

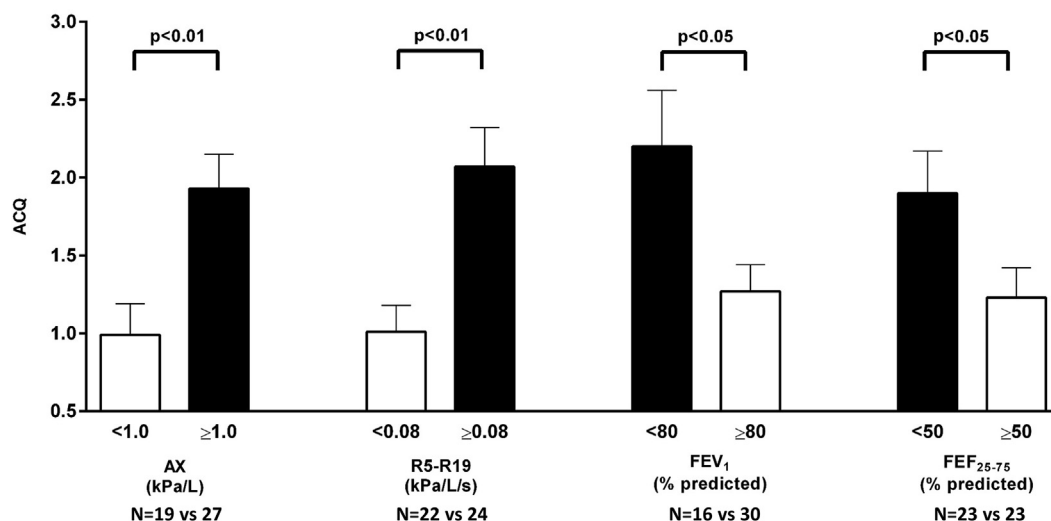


Figure 1. Asthma control questionnaire 6 values are shown as means and standard error of the mean for significant comparisons according to area under the reactance curve (AX), difference between resistance at 5 Hz and 19 Hz (R5–R19), forced expiratory volume in 1 second (FEV₁) % predicted, and forced expiratory flow at 25% to 75% of pulmonary volume (FEF_{25–75}) % predicted.

In conclusion, peripheral lung resistance and reactance measured by AOS are related to patient-reported outcomes of asthma control and quality of life. Airwave oscillometry was also more sensitive at detecting bronchodilator reversibility in relation to asthma control. We propose that measuring AOS should complement spirometry as part of the routine workup of patients with asthma in a real-life clinic setting.

Chris RuiWen Kuo, MBChB
Brian Lipworth, MD
Scottish Centre for Respiratory Research
Ninewells Hospital and Medical School
University of Dundee
Scotland, United Kingdom
b.j.lipworth@dundee.ac.uk

References

- Kuo CR, Jabbal S, Lipworth B. I say IOS you say AOS: Comparative Bias in Respiratory Impedance Measurements. *Lung*. 2019;197:473–481.
- Soares M, Richardson M, Thorpe J, Owers-Bradley J, Siddiqui S. Comparison of forced and impulse oscillometry measurements: a clinical population and printed airway model study. *Sci Rep*. 2019;9:2130.
- Manoharan A, Anderson WJ, Lipworth J, Ibrahim I, Lipworth BJ. Small airway dysfunction is associated with poorer asthma control. *Eur Respir J*. 2014;44:1353–1355.
- Jabbal S, Manoharan A, Lipworth J, Lipworth B. Utility of impulse oscillometry in patients with moderate to severe persistent asthma. *J Allergy Clin Immunol*. 2016;138:601–603.
- Kuo CR, Jabbal S, Lipworth B. Is small airways dysfunction related to asthma control and type 2 inflammation? *Ann Allergy Asthma Immunol*. 2018;121:631–632.
- Meltzer EO, Busse WW, Wenzel SE, et al. Use of the Asthma Control Questionnaire to predict future risk of asthma exacerbation. *J Allergy Clin Immunol*. 2011;127:167–172.
- Bateman ED, Reddel HK, Eriksson G, et al. Overall asthma control: the relationship between current control and future risk. *J Allergy Clin Immunol*. 2010;125:600–608.
- Foy BH, Soares M, Bordas R, et al. Lung computational models and the role of the small airways in asthma. *Am J Respir Crit Care Med*. 2019;200:982–991.
- Díaz Palacios MÁ HMD, Giner Valero A, Colomer Hernández N, Torán Barona C, Hernández Fernández de Rojas D. Correlation between impulse oscillometry parameters and asthma control in an adult population. *J Asthma Allergy*. 2019;12:195–203.
- Short PM, Williamson PA, Lipworth BJ. Sensitivity of impulse oscillometry and spirometry in beta-blocker induced bronchoconstriction and beta-agonist bronchodilation in asthma. *Ann Allergy Asthma Immunol*. 2012;109:412–415.

Persistent food protein–induced enterocolitis syndrome triggered by fish in children



We describe 3 cases of food protein–induced enterocolitis syndrome (FPIES) to sole that persists beyond the age of 6 years in Italian children and compare the age of acquisition of tolerance to fish with that of other foods in relation to the different patients' geographic origins.

Disclosures: The authors have no conflicts of interest to report.

Funding: None.

The first case concerned a 3-year-old boy referred to our allergy clinic for 2 episodes of repetitive vomiting, hypotonia, and lethargy 2 hours after eating sole that occurred at 8 and 10 months of age. The results of a skin prick test (SPT) to sole extract were negative. An oral food challenge (OFC) with sole was performed to assess the acquisition of tolerance. The boy ate 6 g of sole, and after 2 hours 30 minutes he had 10 episodes of vomiting and lethargy. An intravenous (IV) catheter was inserted with prompt rehydration with saline solution and a single dose of methylprednisolone followed by complete recovery within a few hours. A diagnosis of FPIES caused

by sole was confirmed, and the child was prescribed a fish-free diet, except for anchovies, which he tolerated. To verify the acquisition of tolerance, an OFC with sole was performed again at 9 years of age. Within 3 hours after the first 15-g dose, he had 3 episodes of vomiting, pallor, and lethargy. His vital signs were normal except for his temperature, which was 34.9°C. After being treated with IV saline solution, methylprednisolone, and a single dose of ondansetron, he fully recovered in 2 hours. His initial neutrophil count was 2.455/ μ L, which increased to 8.466/ μ L after the onset of symptoms but before the administration of IV corticosteroids. The next OFC to verify the acquisition of tolerance to sole is scheduled in a year's time.

An 8-year-old girl underwent an OFC with sole because at the age of 9 months she had vomited after eating sole on 2 different occasions. The results of an SPT to sole extract were negative. She ate 10 g of sole, and after 2 hours 30 minutes she experienced general malaise, nausea, abdominal pain, vomiting, and hypotonia. An IV saline solution and methylprednisolone were administered. Because the child moved to a different region, we were not able to arrange an appointment for a new OFC.

A 7-year-old boy underwent an OFC with sole because at the age of 9 months he had experienced vomiting, hypotonia, and pallor 2 hours after eating sole. The results of an SPT to sole extract were negative. He underwent an OFC, and 2 hours 30 minutes after eating 10 g of sole he experienced vomiting, hypotonia, pallor, and sweating. An IV saline solution and ondansetron were administered, and the symptoms cleared in 3 hours. He tolerated cod. The next OFC to verify the acquisition of tolerance to sole is scheduled in a year's time.

FPIES is a non-IgE-mediated gastrointestinal food hypersensitivity that causes profuse vomiting and at times diarrhea, leading to dehydration and lethargy in the acute form.¹ Cow's milk is the major culprit food in series in different countries followed by fish as solid food in Italy, Spain, and the United Kingdom.^{2–4} The prognosis of FPIES in general is usually good because more than half the patients acquire tolerance by 5 years of age.^{2,5,6} However, the prognosis depends on the culprit food and differs by geographic areas of the various studies. For example, in the United States, the mean reported age of tolerance to grains is 35 months and 42 months to other solid foods (vegetables, fruit, and meat).¹ In a large population-based cohort study in Israel with patients with cow's milk–induced FPIES, 60% gained tolerance by 1 year, 75% by 2 years, and 85% by 3 years.⁵ In a large US case series, the median age of gaining tolerance to cow's milk–induced FPIES was 5.1 years.⁶

Little is known about the natural course of FPIES to fish, which is believed to be more persistent and is only overcome in a few cases.^{2,3,7} The age of achieving tolerance to fish is significantly higher than for cow's milk. So far there is no valid mechanistic evidence to support a hypothesis that explains why FPIES to solid food persists more than FPIES to liquid food; one possible explanation could be the fact that solid foods are introduced later in life. Vazquez-Ortiz et al⁸ reported a tolerance rate of 75% in Spanish patients with FPIES to fish by 60 months of age, whereas other studies reported a tolerance rate ranging from 33% to 63% by 48 and 53 months of age^{3,7} in Spain and in Italy, respectively.

We have described the clinical cases of 3 Italian children with persistent FPIES to sole beyond the age of 6 years. Vila et al³ described 2 Spanish patients aged 14 and 17 years with persistent FPIES to salmon and hake, respectively. The significant factor of our

clinical cases is that sole was the culprit fish in all 3 patients, which could probably be explained by the fact that in Italy sole, together with cod, is the fish most frequently given during the weaning of infants.

Two of our 3 patients tolerated fish, namely, anchovies and cod. The possibility of patients with FPIES to certain fish tolerating different fish is well known.^{7,9} This tolerability resembles what happens in IgE-mediated fish allergy and supports the similarity of the 2 conditions.¹⁰ Although the prognosis of FPIES is usually good in most patients, some patients may acquire tolerance later than the age reported in the literature. Currently, the only way to verify the outgrowing of FPIES is to perform an OFC every 12 to 18 months after the most recent episode.¹ Because the tolerance to fish is acquired later, before reintroducing fish, in these patients, waiting longer to perform the OFC is recommended. The guidelines should probably modify the OFC timing on the basis of the knowledge acquired regarding the natural history of FPIES for the various foods.

Simona Barni, MD*

Francesca Mori, MD, PhD*

Lucia Liotti, MD†

Giulia Liccioli, MD*

Elio Novembre, MD, PhD*

*Allergy Unit

Department of Paediatrics

Anna Meyer Children's University Hospital

Florence, Italy

†Paediatric Unit

Hospital of Senigallia

Senigallia, Italy

simonabarni@hotmail.com

References

- Nowak-Węgrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: executive summary-workgroup report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2017;139(4):1111–1126.
- Sopo SM, Giorgio V, Iacono ID, Novembre E, Mori F, Onesimo R. A multicentre retrospective study of 66 Italian children with food protein-induced enterocolitis syndrome: different management for different phenotypes. *Clin Exp Allergy*. 2012;42(8):1257–1265.
- Vila L, Garcia V, Rial MJ, Novoa E, Cacharron T. Fish is a major trigger of solid food protein-induced enterocolitis syndrome in Spanish children. *J Allergy Clin Immunol Pract*. 2015;3:621–623.
- Ludman S, Harmon M, Whiting D, du Toit G. Clinical presentation and referral characteristics of food protein-induced enterocolitis syndrome in the United Kingdom. *Ann Allergy Asthma Immunol*. 2014;113(3):290–294.
- Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. The prevalence and natural course of food protein-induced enterocolitis syndrome to cow's milk: a large-scale, prospective population-based study. *J Allergy Clin Immunol*. 2011;127:647–653.
- Ruffner MA, Ruymann K, Barni S, Cianferoni A, Brown-Whitehorn T, Spergel JM. Food protein-induced enterocolitis syndrome: insights from reviews of a large referral population. *J Allergy Clin Immunol Pract*. 2013;1:343–349.
- Sopo SM, Monaco S, Badina L, Barni S, et al. Food protein-induced enterocolitis syndrome caused by fish and/or shellfish in Italy. *Pediatr Allergy Immunol*. 2015;26:731–736.
- Vazquez-Ortiz M, Machinena A, Dominguez O, et al. Food protein-induced enterocolitis syndrome to fish and egg usually resolves by age 5 years in Spanish children. *J Allergy Clin Immunol Pract*. 2017;5(2):512–515.
- Infante S, Marco-Martín G, Sánchez-Domínguez M, et al. Food protein-induced enterocolitis syndrome by fish: Not necessarily a restricted diet. *Allergy*. 2018;73(3):728–732.
- Caubet JC, Nowak-Węgrzyn A. Current understanding of the immune mechanisms of food protein-induced enterocolitis syndrome. *Expert Rev Clin Immunol*. 2011;7(3):317–327.