Response to 'Korean gender differences in hidradenitis suppurativa: nature or nurture?'

Editor

We thank R. Happle for his invaluable comments[1] on our recent article regarding the prevalence of hidradenitis suppurativa (HS) in Korea.[2] We agree with the opinion that the low prevalence of HS in Korean women may be due to the low number of female smokers in Korea. Although the Korean National Health Insurance Claims Database used in our study did not record the smoking habit of each individual, another recent Korean study revealed interesting findings regarding this issue.[3]

Yang *et al.*[3] reviewed the detailed medical records of 438 HS patients in 13 Korean hospitals and showed a male predominance, with a male-to-female ratio of 2.5:1. Of the HS patients included in the study, the overall smoking rate was 38.3%, of which 46.1% of male patients and 14.0% of female patients were smokers. According to the latest statistics from the Ministry of Health and Welfare, the smoking rate of Koreans was 22.3% in 2017, 38.1% for males and 6.0% for females. The smoking rate of female patients was twice as high as that of the general female population in Korea, indirectly suggesting a possible relationship between HS and smoking.

One interesting point is that the reported prevalence of smoking in patients with HS in East Asia is lower than that reported in Western countries. Previous studies with a Western population reported a high prevalence of smoking in HS patients, and some studies had rates as high as 90% in HS populations.[4,5] However, the rate of smoking among HS patients in East Asia is relatively low: 29% in a Japanese study,[6] 34–38.3% in Korean studies[3,7] and 32.8% in Singapore.[8]

A number of potential mechanisms have been suggested for the role of smoking in the pathogenesis of HS, including alteration of neutrophil chemotaxis, release of toxic metabolites in sweat, and the promotion of inflammation via follicular occlusion and inhibition of normal glandular secretion by nicotine.[4] Although smoking is a well-defined major risk factor for developing HS, the influence of smoking may also vary among races. In this respect, epidemiologic studies of various countries would seem to have a number of implications. Further studies are warranted, including an exploration of genetic susceptibilities among races.

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Linked article: R. Happle. *J Eur Acad Dermatol Venereol* 2019; **33**: e256. https://doi.org/10.1111/jdv.15507

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DOI: 10.1111/jdv.15500

Food Protein-Induced Enterocolitis Syndrome in South Tyrol 2012–2016: a population-based study

Dear Editor,

Food protein-induced enterocolitis syndrome (FPIES) is a rare non-IgE-mediated food allergy to protein mainly in cow milk (CM) that typically presents in early infancy. Projectile and

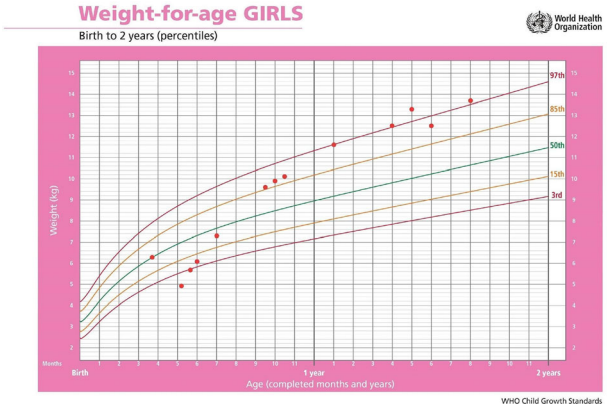

Figure 1 WHO weight-for-age percentile table for girls with values shown for infant 4. Severe underweight is noted before recommending the amino acid based of cow milk (Neocate LCP™). Copyright WHO URL: https://www.who.int/childgrowth/standards/cht_wfa_girls_z_0_2.pdf?ua=1.

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Table 1 Summary of gastrointestinal symptoms, with major and minor criteria of food protein-induced enterocolitis syndrome (FPIES) as clinical outcome and atopic diseases in affected children. The diagnosis of FPIES, according to American guidelines, requires that a patient meets the major criterion and more than three minor criteria

Patient	Patient 1	Patient 2	Patient 3	Patient 4
Symptoms				
Major criterion according American guidelines on FPIES				
Vomiting in the 1- to 4-h period after ingestion (no IgE symptoms)	Present	Present	Present	Present
Minor criteria according American guidelines on FPIES				
A second (or more) episode of repetitive vomiting	Present	Present	Present	Present
Extreme lethargy	Present	n.r.	n.r.	n.r.
Marked pallor	Present	n.r.	Present	n.r.
Need emergency department visit	Present	Present	n.r.	Present
Need intravenous fluid support	Present	n.r.	Present	Present
Diarrhoea in 24 h (* with blood)	Present	Present	Present	Present (*)
Hypotension	Present	n.r.	n.r.	n.r.
Hypothermia	Present	n.r.	n.r.	n.r.
Blood values supporting acute FPIES (Leonard & al., 2012)	Neutrophils (82.3%), thrombocytes (580.000/mmc)	n.r.	n.r.	n.r.
Blood values supporting acute FPIES (Leonard & al., 2012)	n.r.	n.r.	n.r.	Anaemia (transferrin 151 mg/dL, iron 25 μg/dL), hypoalbuminemia (3.2 g/dL)
FPIES				
Interruption of breast feeding (age)	14 days	3 months	4 months	2 months
Age at onset of FPIES	9 days	3 months and 14 days	5 months	2 months, diagnosis established at 5 months and 7 days
Positive OFC for diagnosis or exposure to alternative formulas	2 months		5 months	
Age of tolerance shown by OFC	20 months	2 years and 5 months		20 months
Not recommended autonomous OFC at home (age)	7 months: FPIES symptoms; 14 months: Tolerated		20 months: Tolerated	
Family history of atopy	Not reported	Father with rhinitis and asthma	Brother with atopic dermatitis and dubious FPIES to CM	None
Supplementation	'Colecalcium' (HUMANA), Vit D and Calcium		'Duocal' (NUTRICIA), glucidic-lipidic formula	'Dicoflor' (DICOFARM), probiotics with Lactobacillus GG
Atopy				
Total IgE during first FPIES reaction	Not performed	38 IU/mL (normal <13)	72 IU/mL (normal <13)	54 IU/mL (normal <13)
Atopic eczema (age of confirmed onset)	Not reported	5 months	8 months	2 months
Positive Food Skin Prick Test/Rast Test during FPIES (food)	Not reported	white egg, both tests positive	Not reported	Casein nBos d8, light positive in Rast Test 0.4 kUA/L (<0.35)
IgE Food Allergy Symptoms (age of onset)	Not reported	3 years	Not reported	Not reported
Anaphylaxis (age of onset)	Not reported	4 years	Not reported	Not reported
Allergic rhinoconjunctivitis with asthma (age of onset)	Not reported	4 years	12 months	Not reported

OFC, oral food challenge.

repetitive vomiting are the main clinical symptoms after 1–4 h of trigger food ingestion. Rapid recognition and instalment of a specific diet are important to avoid serious complications in affected children (see Fig. 1).[1] According to a multicenter Italian study[2] atopy as co-morbidity is rarer than in other countries being 9% compared to a much higher frequency of 28% in Spain,[3] 57% in Australia[4] and over 70% in the USA.[5] To analyse this topic further, we retrospectively retrieved all clinical documents reporting FPIES, as described by Sopo *et al.*,[2] from 2012 to 2016 from all paediatric services in South Tyrol, a northern Italian province near the Austrian border with 524.256 inhabitants at 2016 census.

In total four cases of FPIES were diagnosed in the 5 year period and are summarized in Table 1. All mothers suffered from hypogalactia and had to supplement their infants, who all were hospitalized before the age of 5 months. Diagnosis of FPIES was based on typical clinical presentation and improvement after withdrawal of the suspected trigger food and confirmed with the criteria published by Nowak *et al.*, 2017.[1] Atopic dermatitis was finally diagnosed in three of the toddlers, and all three of them showed a significant increase of total IgE. Despite not being surprising, as patients with atopic dermatitis can present an increase of total IgE,[6] this was not previously reported for patients also affected with FPIES. We speculate that elevated total serum IgE could be a laboratory marker for the future development of atopic dermatitis in toddlers affected by FPIES and normal skin, because typically FPIES presents before clear clinical appearance of atopic dermatitis and on the other hand could also give a hint towards the diagnosis of FPIES in doubtful cases.

Making recommendations for the milk replacement can be difficult. Hydrolysed formulas of CM represent the first choice, followed, in case of intolerance, by amino acid-based formulas (AAF). Substitutes based on other protein sources should be avoided due to correlation to FPIES described for soy and oat in America,[1] to rice protein in Australia[7] and fish in Italy.[2] We also found a second intolerance probably related to FPIES to rice, when patient 3 again showed symptoms of FPIES taking formulas containing rice protein.

A recent Australian population-wide study reported an incidence of 15.4/100 000/year, so FPIES could be more frequent but underdiagnosed.[4] One reason for this underdiagnosis is that parents might also directly avoid feeding suspected products without seeking medical attention, as seen with the sibling of patient 3. However, as awareness increases, reported incidence rates will rise and FPIES is thought to be an emerging allergic disease.[8]

According to our study with three atopic toddlers of four found, the association of FPIES with atopy in Italy might well be higher than the 9% previously reported. The main reasons for this probably are that patients in our study were diagnosed by a dermatologist, while in the previous study no dermatologists were involved. Further, the previous study was older (2004–2010), so a higher awareness of the atopic association with FPIES could also have been playing a role. Awareness of atopy or atopic predisposition is important, as it has been shown that very early skin moisturizing reduces the development and severity of atopic disease. Therefore, we conclude that a dermatologic presentation with counselling to consequent skin care should be advised in all affected children at diagnosis of FPIES in order to reduce or even completely avoid burden of atopic disease.[9,10]

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DOI: 10.1111/jdv.15510