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Letter to the Editor

Food allergy to millet and cross-reactivity with rice, corn and other cereals

Dear Editor,

Millet encompasses a group of cereals from the Poaceae family botanically related to wheat, corn (maize) and rice. While a basic foodstuff in many developing countries, millet is consumed in Westernized countries rather as a “healthy” alternative cereal or a gluten-free substitute for wheat. Yet, millet allergy has been mainly recognized in industrialized countries rather than in low-income countries with high millet consumption, because sensitization seems to occur mostly via the respiratory route through millet-containing birdseed in pet bird holders. Until now only a very limited number of cases have been described from the USA, Japan and Central Europe, many of them involving severe anaphylaxis.^{1–6} Millet allergens have not yet been identified in detail and data concerning their potential cross-reactivity with homolog allergens in other cereals are controversial.

Between 2003 and 2015 we identified nine adult patients with a convincing history of millet allergy. Demographic characteristics, clinical symptoms and potential bird exposure are summarized in Table 1. All patients reacted to millet at the very first occasion. Systemic reactions were mostly moderately severe but three patients developed cardiovascular symptoms requiring emergency treatment. Eight patients currently (pts.1–2) or formerly (pts.3–8) kept budgerigars which were regularly fed with foxtail millet or millet-containing birdseed mixtures. Four of them were exposed to the birds only during childhood. In patients having kept a pet bird in the past, the time elapsed between bird keeping and the allergic reaction to millet varied between 8 and almost 50 years (median 30 years).

ImmunoCAP to millet (f56) was positive in 8/9 patients (0.62–20.00 kU/L) and borderline (0.31 kU/L) in one (Table 1). Bromelain was negative throughout excluding irrelevant IgE-binding to CCDs (cross-reactive carbohydrate determinants). Most sera tested positive also for corn (7/9), rice (6/9), and wheat (6/9). Patients 1–8 had similar binding patterns showing highest IgE levels to millet, somewhat lower ones to corn, and lowest levels to wheat and rice. In contrast, patient 9 showed strongest binding to sesame and much weaker binding to millet and other cereals, which was consistent with a history of anaphylaxis from sesame in this patient. Remarkably, this serum was the only one positive for wheat LTP (rTri a 14). Skin prick testing with millet extracts in five patients was positive (≥ 3 mm) in all, 3/5 tested positive also with rice, corn, wheat, rye, barley and oat.

Dose-dependent inhibition of IgE-binding to millet in patient 1 revealed a maximum inhibition of 89% by millet extracts and of 38% by rice extracts, whereas IgE-binding to rice was equivalently inhibited by millet and rice extracts (Fig. 1). This confirms primary sensitization to millet and secondary cross-reactivity with rice. Millet extracts completely inhibited IgE-binding to rice also in patients 2–5 (87–99%), again identifying millet as the primary sensitizer. In contrast, in patient 9, millet allergens inhibited IgE-binding to rice by only 28% and did not significantly block IgE-binding to sesame (12%) (data not shown). Accordingly, millet is unlikely the primary sensitizer in this patient. Though we do not have final evidence from further in-vitro experiments, we assume that this patient was first sensitized to sesame LTP and later cross-reacted with homolog LTPs in millet and other cereals.

Our findings corroborate the crucial role of bird-keeping and concomitant exposure to millet-containing birdseed as the origin of millet allergy.^{1–3} Regarding this, millet allergy exhibits three notable clinical features. One is that anaphylaxis regularly occurs on the very first occasion of millet consumption.^{1–4} This was true for all of our patients and can be reasonably explained by the fact that primary sensitization mostly occurred through the respiratory route. Another feature is that sensitization is amazingly long-lasting.^{2,4} In this study, only two patients have been keeping pet birds at the time of the food-allergic reaction, while in the others exposure ended as long as almost 50 years before. Accordingly, anaphylaxis may occur in late adulthood as a consequence of bird exposure during childhood. Finally, a third noteworthy detail is the striking predominance of females among millet-allergic patients, just like in allergy to bird feathers.⁷ The reasons for this are unknown. Women might be at higher risk because they more often keep pet birds, which, however, is not true for Austria,⁸ or because they feel more responsible to care about feeding birds and cleaning cages. Alternatively, respiratory sensitization to millet might translate more often into food allergy in women because they are more open-minded than men with respect to eating “healthy” foods like millet.

Bird exposure may also induce sensitization to avian serum albumins present in feathers as well as in egg yolk which in turn may result in secondary egg allergy known as bird-egg syndrome.⁷ In agreement with two previous reports mentioning double-sensitization to millet and bird feathers,^{3,4} two out of eight bird-keepers in our study had concomitant bird-egg syndrome (Table 1) supporting the view that pre-existing sensitization to millet allergens facilitates subsequent co-sensitization to avian serum albumins (or vice versa). Accordingly, potential egg allergy should always be addressed during work-up of millet-allergic subjects.

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Table 1
Clinical symptoms, exposure to pet birds and specific IgE levels in nine patients with millet allergy.

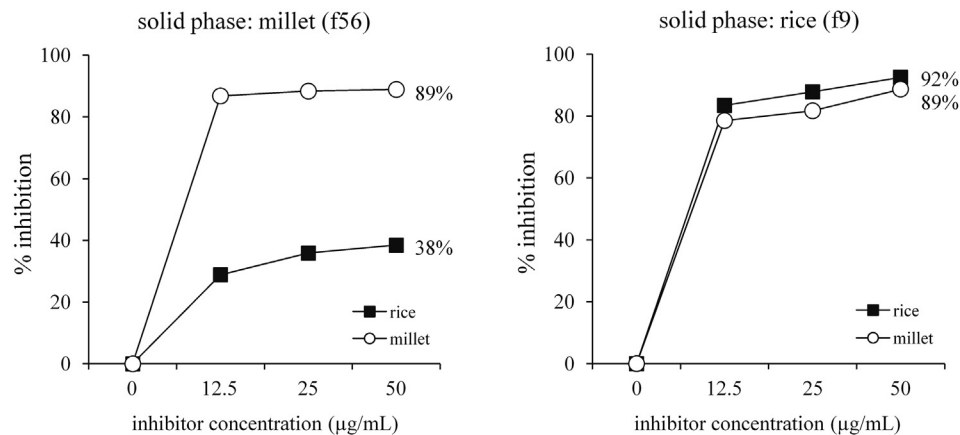
	pt. 1	pt. 2	pt. 3	pt. 4	pt. 5	pt. 6	pt. 7	pt.8	pt.9
Gender/age	f/62a	f/37a	f/50a	f/69a	f/27a	m/88a	f/45a	m/44a	f/42a
Food allergy									
Millet	Dyspnea, angioedema	OAS, erythema, stomach cramps, nausea, palmar itch, hypotension; hospitalization	Dyspnea, hypotension, hospitalization	Severe anaphylaxis; hospitalization	Stomach cramps	Severe OAS, breathing difficulties, nausea	Palmar itch, generalized erythema and edema (incl. tongue), breathing difficulties, vomiting	OAS, angioedema	Urticaria, stomach cramps
Rice	Dyspnea, angioedema	No	No	OAS	No	No	Itch of palms and soles of the feet	No	No
Corn (maize)	No	No	No	Unknown	OAS	Unknown	No	No	No
Wheat, rye	No	No	No	Sneezing when handling flour	Stomach ache from whole grain products	No	No	No	Worsening of atopic eczema
Egg	OAS after fried egg	No	No	No	No	No	No	No	Urticaria
Exposure to birds									
Bird keeping	2–4 budgies since 50 years	2 budgies since many years	1 budgie until 30 years ago	Several budgies until 40 years ago	Extensive exposure to budgies until age of 19	2 budgies until age of 40	Exposure to budgies as a child	1 budgie as a child	Never
Symptoms from bird exposure	Dyspnea when cleaning cage	No	No	sneezing and conjunctivitis when cleaning cage	No	No	No	?	n.a.
Specific IgE (kU/L)									
Millet	20.00	15.80	5.20	4.89	6.52	0.81	0.31	0.62	4.11
Corn	16.10	13.23	3.61	3.97	6.97	0.55	0.16	0.18	2.82
Wheat	15.60	11.80	3.35	1.36	0.59	0.00	0.03	0.05	4.71
rTri a 14	0.06	0.25	0.05	0.07	0.02	0.00	0.00	0.00	1.13
rTri a 19	0.08	0.01	0.00	0.00	0.00	0.00	0.00	0.01	0.53
Rice	4.53	7.03	1.76	2.72	4.51	0.00	0.00	0.04	1.77
Sesame	0.39	0.97	0.23	0.49	0.35	0.00	0.00	0.00	8.59
Budgerigar	29.60	7.60	0.01	0.04	0.03	0.00	0.00	0.01	0.94
Egg yolk	6.46	1.44	0.01	0.03	0.01	0.00	0.02	0.01	28.10
CCDs	0.09	0.04	0.02	0.02	0.05	0.01	0.01	0.02	0.06
Total IgE	2656	350	21	450	100	66	59	31	>2000

OAS, oral allergy syndrome.

Positive ImmunoCAP test results ≥ 0.35 kU/L shown in bold.

Current knowledge concerning cross-reactivity between millet and other cereals is inconsistent and rests upon a very limited number of patients. While some studies observed broad cross-reactivity,^{1,2} others did not.^{4–6,9} These divergent findings may be partly due to the use of distinct and sometimes poorly-validated diagnostics, but also because experimental data are often incomplete, especially with regard to rice and corn. According to the present study, cross-sensitization to other cereals appears to be extensive

in millet-allergy since most of our patients showed positive ImmunoCAP results also to rice, wheat and corn, the latter often revealing binding scores comparable to those for millet. This fits well to new genetic studies in grasses proving a particularly close phylogenetic relationship between millets and corn.¹⁰ Importantly, this cross-reactivity was clinically relevant in more than half of our patients. Though symptoms were mostly mild, all of them permanently avoided eating these cereals. It should be also emphasized that all

**Fig. 1.** Dose-dependent reciprocal inhibition of ImmunoCAP IgE-binding to millet (left panel) and rice (right panel) by millet and rice extracts in a bird-keeper with a history of adverse reactions to both millet and rice (pt. 1).

patients were evidently CCD-negative thereby confirming that the observed in-vitro reactivity with millet and other cereals is protein-specific and not due to clinically irrelevant antibodies against CCDs.

In conclusion, millet allergy is a rare but potentially life-threatening condition mostly resulting from primary sensitization to airborne millet allergens in bird keepers. Cross-reactivity with other cereals and concomitant sensitization to egg and bird feathers should be considered during the diagnostic work-up of such patients.

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Conflict of interest

The authors have no conflict of interest to declare.

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