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Detection of KIT D816V mutation in patients with severe anaphylaxis and normal basal tryptase—first data from the Anaphylaxis Registry (NORA)



To the Editor:

Anaphylaxis is the most severe and potentially life-threatening systemic allergic condition. Insect venom, food, and drugs are the main elicitors.

The diagnosis of anaphylaxis is clinically based on symptoms on exposure to a potential elicitor. Despite improved diagnostic measures including the use of recombinant allergens for IgE diagnostics, reliable biomarkers for the diagnosis, prediction, and risk stratification of anaphylaxis are lacking.¹ The only marker routinely available is total serum tryptase level, which rapidly increases during the acute phase of an anaphylactic reaction. However, total serum tryptase level should be assessed outside the anaphylactic episodes in all patients with a previous moderate to severe allergic reaction. It can serve as a risk indicator for consecutive severe anaphylactic reactions, in particular in patients with insect venom allergy.²

Patients with an increased baseline serum tryptase level may also suffer from an underlying mastocytosis or mast cell activation syndrome.³ Mastocytosis is characterized by an accumulation of mast cells in various tissues. Adult patients mostly suffer from an indolent systemic mastocytosis, in which the skin, the gastrointestinal tract, and the bone marrow are most prominently affected. In more than 95% of patients, the activating KIT mutation D816V is identified as an underlying cause of mastocytosis. Because of the clonal expansion of mast cells, mastocytosis can promote the onset and severity of allergic reactions. Thus, mastocytosis is one of the most important risk factors for severe anaphylaxis, which has recently been confirmed by data

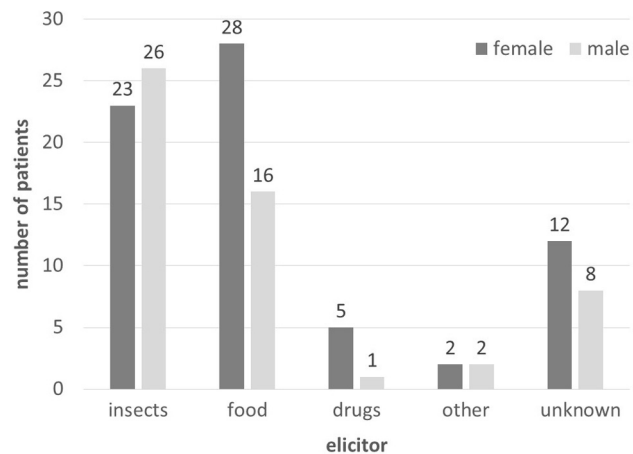


FIG 1. Elicitors and sex distribution within the study cohort (n = 123).

from the European Anaphylaxis Registry.⁴ Despite this striking evidence, mastocytosis is often underdiagnosed in patients with anaphylaxis. One reason for this is that the phenotype of mastocytosis in patients with anaphylaxis is often clinically inapparent because patients may have no or very discrete skin lesions and/or nonelevated basal serum tryptase levels. In particular, when baseline tryptase level is normal, which applies to a subgroup of patients with mastocytosis,⁵ a bone marrow biopsy is routinely not performed to rule out mastocytosis. Thus, patients with severe anaphylaxis may not be diagnosed regarding an underlying mastocytosis because of the absence of clinical signs and the lack of elevated baseline tryptase levels. Today, the KIT D816V mutation can be detected in the peripheral blood with high sensitivity by a PCR-based assay.⁶ In this study, we aimed to determine the frequency of the KIT D816V mutation in a large cohort of patients with severe anaphylaxis, but normal baseline tryptase levels.

A total of 123 patients from the Anaphylaxis Registry were identified (Fig 1) and blood samples were screened for KIT D816V mutation according to the method described elsewhere.⁶ The Ethics Committee at Charité - Universitätsmedizin Berlin (EA01/079/06) approved the study and all patients gave their written informed consent.

The KIT D816V mutation was detected in 6 of the 123 patients (5%) (Table I). For patients 1, 4, 5, and 6, the elicitor yellow jacket was confirmed by history, skin prick test, and specific IgE and venom immunotherapy (VIT) was initiated. Patients 2 and 3 had most likely food-induced anaphylaxis because shrimp and soy/celery were suspected. The workup including oral food challenges was offered to both patients, but they refused. Skin prick test results were positive (shrimp 4 mm, soy 4 mm/celery 5 mm), but specific IgE was negative (Table I). Both patients had low to normal total IgE levels. Low total IgE level is a known phenomenon in patients with mastocytosis.⁷

The patients with a positive screening result for KIT D816V mutation were reevaluated regarding an underlying mastocytosis or mast cell activation syndrome.³ A bone marrow assessment was offered to the patients, but it was initially rejected by all patients. Moreover, an annual monitoring of complete blood count, serum tryptase level, and a bone scan every 2 years were recommended. A lifelong VIT was recommended to the patients with venom allergy.

Five of the 6 patients with positive KIT D816V mutation had no skin lesions of mastocytosis. Our preliminary data support

TABLE I. Summary of patients with severe anaphylaxis and KITD 816V mutation

ID	Sex	Age (y)	Elicitor (c or s)	Tryptase level (μg/L)	KIT D816V+ allele in PB (%)	Skin symptoms		Hypotension during episode	Previous ANA	Grade of ANA (R&M)	First-line therapy	Total IgE level (kU/L)	Specific IgE level (kU/L)
						During episode	Outside episode						
1	F	47	Yellow jacket (c)	2.10	0.400	Angioedema, urticaria	No	No, but loss of consciousness	Yes	III	Corticosteroid IV	NA	Bee (i1): 0.00 Wasp (i3): 4.48
2	F	52	Shrimp (s)	2.27	0.150	No	Yes*	No, but loss of consciousness	No	III	Corticosteroid IV	71.7	rPen a 1 (f351): 0.00
3	F	49	Soy, celery (s)	8.52	0.067	Erythema	No	No	Yes	III	AH IV	31.6	rBet v 1 (ISAC [†]): 7.39 Gly m 4 (ISAC [†]): 0.00 Api g 1 (ISAC [†]): 0.00 Celery (f85): 0.34
4	M	58	Yellow jacket (c)	9.70	0.021	No	No	Yes	Yes	III	Corticosteroid IV AH IV	49.0	Bee (i1): 0.03 Wasp (i3): 3.04
5	M	43	Yellow jacket (c)	5.19	0.084	No	No	No	No	III	Adrenaline IV Corticosteroid IV AH IV	107.0	Bee (i1): 05.97 rApi m 1 (i20): 0.21 Wasp (i3): 10.8 rVes v 5 (i209): 1.24
6	M	78	Yellow jacket (c)	4.00	0.085	Urticaria, pruritus	No	Yes	No	III	Unknown	71.1	Bee (i1): 0.02 Wasp (i3): 9.51

AH, Antihistamine; ANA, anaphylaxis; c, confirmed; F, female; IV, intravenously; m, male; NA, not available; PB, peripheral blood; R&M, Ring and Messmer; s, reasonable suspicion.

*Discrete urticarial skin lesions developed after the anaphylactic event.

[†]Measured with ImmunoCap ISAC ThermoScientific (in IUS).

previous findings in the literature^{6,8} that a mastocytosis can be missed in patients with severe anaphylaxis without clinical signs (elevated baseline tryptase level and visible skin lesions). One limitation of the present study was that no control group was included. However, the detection of the KIT D816 V mutation in the peripheral blood has been shown to highly correlate with the presence of mastocytosis in the bone marrow.⁶ Furthermore, previous studies suggested its use to determine disease burden and monitoring, to assess response to therapy, and to follow disease status in children over time.⁹ We did not detect significant differences in major clinical and laboratory parameters between KIT D816V+ patients and an age-, sex-, and elicitor-matched control group (see Table E1 in this article's Online Repository at www.jacionline.org) except the onset of skin symptoms on anaphylaxis. Three of the 6 KIT D816V+ patients had skin symptoms compared with 10 of the 12 matched control patients. We reproduced this finding in patients with insect venom allergy within the European Anaphylaxis Registry. Anaphylaxis with apparent skin symptoms occurred significantly less often in patients with concomitant mastocytosis (56% vs 82%; $P < .001$). Therefore, the absence of skin symptoms in severe allergic reactions might be a predictive marker in identifying patients with mastocytosis, at least for insect venom anaphylaxis.⁷

Previous findings reported insect venoms and drugs as frequent elicitors of the severe anaphylaxis in mastocytosis. In this study, we identified for the first time 2 patients with food allergy and a KIT D816V mutation in the peripheral blood. Our cohort also included patients with idiopathic anaphylaxis (Fig 1); however, none of the

20 patients were KIT D816V+. These patients were younger (median age, 43 years [range, 20-74] compared with 51 years [range, 43-78]; see Table E1) and had slightly higher total IgE levels (123 kU/L [range, 11.1-453.0] compared with 71.1 kU/L [range, 31.6-107.0]) but no significant differences were detected.

For all 6 patients a multidisciplinary disease control management (regular differential blood count, serum tryptase, bone scan) had been initiated. In 4 of these 6 patients, the KIT D816V result had direct consequence on the causative treatment of anaphylaxis because the initiated VIT had been changed from 5-year to life-long treatment.

In conclusion, the KIT D816V mutation measured in peripheral blood was detectable in 5% of patients with severe anaphylactic reaction. We propose that patients with severe anaphylaxis should be investigated for the presence of the KIT D816V mutation in peripheral blood using a highly sensitive quantitative PCR, regardless of the elicitor and in cases with normal basal tryptase level.

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Sabine Dölle-Bierke, PhD^{a*}

Frank Siebenhaar, MD^{a*}

Thomas Burmeister, MD, PhD^{b,c}

Margitta Worm, MD^a

From ^aCharité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Dermatology, Venereology and Allergology, ^bCharité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of

Hematology, Oncology and Tumor Immunology, and ^cLabor Berlin, Hematology - Tumor Genetics, Berlin, Germany. E-mail: margitta.worm@charite.de.

*Shared first authorship.

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A comprehensive characterization of chronic norovirus infection in immunodeficient hosts



To the Editor:

Chronic norovirus infection (CNI) can be devastating in patients with immunodeficiency.¹ We sought to investigate immunologic and virologic factors associated with chronic infection and document outcomes from a structured treatment algorithm.

We identified 10 patients with CNI (1 referred from Oxford University Hospitals), which was defined as compatible symptoms (diarrhea, weight loss, and vomiting) or malabsorption with stool samples with positive PCR results for norovirus for more than 3 months. We also recruited control groups (see the [Methods](#) section in this article's Online Repository at www.jacionline.org).

Nine patients had CVID, and 1 had chronic lymphocytic leukemia and secondary antibody deficiency. Comorbidities

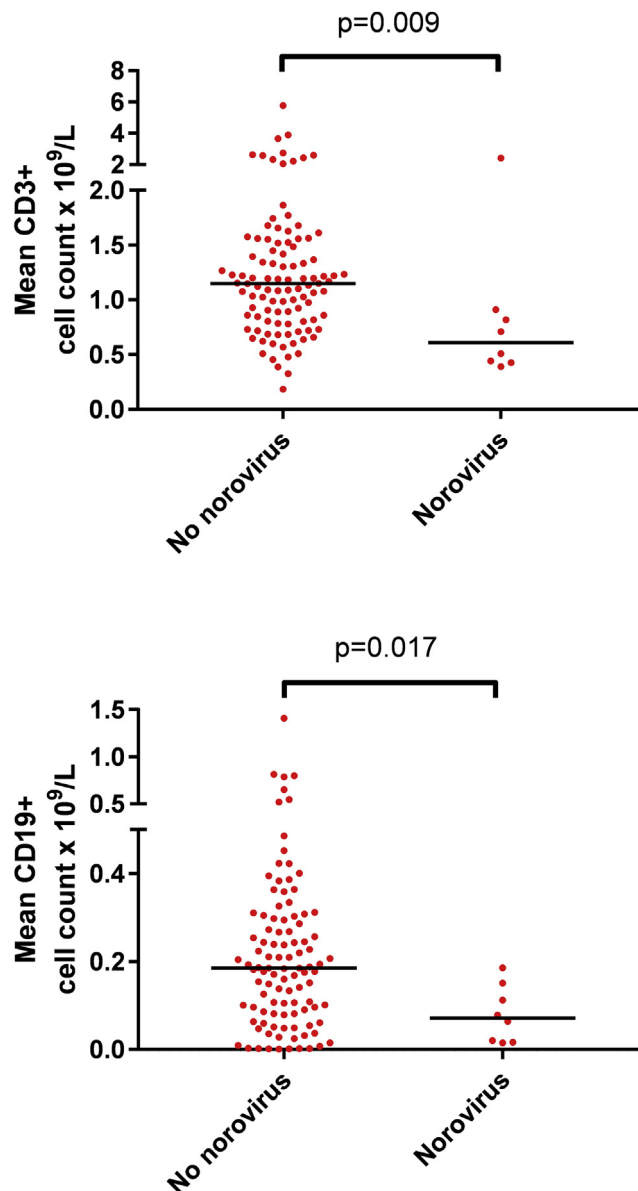


FIG 1. Long-term average (from 2000 [or date of CVID diagnosis, if later] to 2018) CD3⁺ and CD19⁺ values for 8 patients with CVID with CNI versus 113 patients with CVID without CNI. Lines represent medians. P values are from Mann-Whitney tests.

and concurrent infections are detailed in [Table E1](#) in this article's Online Repository at www.jacionline.org. All patients had diarrhea, 3 had significant vomiting, and most had weight loss. The majority had low vitamin E, folate, or B12 levels, and patients A and H had low zinc levels; therefore all 10 patients had evidence of malabsorption. Three required parenteral nutrition.

In comparison with other patients with CVID from our center, those with CNI (n = 8) had lower long-term average CD3⁺ (median, 0.61 vs 1.12 × 10⁹/L; P = .009) and CD19⁺ (median, 0.07 vs 0.18 × 10⁹/L; P = .017) cell counts ([Fig 1](#)). From the earliest available data, 6 patients with CNI were classified as Freiburg group 1A, and 3 were classified as Freiburg group 1B (all of whom eventually met the criteria for group 1A

TABLE E1. Major clinical and laboratory parameters compared between KIT D816 V + patients and an age-, sex-, and elicitor-matched control group (KIT D816V –) as well as compared to patients with idiopathic anaphylaxis (KIT D816V –)

Parameter	KIT D816V+	% or (min-max)	Matched controls (KIT D816V –)	% or (min-max)	Mann-Whitney <i>U</i> <i>P</i> value	Idiopathic (KIT D816V –)	% or (min-max)	Mann-Whitney <i>U</i> <i>P</i> value
Total	6		12			20		
Median age (y)	50.5	43-78	49	41-79	NS	43	20-74	NS
Sex: male	3	50%	6	50%	NS	8	40%	NS
Comorbidities								
Atopy	1	17%	3	25%	NS	6	30%	NS
CVD	2	33%	3	25%	NS	3	15%	NS
Symptoms								
Skin	3	50%	10	83%	.012	17	85%	NS
Gastrointestinal	5	83%	6	50%	NS	17	85%	NS
Respiratory	3	50%	6	50%	NS	13	65%	NS
Cardiovascular	6	100%	12	100%	NS	16	80%	NS
<i>In vitro</i> diagnostic								
Total IgE level (kU/L)	71.1	31.6-107.0	74.2	5.9-1732.0	NS	123	11.1-453.0	NS
sIgE level (kU/L)	6.7	3.04-10.80	12.7	1.63-21.30	NS	NA	NA	
Tryptase level (μg/L)	5.19	4.00-9.70	4.84	2.30-8.20	NS	4.82	1-18.70	NS
Time to onset of symptoms (min)								
00-10	3	50%	3	25%	NS	2	10%	NS
11-30	1	17%	6	50%	NS	7	35%	NS
31-60	0	0%	1	8%	NS	2	10%	NS
61-120	1	17%	2	17%	NS	1	5%	NS
Unknown	0	0%	0	0%	NS	5	25%	NS

CVD, Cardiovascular disease; *max*, maximum; *min*, minimum, NA, not applicable; NS, not significant; *sIgE*, specific IgE.