Higher basal tryptase, asthma and loss of consciousness in anaphylaxis are associated with biphasic reactions

Terence Langlois[1], Pascale Nicaise[2], Camille Taillé[1], Patrick Natta[1], Bruno Crestani[1], Sylvie Chollet-Martin[2], Luc de Chaisemartin[2], and Catherine Neukirch[1]

[1]Hopital Bichat - Claude-Bernard Service Pneumologie A
[2]Hopital Bichat - Claude-Bernard

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Abstract

Background: Anaphylaxis is the more severe form of immediate hypersensitivity. It can be life-threatening and therefore requires fast and appropriate medical management. After a first hypersensitivity phase, a recurrence of symptoms without an elicitor re-exposure may occur, called a biphasic reaction. The aim of this study was to identify biological and clinical predictors of biphasic reactions in patients with anaphylaxis. **Methods:** We retrospectively compared patients with monophasic anaphylaxis to those with biphasic anaphylaxis from an allergology day hospital in a French university hospital between January 2017 and May 2020. **Results:** Among the 237 patients, the rate of biphasic reactions was 5.5% (n = 13). The odds of a biphasic reaction was increased with asthma (p = 0.021; odds ratio = 4 [95% confidence interval 1.05-14.81]) and loss of consciousness during anaphylaxis (p = 0.008) as compared with monophasic anaphylaxis. Basal tryptase levels were significantly higher with biphasic than monophasic anaphylaxis (p = 0.009). **Conclusions:** Asthma and unconsciousness during the first phase of anaphylaxis could be associated with a biphasic reaction **.** Elevated basal tryptase was linked to biphasic reactions, which should be further explored.

Introduction

Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death in its more severe form (1). Therefore, it requires fast and appropriate medical management (1). Individual risk factors and cofactors that affect the severity of anaphylaxis have been described (2, 3).

In the classical form, anaphylaxis is triggered by mediators released by activated mast cells after cross-binding of surface-bound immunoglobulin E (IgE) by an allergen, but it can also be activated by other immunologic and non-immunologic elicitors. This activation leads to a release of mast cell tryptase in the blood, which can be measured and used as a diagnostic tool.

Low levels of tryptase are secreted permanently even in the absence of mast cell activation and reflect total body mast cell burden. Therefore, baseline tryptase levels are elevated in systemic mastocytosis (4) but also slightly increased in older people and in males versus females (5, 6, 7). A high baseline tryptase level is known to be associated with severe anaphylaxis (8, 9, 10, 11).

The acute phase of anaphylaxis typically occurs within minutes after contact with the allergen and then symptoms regress within 4 hr (12). However, anaphylaxis can also be biphasic, which means that after initial symptoms completely resolve, a new onset of symptoms occurs without re-exposure to an elicitor (13). The reported incidence of biphasic anaphylaxis ranges from 0.4% to 23.3%, but more recent data indicate 4% to 5% (14, 15, 16, 17, 18). The mechanism in biphasic anaphylaxis in humans is known to be a prolonged expression of the initial IgE-mediated reaction rather than an additional mechanism (19, 20).

A biphasic reaction usually occurs at 1 to 48 hr after the initial reaction (14, 17, 21, 22) and in rare instances up to 72 hr (23, 24). Symptoms of this second-phase reaction can be less than, as much as, or more severe than the first reaction. (25). Biphasic hypersensitivity reactions are globally more severe than are monophasic reactions (26). Therefore, close monitoring is recommended for 1 to 6 hr after an anaphylactic reaction, depending on the clinical severity, and potentially up to 12 hr in some cases (27, 28). A previous history of anaphylaxis (26), severe anaphylaxis (29), greater number of doses of adrenaline during medical care (30), delay in initiation of medical care or administration of epinephrine (17, 31), cardiovascular disease (32), history of drug anaphylaxis (33, 34), an unknown elicitor (14, 26), an oral allergen elicitor (35) and age 6 to 9 years (36) have been described as risk factors for a biphasic reaction.

Here we analysed the clinical parameters of biphasic reactions. Because the occurrence of a biphasic reaction has been associated with the severity of anaphylaxis (26, 37, 38, 39) and elevated basal tryptase is associated with anaphylaxis severity (40, 41, 42), we also compared plasma tryptase levels in patients with monophasic and biphasic reactions.

Methods

Patients

This was a retrospective, observational and monocentric study. We examined the medical files of patients [?] 15 years old who were referred to the allergology day hospital in one university hospital in Paris for exploring a suspected immediate hypersensitivity event between January 2017 and May 2020. We included patients with basal tryptase level measurement.

We extracted from the medical records the patient's history and anaphylaxis characterization (1) and also severity of the reaction according to the Ring and Messmer classification (43), allergic status, medical antecedents and current treatments.

Patients with asthma were all diagnosed and followed up by a pulmonologist or a general practitioner.

All investigations such as basal tryptase measurement were performed at least 4 weeks after the hypersensitivity reaction. Plasma basal tryptase level was measured by the UniCAP-Tryptase fluoroimmunoassay method (Phadia, Thermo Fisher Scientific, Uppsala, Sweden) following the manufacturer's instructions. Patients with basal tryptase level > 11 µg/L and/or REMA score [?]2 for Hymenoptera venom-elicited anaphylaxis (44) were suspected to have mast cell–related disorder and referred to hematology consultation for additional exploration. Allergy tests performed in the day hospital included skin tests (prick tests and intradermal tests), specific IgE measurements, and challenge tests for allergen reintroduction if necessary (drugs or foods).

We excluded patients if they had a diagnosis of mast cell disease or if their reaction did not meet the anaphylaxis criteria of the 2020 World Allergy Organization (1).

Statistics

Statistical analysis involved using Matlab 2018b. Because tryptase values do not follow a normal distribution, we compared them between monophasic and biphasic anaphylaxis patients by unpaired signed-rank Wilcoxon test (45, 46) Comparison of the clinical parameters involved the non-parametric Fisher exact test. $P<0.05$ was considered statistically significant.

Ethical Considerations

The included patients had been informed beforehand in their letters of consultation or hospitalization that unless they expressed an objection, their medical data could be used in an anonymous form for medical research purposes. No objections were expressed by any of the included patients.

Results

Description of biphasic patients

During the study period, 237 patients with available tryptase measurements and a suspected anaphylaxis event consulted at our allergy center (Figure 1); 13 (5.5%) had a biphasic reaction. Detailed characteristics of these patients are in Table 1.

Six of the 13 patients (46%) presented a severe secondary reaction (Ring and Messmer grade III-IV), whereas 7 patients (64%) had a mild or moderate reaction (Ring and Messmer grade I-II). The mean delay between the first and second reaction was 8 hr (range 1-48). As compared with the first reaction, the second was less severe for 5 (38.5%) patients, as severe for 7 (53.8%) patients and more severe for only one (7.7%) patient. Nine patients required a transfer to an intensive care unit for the biphasic reaction, and 2 were already hospitalized when the biphasic reaction occurred. The identified allergens were Hymenoptera venom for 6 patients, neuro-muscular blocking agents (NMBAs) for 4 patients, antibiotics for 2 patients, and seafood for one patient.

Comparison of biphasic and monophasic anaphylaxis

Patients with monophasic anaphylaxis (n = 224) and biphasic anaphylaxis (n = 13), did not differ by sex, mean age or age distribution (Supplemental Figure), cardiovascular disease, diabetes, dysthyroidism, chronic urticaria, renal failure, beta-blocker treatment, inhaled corticosteroids use, proton pump inhibitor use or smoking habits (Table 2). However, asthma was more frequent with biphasic than monophasic anaphylaxis (n=6/13, 46.1%; vs 38/224, 16.9%; odds ratio = 4 [95% confidence interval 1.05-14.81], p = 0.02). In the monophasic group, 19 patients had mild asthma, 16 moderate asthma and 3 severe asthma. In the biphasic group, 4 patients had mild asthma and 2 moderate asthma. The proportion of patients with atopic disease was similar in both groups (34/38, 89%; and 5/6, 83%). The two groups did not differ in the use of inhaled corticosteroids (n=19/38, 50%; and 2/6, 33%, odds ratio= 0.341 [95% confidence interval 0.03-2.23], p = 0.26).

The two groups did not differ in history of allergic rhino-conjunctivitis, atopic dermatitis, contact eczema, history of Hymenoptera venom allergy, food allergy or drug hypersensitivity (Table 2) or severity grade of anaphylaxis, skin involvement, respiratory symptoms, digestive symptoms and use of epinephrine (Table 3). However, loss of consciousness during the first phase was more frequent with biphasic than monophasic anaphylaxis (100% of biphasic patients vs 58.9% of monophasic patients, p= 0.008) (Table 3). The distribution of culprit allergens was similar in both groups, with Hymenoptera venom and NMBAs the most frequently reported in our allergy center (Table 4).

Basal tryptase levels were significantly higher with biphasic than monophasic anaphylaxis (median: 6.1 µg/l, n = 13 vs 4.2 µg/l, n = 224, p=0.009) (Figure 2). For asthma patients, basal tryptase level was significantly higher for those with biphasic than monophasic anaphylaxis (median: 5.3 µg/l, n = 6 vs 3.7 µg/l, n = 38, p=0.015). Of note, although with Hymenoptera venom allergy, basal tryptase level was similar with biphasic and monophasic anaphylaxis (median 4.9 vs 4.5 µg/l, p=0.46), for drug allergy, the level was significantly higher with biphasic than monophasic anaphylaxis (median 11.2 vs 4.2 µg/L, p=0.0004).

Discussion

In this monocentric retrospective study, 13/237 (5.5%) patients with an anaphylaxis event had a biphasic reaction. The mean time of onset for the biphasic reaction was 8 hr. This observed prevalence, time of onset and range are in line with the current literature (14, 15, 16, 17, 18). However, our results differ from the literature in the distribution of the severity grade according to the Ring and Messmer classification (25), which is described in equal proportions for mild, moderate and severe reactions (47).

Patients with biphasic and monophasic anaphylaxis did not differ in clinical and allergological features, except for loss of consciousness during anaphylaxis and asthma, both more frequent with biphasic than monophasic anaphylaxis. Furthermore, basal tryptase levels were significantly more elevated with biphasic than monophasic reactions.

That we found more loss of consciousness with biphasic than monophasic reactions suggests a more severe reaction with the former. However, the Ring and Messmer classification did not significantly differ between

the groups. The association between severe anaphylaxis and biphasic reactions was recently investigated in a large cohort (42): gastrointestinal, skin symptoms, respiratory arrest, cardiac symptoms, and chronic urticaria were associated with the occurrence of biphasic reaction. Such a difference with our results can be explained by the limited number of biphasic patients in our study.

There are no reports of a link between asthma comorbidity and biphasic anaphylaxis (48, 49), which could be explained by recruitment bias because our hospital service also includes an asthma center. However, none of the asthmatic patients with a biphasic reaction were followed by fellow pulmonologists. Moreover, the proportion of asthmatic patients we found is lower than in the literature (18.5% of 237 patients vs 22.5% in a large anaphylaxis registry (3)).

Although asthma was more frequent with biphasic than monophasic anaphylaxis, the former group exhibited no severe asthma, and respiratory symptoms during anaphylaxis were similar in both groups. Asthma is known to increase the severity of anaphylaxis (48, 50, 51), and severe asthma is also associated with a predominance of mast cells positive for tryptase and chymase in the airway submucosa and epithelium (52). Furthermore, severe asthma was recently found associated with elevated basal tryptase level (even independently of type 2 inflammation) (53). We cannot conclude a potential link with asthma treatment because only two patients used inhaled corticosteroids in the biphasic group.

In our study, basal tryptase level was higher with biphasic than monophasic anaphylaxis. To our knowledge, this has never been reported. A potential explanation could be the more frequent history of asthma in the biphasic than monophasic group because basal tryptase level was higher with biphasic than monophasic anaphylaxis for asthmatic patients. Older age and renal failure increase tryptase levels and could be confounding factors, so we examined the distribution of age between our two groups and it was similar. Additionally, none of our biphasic patients had renal failure. Kraft et al (42) found no significant difference in mean basal tryptase level between monophasic (n = 4786) and biphasic anaphylaxis (n = 237). However, the authors included patients with systemic mastocytosis in their analysis, which could perhaps mask a difference in basal tryptase level and explain the discrepancy with our results. Other factors regulating the activation of mast cells, such as the cytokine environmental network or genetic regulation of tryptase production could be involved (54).

We found no significant difference in culprit allergens between monophasic and biphasic anaphylaxis. The most common allergens in our study were drugs and Hymenoptera venom, which agrees with the literature on epidemiological prevalence for the cause of anaphylaxis in adults (51, 55) and could explain the few patients with a food elicitor in our study. In addition, the basal tryptase level in biphasic and monophasic groups with an allergy to Hymenoptera venom was similar but was higher in biphasic patients with drug allergy. This has not been reported before and warrants confirmation in further studies.

The main strength of this study is the detailed information on patient characteristics. Furthermore, symptoms and medical management of biphasic phases were well documented. All patients with an anaphylaxis reaction had documented basal tryptase level, allergy test results and a complementary interview in our center.

The retrospective monocentric design of the study is its main limitation. The lack of power due to a small number of participants with biphasic reactions did not allow for applying a multivariate analysis of risk factors.

In conclusion, we show for the first time that elevated basal tryptase is linked to biphasic reactions. The role of basal tryptase level as a risk factor for biphasic reaction requires further investigations. Additionally, asthma and unconsciousness during the first phase of anaphylaxis could be associated with a biphasic reaction. These findings advocate for prolonged monitoring of these patients during their care.

Conflict of interest

The authors declare that they do not have conflict of interests related to the contents of this article.

ORCID

Terence Langlois*https://orcid.org/0000-0002-6814-2983*

Bruno Crestani*https://orcid.org/0000-0002-2961-3455*

Sylvie Chollet-Martin*https://orcid.org/0000-0003-1434-4114*

Luc de Chaisemartin*https://orcid.org/0000-0001-8973-1536*

Catherine Neukirch*https://orcid.org/0000-0002-0778-4165*

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Table 1. Profile of biphasic reactions

Age/sex	Allergen	Basal tryptase level (µg/L)	Severity of first reaction	Treatment of first reaction	Severity of second reaction	Time to second phase (hr)	Biphasic manifestations	Management location	Asthma	Cardiovascular	Cardiovasc	Cardiovasc
41/F	ATB	10.8	III	EPI, AH, CS	III	2	Cutaneous, cardiovascular	ED	No	No	No	Y
23/M	ATB	5.4	II	AH, CS	I	14	Cutaneous	Outpatient	Yes	Yes	No	Y
59/M	NMBAs	12.4	III	EPI, AH, CS	II	3	Cutaneous, respiratory	Hospital	No	No	No	N
38/F	NMBAs	22.2	II	EPI. AH	I	2	Cutaneous	Hospital	Yes	Yes	Yes	N
29/F	NMBAs	5.2	II	EPI, AH, CS	III	2	Cutaneous, cardiovascular	ICU	Yes	Yes	No	Y
26/M	NMBAs	11.6	III	EPI, AH, CS	III	1	Cutaneous, respiratory, cardiovascular	ICU	No	No	No	Y
76/F	Hymen.	8.5	III	EPI, AH, CS	III	8	Cardiovascular, cutaneous, respiratory	ICU	No	No	No	N
62/M	Hymen.	6.5	III	EPI, AH, CS	III	1.5	Cutaneous, cardiovascular	ED	No	No	Yes	N

Age/sex	Allergen	Basal tryptase level (µg/L)	Severity of first reaction	Treatment of first reaction	Severity of second reaction	Time to second phase (hr)	Biphasic manifestations	Management location	Asthma	Cardiovascular	Cardiovasc
56/M	Hymen.	3.9	III	EPI. AH	II	12	Cutaneous, respiratory	ED	Yes	Yes	No
47/F	Hymen.	1.7	III	EPI, AH, CS	III	3	Cutaneous, cardiovascular	ICU	No	No	Yes
53/F	Hymen.	3.2	II	AH, CS	I	48	Cutaneous	Outpatient	No	No	No
71/F	Hymen.	6.1	II	AH, CS	II	5	Cutaneous, cardiovascular	ED	Yes	Yes	Yes
67/F	Food	4.6	II	AH	II	1.5	Cardiovascular, digestive	ED	Yes	Yes	No

Abbreviations: ATB: antibiotic; NMBAs: neuromuscular blocking agents; ED: emergency department; ICU: intensive care unit; EPI: epinephrine; AH: antihistamine; CS: corticosteroids; Hymen. Hymenoptera venom

Table 2 . Clinical characteristics

	Monophasic anaphylaxis n=224	Biphasic anaphylaxis n=13	P-value
Men	87 (38.8%)	5 (38.5%)	p = 1
Age, mean (SD)	49.2 (16.7)	49.8 (17.4)	p = 1
Asthma	38 (16.9%)	6 (46.1%)	**p = 0.021***
Inhaled steroids	19 (8.5%)	2 (15.4%)	p = 0.34
Atopic dermatitis	16 (7.1%)	1 (7.7%)	p = 1
Contact eczema	41 (18.3%)	3 (23.1%)	p = 0.72
Chronic urticaria	5 (2.2%)	0	p = 1
Allergic rhino-conjunctivitis	77 (34.4%)	7 (53.8%)	p = 0.24
History of Hymenoptera venom hypersensitivity	4 (1.8%)	0	p = 1
History of drug hypersensitivity	13 (5.8%)	0	p = 1
History of food hypersensitivity	34 (15.2%)	3 (23.1%)	p = 0.44
Cardiovascular disease	73 (32.6%)	4 (30.8%)	p = 1
Diabetes	14 (6.2%)	1 (7.7%)	p = 0.58
Dysthyroidism	18 (8.0%)	1 (7.7%)	p = 1
Renal failure	1 (0.4%)	0	p = 1
PPI treatment	44 (19.6%)	2 (15.4%)	p = 1
Beta-blocker treatment	26 (11.6%)	0	p = 0.37
Smoking	85 (37.9%)	7 (53.8%)	p = 0.26

PPI, proton pump inhibitor

***** OR = 4, confidence interval [1.05–14.81]

Table 3 . Clinical features

* OR=Inf [CI95]

	Monophasic anaphylaxis n=224	Biphasic anaphylaxis n=13	P-value
Severity grade II III + IV	112 (50%) 112 (50%)	6 (46.1%) 7 (53.8%)	p = 1 p = 1
Skin signs	182 (81.2%)	11 (84.6%)	p = 1
Respiratory signs	118 (52.7%)	7 (53.8%)	p = 0.98
Digestive signs	39 (17.4%)	5 (38.5%)	p = 0.14
Loss of consciousness	132 (58.9%)	13 (100%)	**p = 0.008***
Epinephrine treatment engaged	99 (44.2%)	9 (69.2%)	p = 0.39

Table 4. Elicitors for monophasic and biphasic anaphylaxis

Elicitors	Monophasic anaphylaxis N=224	Biphasic anaphylaxis n=13	p-value
ATB	34 (15.2%)	2 (15.4%)	p = 1
NMBAs	57 (25.4%)	4 (30.8%)	P = 0.745
ICM	11 (4.9%)	0	p = 1
Hymenoptera venom	50 (22.3%)	6 (46.2%)	p = 0.39
NSAIDs/aspirin	15 (6.7%)	0	p = 1
Food	3 (1.3%)	1 (7.6%)	p = 0.22
Paracetamol	1 (0.4%)	0	p = 1
Other	1 (0.4%)	0	p = 1
Non-IgE mediated/ idiopathic	52 (23.2%)	0	p = 0.08

ATB: antibiotic; NMBAs: neuromuscular blocking agents; ICM: iodinated contrast media; NSAIDs: nonsteroidal anti-inflammatory drugs; IgE, immunoglobulin E

Figure legends

Figure 1. Flowchart of the study

Figure 2. Basal tryptase concentrations

Box plot according to monophasic anaphylaxis and biphasic anaphylaxis; horizontal bars are median, box edges are interquartile range and whiskers are range.

Monophasic (µg/L): median (range) = 4.2 (1–19.5); SD = 3.1 (n=224)

Biphasic (µg/L): median (range) = 6.1 (1.7–22.2); SD = 5.4 (n=13)

*p = 0.009 (after unpaired signed-rank Wilcoxon test)

Appendices

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`image1.emf` available at https://authorea.com/users/464306/articles/713455-higher-basal-tryptase-asthma-and-loss-of-consciousness-in-anaphylaxis-are-associated-with-biphasic-reactions

Supplemental figure: Age distribution at anaphylaxis onset with monophasic and biphasic anaphylaxis. y, years

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`Original figures.docx` available at https://authorea.com/users/464306/articles/713455-higher-basal-tryptase-asthma-and-loss-of-consciousness-in-anaphylaxis-are-associated-with-biphasic-reactions