Curr Treat Options Allergy (2015) 2:183–192
DOI 10.1007/s40521-015-0059-8

Anaphylaxis (M Sánchez Borges, Section Editor)

Idiopathic Anaphylaxis—A Diagnostic and Therapeutic Dilemma

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Published online: 24 June 2015

This article is part of the Topical Collection on *Anaphylaxis*

Keywords Idiopathic anaphylaxis · Mast cell activation · Treatment · Omalizumab · Rituximab · Diagnosis · Bone marrow biopsy

Opinion statement

Idiopathic anaphylaxis is a diagnosis of exclusion which falls in the spectrum of mast cell activation disorders. The role of bone marrow biopsy remains controversial, but in the appropriate clinical context, this diagnostic tool may be useful in ruling out a potential systemic mast cell process. There is no definitive treatment for idiopathic anaphylaxis, but omalizumab and rituximab show a promising role in prevention. At this time, data suggesting a role for these two monoclonal antibodies come from case reports but do not prove causation or efficacy of therapy. Clinical trials further investigating efficacy of these options are warranted.

Introduction

Idiopathic anaphylaxis (IA), first described in 1978, is anaphylaxis that cannot be explained by a proven or presumptive cause or stimulus. It is generally a diagnosis of exclusion after other causes have been considered, including foods, medications, exercise, insect stings, mastocytosis, and hereditary angioedema. IA may be found in conjunction with urticaria or angioedema, and because of its association with possible upper airway obstruction, bronchoconstriction, gastrointestinal symptoms, and hemodynamic instability (including hypotension and syncope), it is often associated with significant morbidity, particularly if not recognized and treated appropriately. However, fatalities from IA generally appear to be rare, as only two deaths have been reported [1, 2]. The mechanism surrounding IA is unclear but appears to involve mast cell activation, as evidenced by elevated levels of urinary histamine and its metabolite methylimidazole acetic acid, along with elevated plasma histamine and serum tryptase levels [2]. The mainstay of treatment has generally been empiric therapy with oral antihistamines and corticosteroids, with self-injectable epinephrine available for intramuscular use in the event of acute anaphylaxis. The efficacy of corticosteroids in suppression of idiopathic

anaphylaxis is controversial given the lack of randomized controlled trials demonstrating its superiority over other modes of therapy. A retrospective review by Khan and Yocum demonstrated improvement or remission of IA with use of only antihistamines and adrenergics alone as frequently as when treated with chronic corticosteroids [3]. Tejedor Alonso et al. also noted one-third of patients with IA who met criteria for corticosteroid therapy had spontaneous improvement prior to treatment consideration and suggested that the improvement in patients with IA treated with corticosteroids may be explained by the natural evolution of the disease toward improvement [4]. For patients who are not able to taper off corticosteroids, the use of mast cell stabilizers (such as ketotifen and oral cromolyn) has been described, but evidence surrounding this option is weak [5, 6]. In recent years, monoclonal antibodies have revolutionized the treatment of several allergic diseases, and this has impacted treatment for IA as well.

Mimics of idiopathic anaphylaxis

Idiopathic anaphylaxis can be difficult to diagnose and often requires objective evidence for further validation. As these patients are often evaluated in the outpatient clinic setting in a retrospective fashion, review of medical records can provide important clues to the history and presentation. Documentation of hypotension, urticaria, and/or angioedema (including tongue, oropharyngeal, or laryngeal confirmed by either direct laryngoscopy or radiographic exam) should be present in true anaphylaxis. If objective data is difficult to ascertain or is largely absent, mimics of idiopathic anaphylaxis should be considered. One variant is somatoform idiopathic anaphylaxis in which patients may develop symptoms that appear genuine but lack objective evidence of true anaphylaxis. Further investigation into these episodes may include identification of normal hemodynamics (normal blood pressure or heart rate despite syncope), hyperventilation without airway obstruction, stridorous noises from the upper airway, and transient hypoxia by pulse oximetry that resolves with distraction and normal respiration. These patients may ultimately be diagnosed with vocal cord dysfunction or panic attacks, and empiric treatment with prednisone may increase the frequency of episodes rather than the expected decrease in IA [2, 7, 8]. In our experience, vocal cord dysfunction itself is a common diagnosis in patients labeled with IA who present chiefly with a complaint of "throat swelling." Many of these patients will report subjective swelling of the lips and tongue and sometimes may have some objective findings such as mild flushing or an exaggerated blush response. These patients are often triggered by a variety of substances including odors, foods, and sometimes drugs. Careful review of records from emergency department visits for objective findings may be helpful. In patients with known triggers, intentional provocation followed by laryngoscopy can help secure a diagnosis of vocal cord dysfunction.

Another mimic of IA is Munchausen anaphylaxis in which true episodes of anaphylaxis are self-induced by surreptitious ingestion of known trigger allergens with conscious fibbing on the part of the patient. This presents as true anaphylaxis whereas somatoform IA does not [9, 10]. Ingestion of hidden allergens, such as can occur in oral mite anaphylaxis in which severe allergic symptoms may occur soon after eating mite-contaminated wheat flour [11], should be considered. Scombroidosis is histamine poisoning that can occur after ingestion of spoiled fish when histidine is converted to histamine by

histidine decarboxylase derived from bacteria and can happen with a variety of both scombroid (tuna, mackerel) and non-scombroid fish (sardines, herrings, salmon, etc.) [12] which may also present similarly. Other metabolic conditions to consider in the differential diagnoses of IA include carcinoid syndrome, pheochromocytoma, and other types of endocrine tumors [7]. However, most of these patients do not have multi-organ involvement, and routine screening for these conditions is generally not helpful in the evaluation of anaphylaxis patients [13].

Emerging role of alpha-gal in anaphylaxis

Alpha gal (or galactose-alpha-1,3-galactose) is a mammalian oligosaccharide that has garnered much attention in the past several years after Platts-Mills and Commins identified a novel IgE antibody to this carbohydrate that has been associated with delayed-onset anaphylaxis [14]. Alpha-gal is found ubiquitously in all non-primate mammals and is a target of IgG antibodies that are present in all individuals who are immune competent. Patients become sensitized to alpha-gal after being bitten by ticks, most commonly the Lone Star tick (*Amblyomma americanum*) which is most prevalent in the southern USA. However, sensitization can also occur with other tick species found in other countries. An important historical feature is that patients may report 2 to 3 weeks of pruritus, edema, or swelling after a tick bite [15]. Anaphylaxis typically occurs 3 to 6 h after ingestion of mammalian food products such as pork, beef, or lamb and is an important consideration in the diagnosis of IA when symptoms of anaphylaxis occur 3 to 6 h postprandially. Initial symptoms may be limited to palmar or plantar pruritus or erythema [16•]; however, these symptoms may also occur with other forms of anaphylaxis, including idiopathic anaphylaxis. Due to the delay in symptoms after ingestion, many patients and health care providers do not make the connection between meat ingestion and their symptoms, and these patients may be diagnosed with IA. Skin testing with commercially available extracts to meats is often negative, but serum-specific alpha-gal IgE levels are typically elevated and may be very high titer, accounting for 10–50 % of the total IgE [17, 18]. Recently, Commins et al. have performed open challenges confirming the delayed nature of these reactions with no patient having symptoms at 2 h post-challenge [16•].

Idiopathic anaphylaxis in the spectrum of mast cell activation

There is some debate about where IA falls within the spectrum of mast cell activation disorders. Diseases involved in mast cell activation can be divided into three categories: primary, secondary, and idiopathic. Primary disorders include cutaneous mastocytosis, systemic mastocytosis (SM), mastocytoma, and monoclonal mast cell activation syndrome (MMAS), manifesting as episodes of unprovoked hypotension and meeting only one or two minor diagnostic criteria for mastocytosis [19]. Secondary disorders include allergic disorders, mast cell activation associated with chronic inflammation or neoplastic disorders, and urticaria. Idiopathic disorders include anaphylaxis and mast cell activation syndrome. The term "mast cell activation syndrome" (MCAS) is used to describe a category of patients who exhibit episodic symptoms consistent

with mast cell mediator release affecting two or more organ systems without any known mast cell abnormality or causative external triggers. Diagnosis of MCAS requires objective evidence of mast cell activation, including an increase in mediators (such as serum tryptase) and exclusion of any other primary and secondary mast cell disorders [20]. Some, but not all, patients with idiopathic MCAS may have elevations in baseline serum total tryptase levels. Although some authors consider it a separate clinical entity, IA may have identical clinical features with MCAS, including evidence of mast cell mediator release [21–23]. Both MCAS and IA patients may respond to anti-mediator therapy, such as antihistamines, leukotriene receptor antagonists, or mast cell stabilizers [20]. Thus, it is often difficult to clinically distinguish between the two disorders, particularly in those with normal baseline total tryptase levels. Thus, at the present time, it is unclear whether idiopathic MCAS and IA are distinct clinical entities.

Evidence for mast cell activation is provided by the detection of urinary histamine, urinary methylimidazole acetic acid (a metabolite of histamine), plasma histamine, and elevated serum tryptase [2]. Skin biopsies obtained from presumed IA patients have also shown an increased number of mast cells when compared with normal subjects. However, skin biopsies from IA patients appear to have a decreased number of mast cells when compared to non-lesional skin of patients with urticaria pigmentosa or SM [24]. IA also appears to be corticosteroid-responsive, which may allude to its pathophysiology. Although the mechanism is not completely known, corticosteroid administration may suppress cytokine activation of mast cells or neuropeptide-stimulated mast cell mediator release that may result in IA [2].

Diagnosis of idiopathic anaphylaxis—the role of bone marrow biopsy

Idiopathic anaphylaxis is a diagnosis of exclusion, and the patient's history must be thoroughly evaluated for any potential triggers, such as medications, foods, exercise, and insect stings or bites. Further diagnostic work-up should be guided by a reasonable suspicion for an associated etiology (see Figure 1). Pursuit of a bone marrow biopsy has been the subject of debate as this has typically been undertaken in patients with suspicion for potential mast cell disorders, including those for whom a causative agent for anaphylaxis has not been ascertained. It has been suggested that certain patients with IA may have underlying mast cell disorders [25, 26].

The substantial overlap between signs and symptoms of clonal mast cell disorders (such as SM and MMAS) often make it difficult to distinguish between the two [27]. Some clinical features may help differentiate SM from IA (see Table 1). Urticaria or angioedema is quite common in IA but much less so in SM, with the exception of dermographism. Flushing without urticaria is more common in SM than IA. Chronic symptoms such as diarrhea and abdominal pain can occur in some patients with SM but not with IA. Alcohol and hymenoptera stings are known triggers for symptoms with SM but not in IA [7, 21, 28].

In most patients with SM, the c-kit D816V mutation is present, even in peripheral blood [29]. If bone marrow biopsy is pursued, a typical finding in SM is identification of a compact, dense, and multifocal infiltrate that consists

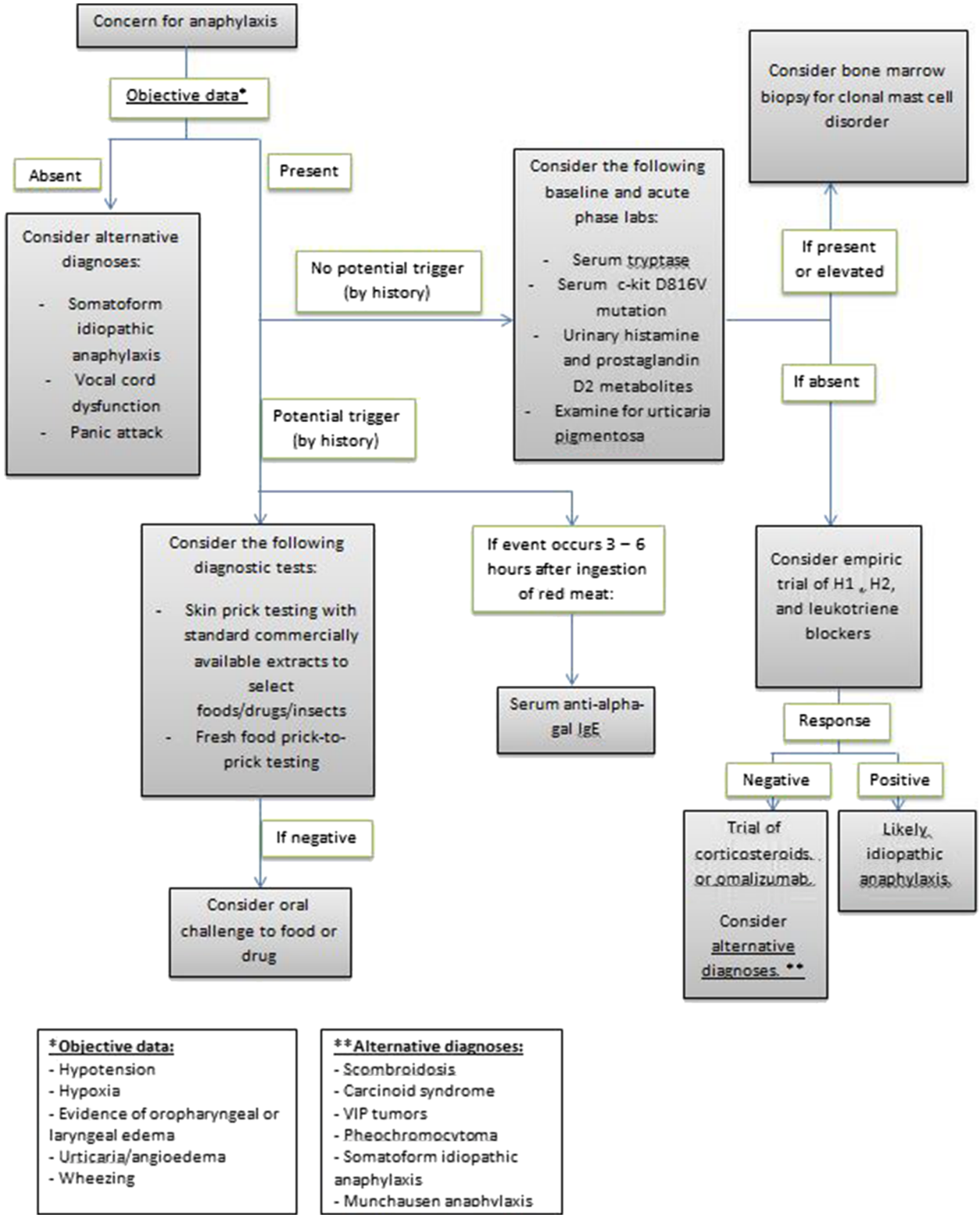

Fig. 1. Diagnostic work-up.

Table 1. Differentiating clinical features of idiopathic anaphylaxis and systemic mastocytosis

	Idiopathic anaphylaxis	Systemic mastocytosis
Gender predominance	Female	Male
Associated conditions	Atopy	
Triggers	None identified	Alcohol Drugs Heat Hymenoptera stings
Cutaneous symptoms	Urticaria Angioedema	Dermatographism Urticaria pigmentosa Flushing (without urticaria)
Differentiating systemic symptoms	Respiratory symptoms	Chronic abdominal pain/diarrhea Dizziness/syncope*
Baseline tryptase	Usually normal	Elevated (usually >25 ug/L)
D816V KIT mutation	Absent	Present
Bone marrow findings	Normal	Multifocal mast cell aggregates

Data compiled from references [7, 20, 27]
*Syncope more common in mastocytosis than IA

of at least 15 coherently aggregating mast cells expressing tryptase [30]. In true IA, one would expect to find a completely normal bone marrow biopsy and bone scans [31]. Bone marrow biopsy should only be performed depending on the patient's clinical features and serum tryptase level. Episodes of unexplained anaphylaxis, presence of urticaria pigmentosa, and a baseline tryptase level greater than 20 ng/mL have all been suggested as indications for bone marrow biopsy. In addition, abnormalities on complete blood count in patients with already known mast cell activation disorder and/or presence of unexplained osteoporosis or organomegaly have been named additional criteria to consider a bone marrow biopsy [21].

A recent study by Gulen et al. evaluated the role of bone marrow biopsy in patients with unexplained anaphylaxis [32•]. This retrospective study was from a tertiary care center, the Mastocytosis Centre Karolinska, evaluating 30 patients with unexplained anaphylaxis who also lacked cutaneous manifestations of SM. In this group of patients, syncope was observed in 93 % of patients, a much higher rate than is typical for studies of IA. The authors found that 47 % of 30 subjects with unexplained anaphylaxis had a clonal mast cell disorder as demonstrated by the presence of an aberrant mast cell population expressing clonal markers. When stratified by a tryptase greater than or equal to 11.4 ng/ml, 75 % had a clonal mast cell disorder. In contrast, only 14 % with normal tryptase levels were found to have a clonal mast cell disorder. Frequent episodes of unexplained anaphylaxis were not predictive of abnormal bone marrow biopsies. The authors also retrospectively applied a modified Spanish Network on Mastocytosis REMA score (using cutoff values of 11.4 to 20 ng/ml for serum tryptase) which resulted in the best sensitivity (93 %) and specificity (94 %). The findings of this study are certainly provocative, but it is difficult to know how generalizable they are in a group of IA patients without hypotension. Whether analyzing for c-kit D816V mutation in peripheral blood would be an even better alternative remains to be studied.

The benefits of bone marrow biopsy include reassurance that there is no underlying mast cell disorder contributing to symptoms of anaphylaxis and allows for the elimination of a malignancy as a potential etiology. However, the risks of pursuing this study include cost and subjecting patients to an often invasive and uncomfortable procedure. Even when performed appropriately, mastocytosis may be missed [33] and bone marrow biopsy may be performed incorrectly [34]. Alvarez-Twose et al. has proposed using the Spanish Network on Mastocytosis (REMA) score to screen for a clonal mast cell disorder after demonstrating that it has better specificity but similar sensitivity to tryptase levels, with a score of two or more indicating a high probability for clonal mast cell disorder [28, 35•]. As discussed earlier, a modified version of this tool may be helpful in determining which patients truly warrant further evaluation with a bone marrow biopsy.

Treatment of idiopathic anaphylaxis—novel therapies

The mainstay of treatment has generally been empiric therapy with oral antihistamines and in some cases corticosteroids, with self-injectable epinephrine available for use in the event of acute anaphylaxis. For patients who are not able to taper off corticosteroids, the use of mast cell stabilizers (such as ketotifen and oral cromolyn) has been described, but evidence surrounding this option is limited to small cases series [5, 6]. In the recent years, monoclonal antibodies have revolutionized the treatment of several allergic diseases, and this has impacted treatment options for IA as well.

Omalizumab is a 95 % humanized monoclonal antibody that recognizes and binds to the Fc portion of IgE at the same site it uses to attach to FcεR1, thereby preventing IgE expression on effector cells and subsequent allergen-induced cross-linking of IgE. The exact mechanism of action of omalizumab on anaphylaxis is not completely clear. By binding to free IgE in circulation, omalizumab has been shown to decrease FcεRI expression on many cell types, including mast cells and basophils, thus preventing mast cell degranulation [36]. Several case reports have reported the use of omalizumab in the setting of IA after potential allergic etiologies were ruled out [37–41] with evidence of remission. However, none of these case reports have been able to report long-term follow-up occurring more than 1 year out. The National Institute of Allergy and Infectious Diseases (NIAID) is currently conducting a randomized, double-blind controlled trial of omalizumab for idiopathic anaphylaxis in an attempt to determine whether treatment will reduce or prevent episodes of unprovoked anaphylaxis. This will be the first randomized controlled study of any therapy in IA. Additional objectives are to identify IA patients with undiagnosed mastocytosis and to further elucidate the cellular and molecular effects omalizumab may have on mast cells and basophils [42].

Rituximab is a chimeric anti-CD20 monoclonal antibody that depletes circulating B cells. There is one published case report of a 17-year-old female with IA who underwent rituximab therapy after failing treatment with high-dose antihistamines, leukotriene antagonists, systemic corticosteroids, mycophenolate mofetil, and even omalizumab. She had complete remission of her disease while her B cell count was undetectable but had recurrence once her B

cell counts normalized again. Full remission of anaphylaxis was achieved after re-treatment with rituximab [43•]. Patients with acute IA and in remission have been found to have a significantly higher percentage of activated B cells when compared to controls, suggesting the prominent role of B cells in the pathogenesis of this disease. It has been theorized that depletion of B cell producing IgG antibodies may mediate a decrease in pathogenic autoantibodies and improvement in clinical symptoms. Postulated mechanisms of rituximab in IA include depletion of putative pathogenic IgG autoantibodies or depletion of circulating total or specific IgE. There may also be a cellular effect of depleting activated circulating B cells that are increased in IA, which could affect effector cell interactions [44].

There has been one case report published describing the use of methylene blue in the treatment of a 43-year-old woman with an initial diagnosis of IA who presented to the emergency department with oral papules, dyspnea, and a choking sensation [45]. On examination, she was noted to have normal oxygenation, wheezing, and an abnormal voice but no urticaria, angioedema, stridor, or hypotension. Her respiratory symptoms failed to reverse with administration of four doses of intramuscular epinephrine 0.3 mg, in addition to IV doses of corticosteroids, antihistamines, and nebulized albuterol. She thus received methylene blue 1 % at 1.5 mg/kg in 100 mL of 5 % dextrose over a 20-min infusion, with her dyspnea improving 6 min into the infusion. Since laryngoscopy was not performed, it is unclear if some of her symptoms may have been attributed to vocal cord dysfunction. This patient was ultimately diagnosed with catamenial anaphylaxis as her subsequent episodes had strong correlation with her menstrual cycles, and her anaphylaxis underwent remission after an elective hysterectomy and bilateral salpingo-oophorectomy. Several other case reports suggest efficacy of methylene blue in other forms of anaphylaxis with documented hypotension; however, these reports often lacked details regarding concomitant vasopressors and thus whether the observed effects were indeed independent of methylene blue is unclear [46]. As a competitive inhibitor of guanylate cyclase, methylene blue blocks the smooth muscle relaxation and vasodilatation, along with other downstream effects of nitric oxide, including blockage of other mediators of mast cell degranulation (such as histamine and platelet-activating factor). However, it must be used with caution as it can induce hemolysis, hypotension, methemoglobinemia, arrhythmias, among other side effects.

Compliance with Ethics Guidelines

Conflict of Interest

Julie K. Kim declares no conflict of interest.

David A. Khan declares the receipt of speaker fees from Genentech (chronic urticaria).

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the authors.

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