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Jesper Jarkvist, MD, Knut Brockow, MD, PhD, Theo Gülen, MD, PhD

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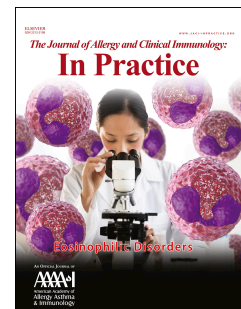
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Low frequency of IgE-mediated food hypersensitivity in mastocytosis

^{1,2,3} Jesper Jarkvist MD, ⁴Knut Brockow MD, PhD, ^{1,2,3}Theo Gülen*, MD, PhD

¹Department of Respiratory Medicine and Allergy, Karolinska University Hospital Huddinge, Stockholm, Sweden; ²Clinical Immunology and Allergy Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; ³Mastocytosis Center Karolinska, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden; ⁴Department of Dermatology and Allergy Biederstein, School of Medicine, Technical University of Munich, Munich, Germany.

***Corresponding author:**

Theo Gülen,
Department of Respiratory Medicine and Allergy, K85, Karolinska University Hospital Huddinge, SE-141 86 Stockholm, Sweden.

Cell phone: +46 737 765476

Mail: Theo.Gulen@sll.se

E-mails of other authors:

Jesper Jarkvist: jesper.jarkvist@stud.ki.se

Knut Brockow: knut.brockow@tum.de

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CONFLICTS OF INTEREST

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ABSTRACT

Background

Patients with mastocytosis have an increased risk for severe anaphylaxis, particularly to hymenoptera venoms. These patients may also develop more often systemic hypersensitivity reactions to certain foods. However, this issue has not been systematically investigated.

Objective

We aimed to determine prevalence and severity of food-related hypersensitivity (FH) reactions among patients with clonal mast cell disorders (CMD).

Methods

A retrospective study was conducted among 204 (≥ 18 years) consecutive patients who presented with confirmed CMD (170 with mastocytosis and 34 with monoclonal mast cell activation syndrome [MMAS]). All patients underwent thorough allergy work-up where self-reported FH-reactions were evaluated.

Results

The prevalence of self-reported FH was 20.6%. The frequency of immunologically mediated reactions was uncommon, as only 3.4% were confirmed by relevant history and IgE-sensitization. Among patients with FH, five had severe anaphylaxis corresponding to an overall prevalence of 2.5%. Most symptoms were restricted to skin (86%), followed by gastrointestinal tract (45%); similar to symptoms that occur in mastocytosis patients also without food-intake. Nuts, spicy foods, seafood and alcohol were the most common

incriminated elicitors. There was no significant difference between the groups regarding age, gender, atopic status or IgE levels.

Conclusion

Anaphylaxis from foods in mastocytosis does exist and is severe, although foods are less frequent elicitor than insect venoms. Further, the frequency of overall FH-reactions is comparable to the general population and most reactions are mild, non-allergic and unconfirmed. Consequently, our results do not support the elimination of any diet in CMD patients without history of FH.

Highlights box**What is already known about this topic?**

Patients with clonal mast cell disorders (CMD) convey increased risk for severe anaphylaxis, particularly to hymenoptera venom. However, it is not systematically investigated whether these patients may also develop more often anaphylaxis to certain foods.

What does this article add to our knowledge?

The estimated frequency of food hypersensitivity is comparable to the general population and most reactions are mild, non-IgE-mediated. Severe anaphylaxis from foods in CMD exist; however, foods are less frequent elicitor than insect venoms.

How does this study impact current management guidelines?

Our results do not support the elimination of any diet in CMD patients without history of food hypersensitivity.

Keywords: D816V mutation, anaphylaxis, prevalence, food allergy, food hypersensitivity, mastocytosis, mast cell, tryptase, IgE, biogenic amines

Abbreviations

CMD – Clonal mast cell disorders

SM – Systemic mastocytosis

MMAS - Monoclonal mast cell activation syndrome

- 122 MIS: Mastocytosis in the skin
- 123 MC – Mast cell
- 124 FH – Food-related hypersensitivity
- 125 FA – Food allergy
- 126 FIA – Food-induced anaphylaxis
- 127 VIA – Venom-induced anaphylaxis
- 128 sBT – Serum baseline tryptase
- 129 SPT – Skin prick test
- 130 WHO - World Health Organization

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INTRODUCTION

Food-related hypersensitivity (FH) is commonly suspected in adults. Whereas food allergy (FA) involves a specific, mostly IgE-mediated immune response to a given food, exceptionally non-IgE-mediated FH also exist (1). Diagnostic procedures include clinical history, allergy tests such as skin prick test (SPT), specific IgE measurement and oral food challenges (1). Furthermore, severe reactions many hours following ingestion of mammalian food is a novel type of FA, in which IgE antibodies are directed against the carbohydrate galactose- α -1,3-galactose (alpha-Gal) (2). Additionally, oral allergy syndrome (OAS) occurs when IgE antibodies against aeroallergens cross-react with certain food proteins, such as birch-fruit, mugwort-celery-spice, and ragweed-melon-banana (3).

The general population frequently overestimates the prevalence of “true” FH in self-reports, as FH can be confirmed by clinically relevant sensitization or by challenge only in a fraction of patients (1,4,5). The estimated FH prevalence in Europe is approximately 17% (4) and suggested to be increased during last two decades (6). In adults, foods as elicitors of anaphylaxis have not been as excessively studied as in children, where over 80% of all anaphylaxis are attributed to foods (7). In Europe, foods have been reported to cause 8 % to 17% of all anaphylaxis in adults (8-10), whereas food-induced anaphylaxis (FIA) was estimated to be the trigger in 32% of adults in an American survey (11), emphasizing the influence of geographical locations. Risk factors for FIA include an existing FA, age, gender, presence of atopic diseases, and possibly low levels of vitamin D (7,12).

Anaphylaxis is a well-known feature in patients with clonal mast cell disorders (CMD), which comprise mastocytosis and monoclonal mast cell activation syndrome (MMAS) (13-15). Mast cells (MCs) of these patients carry an activating gain-of-function mutation (D816V) in the

tyrosine kinase receptor *KIT* and/or immunophenotypically aberrant MCs expressing CD25 (16). Mastocytosis can be systemic (SM) or cutaneous (CM) and in patients with MMAS, the World Health Organization (WHO) criteria for SM are not fully met (16). Due to underlying intrinsic MC defects and MC dysfunction, MC mediator release may be increased (17). Anaphylaxis in these patients often present with severe cardiovascular symptoms including syncope (15, 18-20). Anecdotal cases of FIA in patients with mastocytosis exist (14, 21-23); however, without doubt Hymenoptera venoms constitute the most common cause of anaphylaxis (15, 24).

Widespread beliefs in the lay press and within patient support groups encourage mastocytosis patients to avoid certain foods. Particularly, it has been suggested that biogenic amines and histamine-releasing foods may cause severe, allergy-like symptoms. Since no study has yet systematically explored FH-reactions in patients with mastocytosis, it is largely unknown as to what extent these patients are affected by food elicitors (25). Consequently, there is an apparent need for more data on FH-reactions. Here, we sought to evaluate the prevalence and clinical features of FH-reactions in a large cohort of patients with CMD. Also, we analyzed the elicitor foods and explored whether the occurrence and severity of reactions was influenced by certain risk factors, such as baseline tryptase levels (sBT), total IgE levels, atopic status/disease, gender or type of CMD.

METHODS

Patients and clinical procedures

The Mastocytosis Center Karolinska was established in 2006 at Karolinska University Hospital and Karolinska Institute in Stockholm, Sweden, and receives referrals from the entire country. As of March 31st, 2019, 416 consecutive adult patients had been referred to the center due to suspected mast cell disorders. In accordance with WHO-criteria (16, 26), the diagnostic workup included histopathological evaluation of bone marrow, flow cytometry, *KIT* D816V mutation analysis, and measurement of sBT (Thermo Fisher®). Anaphylaxis was diagnosed in accordance with NIAID clinical criteria (27), i.e. presence of a reaction involving at least two different organs simultaneously (such as associated symptoms of reduced blood pressure such as syncope) and/or respiratory compromise, and/or non-local involvement of skin/mucosal tissue and/or gastrointestinal symptoms after contact with a potential known elicitor, presence of a skin reaction together with cardiovascular and/or respiratory symptoms, or symptoms of reduced blood pressure after contact with a known and confirmed elicitor for the patient, and if these symptoms were objective or required immediate therapy.

Study design

In a retrospective study, data were collected through review of electronic patient records. From 416 consecutively investigated patients (≥ 18 years of age), a total of 235 patients with CMD diagnoses were identified. After excluding 31 patients due to lack of allergy work-up, 204 patients were included in the study (Figure 1). Of patients, 170 obtained a diagnosis of mastocytosis (157 met the criteria for the diagnosis of SM and an additional 13 patients obtained diagnosis of mastocytosis in the skin [MIS] since they refused to undergo bone-

marrow investigation) and 34 patients were diagnosed with MMAS as they only fulfilled 1 or 2 minor criteria for SM.

Ethical approval was obtained from Regional Ethical Review Board, Stockholm, Sweden (approval no. 2011/1750-31/3 and 2018/2621[31]), and all patients provided their written consent.

Clinical symptoms were for the purpose of this study collectively classified to belong to a particular organ system, using one single phrase. Skin and mucosal symptoms encompassed urticaria, flushing, pruritus, angioedema, and oral tingling. Cardiovascular symptoms involved vertigo, palpitations, pre-syncope and syncope. Moreover, syncope was also separately reported. Throat congestion, dyspnea, cough and wheezing were respiratory symptoms. Finally, gastrointestinal symptoms included abdominal pain, cramping, diarrhea and nausea.

Allergy work-up

Patients went through a complete allergic work-up at Karolinska University Hospital Huddinge Allergy Outpatient Clinic including a detailed medical history, SPT with commercial extracts (ALK-Abelló A/S, Horsholm, Denmark) of standard aeroallergens (birch pollen, Timothy-grass pollen, mugwort pollen, animal danders, dust mites, moulds) and food allergens including cow's milk, egg, peanut, hazelnut, wheat/rye/oat flour, fish, shrimp, soy and chicken meat. When necessary, a specific IgE antibody test (ImmunoCAP®, Thermo Fisher Scientific, Uppsala, Sweden) was performed as a complementary tool. Additionally, total IgE levels were measured concurrently with sBT levels, while IgE specific alpha-Gal

antibody levels were determined in 71 patients with compatible history. Specific IgE levels >0.10 kU/L were considered positive. The levels of 25-OH-Vitamin D was also routinely measured.

Statistical analysis

All analyses were performed using IBM SPSS Statistics 25.0 (IBM). Values of $P < 0.05$ were considered statistically significant. Data distribution was analyzed with the Shapiro-Wilk test and accordingly not found normal. Frequencies were reported for categorical variables, and group differences were analyzed by using the chi-square/Fisher's exact test. Continuous variables were presented as median values and ranges and group differences were analyzed by using nonparametric Mann-Whitney U -test.

RESULTS

Patient characteristics

In the cohort, 53 % were women (n=109) and the median age at diagnosis was 52 years (range 18-84) (Table 1). Median sBT-levels were 24 ng/ml (range 2.8-650 ng/ml) and total IgE levels were 16 kU/L (range 1-1600 kU/L). Almost one third of the patients showed presence of atopy and atopic diseases, such as asthma or rhinoconjunctivitis (29 % and 28 %, respectively). Although 50% of the included patients (n=102) had suffered at least one episode of anaphylaxis of any type, the overall prevalence of MC mediator-related symptoms in the cohort was 86% (n=175).

Prevalence of food hypersensitivity reactions and food-induced anaphylaxis

We identified a total of 52 (25.5 %) patients with self-reported FH-reactions. After re-assessing the clinical history, reaction patterns and allergy test results in conjunction with allergy work-up, 10 patients were excluded due to lack of a convincing chronology of food ingestion to symptoms (Table 2). Hence, the allergist-diagnosed prevalence of FH in patients with CMD was 20.6 %. Seven of these patients with milder symptoms were diagnosed with localized OAS due to cross-reactivity with birch pollen. Thus, the adjusted prevalence of systemic FH was 17.2 %. Finally, the prevalence of FIA was 2.5 %, as five patients with anaphylaxis were identified in the entire cohort.

In the diagnostic subgroups of CMD, patients with mastocytosis represented the majority of patients and therefore closely reflected the prevalence presented above (Table 2). In patients with MMAS, the self-reported frequency of FH reactions was slightly higher (32.4 %). However, the allergist-diagnosed prevalence was 26.5 % and following adjustment for OAS, the prevalence of FH was also only 20.5 % in MMAS.

Risk factor analysis of hypersensitivity reactions to foods and food-induced anaphylaxis

Patients with FH were slightly younger, and most patients were women (59%) (Table 3). Additionally, median levels of sBT, total IgE and vitamin-D were slightly higher, and the presence of atopy and atopic diseases were more frequent in patients with FH. Frequency of any type of anaphylaxis was marginally lower in patients with FH. Even so, none of these differences were statistically significant, and no risk factor for FH reactions could be established (Table 3). This also held through for the subgroup analysis, where we compared FH patients with mastocytosis vs. MMAS.

Clinical symptoms

Among 42 patients with FH, symptoms ranged from isolated pruritus or oral tingling to anaphylaxis involving more than one organ system. Most frequently described symptoms involved the skin and oral mucosa (86 %), followed by GI-symptoms (45 %) (Fig. 2A). Moreover, cardiovascular symptoms were reported in 33 % and respiratory symptoms in 14 % of patients. Anaphylaxis was reported in 5 patients (12 %) as all these patients had lost consciousness after having ingested foods.

The most commonly reported cutaneous symptoms were pruritus (31 %) and flushing (29 %), followed by urticaria (14 %) and angioedema (10 %) (Fig. 2B). The OAS was observed in 7 patients (17%) and sensation of oral tingling was the primary symptom. Additionally, the most common symptom combination was cutaneous symptoms in conjunction with GI-symptoms as observed in 13 of 42 patients (31 %) with FH.

Common reported food elicitors

Forty-two patients with FH reported 74 possible elicitors of food and beverages causing symptoms. The largest category included all plant-based foods as reported by 19 patients. Nevertheless, this was a heterogeneous group of foods containing a large spread of fruits, vegetables, etc. Six of the OAS patients (86%) reported reactions from ingesting plant-based foods including apple, kiwi, strawberry and plums, whereas nuts were also common (57 %) OAS elicitors. The remaining categories of reported food-elicitors were nuts, spices/spicy foods, alcohol, seafood, cheese and meat (Fig. 2C). Other eliciting foods as reported by nine patients could not easily be categorized. In some cases, the elicitor was a combination of foods, most frequently being red wine together with spicy foods (4 patients).

IgE- sensitization

The prevalence of IgE-sensitization to any tested food was 13% (n=27) in the entire cohort (Table 2) and only 48% (13 patients) in patients with FH (Table 4). FIA was IgE-mediated in three cases (60%) and elicited by seafood in two patients (one shrimp, other mixture shellfish) and by beef/ α -GAL in the third patient. The remaining elicitors were unknown fish in one case, where we could not detect any IgE sensitization to fish, and reportedly a mixed Asian dish without further specification (Table 5). Additionally, 13 % of the subjects were found to be sensitized against birch pollen including all seven patients with OAS. However, in only 4 of the 7 OAS patients we could detect IgE-sensitization to incriminated foods, mainly hazelnut. The remaining 3 OAS patients reacted to apple, kiwi and/or plum, which we confirmed clinically, but not by allergy tests. The component-resolved diagnostic tests for food allergies was not applied in the patients with OAS symptoms in this study, since none of the OAS patients here experienced systemic reactions.

Alpha-gal sensitization

Total of 71 patients were screened for sensitization of alpha-Gal and 13 patients (18 %) were positive, of whom four (6 %) had a history of FH. Thus, neither frequency of sensitization nor the measured levels of alpha-Gal rendered any statistically significant difference between the two groups.

DISCUSSION

This is the first systematic study on food-hypersensitivity in CMD patients showing that one in five adults with CMD reported FH-reactions. This is comparable to the prevalence in the general population. Although true FA does exist (3.4%), most reactions were non-allergic, mild, limited to skin or GI-tract and similar to symptoms that commonly reported by patients with mastocytosis unrelated to food ingestion. Furthermore, FIA occurs more severely in mastocytosis patients and is not always easy to distinguish from idiopathic anaphylaxis (IA).

The clinical characteristics and severity of FH-reactions varied, and most reported symptoms were from the skin and oral mucosa (86 %), followed by GI-symptoms (45 %), cardiovascular symptoms (33 %) and respiratory symptoms (14 %) (Figure 2A). Only 5 patients (12%) developed anaphylaxis, as all had a severe reaction with syncope (Table 5). Among patients with cutaneous reactions, pruritus (31 %) and flushing (29 %) were the most commonly reported symptoms (Figure 2B). Notably, a study in the general population reported most symptoms related to the GI-tract in patients with FH (5), whereas in our study, most reported symptoms were cutaneous. Although a total of 91 patients (45%) in the cohort reported some GI-symptoms, the prevalence of GI-symptoms differed significantly between the groups as being higher among the patients with FH ($p= 0.015$). Additionally, 31% of patients with FH had GI-symptoms combined with cutaneous symptoms. Interestingly, 17 patients in the cohort has isolated GI-symptoms, of whom four were with FH.

The prevalence of self-reported FH in an adult population ranged from 3% to 35% and appeared to be less common in Southern Europe but higher in Northern Europe (28).

390 Additionally, estimated prevalence of FH in adults was 11% in the US (29) and 18% in
391 Northern China (30). The discrepancies between different reports may be due to different
392 study design, participation rates among different age groups, geographical localization of
393 participants and definition of FH-reactions used to determine prevalence. As self-reported
394 FH-reactions tend to overestimate the prevalence, the “golden standard” used to verify FH
395 remains a double-blind, placebo-controlled food challenge (DBPCFC) (1, 6). However, most
396 centers avoid it in CMD patients because of higher risk. Hence, we applied a standardized
397 allergy work-up by combining clinical history with SPTs and specific IgE tests to provide a
398 better estimation of the prevalence, thereby determined 20.6% convincing FH among patients
399 with CMD. Notably, this is in line with a Nordic epidemiological study showing a FH
400 prevalence of 21% (31), but less frequent than a recent Swedish study (32%) (5).

401
402 In contrast, studies regarding prevalence of FIA in adults are sparse and less reliable, as
403 several studies were conducted among children and/or among patients seeking the emergency
404 ward due to food-related reactions. In a recent American survey, among 11% of adults with
405 FH, 8.6% of patients visited the emergency care due to a severe reaction (29). Additionally,
406 the prevalence of FIA among 1110 adults with IgE-dependent FA was estimated at 5% in an
407 Italian multi-center study (32). Here, an overall prevalence of FIA was 2.5% in our CMD
408 cohort. Also, if we consider the life-time prevalence of anaphylaxis being around 0.3% to 1.6
409 % in general population (11, 33), and assume that 1 in 10 reactions would be triggered by
410 foods in adults, this would give around 20 to 100-fold increased risk for FIA in CMD patients.
411 However, if we compare the risk of FIA to risk of venom-induced anaphylaxis (VIA) in CMD
412 patients, there are still huge differences. In the investigated cohort, among 104 patients who
413 had anaphylaxis, 57% reacted to insect venoms, 6% to drugs, 4% to foods and 33% had IA.
414 Thus, the overall risk for FIA is still 14-fold lower compared to VIA in this cohort.

The prevalence of IgE-sensitization to any food in the cohort was 13%, which is comparable to the general adult population in Sweden, 16% (5). However, the prevalence of clinically relevant IgE-mediated food allergy was observed only in 3.4% (7 patients). Notably, we could identify a relevant IgE-mediated culprit food allergen in 3 of 5 patients with FIA. These observations may support that mostly IgE-mediated food reactions may cause severe FH in CMD patients. Nevertheless, in one patient with FIA, we were unable to detect specific IgE-sensitization to fish, although patient had clear temporal correlation in two anaphylaxis episodes (Table 5). This could be due to the fact that specific-IgE levels are, in general, low in mastocytosis patients (24). In the fifth patient, who had an anaphylaxis after eating mixed Asian food, it was not possible to determine any specific elicitor due to insufficient medical history. However, observing these two undefined FIA cases, one should consider mechanisms other than IgE-mediated ones or alternatively non-food causality, i.e., IA.

Recent research has demonstrated an increasing prevalence of red meat allergy and IgE-sensitizations to α -Gal (34). In general adult populations, the prevalence of α -Gal sensitization ranges between 5.5 and 8.1% in an urban environment (35), whereas the prevalence can reach 24.5% in rural areas (36). The sensitization route includes tick-bites, however, not all sensitized patients will experience symptoms (37). In this study, the overall prevalence of α -Gal sensitization was 18%, but only 6% of those (4 patients) had history of FH (one of whom reacted with FIA). Interestingly, this patient was previously diagnosed with IA. However, in this study the relation to tick bites were not further assessed. Thus, α -Gal sensitization and related symptoms in CMD patients appear to be comparable to those of the general population.

Moreover, the prevalence of pollen-related OAS in general population is inconsistent and varies from 2 to 70% among adults with pollen allergy in different geographical regions (3) as being the lowest in the UK (2%) (38). Interestingly, in an American survey performed among allergists, the prevalence of OAS in adult patients with pollen allergy was 8% (39). In our study, birch pollen sensitization in the entire cohort was 13%, and consequently we found an overall OAS prevalence of 3.4% (corresponding 17% in patients with FH). Thus, it appears that the prevalence of OAS is not increased in CMD patients. Most of the patients reported oropharyngeal symptoms of tingling and pruritus. Even though, OAS theoretically might display systemic symptoms/anaphylaxis in presence of co- or augmentation - factors together with contact to food allergens, surprisingly we have not observed OAS reactions progressing to systemic symptoms in our cohort.

In the present study, 42 patients reported 74 possible food elicitors. Interestingly, the most frequently reported individual elicitor was red wine (in eight patients with FH, corresponding to 4% in the entire cohort). However, this is comparable to reported frequency of alcohol-related reactions in the general population (4.6%) (5). Interestingly, the wine hypersensitivity was reported to be associated with sensitization to Hymenoptera venom without previous stings (40), nevertheless, such association was not observed in our cohort. Among eight patients with wine-induced reactions, only one patient found to be sensitized to venom but after experiencing venom-induced anaphylaxis. Additionally, when we looked at the food elicitors as groups, nuts were the most common (15%) triggering agents, followed by undefined spices (14%), alcohol (12%) and seafood (11%) (Fig. 2C).

To assess clinical significance of biogenic amines/histamine-containing/releasing foods remains a difficult task due to lack of consensus definitions, the poor evidence in literature

and lack of challenges (25, 41, 42). Notably, 16% of the reported 74 foods in this cohort were containing high biogenic amines (including seafoods, cheese, vegetables, and wines) and 28% were suggested to be histamine-releasing, such as citrus fruits (data not shown). However, it is difficult to evaluate their clinical relevance or prevalence since there is no systematic study including challenges in the general population and in CMD patients. After excluding IgE-mediated OAS and anaphylactic reactions, in 16 cases biogenic amines/histamines were thought to be possible elicitors. Of those, 15 presented with cutaneous reactions (in 4 cases isolated), 9 with GI symptoms, 6 with palpitation and 5 with milder respiratory symptoms. Therefore, although possible, there were not substantial evidence to support the role of biogenic amines as causative agents in development of FH without performing challenge tests. Hence, available reference sources do not reflect a homogeneous consensus, and the variation between biogenic amine contents of foods (42) makes it impossible for dieticians/clinicians to provide accurate advises in mastocytosis patients.

Influence of gender or atopic predisposition/disease were reported as risk factors for FH in the general population (31). Here, we could not detect any risk factors regarding gender, atopic predisposition or comorbidity with asthma and/or rhinitis. Additionally, low levels of vitamin D have been suggested to increase the risk of FA, and a higher incidence of FIA has been shown to exist in regions where measured levels of vitamin D was low (12). Although the levels of vitamin D were in fact higher in patients with FH (68 vs 60.5 nmol/L), we could not detect any significant association in this cohort.

The main limitation of our study was that food provocations tests were not performed to confirm diagnosis due to higher risk for anaphylaxis in this cohort. It may be argued that they could have been done in those patients with oral allergy syndrome and sensitivity to plant-

derived food. However, the diagnosis of FH was based on a reported history and further assessment by an allergist. All patients were investigated in a standardized manner and underwent a comprehensive allergy work-up including wide panel of allergy tests. This is the main strength of this single-center study. Other possible limitations included a recall bias as self-reported histories were unavoidably used, and the relative paucity of study subjects enrolled. Nevertheless, since this is the first systematic study on food-hypersensitivity in CMD patients, data may provide important information about frequency, severity and safety of foods in these patients.

The lack of well-designed studies investigating the role of FH-reactions in adult CMD patients made it difficult to adequately advice patients. However, the current study, for the first time, systematically shows that although rare, severe FIA exist in mastocytosis patients and may become dangerous due to the inherent MC dysfunction. Nevertheless, the prevalence of FH in CMD patients is comparable to the general adult population. The frequency of immunologically mediated reactions is uncommon (3.4%), and OAS appears to be the most common IgE-mediated adult FA in this cohort. Conclusively, most reported FH-reactions are mild, non-allergic and unconfirmed and occur in patients also reacting in the skin or the GI-tract independent of food ingestion. Hence, our results do not support the elimination of any diet in CMD patients without history of FH.

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AUTHOR CONTRIBUTIONS

JJ took active part in the acquisition, analysis and interpretation of the data, and drafting and revising of the manuscript. KB analyzed and interpreted the data and revised the manuscript critically. TG conceptualized and designed the study; collected, analyzed and interpreted the data; and wrote and revised the manuscript. All authors approved the final submitted manuscript.

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Table 1: Baseline characteristics of patients with clonal mast cell disorders

	CMD (<i>n</i> = 204)	SM _{TOTAL} (<i>n</i> = 157)	ISM (<i>n</i> = 146)	SM-AHN/ASM (<i>n</i> = 11)	MIS/CM (<i>n</i> = 13)	MMAS (<i>n</i> = 34)
Age ≥ 18 years						
Male gender, <i>n</i> (%)	95 (47)	72 (46)	66 (45)	6 (55)	6 (46)	17 (50)
Age at diagnosis (years), median (range)	52 (18 – 84)	52 (13 – 84)	51 (13 – 83)	67 (43 – 84)	37 (18 – 76)	54 (28 – 74)
Basal tryptase (ng/mL), median (range)	24 (2.8 – 650) (1 NA)	30 (6 – 650) (1 NA)	29 (6 – 650) (1 NA)	110 (8 – 620)	12 (2.8 – 160)	9.7 (3.1 – 23)
Total IgE (kU/L), median (range)	16 (1 – 1600) (3 NA)	14 (1 – 1600) (2 NA)	14 (1 – 1600) (2 NA)	16 (6 – 280)	22 (2.3 – 110) (1 NA)	37 (5.8 – 1100)
Presence of major criterium at BM-biopsy, <i>n</i> (%)	87 (46) (13 NA)	87 (56) (2 NA)	77 (54) (2 NA)	10 (91)	0 (0) (10 NA)	0 (0) (1 NA)
Presence of atypical morphology at BM-biopsy, <i>n</i> (%)	155 (82) (15 NA)	148 (96) (3 NA)	138 (97) (3 NA)	10 (91)	0 (0) (10 NA)	7 (22) (2 NA)
Presence of D816V mutation, <i>n</i> (%)	132 (72) (20 NA)	116 (84) (18 NA)	106 (83) (18 NA)	10 (91)	7 (64) (2 NA)	9 (27)
Presence of CD2 at BM-biopsy, <i>n</i> (%)	126 (77) (41 NA)	103 (81) (29 NA)	96 (82) (29 NA)	7 (61)	1 (33) (10 NA)	22 (69) (2 NA)
Presence of CD25 at BM-biopsy, <i>n</i> (%)	183 (97) (16 NA)	153 (100) (4 NA)	143 (100) (3 NA)	10 (1 NA)	1 (33) (10 NA)	29 (91) (2 NA)
Presence of atopy, <i>n</i> (%)	59 (29) (3 NA)	43 (28) (1 NA)	42 (29) (1 NA)	1 (9)	4 (33) (1 NA)	12 (36) (1 NA)
Presence of asthma and/or rhinoconjunctivitis, <i>n</i> (%)	56 (28) (2 NA)	39 (25) (1 NA)	37 (26) (1 NA)	2 (18)	3 (23)	14 (42) (1 NA)
Presence of cutaneous lesions, <i>n</i> (%)	111 (54)	98 (62)	95 (65)	3 (27)	13 (100)	0 (0)
Occurrence of any kind of anaphylaxis, <i>n</i> (%)	102 (50)	78 (50)	76 (52)	2 (18)	0 (0)	24 (71)
Vitamin-D (nmol/L), median (range)	61 (7 – 163) (35 NA)	60 (7 – 163) (19 NA)	60.5 (7 – 163) (18 NA)	51.5 (17 – 128) (1 NA)	76 (26 – 120) (2 NA)	62 (17 – 136) (14 NA)

Abbreviations: CMD, clonal mast cell disorders; SM, systemic mastocytosis; SM-AHN/ASM, SM-associated hematologic neoplasm/Aggressive systemic mastocytosis; MIS, mastocytosis in the skin; MMAS, monoclonal mast cell activation syndrome; NA, not analyzed.

Table 2: Prevalence of food hypersensitivity and food-induced anaphylaxis in patients with clonal mast cell disorders

Age ≥ 18 years	CMD (n = 204)	SM _{TOTAL} (n = 157)	ISM (n = 146)	SM-AHN/ASM (n = 11)	MIS/CM (n = 13)	MMAS (n = 34)
Prevalence self-reported FH, n (%)	52 (25.5)	40 (25.5)	39 (26.7)	1 (9.1)	1 (7.7)	11 (32.4)
Prevalence FH - reassessed following allergy work-up, n (%)	42 (20.5)	32 (20.4)	31 (21.2)	1 (9.1)	1 (7.7)	9 (26.5)
Prevalence FH – reassessed and corrected for OAS, n (%)	35 (17.2)	27 (17.2)	27 (18.5)	0 (0)	1 (7.7)	7 (20.5)
Prevalence of sensitization to any foods (SPT, sIgE)	27 (13) (3 NA)	23 (15) (1 NA)	21 (14) (1 NA)	2 (18)	1 (8)	3 (9)
Food-induced anaphylaxis, n (%)	5 (2.5)	4 (2.5)	4 (2.7)	0 (0)	0 (0)	1 (2.9)
Presence of GI-symptoms, n (%)	91 (45)	70 (45)	67 (46)	3 (27)	5 (39)	16 (47)

Abbreviations: CMD, clonal mast cell disorders; SM, systemic mastocytosis; SM-AHN/ASM, SM-associated hematologic neoplasm/aggressive systemic mastocytosis; MIS, mastocytosis in the skin; MMAS, monoclonal mast cell activation syndrome; FH, food hypersensitivity; OAS, oral allergy syndrome; SPT, skin prick test; sIgE, specific IgE; GI, gastrointestinal; NA, not analyzed.

Table 3: Risk factor analysis - comparison of patients with food hypersensitivity and patients without reactions to foods.

	No food hypersensitivity (<i>n</i> = 162)	Food hypersensitivity (<i>n</i> = 42)	<i>P</i> -value
Age ≥ 18 years			
Male gender, <i>n</i> (%)	78 (48)	17 (41)	0.392 ^a
Age at diagnosis, median (range)	53 (18 – 84)	49.5 (20 – 72)	0.082 ^b
Basal tryptase (ng/mL), median (range)	23 (3.2 – 650) (1 NA)	28 (2.8 – 140)	0.964 ^b
Total IgE (kU/L), median (range)	15 (1 – 1000) (2 NA)	21 (1 – 1600) (1 NA)	0.221 ^b
Presence of atopy, <i>n</i> (%)	45 (28) (2 NA)	14 (34) (1 NA)	0.448 ^a
Presence of asthma and/or rhinoconjunctivitis, <i>n</i> (%)	40 (25) (1 NA)	16 (39)	0.080 ^a
SM ⁺ (presence of cutaneous lesions), <i>n</i> (%)	87 (54)	24 (57)	0.731 ^a
Occurrence of anaphylaxis, <i>n</i> (%)	83 (51)	19 (45)	0.604 ^a
Positive alpha-Gal, <i>n</i> (%)	9 (17) (109 NA)	4 (22) (24 NA)	0.726 ^a
Vitamin-D (nmol/L), median (range)	60.5 (7 – 163) (26 NA)	68 (17 – 116) (9 NA)	0.610 ^b

^a*P*-values were calculated using Fisher's exact test; ^b*P*-values were calculated using a 2-tailed Mann-Whitney *U*-test. Statistical significance was determined as a *p*-value of < 0.05. Abbreviations: MIS, mastocytosis in the skin; NA, not analyzed.

744 Table 4: Patients with IgE sensitization to foods

Patient no	History of food hypersensitivity (Yes/No)	IgE-sensitization to food	IgE-sensitization to birch pollen/grass-timothy	Reaction pattern
1	No	(+) hazelnut	Pos / Neg	Clinically irrelevant
2	Yes	(+) beef (+) α -Gal 6.6 kU/L	Neg / Neg	Anaphylaxis (beef)
3	No	(+) hazelnut	Pos / Pos	Clinically irrelevant
4	Yes	(+) hazelnut (+) soy	Pos / Neg	OAS
5	Yes	(+) shrimp	Neg / Neg	Anaphylaxis (Asian dish with unclear elicitor)
6	Yes	(+) shrimp (+) lobster	Neg / Pos	Anaphylaxis (seafood)
7	No	(+) sesame (+) walnut	Pos / Neg	Clinically irrelevant
8	No	(+) wheat	Neg / Neg	Clinically irrelevant
9	No	(+) rye (+) hazelnut	Pos / Pos	Clinically irrelevant
10	No	(+) rye	Pos / Pos	Clinically irrelevant
11	No	(+) peanut (+) chicken	Pos / Neg	Clinically irrelevant
12	Yes	(+) hazelnut	Pos / Pos	Clinically irrelevant
13	No	(+) celery (+) oats (+) rye	Neg / Neg	Clinically irrelevant
14	No	(+) hazelnut	Pos / Pos	Clinically irrelevant
15	Yes	(+) hazelnut; (+) α -Gal 5.9 kU/L	Pos / Pos	OAS Clinically irrelevant
16	Yes	(+) wheat	Pos / Pos	Anaphylaxis (fish)
17	Yes	(+) rye	Pos / Pos	OAS
18	No	(+) beef	Neg / Neg	Clinically irrelevant
19	No	(+) egg white (+) rye	Neg / Pos	Clinically irrelevant
20	Yes	(+) hazelnut (+) rye	Pos / Neg	OAS
21	No	(+) shrimp (+) hazelnut (+) peanut (+) rye	Pos / Pos	Clinically irrelevant
22	Yes	(+) rye	Neg / Pos	Clinically irrelevant
23	No	(+) rye	Pos / Pos	Clinically irrelevant
24	No	(+) hazelnut	Pos / Neg	Clinically irrelevant
25	Yes	(+) shrimp (+) crab	Neg / Pos	Anaphylaxis (seafood)
26	Yes	(+) α -Gal 0.44 kU/L	Neg/Neg	Clinically irrelevant
27	Yes	(+) α -Gal 41 kU/L	Neg / Neg	Clinically irrelevant

Abbreviation: no; number

Table 5. Details of patients with food-induced anaphylaxis.

Patient no.	# 2	# 5	# 6	#16	#25
Gender, age at diagnosis	Male 70 years	Male 49 years	Female 62 years	Female 36 years	Male 58 years
Diagnosis	ISM ⁻	ISM ⁺	ISM ⁺	ISM ⁺	MMAS
Baseline total IgE (kU/L)	59	12	25	22	140
Baseline tryptase (ng/mL)	21	82	36	47	11
Atopy	Yes	No	Yes	Yes	Yes
Atopic disease	No	No	No	Rhinitis	No
Nr of anaphylaxis episodes	2	1	2	2	1
Reported food elicitor	Beef x 2	Mixed Asian food (unclear elicitor) x1	Seafood (shrimp) x 2	Fish x 2	Seafood x 1
Time between reaction and food intake	2-3 hours	30 min	1-2 hours	30 min	5-10 min
Clinical reaction pattern	Skin, GI Syncope	Skin, Resp, GI, Syncope	Skin, Resp, GI, Syncope	Skin, GI Syncope	Skin, GI Syncope
IgE-Sensitization (SPT/s-IgE)	Alpha-Gal (6.6 kU/L) Beef (0.24 kU/L)	Shrimp (SPT 5x6 mm) (clinically irrelevant!)	Shrimp (2.7 kU/L) Lobster (1.9 kU/L)	Fish (neg/neg)	Shrimp (2.1 kU/L) Crab (0.71 kU/L)
Non-food anaphylaxis	IA x10	Wasp x1	N/A	N/A	IA x1
Comment	Very likely FIA	Likely FIA	Very likely FIA	Very likely FIA	Likely FIA

Abbreviations: ISM; indolent systemic mastocytosis, and ^{+/+} indicates presence of cutaneous involvement, MMAS; monoclonal mast cell activation syndrome, SPT; Skin prick test, s-IgE; specific IgE, IA; Idiopathic anaphylaxis, FIA; Food-induced anaphylaxis, no; number.

FIGURE LEGENDS

Figure 1. The flow chart illustrates the selection process of the study subjects.

*Of 204 CMD patients, 157 met the criteria for the diagnosis of systemic mastocytosis, 13 patients obtained diagnosis of mastocytosis in the skin and 34 patients were diagnosed with monoclonal mast cell activation syndrome.

Figure 2: Food hypersensitivity reaction patterns, cutaneous symptoms and reported elicitors.

2A – Reaction patterns of food hypersensitivity in patients with clonal mast disorders. 2B –

Distribution of skin symptoms from patients with food hypersensitivity in 36 patients with

clonal mast cell disorders. 2C. The most frequently reported elicitors of food hypersensitivity

reactions. Note that some patients may have reported multiple elicitors. Abbreviations:

Cardiovasc; cardiovascular symptoms, Resp; Respiratory symptoms, GI; Gastrointestinal symptoms.

Figure 1

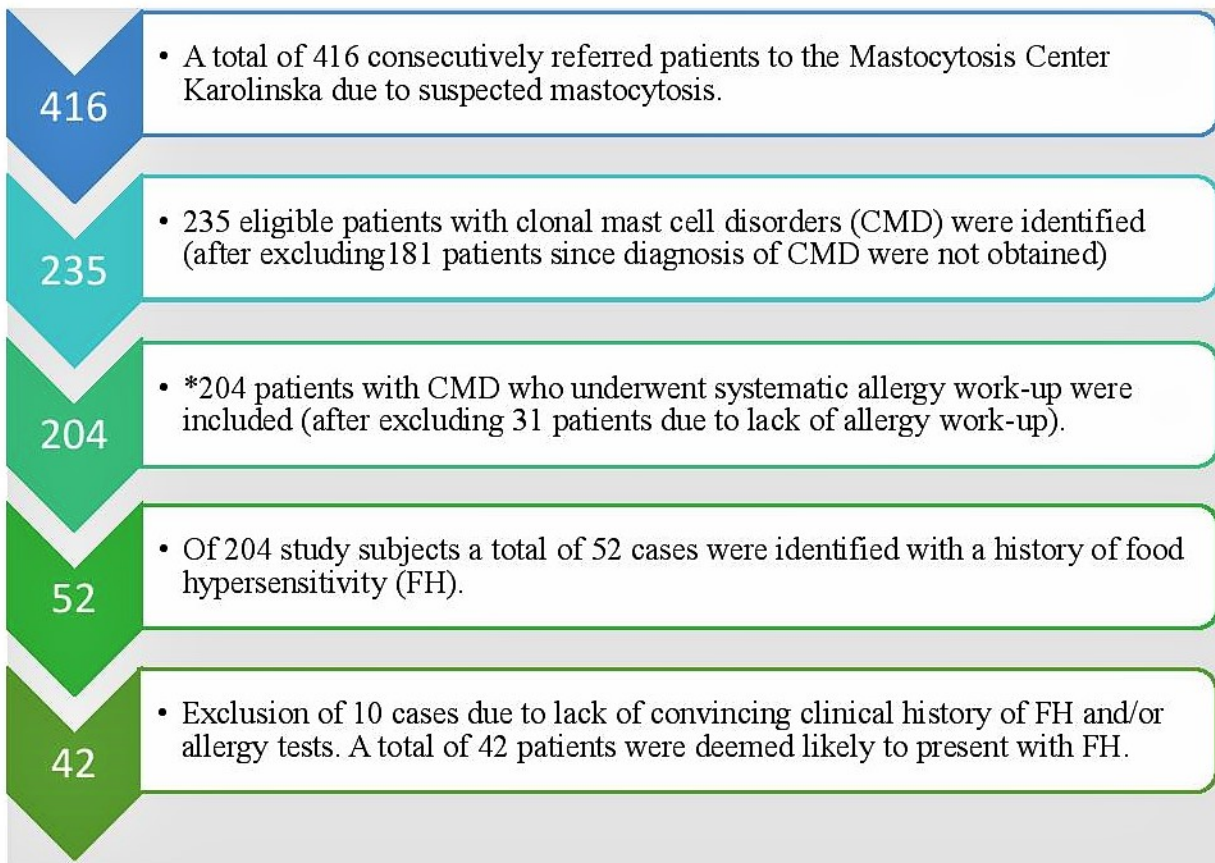


Figure 2A

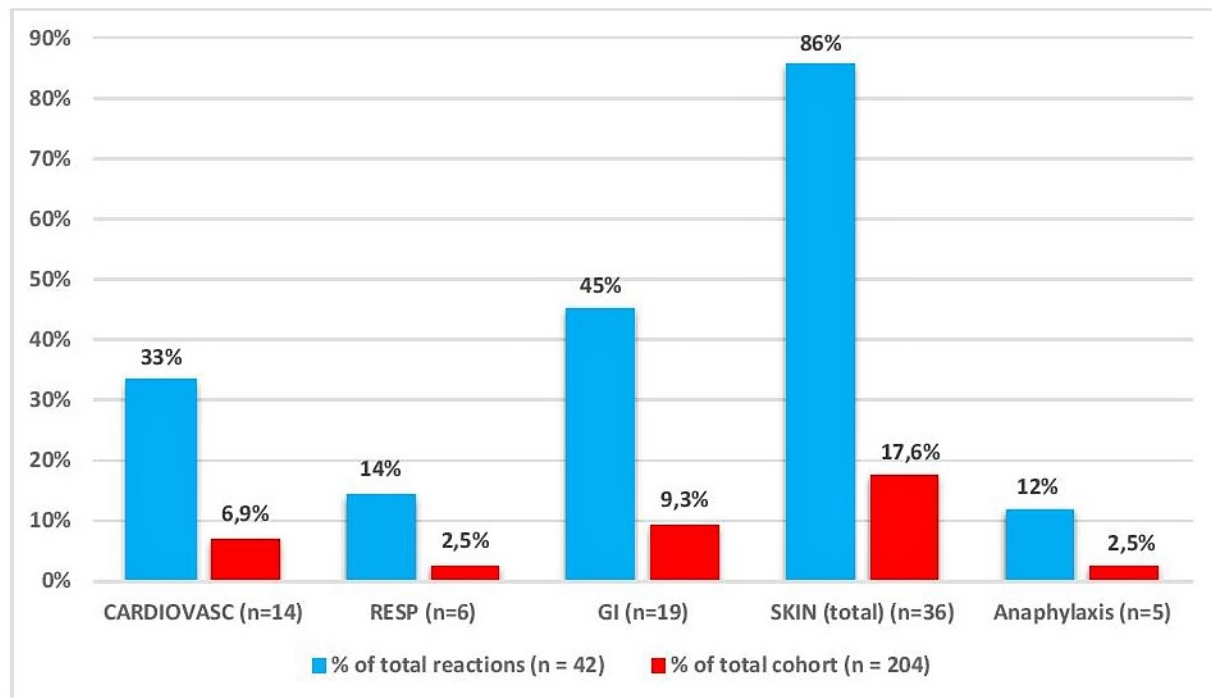


Figure 2B

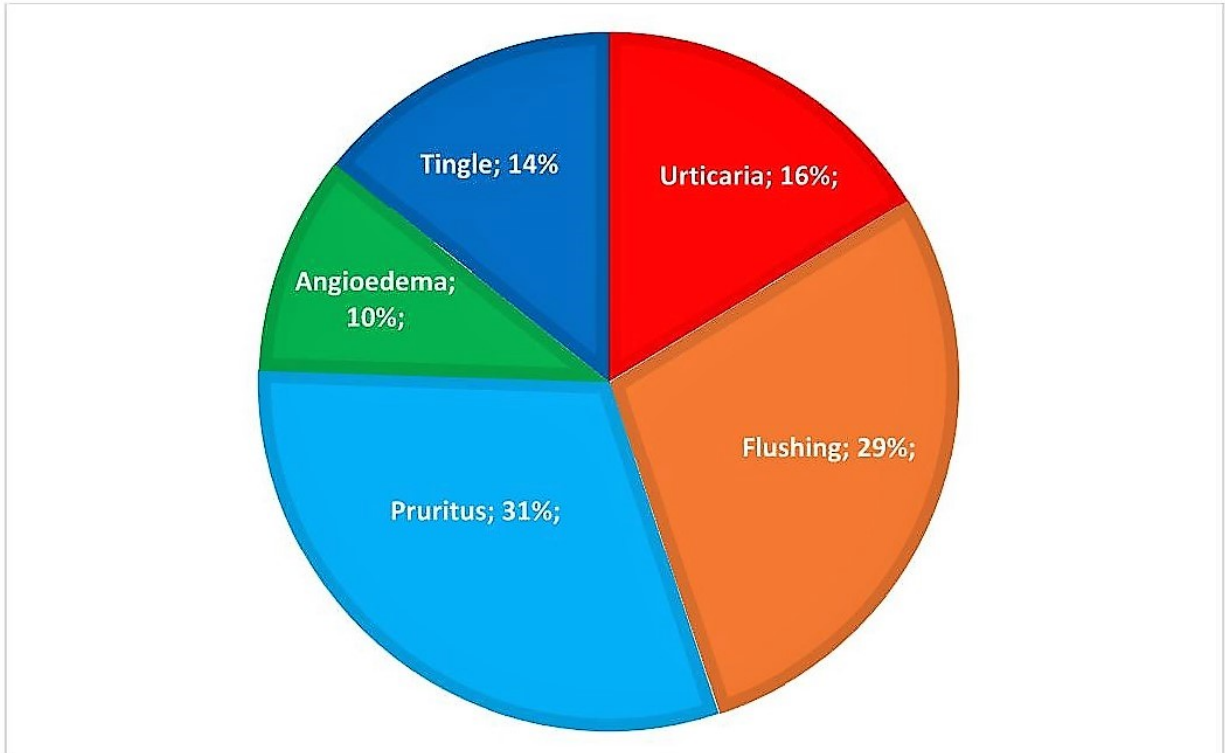


Figure 2C

