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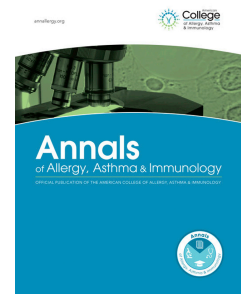
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Psychosocial and Neurodevelopmental Aspects of FPIES

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~~Systematic Literature Review of~~ Psychosocial and Neurodevelopmental Aspects of FPIES

Food Protein-Induced Enterocolitis Syndrome (FPIES) is a non-IgE-mediated food allergy that presents with severe vomiting and lethargy, with or without diarrhea, within 1-4 hours of ingestion of a trigger food antigen¹. In about 15% of cases, the reaction may be severe enough to cause hypotension and shock. Prevalence of FPIES is likely underestimated, with a reported incidence of 0.34% to 0.7% amongst infants^{2,3}. Although FPIES in adults has been reported, it is typically a disease of young children. Symptoms are often triggered by the first food introduced in the infant's diet. Cow's milk is the most common trigger in infants, although any food can trigger symptoms⁴, including fruits, vegetables, or grains.

Numerous aspects of FPIES can heighten risk of parent psychosocial concerns. Children can have more than one food trigger, and there is no test to predict future food triggers, leaving families fearful of new food introduction. FPIES remains under-recognized in the medical community, and symptoms can mimic other childhood diseases (e.g., viral illness), resulting in delayed or misdiagnosis. The frightening nature of symptoms (e.g., vomiting to shock) may be experienced as traumatic, causing ongoing hypervigilance and stress around feeding and monitoring one's child⁵. Some parents even suggest anecdotal "obsessive-compulsive disorder" (OCD) tendencies around tracking foods and reactions. Breastfeeding mothers of babies with FPIES may try an elimination diet to improve their baby's health, which may be stressful. Other mothers may choose to wean before they are ready to start their baby on hypoallergenic formula. These mothers may be at risk for postpartum depression due to feeding decisions. Anecdotally, parents report fear, anxiety, and even post-traumatic stress

disorder (PTSD) around their baby's most severe reactions. Additionally, babies with multiple FPIES triggers or chronic reactions may be at risk for growth stunting⁶ and nutrient deficiencies (iron, vitamin D, zinc)⁷. Because poor growth and nutrition could impact overall development, it is important to examine neurodevelopmental outcomes of babies with FPIES. The FPIES guidelines do not address neurodevelopment in a child with FPIES.

We conducted a systematic review of the FPIES literature to assess the state of the science on psychosocial and neurodevelopmental aspects of FPIES. Using PubMed with no restrictions, we searched "FPIES" with the "AND" operator with each of the following terms addressing parent psychosocial functioning and potential neurodevelopmental outcomes of poor nutritional status: "psychological;" "psychosocial;" "depression;" "postpartum;" "anxiety;" "panic;" "OCD;" "obsessive;" "trauma;" "PTSD;" "quality of life;" "development;" "neurodevelopment;" "cognitive;" "functional;" "academic;" "attention;" "memory;" "intelligence;" "motor;" "processing;" "executive function." The same searches were conducted again using "gastrointestinal allerg*" as the allergy search term to pull both "allergies" and "allergy." All article titles were reviewed by the first author to determine if they were appropriate for inclusion. If article titles were not clear, abstracts were reviewed. A total of four articles were returned on the "quality of life" (QOL) search (two with "FPIES" and two with "gastrointestinal allerg*"). Full texts of these four articles on QOL were reviewed. References of the included articles were reviewed; no additional studies were identified.

The four papers in this review described QOL in families managing non-IgE-mediated, gastrointestinal food allergies. One paper⁵ was an opinion paper describing psychosocial issues experienced by parents of children with FPIES, although no empirical data were reported. The

second FPIES paper⁸ reported health-related QOL data in parents of children with FPIES, indicating that parents of children with FPIES report lower QOL than parents of children with IgE-mediated allergies. This paper used a validated, food allergy-specific QOL measure (the Food Allergy Quality of Life – Parent Burden measure) and delineated specific domains of QOL in which FPIES caregivers fared worse psychosocially than caregivers of children with IgE-mediated allergies. The Greenhawt et al. study did not assess specific clinical constructs that may guide intervention, e.g., parental postpartum distress, general anxiety, or trauma. A study by Foong et al.⁹ reported on 52 parents of children with gastrointestinal allergies (including FPIES and other diagnoses). They found that QOL was higher in patients with gastrointestinal allergies than patients with abdominal pain, but some domains, particularly physical QOL, were lower than in IgE-mediated allergies. Meyer et al.¹⁰ found lowered QOL in families of children with gastrointestinal allergies on elimination diets compared to children with intestinal failure and children with sickle cell disease. The Foong et al. and Meyer et al. studies were not limited to just FPIES diagnoses, and the Meyer et al. sample consisted of children on an elimination diet, perhaps not representative of all families coping with FPIES. Nevertheless, these four papers indicate notable concerns with impaired QOL in the FPIES population.

Other than the four included articles, no other research was identified that delineated psychological symptoms in parents (e.g., postpartum depression, trauma/PTSD, or other anxiety disorders) despite anecdotal reports of such. No studies were identified that examined neurodevelopmental outcomes or cognitive concerns in young children with FPIES, despite risk for nutrition-related issues that might affect growth and brain development. Although psychosocial aspects of IgE-mediated allergies have been reported, this review indicates that

there is far less literature on FPIES. The burgeoning FPIES literature focuses on medical and nutrition management but without addressing the parent psychosocial experience of managing this distressing condition. Researchers should explore specific clinical outcomes beyond QOL, including parent psychological functioning (depression, anxiety), to inform specific parent interventions. There is also a need to systematically assess developmental concerns (e.g., oral-motor development) in young children with FPIES, particularly in those with nutritional or growth concerns.

Child developmental outcomes are difficult to conceptualize and test in preliminary research, as there are likely cyclical or bidirectional associations between variables: proper nutrition, age-appropriate growth, age-appropriate oral-motor development and feeding, positive parent functioning, and positive parent-child relationships all interact in complex ways. These research questions are best addressed through interdisciplinary collaborations with allergists, psychologists, dietitians, and other allied health providers. Multi-site or registry studies are necessary for adequate statistical power. Ultimately, clinicians would benefit from brief screening tools to screen parent psychosocial functioning and child development to facilitate early intervention and comprehensive care of young children with FPIES.

References

1. Nowak-Wegrzyn 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.e1114.
2. 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(3):647-653.e641-643.
3. Alonso SB, Ezquiaga JG, Berzal PT, et al. Food protein-induced enterocolitis syndrome: Increased prevalence of this great unknown-results of the PREVALE study. *J Allergy Clin Immunol*. 2019;143(1):430-433.
4. Ruffner MA, Ruymann K, Barni S, Cianferoni A, Brown-Whitehorn T, Spergel JM. Food protein-induced enterocolitis syndrome: insights from review of a large referral population. *J Allergy Clin Immunol- In Practice*. 2013;1(4):343-349.
5. Schultz F, Westcott-Chavez, A. Food protein-induced enterocolitis syndrome from the parent perspective. *Curr Opin Allergy Clin Immunol*. 2014; 14:263–267.
6. Meyer, R, De Koker, C, Dziubak, R et al. The impact of the elimination diet on growth and nutrient intake in children with food protein induced gastrointestinal allergies. *Clin Transl Allergy*. 2016;6:25.

- 107 7. Cherian, S., Varshney, P. Food Protein-Induced Enterocolitis Syndrome (FPIES): Review
108 of recent guidelines. *Curr Allergy Asthma Rep.* 2018;18:28.
- 109 8. Greenhawt, M, Schultz, F, DunnGalvin, A. A validated index to measure health-related
110 quality of life in patients with food protein–induced enterocolitis syndrome. *J Allergy*
111 *Clin Immunol.* 2015;137(4):1251-3.
- 112 9. Foong, RX, Meyer R, Godwin H, et al. Parental perception of their child’s quality of life in
113 children with non-immunoglobulin-E-mediated gastrointestinal allergies. *Pediatr Allergy*
114 *Immunol* 2017;28:251-6.
- 115 10. Meyer, R, Godwin, H, Dziubak, R, et al. The impact on quality of life on families of
116 children on an elimination diet for Non-immunoglobulin E mediated gastrointestinal
117 food allergies. *World Allergy Organization Journal.* 2017;10:8.

References

1. Nowak-Wegrzyn 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.e1114.
2. 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(3):647-653.e641-643.
3. Alonso SB, Ezquiaga JG, Berzal PT, et al. Food protein-induced enterocolitis syndrome: Increased prevalence of this great unknown-results of the PREVALE study. *J Allergy Clin Immunol*. 2019;143(1):430-433.
4. Ruffner MA, Ruymann K, Barni S, Cianferoni A, Brown-Whitehorn T, Spergel JM. Food protein-induced enterocolitis syndrome: insights from review of a large referral population. *J Allergy Clin Immunol- In Practice*. 2013;1(4):343-349.
5. Schultz, F, Westcott-Chavez, A. Food protein-induced enterocolitis syndrome from the parent perspective. *Curr Opin Allergy Clin Immunol*. 2014; 14:263–267.
6. Meyer, R, De Koker, C, Dziubak, R et al. The impact of the elimination diet on growth and nutrient intake in children with food protein induced gastrointestinal allergies. *Clin Transl Allergy*. 2016;6:25.
7. Cherian, S., Varshney, P. Food Protein-Induced Enterocolitis Syndrome (FPIES): Review of recent guidelines. *Curr Allergy Asthma Rep*. 2018;18:28.
8. Greenhawt, M, Schultz, F, DunnGalvin, A. A validated index to measure health-related quality of life in patients with food protein–induced enterocolitis syndrome. *J Allergy Clin Immunol*. 2015;137(4):1251-3.
9. Foong, RX, Meyer R, Godwin H, et al. Parental perception of their child's quality of life in children with non-immunoglobulin-E-mediated gastrointestinal allergies. *Pediatr Allergy Immunol* 2017;28:251-6.
10. Meyer, R, Godwin, H, Dziubak, R, et al. The impact on quality of life on families of children on an elimination diet for Non-immunoglobulin E mediated gastrointestinal food allergies. *World Allergy Organization Journal*. 2017;10:8.