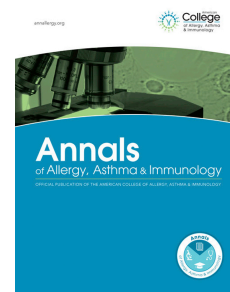


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Food protein induced enterocolitis syndrome to nuts – an increasing phenomenon.

Dr Samara Baldwin, MBBS, Dr Rebecca Werther, FRACP, Dr Ania Hargrove, FRACP, Dr Aikaterini Anagnostou, MD, PhD, Dr Sam Mehr, FRACP, FRCPA



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Title: Food protein induced enterocolitis syndrome to nuts – an increasing phenomenon.

Authors: Dr Samara Baldwin, MBBS^{1,2}, Dr Rebecca Werther, FRACP³, Dr Ania Hargrove, FRACP¹; Dr Aikaterini Anagnostou MD, PhD^{4,5}, Dr Sam Mehr, FRACP, FRCPA^{1,2}

Institutional Affiliations: 1. Epworth Allergy Specialists, Epworth Hospital, Richmond, Victoria, Australia. 2. Department of Allergy/Immunology, Royal Children's Hospital, Melbourne, Victoria, Australia. 3. Stem Allergy and Paediatric Specialists, Glen Iris, Victoria, Australia. 4. Baylor College of Medicine, Department of Pediatrics, Section of Immunology, Allergy and Retrovirology Houston, TX. 5. Texas Children's Hospital, Department of Pediatrics, Section of Immunology, Allergy and Retrovirology, Houston, TX

Corresponding Author: Sam Mehr, Epworth Allergy Specialists, 34 Erin Street, Richmond, VIC, Australia, 3121. Phone: +61394266888. Fax: +61 394266889. Email: sam.mehr@rch.org.au

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Abbreviations/Acronyms: ALD, almond; BZN, brazil nut; CSW, cashew; D, Diarrhoea; E, eczema; F, floppy; FPIES, food protein induced enterocolitis syndrome; HZN, hazelnut; IgE FA, IgE mediated food allergy; L, lethargy; MDM, macadamia; P, pale; PN, peanut; PCN, pecan; PST, pistachio; PV, profuse vomiting; SPT, skin prick test; ssIgE, serum specific IgE; WN, walnut.

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Food protein induced enterocolitis syndrome (FPIES) is a non-IgE mediated food allergy, which typically presents in infancy. Whilst rice is a rare cause of IgE mediated food allergy, it is one of the commonest triggers of FPIES in Australia and the USA^{1,2}. Conversely, peanut and treenuts are rarely described to cause FPIES, but are common triggers of IgE mediated food reactions. Ruffner et al reported peanut and treenuts FPIES in only 2% and < 1% of children respectively, in a retrospective cohort of 462 children from a single institution². Mehr et al reported a single case (0.5%) of peanut FPIES in a prospective population-based study of 230 children¹. Case reports of peanut FPIES have been published⁴, and one case of peanut FPIES was noted as a reason for discontinuation in the LEAP trial⁵. We recently noted an increase in the number of children being referred with peanut FPIES to our private allergy services, in Melbourne, Australia.

We undertook a retrospective study to determine the clinical characteristics of infants with peanut and treenut FPIES over the last 12 months. Searching our correspondence letters using key words initially identified cases. Key words included nut FPIES and nut and vomiting. All children had to fulfil the international criteria for acute FPIES⁶. Following ethics approval, all parents were then contacted by phone to ensure complete capture of complete demographic, clinical and laboratory information.

We report 9 with peanut FPIES and 1 with hazelnut FPIES (Table 1). 8 children were diagnosed between January to October 2020; two were diagnosed in 2017 and 2019 and both reviewed in 2020. 7/10 were male, all were born at term via normal vaginal delivery, and all presented with their first peanut or hazelnut FPIES reaction less than 12 months of age (mean 7.3 months, SD 1.8). The average age of diagnosis was 9.8 months (SD 2.6). 6/10 had eczema, with only 1/10 having an IgE mediated food allergy (the infant with hazelnut FPIES had had an IgE mediated reaction to egg). 9/10 had a family history of atopic disease in at least one first degree relative, but none had a family history of FPIES.

23 separate episodes of FPIES to either peanut or hazelnut occurred in the 10 cases. One case of peanut FPIES had 4 separate episodes, 3 cases of peanut FPIES had 3 episodes, 4 had 2 episodes (including the one child with hazelnut FPIES), and 2 had a single episode of peanut FPIES (Table 1). Five children (4 with peanut and 1 with hazelnut FPIES) also had FPIES to another non-nut food (Table 1). Out of the 9 children with peanut FPIES, 4 had been exposed and tolerated soy (5 had not yet been exposed). Three children with peanut FPIES reacted on their first known exposure, whilst the remaining 6 children with peanut FPIES reacted following at least one prior tolerated exposure. The child with hazelnut FPIES had tolerated hazelnut on 4 prior occasions.

All children presented with delayed profuse vomiting to the triggering nut (mean time to reaction of 2.7 hours, SD 0.8). Out of the 23 episodes, 17 also presented with concomitant lethargy, pallor and/or floppiness (in 12 cases, both pallor and floppiness/lethargy were noted). Only one child with peanut FPIES did not have a skin prick test (SPT)/serum specific IgE (ssIgE) at the time of diagnosis. The remaining all had negative SPT or ssIgE to the triggering nut.

All children were encouraged to eat other nuts following their initial consultation and some had already introduced other nuts (Table 1). No child had FPIES or an IgE mediated reaction to another introduced nut. Of the 9 with peanut FPIES all had eaten at least one other treenut and 6 children had tolerated at least 3 treenuts. The infant with hazelnut FPIES had also tolerated peanut and three treenuts. All children except one were continuing to avoid their nut trigger. One patient (patient 8) diagnosed with peanut FPIES at 10 months of age was reviewed at 19 months of age, had a negative SPT to peanut and then tolerated peanut at 20 months of age.

Based on our data, peanut FPIES appears to be increasingly recognised. One Australian population-based study reported a single case of peanut FPIES over 2 years¹. This was prior to the publication of the LEAP trial⁵, and therefore before the active promotion of early nut introduction by Allergy societies. In contrast we report 10 cases of nut FPIES from a single institution, 8 of whom presented over the last 10 months. We found no cases of peanut or treenuts FPIES presenting to our institution before 2017. Whether this is due to better recognition of FPIES, or due to a true increase in incidence due to early nut introduction will require on going surveillance. Given early egg introduction is also promoted, a subsequent rise in egg FPIES should be noted if what we are witnessing is a “LEAP effect”.

Although no child in our cohort had a confirmatory food challenge, all fulfilled the criteria set by international experts for FPIES⁶. Food challenge is encouraged in children with single FPIES episodes. Only 2 of the 10 cases had single episodes, but both had stereotypical reactions of FPIES and FPIES to another non-nut trigger.

Robbins et al published a case series of 3 children with peanut FPIES. All three infants had eczema, 2 tolerated peanut multiple times before reacting, but none had a history of FPIES to another food, and all had low level sensitisation peanut ssIgE at diagnosis. No information regarding treenut tolerance was provided.

Our cohort provides insights into infants with nut FPIES. All presented under 12 months of age, eczema was common, but concomitant IgE mediated food allergy was uncommon, and FPIES to another non-nut food was present in half of the cases. All children with peanut FPIES tolerated at least one treenut, although our cohort did not include any infants with cashew or walnut FPIES to determine a potential co-allergy to pistachio or pecan respectively (as is often reported in IgE mediated allergy).

72 Nut FPIES may not be as rare as once thought. Further research is required to determine if
73 others are noting an increase in nut FPIES, and whether such children are at risk of IgE
74 mediated transformation or potentially have better rates of tolerance than children with
75 peanut or treenut IgE mediated allergy.

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Table 1 – Clinical characteristics of the 10 children with nut FPIES

Patient number	Gender	Age at reaction (months)	Atopic disorder at diagnosis	Triggering nut	Number times tolerated before FPIES	Symptoms at reaction	Time to reaction (hours)	SPT/ssIgE to nut trigger at diagnosis	FPIES to other foods	Introduced and tolerated nuts
1	M	R1: 6 mo R2: 6mo + 2 wk R3: 7 mo	E	PN	3	R1: PV, L R2: PV, L R3: PV, L	R1:2hr R2:2hr R3:2hr	ssIgE 0.02 KuA/L	No	HZN, ALD, WN
2	F	R1: 6 mo R2: 6mo + 1 wk R3:9 mo	Nil	PN	3	R1: PV, L, P R2: PV, P R3: PV, L, P	R1:2hr R2:4hr R3:4hr	ssIgE <0.1 KuA/L	Fish (Snapper)	HZN, WN, ALD
3	M	R1: 6 mo R2: 6mo + 2 wk R3:8 mo	E	PN	3	R1: PV R2: PV R3: PV	R1:3hr R2:3hr R3:2hr	SPT 0mm	No	ALD, CSW, WN
4	M	R1: 8 mo R2: 8 mo + 1 wk	E	PN	3	R1: PV R2: PV, L, P	R1:4hr R2:2hr	SPT 0mm	Banana	ALD
5	M	R1: 5 mo	Nil	PN	3	R1: PV, L, P	R1:2hr	SPT 0mm	No	CSW, PST,

		+ 2 wk R2: 5 mo + 3 wk				R2: PV, L	R2:2hr			PCN, WN, MDM, ALD, HZN
6	M	R1: 10mo R2: 10mo + 2 wk	E, IgE FA (egg)	HZN	4	R1: PV, L, P, F R2: PV, L, P, F, D	R1:3hr R2:2hr	SPT 0mm	Fish (Rockling)	ALD, BZN, PST, PN
7	F	R1: 5mo + 2 wk R2: 5mo + 3 wk	Nil	PN	2	R1: PV, L, P, F R2: PV	R1:2.5hr R2:2hr	SPT 0mm	No	CSW, HZN MDM, PCN
8	F	R1: 10mo	E	PN	0	R1: PV, L, P, F	R1:2hr	N/A	Avocado	ALD
9	M	R1: 8mo	Nil	PN	0	R1: PV, D	R1:4hr	SPT 0mm	Oats, Rice	PST, ALD
10	M	R1: 8mo R2: 9mo R3: 10mo R4: 16mo	E	PN	0	R1: PV, P, F R2: PV, P, F R3: PV, P, F R4: PV, P, F	R1:2hr R2:2hr R3:2hr R4:2hr	SPT 0mm	No	CSW, MDM, ALD, HZN, BZN

Abbreviations: ALD, almond; BZN, brazil nut; CSW, cashew; D, Diarrhoea; E, eczema; F, floppy; HZN, hazelnut; IgE FA, IgE mediated food allergy; L, lethargy; MDM, macadamia; P, pale; PN, peanut; PCN, pecan; PST, pistachio; PV, profuse vomiting; SPT, skin prick test; ssIgE, serum specific IgE; WN, walnut.