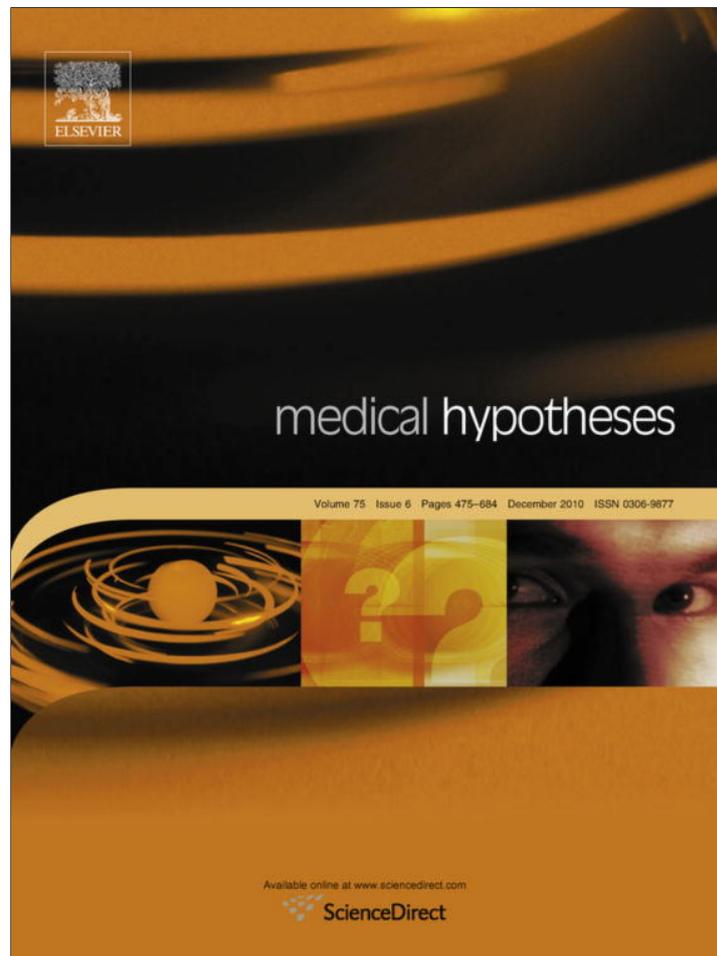


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# Medical Hypotheses

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## The hidden sense of symptoms: Urticaria can be beneficial<sup>☆</sup>

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### SUMMARY

Evolutionary Medicine can be useful when analysing the origin of disease and symptoms. Acute urticaria or anaphylaxis is bothersome and potentially life-threatening. We analyse this symptom-complex in the context of Gastro-allergic Anisakiasis (GAA), where the human is an incidental host for the cosmopolitan fish-nematode *Anisakis simplex* (*A. simplex*). The immunological response against this nematode resembles that against other helminths, but overt expression of allergic symptoms is by far more frequent in GAA. This could be due to the missing co-evolutionary relationship between host and parasite. Features of acute gastric parasitism with and without overt allergic type 1 hypersensitivity symptoms are compared with the abdominal complications in intestinal Anisakiasis, where clinically visible IgE mediated symptoms are missing. In GAA, parasite induced chronic abdominal complications are missing. We postulate that urticaria in GAA can be considered the price for rapidly expelling the live larva of *A. simplex* in those subjects whose evolutionary history made them more resistant to other helminth parasites. Further, urticaria is explained as a possibly exaggerated immunopathological feature in this special type of acute parasitism, where sensitized mast-cells are not only present in the skin, but also in the gastro-intestinal mucosa. This evolutionary analysis of clinical observations is the first known report that addresses the possible beneficial feature of hypersensitivity type 1 response with overt allergic urticaria-anaphylaxis in GAA and confers an evolutionary based sense to the acute IgE-mediated reaction.

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### Introduction

Emerging Evolutionary Medicine is recently gaining more importance in the interdisciplinary fields between Biology and Medicine and can be useful when analysing the origin of disease and symptoms [1]. An evolutionary perspective suggests that many defensive reactions are excessive or entirely unnecessary in our current environment but could have its sense in a different historical environment [2].

We construct an hypothesis mainly on an evolutionary perspective of an annoying or even life threatening symptom-complex as is urticaria/angioedema or anaphylaxis (UA/A) in the context of Gastro-allergic Anisakiasis (GAA) [3]. We analyse the possible origin of the hypersensitivity type 1 response and search for an evolutionary explanation for the overt expression of clinical features, such as UA/A.

### Parasites and allergic symptoms

The host response against nematodes and allergy share common immunological features as are the Th2-driven IgE production, the activation of mast cells and eosinophils. This response has been claimed to be protective against a high parasite burden or re-infection, but in allergy this response is clearly associated with clinical symptoms [4,5].

Whereas allergic symptoms are not frequent in most helminth infections, allergic type syndromes can develop in zoonotic helminth infections, like *Toxocara*, *Ascaris* or hookworms, which cannot develop to maturity in the human and migrate in the tissues [4]. Here, cutaneous or pulmonary symptoms are witness of the actual parasite migration.

The revised hygiene hypothesis suggests that some of the increased prevalence of chronic inflammatory disorders is the result of a defective regulation of the immune system resulting from diminished exposure to microorganisms [6]. In relationship with the allergy epidemic the lack of regulatory features corresponds to missing chronic helminth infections. Thus, chronic parasite infections are associated with a regulatory network, where the cytokines IL-10 and TGF-beta are responsible to prevent clinical expression of the highly expressed Th2 phenotype in helminth infection. On the other hand, Yazdanbakhsh et al. already pointed to the existing positive association of some clinical allergic pheno-

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types like asthma with parasitic disease, when these are only sporadically or light [7]. In these cases, the Th2 response mounted by the host is not sufficiently counter-regulated by the challenged parasite and gives rise to overt clinical allergic features.

### Gastro-allergic Anisakiasis

This clinical entity has been described in 2000 as a concept, in which an acute allergic reaction (ranging from urticaria or angioedema to anaphylaxis) accompanies the penetration of the fish-nematode *Anisakis simplex* (*A. simplex*) through the gastric mucosa [3].

For a better comprehension of the evolving hypothesis the special features of this parasitism are described.

1. Humans are incidental hosts for *Anisakis* larvae, as they do not moult nor reproduce in them. Further, survival is limited to probably only some days or weeks.
2. As a consequence, for humans this parasitism is only an acute infection, as opposed to most knowledge about other human helminth parasites. The special feature of GAA makes it possible to know the exact moment of parasitic contact, a fact that was immensely helpful in clarifying some immunologic features with respect to this parasite.
3. We have learned that the infection is self-limiting in GAA, with the expulsion of the larva mainly in the very first hours after infection. Further details are mentioned in the following chapters.

GAA can be considered a natural human experiment, as the allergic reaction is simultaneous to the entrance of the nematode to the gastric mucosa. This made it possible to follow up immunologic parameters in the course of the parasitism. Whereas we have no information about possible immunologic features in a human primary infection, GAA, considered as a secondary infection, gives rise to a polyclonal stimulation of all immunoglobulin isotypes, including Th1 and Th2 associated IgE, IgG, IgG4 or IgA, and by immunoblotting analysis we could show that within the already present IgE repertoire, new antibodies are produced. The interesting fact is, that being the allergic reaction witness of an immediate secondary response, this very short-lasting infection is yet able to induce a new secondary response, as has also been demonstrated by the induction of new specific IgM antibodies [8,9].

### IgE in other Anisakiasis forms

Early studies from Japan showed that patients with gastric Anisakiasis displayed positive Skin Prick tests (SPT) against *A. simplex*. It has even been postulated, that the gastric symptoms as are epigastric pain, nausea or vomiting are produced as an "allergic response" due to the finding of specific IgE in these patients [10]. In intestinal Anisakiasis the larva has penetrated the gastro-intestinal wall and in its chronic form a granuloma is formed around dead and sequestered nematode material.

In studies of intestinal Anisakiasis, specific IgE against the nematode is a constant finding [10]. All together, in all forms of Anisakiasis, independent of the localization, or being an acute or chronic form (as when granuloma formation is present), the finding of specific IgE against *A. simplex* demonstrates that IgE production is a generally maintained feature of contact with this helminth, independently of accompanying allergic symptoms.

### The Japanese and the Spanish experience

Due to its fish eating habits, after the initial description of human Anisakiasis by Van Thiel in The Netherlands, most clinical

studies series on clinical features of Anisakiasis came from Japan [11]. In 1980, Asaishi described in a series the symptoms of gastric Anisakiasis, revealing that urticaria can be present in 8.4% of cases [10]. In the same study he confirms that urticaria was not present in 45 cases of intestinal Anisakiasis, diagnosed by surgery.

With the complete clinical description in Spain of Gastro-allergic Anisakiasis from the year 2000 on, allergic features were given a different significance [3]. In only one year, we were able to recruit in the emergency room of one hospital with a reference population of about 500,000 patients, 96 patients, who were diagnosed on clinical and immunological basis as GAA. In these patients, 47 gastroscopies were performed in the emergency room. In 24 of these gastroscopies, at least one larva of *A. simplex* could be visualized and removed [12]. But gastroscopic findings (mainly erosions or ulcerations) in the other group of patients without attached larva, together with clinical history and further allergological workup, showed us that the larva has recently been in contact with the gastric mucosa [13]. Further, epidemiologic studies in our region showed us, that there is a clear association between sensitization against *A. simplex* and raw fish eating habits [14].

Special findings in the Spanish experience were:

1. The absence of gastric symptoms in the majority of patients with urticaria and acute parasitism by *A. simplex*, and if present the abdominal symptoms were only light and overshadowed by the allergic reaction.
2. The rapid resolution of gastric parasitism in many patients, where the larva could not early be visualized by gastroscopy in the emergency room only some hours after the onset of the allergic reaction.
3. Most importantly, searching not only for GAA, but also for gastric Anisakiasis in the study protocol, only two patients were recruited with gastric Anisakiasis versus 96 with GAA in the same period of time.

### What makes the difference between gastric Anisakiasis and Gastro-allergic Anisakiasis?

Clinically, the differences are clear from the reported studies. Gastric Anisakiasis is accompanied by severe gastric or abdominal symptoms that guide the patient to the emergency room and in the Japanese experience frequently to a gastroscopic evaluation. Urticaria is present only rarely. On the other side, in GAA it is the acute allergic reaction, that leads the patient to the emergency room, but gastric symptoms are of secondary importance or even absent.

It is difficult to get epidemiological data about the frequency of gastric or intestinal penetration when contacting the live larva, as we probably have only knowledge of parasitism when symptoms are sufficiently important to lead the patient to the doctor, and as we have seen, this seems only to be the case when specific IgE is already present in a secondary contact [9]. Further it would be interesting to have epidemiological data about the fate of the larva after penetrating the gastric mucosa in gastric Anisakiasis (without allergy): how long will the larva remain attached? How many larvae "succeed" in penetrating completely the gastric wall or get into other organs after not finding their ideal habitat? The interesting conclusion of our Spanish experience is that in a prospective series of nearly 100 patients with GAA, no surgical complication was stated, and that penetration of the larva into the gastric mucosa was only superficial and self-limiting. Our clinical experience showed us even not to perform further gastroscopies as a diagnostic or more importantly therapeutic means. Worms were expelled by natural means mostly in a few hours.

Thus, we hypothesize, that the allergic reaction (mainly urticaria, but also angioedema or anaphylaxis) is the accompanying exterior and visible feature of a local allergic reaction, whose aim

is to expel the larva. Oedema at the penetration site could not only be responsible for the gastric symptoms, but also corresponds to the host's response drawn up to get rid of the nematode. Interestingly, this leads us to a possible mechanism that explains the special features evolved for IgE: the immediacy of the response, that can only be achieved by an immunologically innate response or, when adaptative, by IgE bound to mast cells. These encounter the allergen and release the mediators responsible for the acute reaction. From this hypothesis, we could infer that gastric Anisakiasis with its "allergic type" gastric symptoms would equally be an effective response for expelling the larva, and have to further analyse the possible sense of a distant response, such as with UA/A.

### What makes the difference between Gastro-allergic Anisakiasis and intestinal Anisakiasis?

Intestinal Anisakiasis can be acute or chronic, the last referring to the mainly intra-operative findings of granuloma formation when patients are evaluated for abdominal symptoms, frequently mimicking other disorders like appendicitis or inflammatory bowel disease. Here the larva of *A. simplex* has "succeeded" in penetrating completely the gastro-intestinal wall in its search for other habitats. In Japan in a series of 45 intestinal Anisakiasis, no urticaria was reported [10]. We have performed a bibliographic research of series of Anisakiasis reported in Spain in the first years when *A. simplex* began to be a general concern of health. Table 1 lists those studies with sufficient clinical information useful for our evaluation. From a total of another 45 cases with intestinal Anisakiasis, no urticaria was present in the clinical course, neither.

Thus intestinal Anisakiasis is not preceded by overt allergic symptoms. Note however that specific IgE is produced in these cases, too.

Following our hypothesis, in intestinal Anisakiasis, no clinically relevant allergic symptoms have prevented the larva from penetrating the gastro-intestinal wall and have produced a probably more disabling effect. In other words: it could be concluded that urticaria is associated with the acute expulsion of the worm and thus is able to prevent a chronic form of intestinal parasitism.

If this hypothesis is certain, one practical consequence would be to study the suitability of early pharmacological treatment of acute urticaria in the case of GAA. However, all patients in the described Spanish series were treated in the Emergency room with at least anti-Histamines. This fact could explain the rare finding of local oedema at gastric penetration sites in our patients compared to those of the Japanese experience.

### Evolutionary considerations

As has been said, *A. simplex* does not produce a chronic infection, only in some cases a chronic immunological reaction is maintained, mainly in the form of a granuloma surrounding dead and

sequestered material of *A. simplex*. Thus, without the certainty of which effect would produce a significant selective pressure (urticaria/anaphylaxis versus chronic granuloma formation), and bearing in mind, that *A. simplex* due to the human dead end-host has certainly not have had any selection pressure with respect to the human immunologic response, the variety of human responses has to be interpreted in the context of a more general anti-helminth strategy. IgE production against allergens of parasites is an overall feature of anti-helminth immunology [5]. The rapid-onset of IgE-mediated local oedema is useful for the expulsion of the nematode, as we have observed in our clinical experience. But we have to address the last question.

### Why urticaria and not only local IgE mediated symptoms?

*A. simplex* parasitism, being per se only acute, produces a helminth-specific Th2 response but not sufficient regulatory elements as in other chronic parasitic diseases, so that an allergic phenotype is preponderant, in this case in form of urticaria. This fits well to the revised hygiene hypothesis, where regulatory features, which inhibit allergic responses, are associated with chronic parasite infections [7]. Thus, whereas we postulate urticaria—as a generalized response, that includes the gastro-intestinal mucosa—in GAA to be protective against the complete penetration of the gastric wall, in this case without a co-evolving relationship between parasite and host, immunopathology produces more symptoms as would reasonably be necessary [15]. Further, if evolution would render us with the appropriate response, it is clear that a local IgE-mediated reaction would be sufficient for expelling this nematode. But evolution gives rise to different phenotypes and these depend further on environmental factors. Different helminth parasites enter the host by different routes, such as the intestinal tract or the skin. Whereas the host is able to detect pathogen associated molecular patterns in order to mount the appropriate response (here Th2-associated), it is possible, that the sensitization of mast cells not only in the gastro-intestinal mucosa, but also in the skin, reflects the fact, that the host is not able to localize exactly the region of pathogen entry. Alternatively, in an environment with presence of intestinal helminths, there is a higher possibility of encountering also helminths, whose entry-organ is the skin. In fact, parasites like hookworms have both an intestinal and cutaneous phase. We don't know, if the different phenotype distribution in gastric (Japan) versus gastro-allergic (Spain) Anisakiasis is genetically mediated. If urticaria results from a missing regulatory axis, current knowledge on human–parasite relationship leads us to propose other, in developed countries frequently missing helminths to be the real target of the allergic response. These helminths should produce—by chronic or recurrent parasitism in a co-evolutionary context—a diminished immunopathology by inducing more balanced regulatory features. Thus, the actual (but in geographic and socio-cultural different environments) and historical encounter with other ascarid helminths, such as *Ascaris* or *Toxocara* would be a candidate possibility.

### Testing the hypothesis

We have shown that in GAA, *A. simplex* does not complete penetration to other organs. Otherwise, in intestinal Anisakiasis no report has described initial symptoms when the parasite penetrates the gastrointestinal barrier. One means to validate our hypothesis would be to perform an epidemiological survey of asymptomatic subjects with serological features of a recent parasitism contact and perform wide scale radiological image studies in order to search for possible subclinical granuloma formation. The control group would be patients with GAA. It is clear that too high a num-

**Table 1**  
First published series of gastrointestinal Anisakiasis in Spain without allergy.

Author	Source	Year	Region	Diagnoses
Olveira et al.	[17]	1999	Madrid	5 Gastric 2 Intestinal
López-Peñas et al.	[18]	2000	Córdoba	13 Intestinal
Castán et al.	[19]	2002	Pamplona	8 Gastric 15 Intestinal
Repiso Ortega et al.	[20]	2003	Toledo	10 Gastric 15 Intestinal

In these reports sufficient clinical information is available about the studied patients and no urticaria has preceded or accompanied chronic intestinal granuloma formation.

ber of studied subjects would be needed in order to elaborate a reasonable study protocol. Further, it would be interesting to perform genetic studies in order to compare these two groups of patients for geographical ancestry and possible historical encounter with chronic parasitism producing helminths. A more recent tropical origin, where parasitic infections were and are endemic would be correlated with a now higher “inappropriate” inflammatory reaction, as seen in GAA, whereas a longer history of temperate region origin would have shifted the populations’ genetic profile of immune response to become less inflammatory as in chronic intestinal Anisakiasis [16].

## Conclusion

Based on clinical and immunological observations and considering evolutionary thinking, this is the first known hypothesis conferring urticaria a possible protective role in GAA. Urticaria or anaphylaxis would be the price for expelling the live larva of *A. simplex* in those subjects whose evolutionary history made them more resistant to other helminth parasites.

## Conflicts of interest

None declared.

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