°F per decade in Indiana, and 0.2°F in Ohio (NOAA Climate at a Glance Database).

The same weed pollens were reported in Indianapolis and Dayton—Ragweed (*Ambrosia*); English plantain (*Plantago*); dock/sorrel (*Rumex*); nettle (*Urtica*); chenopods (*Chenopodiaceae*); and mugwort/sagebrush (*Artemisia*). The start and end of a pollen season were defined as the first 2 and the last 2 consecutive days on which at least 5 pollen grains/m³ were reported. Weed pollens other than *Ambrosia* are grouped together as “other weeds.”

No significant differences were seen between Indianapolis and Dayton regarding *Ambrosia* season length ($P = .51$) or other weeds' pollen season length ($P = .84$) from 2003 to 2009 (Table 1). In Dayton, between 2003 to 2009 and 2010 to 2018, no significant changes were seen regarding *Ambrosia* or other weeds' pollen season length (*Ambrosia* $P = .33$; other weeds $P = .14$). From 2003 to 2009, *Plantago* and *Rumex* were detected on significantly more days in Dayton vs Indianapolis (*Plantago* $P = .01$; *Rumex* $P = .01$). *Plantago* and *Rumex* also were detected on significantly more days from 2003 to 2009 in Dayton, vs 2010 to 2018 (*Plantago* $P = .01$; *Rumex* $P = .02$).

Disclosures: none.

Funding Sources: none.