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Case report

Honey-Induced FPIES: A Rare Presentation and Pathogenetic Insights

Fabrizio Leone [1,2], Martina Vetrò[1], Ottavia De Angelis[1], Serena Marangio[1], Gabriella Cusa[2], Matteo D'Ambrosi[2], Sonia Iavarone[1], Anna Maria Zicari[1], Caterina Anania[1]

[1] Department of Maternal Infantile and Urological Sciences, Sapienza University of Rome, Rome, Italy; [2] Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy

SUMMARY

Introduction. Food protein-induced enterocolitis (FPIES) is a non-immunoglobulin E (IgE)-mediated food allergy syndrome typically diagnosed in infancy and childhood presenting with delayed onset of repeated vomiting. The most common allergens causing FPIES reactions are cow's milk, soy, cereals, and rice. However, honey, propolis and royal-jelly can also trigger allergic reactions. Cases of food allergy related to honey described in the literature are very rare. Honey is mainly composed of water, sugars such as fructose and glucose, a very small quantity of proteins drived from the pharyngeal and salivary glands of bees (Apis Mellifera), and spores, algae, vitamins, minerals, etc.

Materials and methods. We describe a case of a 4-year-old boy who had recurrent episodes of repetitive emesis, each lasting at least 2 hours after consuming honey or royal-jelly or any food containing honey. No evidence of IgE-mediated sensitization was documented, either by skin prick tests or by the assay of specific IgE for honey, pollen and bee venom.

Results. We performed an oral food challenge (OFC) with acacia honey: two hours after ingestion our patient presented repetitive emesis and two more episodes of vomiting occurred in the following two hours.

Discussion and Conclusions. This case shows the importance of considering isolated vomiting as a possible symptom of honey allergy, even in the absence of positive standard diagnostic tests. We hypothesized that it could be a FPIES triggered by honey, given the isolated repetitive gastrointestinal manifestation, the absence of any symptoms of IgE-mediated food allergy and the negativity of IgE test. Further tests (blood count, tryptase dosage and calprotectin) during the next OFC may be useful for diagnosis. Clinical management involves a correct diagnostic process, an avoidance diet and patient education.

KEY WORDS: FPIES, food allergy, vomiting, honey, royal jelly

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CORRESPONDENCE

Fabrizio Leone
simonabarni@hotmail.com
fabrizio.leone@uniroma1.it
fabrizioleone22@gmail.com

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INTRODUCTION

Food protein-induced enterocolitis (FPIES) is a non-immunoglobulin E (IgE)-mediated food allergy syndrome typically diagnosed in infancy and childhood presenting with delayed onset of vomiting often accompanied by lethargy, pallor and sometimes followed by diarrhea, always in the absence of cutaneous and respiratory symptoms [1]. Symptoms of acute FPIES are usually resolved within 24 hours after food ingestion. Acute FPIES is diagnosed when the major criterion and at least three minor criteria are fulfilled (Tab. I) [2].

In infancy, FPIES is most commonly triggered by cow's milk, followed by soy, oats, and rice [2,3]. Clinical features range from mild-to-moderate to severe acute reactions. Laboratory findings

TABLE I. Acute FPIES criteria according to Nowak-Wegrzyn et al., 2017.

Major criteria	Minor criteria
1. Vomiting 1-4 h following food trigger ingestion	1. A second (or more) episode of repetitive vomiting after eating the same suspect food
2. Absence of IgE-mediated skin and respiratory symptoms	2. Repetitive vomiting episode 1-4 h after eating a different food
	3. Lethargy
	4. Pallor
	5. Hypotension
	6. Hypothermia
	7. Diarrhea within 24 h (typically within 5 to 10 h)
	8. Need for emergency department visit for suspected reaction
	9. Need for intravenous fluid support with any suspected reaction

during mild-to-moderate acute episodes may include leukocytosis with neutrophilic predominance, thrombocytosis, and the presence of fecal leukocytes or eosinophils [2].

In severe acute episodes, metabolic acidosis and methemoglobinemia may also be observed [3]. The primary treatment for an acute FPIES reaction is supportive care, including oral or intravenous rehydration, while ondansetron is recommended for severe episodes [2].

In the pediatric population, food allergies related to honey are rarely reported in the literature, whereas IgE-mediated allergies to bee venom allergens are well understood. Honey is one of the many products derived from honey bees (Apis mellifera) [4]. It is mainly composed of a mixture of different sugars (80-85%), water (15-17%), and a very small quantity of proteins (0.1-0.4%), but it also contains enzymes, organic acids, vitamins, minerals, and phenolic compounds [5]. Api m 1, Api m 2, Api m 3, Api m 4, and Api m 10 are components of bee venom that are not intrinsic allergens of honey. However, these proteins can be found in honey due to contamination from bees. The primary allergens responsible for honey-related reactions are thought to be pollen proteins, particularly from the Compositae family, as well as glandular secretions and other bee-derived materials. Allergens include also the major royal jelly protein 1 (MRJP1): the most represented protein in royal-jelly [6]. Furthermore, due to the different biological components, honey may contain cross-reactive carbohydrate determinants (CCD), carbohydrate structures capable of inducing reactions cross allergies for their ability to interact with different allergenic glycoproteins, causing false positive in diagnostic evaluations [7]. These data show the complexity in diagnosis of honey allergy.

CASE PRESENTATION

A 4-year-old boy presented to our Allergy and Immunology department with a history of repetitive emesis after consuming honey, royal-jelly, or food containing honey in three different episodes. The child was diagnosed with non-IgE-mediated cow's milk protein allergy (CMPA) at 15 days of life, which completely resolved by 6 months. The child had a history of mild atopic dermatitis and family history of allergy to inhalants and drugs. At one year of age, he experienced repetitive projectile vomiting within two hours of consuming honey biscuits, without diarrhea or other symptoms suggestive of IgE-mediated food allergy. Similar episodes occurred at 18 months and 2 years of age after consuming acacia honey and royal jelly. In all three instances, symptoms resolved spontaneously at home without medical intervention.

Diagnostic investigations included skin prick test (SPT) using fresh royal jelly (Mayasprint) and acacia honey; other tests resulted negative and prick-by-prick-test (PbP) with honey and royal jelly were negative. Total IgE was 17.9 U/mL with no peripheral eosinophilia. Specific IgE and molecular diagnostics, summarized in Table II, were also negative. An Oral Food Challenge (OFC) was conducted using 4.8 mL of acacia honey, divided into four equal portions and administered over the course of approximately one hour.

Two hours after ingestion, the patient experienced repetitive vomiting, followed by two additional episodes within the next two hours. The child appeared both pale and lethargic, but did not exhibit diarrhea, cutaneous reactions, or cardiorespiratory symptoms. Vital signs remained stable throughout the observation period. The patient was discharged with instructions to avoid honey and honey-containing foods. Based on FPIES diagnostic criteria (Tab. I), the challenge was deemed positive.

CONCLUSION

According to our knowledge, just one case of FPIES induced by honey has been reported in the literature [8]. Our case shows the importance of considering isolated vomiting as a possible symptom of honey allergy, even in the absence of positive standard diagnostic tests. We hypothesized that it could be a FPIES

TABLE II. Laboratory Tests and Diagnostic Procedures in the Patient Evaluation.

Test		Results
Total IgE		17.9 (n.v.:4-1 00 U/mL)
Eosinophils		0.13 (n.v.: 0-1.8 x 10^9/L)
	Source	
FEIA	f247 (honey)	0 (n.v. ≤ 0.35 kU/L)
SPT	Fresh royal jelly and acacia honey	0 mm (n.v. < 3 mm)
Molecular components		Negative (n.v. ≤ 0.35 kU/L)
Api m 1-4 /m10	Honeybee venom (Apis mellifera)	0
Bet v 1	Birch pollen (Betula verrucosa)	0
Phl p 1	Timothy grass pollen (Phleum pratense)	0
Amb a 1	Ragweed pollen (Ambrosia artemisiifolia)	0
Art v 1	Mugwort pollen (Artemisia vulgaris)	0
Ole e 1	Olive tree pollen (Olea europaea)	0
Cup a 1	Arizona cypress pollen (Cupressus arizonica)	0
Profilin	Plant protein (cross-reactive allergen)	0
CCD (Hom s LF)	Cross-reactive carbohydrate determinants	0

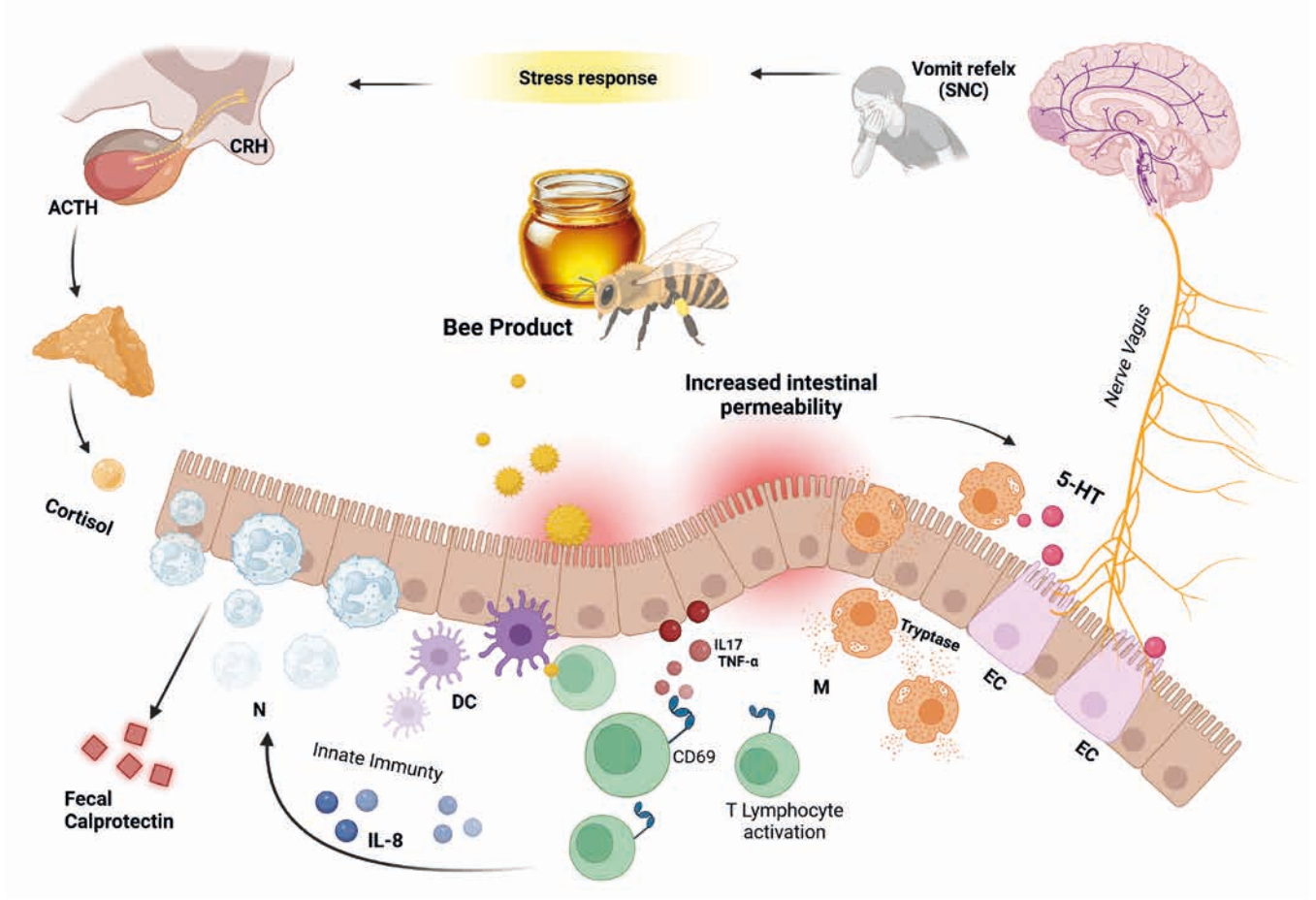
FEIA: Fluorescent Enzyme Immunoassay; SPT: Skin Prick Test; n.v.: normal value.

triggered by honey, given the isolated repetitive gastrointestinal manifestation, the absence of any IgE related symptoms and the negativity of specific IgE.

Vomiting is a hallmark of FPIES, typically occurring 1 to 4 hours after ingestion of the triggering food. The mechanism underlying this symptom involves a complex interplay of immune-mediated and possibly neuroimmune pathways [9] (Fig. 1). Evidence from studies suggests that antigen-specific T lymphocytes may play a pivotal role, with peripheral lymphocytes showing activation and increased expression of CD69 during reactions [10]. Elevated levels of cytokines such as IL-17 and TNF-α have been reported, contributing to intestinal inflammation and increased gastrointestinal permeability. This disruption of barrier function is further exacerbated by a decrease in TGF-β, which normally preserves gastrointestinal integrity [9].

The vomiting observed in FPIES may also involve the autonomic nervous system. This condition has been hypothesized to result, in part, from dysregulation of the autonomic response, triggered by cytokine release and gastrointestinal fluid shifts. Supporting this, ondansetron – a selective serotonin receptor antagonist – has proven effective in alleviating vomiting, suggesting that serotonin release in the gastrointestinal tract may contribute to the symptoms. Immune cells, mast cells, and enterochromaffin cells have been implicated as potential sources of this serotonin release during inflammatory responses [9].

Honey contains small amounts of proteins, such as those derived from Apis mellifera, and other bioactive components that could theoretically act as antigens. Although limited data exists on honey-induced FPIES, the repetitive vomiting seen in such cases aligns with the characteristic clinical presentation of the syndrome, further underscoring the need to explore uncommon triggers and the complex mechanisms behind these non IgE-mediated reactions. The repeated episodes triggered by different types of honey and honey-containing products, along with the rarity of mad honey in common commercial products, allowed us to exclude grayanotoxin-related intoxication. Additionally, the patient did not present the typical neurological symptoms of mad honey poisoning, such as confusion, dizziness, or excessive sweating. Furthermore, there was no history of honey sourced from regions where grayanotoxin-containing honey is endemic, making this diagnosis highly unlikely. [11]. In FPIES, neutrophilia is a well-documented response, with an increase in neutrophil count often observed after a positive OFC, likely driven by stress responses involving cortisol and IL-8 [12]. Elevated fecal calprotectin reflects neutrophilic inflammation in the gastrointestinal tract, while serum tryptase, though less consistently elevated, may indicate mast cell activation contributing to the pathophysiology. OFC remains the gold standard for diagnosis of FPIES, and our patient's clinical history and positive OFC were sufficient to confirm the diagnosis. While additional tests such were not performed, they might provide further insights into the inflammatory response but are not required for diagnostic confirmation. Clinical management involves a correct diagnostic



ACTH: Adrenocorticotropic Hormone; CD69: Cluster of Differentiation 69; CRH: Corticotropin-Releasing Hormone; DC: Dendritic Cell; EC: Enterochromaffin Cell; IL-8: Interleukin-8; IL-17: Interleukin-17; M: Mast Cell; N: Neutrophil; SNC: Central Nervous System; TNF-α: Tumor Necrosis Factor Alpha; 5-HT: Serotonin (5-Hydroxytryptamine).

FIGURE 1. Proposed pathophysiological mechanism of honey-triggered FPIES. The diagram illustrates the complex interplay of immune, neuroimmune, and endocrine responses in FPIES triggered by honey. Bee products introduce bioactive components that compromise the intestinal barrier, leading to increased permeability and the activation of innate immunity through dendritic cells, neutrophils, and T lymphocytes. IL-8 drives neutrophil recruitment, which contributes to the release of fecal calprotectin, a marker of neutrophilic intestinal inflammation. Mast cells release tryptase, exacerbating intestinal inflammation and permeability, along with serotonin, which acts on enteric and vagal nerve endings. Enterochromaffin cells also release serotonin, further activating the vagus nerve and triggering the vomiting reflex via the central nervous system. Additionally, cortisol, released during the stress response, amplifies neutrophil activation and contributes to the inflammatory process within the intestinal mucosa

process, an avoidance diet and patient education. It is worth noting that FPIES often resolves spontaneously with age, particularly for common triggers such as cow's milk, although data on rare triggers like honey remain limited and warrant further investigation.

Conflict of interest

The authors declare that they have no conflicts of interest.

Authors contributions

FL, MV, OTD, SM, GC and MD made the diagnosis and wrote the paper; FL, SI, CA and AMZ revised the manuscript. All authors read and approved the final manuscript.

References

1 Nowak-Wegrzyn A, Berin MC, Mehr S. Food Protein-Induced Enterocolitis

Syndrome. J Allergy Clin Immunol Pract 2020;8:24-35. https://doi.org/10.1016/j.jaip.2019.08.020.

2 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;139:1111-1126.e4. https://doi.org/10.1016/j.jaci.2016.12.966.

3 Mathew M, Leeds S, Nowak-Węgrzyn A. Recent Update in Food Protein-Induced Enterocolitis Syndrome: Pathophysiology, Diagnosis, and Management. Allergy Asthma Immunol Res. 2022;14:587. https://doi.org/10.4168/aair.2022.14.6.587.

4 Palma-Morales M, Huertas J, Rodríguez-Pérez C. A Comprehensive Review of the Effect of Honey on Human Health. Nutrients 2023;15:3056. https://doi.org/10.3390/nu15133056.

5 Baloš MMŽ, Popov NS, Radulović JZP, et al. Sugar profile of different floral origin honeys from Serbia. J Apicult Res 2020;59:398-405. https://doi.org/10.1080/00218839.2020.1714193.

6 Hayashi T, Takamatsu N, Nakashima T, et al. Immunological Characterization of Honey Proteins and Identification of MRJP 1 as an IgE-Binding Protein. Biosci Biotechnol Biochem 2011;75:556-560. https://doi.org/10.1271/bbb.100778.

7 Matricardi PM, Potapova ES. Cross-reactive Carbohydrate Determinants (CCD): biochimica, epidemiologia, impatto diagnostico e clinico. Italian Rivista di Immunologia e Allergologia Pediatrica 2021;35:10-16. https://doi.org/10.53151/2531-3916/2021-9.

8 Villamor Martín T. La miel como causa de enterocolitis inducida por proteínas alimentarias. Reporte de un caso y revisión de la literatura. Revista Electrónica de PortalesMedicos.com 2023;XVIII(14);801.

9 Baker MG, Cecilia Berin M, Sicherer S. Update on Food Protein–Induced Enterocolitis Syndrome (FPIES). Curr Allergy Asthma Rep 2022;22:113-122. https://doi.org/10.1007/s11882-022-01037-y.

10 Goswami R, Blazquez AB, Kosoy R, et al. Systemic innate immune activation in food protein–induced enterocolitis syndrome. J Allergy Clin Immunol 2017;139:1885-1896.e9. https://doi.org/10.1016/j.jaci.2016.12.971.

11 Ullah S, Khan SU, Saleh TA, et al. Mad honey: uses, intoxicating/poisoning effects, diagnosis, and treatment. RSC Adv 2018;8:18635-18646. https://doi.org/10.1039/C8RA01924J.

12 Shimomura M, Ito Y, Tanaka H, et al. Increased serum cortisol on oral food challenge in infants with food protein-induced enterocolitis syndrome. Pediatr Int 2018;60:13-18. https://doi.org/10.1111/ped.13449.