Urticaria as Symptom of Parasite Migration Through the Biological Barriers

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Abstract: The absence of a consistent link between parasitoses and urticarial symptoms in the clinical investigations contrasts to the fact that some parasites are the most potent inducers of immunoglobulin E that exist in nature. To shed some light into this question, this review is focused on the actual knowledge regarding parasites life cycle, interactions with host immunity, the influence on host behavior, and finally the role of all these factors on the urticaria development. The collected data demonstrate that parasites could manipulate the host behavior for its own benefit in different ways, inducing urticarial reactions during penetration into different biological barriers. In this context, urticaria may be associated with certain stages of the parasites' life cycle or with host tissue location, but not necessarily only with their presence in the host organism. As compared to T helper (Th) 1, the Th2 response, the eosinophilic infiltration and the complement inhibition could assure a more pleasant surrounding area for the development of some parasites. Taken together, these concepts could explain the epidemiological discrepancy between low rates of urticaria occurrence, and the usual parasites-induced Th2 response. However, further studies are necessary to provide better-based conclusions.

Key Words: Eosinophil attraction, host behavior, parasites life cycle, urticaria, Th1/Th2 response.

INTRODUCTION

Parasitic diseases are considered as potential cause of urticaria [1-3]. Nevertheless, laboratory and clinical investigations greatly vary from one centre to the other. Thus, a high prevalence of *Toxocara canis* markers in chronic urticaria is not associated with constant effects during the anti-parasitic treatment [4]. Similarly to this, *Giardia lamblia* is reported to be an urticaria-inducer only in a few case reports [5-7]. However, some authors consider the urticaria a secondary symptom of the gastrointestinal infection due to its cysts and trophozoite forms, as they may disappear under specific treatment [7]. Also, the presence of urticaria associated with *Blastocystic hominis* infection has been described only in casuistic studies [8, 9].

The absence of a consistent link between parasitoses and skin allergic symptoms in the clinical investigations contrasts to the fact that some parasites are possibly the most potent inducers of immunoglobulin (Ig) E that exist in nature [10-14]. In effect, the immuno-inflammatory response to helminthic infections and allergic pathologies have some similarities, the most profound being the increases in eosinophils and serum total IgE concentration [10-13, 15, 16]. Both entities – helminthic infections and atopic response are Th2/interleukin (IL)-4 inducers, but helminthic infections do not only stimulate specific IgE responses against their own antigens, but also they may induce a strong non-specific polyclonal synthesis of this Ig [10-14].

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Irrespective of the abundant literature regarding the association between exposure to parasites and the enhancement of IgE response, no definite conclusions about the causality of the weak association between these findings and the low frequency of urticarial reactions are yet warranted. To shed some light into this question, this review is focused on the actual knowledge about parasites life cycle, interactions with host immunity, influence on host behavior as well as the role of these factors on the urticaria development.

HOST-PARASITE INTERACTION AND PARASITOSIS-URTICARIA RELATIONSHIP

Parasites are designed by evolution to invade the host and survive in its organism until they are ready to reproduce [17]. They can release a variety of molecules that help them to penetrate the defensive barriers and avoid the host immune attack. Thus, while various hostile or parasitic proteinases are involved in tissue invasion and extracellular protein digestion, helminths secrete also serpins, aspins, and cystatins to inhibit these enzymes. These mediators, as well as helminth cytokines homologues can influence the immune response of the host, biasing it towards the Th2 type [11-13, 17]. The IgE response as component of the Th2 profile, together with eosinophilic infiltration, is assumed to be a cornerstone of host defense during parasitoses [10-14, 18].

Meanwhile, current reports suggest that interaction between parasites and hostile immunity is more complex than previously estimated. In nematodes, the Th2 type response is affected by parasitic challenge [18]. For *Trichiuris muris* infections, Th1-type immune responses occurred in animals given repeated low parasite burden infections; latterly, the immune response developed into a protective Th2-type re-

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sponse. During *Strongyloides ratti* infections, the host immune response changes both qualitatively from a Th1- to a Th2-type immune response and the Th2-type response increases quantitatively with higher parasite burden infections [18].

In contrast to the IgE, the parasitic survivorship was significantly negatively related to the concentration of parasite-specific IgG1 and IgA [19, 20]. At the metacestode stage of *Echinococcus* infection, studies of the immune responses in the experimental murine model as well as in humans have shown that cellular immunity induced by a Th1-type cytokine secretion was able to successfully kill the metacestode at the initial stages of development, whereas antigenic proteins and carbohydrates of the oncosphere/metacestode were able to interfere with antigen presentation and cell activation [21]. This leads to the production of IL-10 and other mediators by host lymphocytes and other immune cells, and therefore, to the inhibition of the effector phase of cellular immune reaction [21].

With respect to anisakiasis, acute symptoms are caused by an IgE-mediated allergic reaction in the gastrointestinal wall. Similarly to this pathology, the majority of chronic patients with schistosomosis presented a Th2 profile with low production of gamma interferon (IFN-γ) as compared to subjects resistant to this infection, while the IL-10 production depends on the infection intensity [22]. In addition, the blockade of IL-4 and IL-5 as well as the addition of the recombinant IL-10 significantly reduced the peripheral blood mononuclear cell proliferative response to soluble egg and adult worm antigens [23]. In addition, experiments in mice have shown that the relative success of *Giardia muris* in completing its life cycle in a primary infection might be due, in part, to the stimulation of a Th2-type response. In contrast, a stronger Th1 response may lead to a better control of the infection [24]. These data suggest that IL-10 is an important cytokine in regulating the immune response and possibly controlling morbidity in human parasitoses, while the IFN-γ production may be associated with resistance to infection [23]. However, increased IL-10 and IgG4 plasma concentration have been also reported in hypo-responsive and asymptomatic cases of helminth infection, such as human filaria [25].

These findings may suggest that hostile IgE/Th2 response has defensive effects, but the IgG/Th1 subtype may also provide such qualities, which in some situations seem to be superior to the Th2 phenotype. *In vivo*, the Th2 profile might be not simply a host-chosen reaction, but rather the most efficient permitted humoral response during host-parasite interaction. The fatal outcome in apparently immunocompetent patients due to multiorgan failure after *Strongyloides stercoralis* septicaemia following a short course of prednisolone therapy could lead to the additional suggestion that glucocorticoids may suppress the parasite-attenuated host immune defenses [26].

The afore-mentioned data may indicate that even hostile cytokines used for cell-cell communication can also be exploited by the parasite as clues to find suitable target organs [27]. We share the opinion that Th2 deviation may permit parasites to invade the host organism, and to select specific organs or host cell types as predilection site to reside, maturate or even proliferate [11, 28, 29]. While many microparasites escape immune attack by antigenic variation or sequestration in specialized niches, helminths appear to thrive in exposed extracellular locations, such as the lymphatics, bloodstream, or gastrointestinal tract [29, 30]. Key events among the host cell population are dominance of the Th2 cell phenotype and the selective loss of effector activity against a background of regulatory T cells, alternatively activated macrophages, and Th2-inducing dendritic cells. The sum effect of these changes to host reactivity is to create an environment, which is most favorable to parasite survival [30]. In *Echinococcus multilocularis* infection, a combined Th1 and Th2 cytokine profile appears crucial for prolonged metacestode growth and survival. Vuitton has demonstrated that Th1 cytokines promote the initial cell recruitment around the metacestode and are involved in the chronicity of the cell infiltrate leading to a fully organized periparasitic granuloma and its consequences, fibrosis and necrosis [21]. Meanwhile, the Th2 cytokines could be responsible for the inhibition of a successful parasite killing, especially because of the immuno-modulatory potency of IL-10. This combination of various arms of the immune response results in a partial protection of both *Echinococcus metacestode* and host [21, 31]. However, it may also be considered responsible for several disease complications. The Th2-related IgE synthesis and mast cell activation are more rarely involved in "allergic" complications of alveolar echinococcosis [21]. With respect to *Anisakis simplex*, it shares several epitopes with IL-4, important for the Th2 response development in human anisakiasis, where the parasite may modulate the Th1-Th2 dichotomy for its own benefit by mucosal inflammation control in an attempt to avoid the larval expelling [32].

Apart from the increasing of the tissue permeability and larvae penetration, the induction of IgE response could have an additional effect in the development of parasites within the hostile organism. In contrast to IgG, the IgE antibody does not activate the complement system. In animal experiments, IgG is shown to activate complement, and therefore, to kill the L3 larvae of *Angiostrongylus cantonensis* [33]. *In vivo*, however, the classic pathway activation can be avoided because IgE does not interact with C1 fraction of the complement [34]. Regarding the complement inhibition in humans, the larval L3 products of *anisakis* exercised a stronger effect on the classical pathway than on the alternative one, constituting a mechanism to evade host defenses, similarly to other parasitic diseases. Detailed studies revealed that larval products of *Anisakis simplex* act at the level of the C3 and C2 proteins, which are early components of the classical complement pathway [35, 36]. In contrast, the asymptomatic infections of human lymphatic filariasis and onchocerciasis are characterized by high plasma concentrations of IgG4 (compared with those of IgE) and of the complement-fixing antibodies IgG1, IgG2 and IgG3 [25]. Notably, elevations in IgG4 are also often associated with high worm loads [25]. These findings indicate that parasites cannot "switch off" the humoral host immunity, but they could induce the Th2 profile, or at least the IgG4 production. The Th2/IgE or IgG4 responses may assure better survival possibilities for the parasites within the host due to parasitic avoidance of the complement system activation.

Apart from parasitoses, the IgE response is also strongly associated with pathogenesis of the immediate allergic diseases such as urticaria, angioedema, etc. Despite expectations, the association of the urticarial reactions with presence of parasitic infections does not agree with epidemiological data [4]. Recently, much evidence is collected about the interaction's details between the hosts and parasites, but fewer attempts are made to clarify the urticarial puzzle during parasitoses. Reflecting on these findings, it could be mentioned that urticaria is a skin manifestation, related to helminths or arthropods with a cutaneous phase: *Schistosoma*, *Sarcoptes scabiei*, as well as ticks and other blood sucking arthropods have been involved in Th2-based immunologic mechanisms [37, 38]. Among patients with toxocariasis, an elevated eosinophil cationic protein (ECP) level was significantly associated with both cough and rhinitis, a high level of specific anti-toxocara IgE with itchy rashes [39]. Loeffler's syndrome, which resembles the pathophysiological features of chronic asthma with its Th2-related immunologic feature, is related to *Ascaris* and *Necator* infection, both of which have an obligatory pulmonary phase [40]. Some helminths like *Necator* and *Schistosoma* have even both a cutaneous and pulmonary phase [41]. Such pathologies as larva migrans or cercarial dermatitis are also examples of the skin migration. Being attempts to find the suitable host environment, the parasitic induction of urticaria, atopic phenotype, itching and the increased tissue permeability could favorise larvae migration and therefore, the completing of the parasitic life cycle [11, 14]. In the case of human anisakiasis, this would be a hopeless attempt to destroy hostile barriers (intestinal wall, etc) to search for the missed suitable environment, because they cannot develop within terrestrial mammalians. Consequently, the type I allergic reaction takes at least 2 to 6 hours to be triggered by alive larvae, while the ingestion of lyophilized larvae, or its equivalent in antigen, does not induce clinical symptoms in sensitized individuals [42, 43]. A similar scenario develops also within paratenic hosts during larvae migration in different visceral organs, like in case of *Toxocara canis* [44]. These data suggest that the development of allergic symptoms could be an active effect of parasites and not only a host defense reaction.

In some particular cases, IgE and IgG values will differ depending on the time relapsed between the parasitic contact and therefore on its developing phase [45]. During infection of mice with *Litomosoides sigmodontis*, female adult worms from prepatent infections protects mice injected with lipopolysaccharide due to inhibition of the host Th1 response, whereas microfilariae worsen lipopolysaccharide-induced sepsis through the induction of the Th1-related cytokines in the peripheral blood [28]. Similarly to the immune modulation, *Giardia lamblia* can express different kinds of variant surface proteins (VSP). The giardial variant-type formation and VSP mRNA levels after infection of mice with cysts lead to an antigenic reset of the parasite, which appears to be associated with excystation [46]. In this respect, the VSP H7 type has to be regarded as a predominant variant of *Giardia lamblia* clone GS/M-83-H7 that emerges during early-stage infection and may contribute to an optimal establishment of the parasite within the intestine of the experimental murine host [46]. In summary, the Th2 response seems to be a host reaction, induced under the parasites' influence. It may permit the migration of parasites under the skin, in lymphatic ways and into some parenchimatous organs. In a few cases, this response may be induced in some developing phases, such as in case of excystation (also a kind of barrier penetration), or *Giardia* inoculation in the enteric epithelium. These data indicate that urticarial symptoms may be related to the larval stage or hostile tissue penetration, but not necessarily only to the presence of parasitic infection in the hostile organism. This may explain the lack of clear evidence regarding the correlation between the parasitic diseases and the urticaria development.

In spite of the humoral mechanisms, there is evidence of important parasite-induced effects on innate cell types, particularly mast cells and eosinophils. According to Maizels et al., the sum effect of these changes to host reactivity is to create an "anti-inflammatory environment", which is most favorable to parasite survival [13, 30]. However in our opinion, the role of eosinophils is more complex. The eosinophils like the complement system can induce increased cell membrane permeability [47, 48]. This eosinophil-induced role is also shown on various biologic barriers, including the parasite surfaces, and it is called "frustrated phagocytosis" [46, 49]. Thus, Kaji *et al*. reported about an urticarial reaction, eosinophilic cholecystitis and a simultaneous onset with pericarditis after an *Ascaris* infection [50]. Meanwhile, infection from *Angiostrongylus cantonensis* is generally associated with damage of blood-brain barrier and neurological disorders, which is assumed to be a consequence of eosinophilic meningitis [48, 51].

Besides the host-influence, eosinophils migration close to parasites could be also a strategic step induced even from the parasite, leading to the allergic symptoms. While a hypereosinophilia is an argument in favor of a progressive toxocara infection, high total IgE level is considered a hallmark of visceral infections by parasites [52, 53]. A study, conducted by Stein *et al.* demonstrated that another nematode, *Strongyloides stercoralis*, expresses one or more eosinophil chemoattractants, leading to the conclusion that helminths may have evolved unique mechanisms that actually exploit the LIAR-based eosinophil activities as part of their life cycle (LIAR – localized immune and remodeling/repair) [54, 55]. *Anisakis* larvae extract, also exercises chemotactic effect for eosinophils [56]. In this context, alive L3 larvae can exhibit the main hyperergic response in the duodenum, decelerating their transit into the successive parts of intestinum, but also inducing the transit into the tissues outside the duodenal lumen [57]. In other words, since parasites affect the behavior traits with selectively benefit the parasite, rather than causing a general alteration of the host behavior, the induction of the urticaria might be only a sign of efficient or hopeless larval attempt to find the suitable host to produce eggs. The IgE-response, the eosinophilic chemotaxis, or the general itching cannot be only host defenses, but also larval attempts to destroy hostile barriers to search for the missed suitable hostile environments. Taken together, these findings indicate that eosinophils as biological barrier perforators are implicated under the simultaneous influence of the host and parasites in a double game. This hypothesis is supported for example by the presence of local eosinophil infiltration in the skin when *Dracunculus medinensis* larvae emerge from the inferior limbs in the

ponds water [58]. In these circumstances, the eosinophils could help parasites to destroy the skin integrity, because in this stage dracunculae larvae can be developed only within thermocyclops living in ponds. This also demonstrates that helminths display highly complex life cycles, in which the establishment of adults or larvae within hostile target organs as well as the transition of a developmental stage to the successive one is influenced by host-derived factors [27].

The parasite-manipulated involvement of host immune mechanisms supports the opinion that parasites can be efficient manipulators of the host behavior [57]. The parasitic ability to affect the behavior of infected host has been documented by different authors [11-14, 59, 60]. Although changes in the behavior of infected hosts do occur for pathogens with direct life cycle, they are most commonly recorded in the intermediate hosts of parasites with complex life cycle. In this case, because sexual reproduction of *Toxoplasma gondii* can be accomplished only in felines, there are strong selective pressures on the parasite to evolve mechanisms to enhance transmission from the intermediate host to the definitive feline one, and thereby complete its life cycle [61, 62]. The predilection of this protozoon for the brain of its intermediate host places it in a privileged position to cause such manipulation [62]. Ferreira et al. recently demonstrated that the host cell transcriptome, including the expression of distinct host cell genes, can trigger bradyzoite development and cyst formation, indicating that the complex cellular environment may govern the developmental differentiation of this protozoon [63]. Moreover, the pattern of histone H3 arginine methylation distinguishes certain promoters, illustrating the complexity of the histone modification machinery in toxoplasmosis [64, 65]. Being placed in the intermediate host brain, the *toxoplasma*-expressed epigenomic mechanisms may lead to variations in gene expression during the transformation of tachisoites into bradysoite, waiting then for the definitive host. This way, *Toxoplasma gondii* dispose the ability to manipulate the personality profile of the intermediate host [14, 59]. The toxoplasma-infected people are more predisposed to take a risk, or are less watchful for example in the motorways, whereas toxoplasmosis-infected rats can even lose the cat predation risk [14, 61, 66, 67]. The loss of predation risk by rats or the loss of watchfulness by humans at least at the prehistoric time before the invention of entombment, after a toxoplasmic infection, led usually to the rip of their bodies from some carnivore and therefore to the transmission of the parasite into its definitive host like felines [14]. This parasite, thus manipulates the behavior of its intermediate host to enhance its transmission to the definitive one [66, 67]. In a similar manner, the experimentally *Toxocara canis*-infected BALB/c mice take significantly longer to drink from a water source compared with control mice [68]. Moreover, infected mice displayed reduced levels of anxiety to aversive and exposed areas of the maze, particularly in the case of the moderate and high intensity mice [69]. These findings lead to the suggestion that a *Toxocara*-infected paratenic host can be an easier prey for their predators. During dracunculiasis, the burning effect in patient's lower limbs during pregnant larvae extrusion is also a host behavior manipulation, because the expelling first-stage larvae can be developed only within copepods of the ponds [58]. Consequently, the patient hurries to immerse the burning limbs in the ponds in order to cool them.

The reduction of respiratory allergic symptoms (like wheezing or airway hyperreactivity) in intensive helminth–infected populations is another example of host behavior manipulation and an evolutionary adaptation from the point of view of parasites [14]. This reduction assures those better chances for their reproduction and development in the environment "host", because the liberation mammalian efforts against these parasites are suppressed. Thus, *Toxocara*, *Ascaris*, *Trichiuris*, and hookworm have a phase of larval migration into the respiratory system or at least, their entrance way (as eggs) in the human body is the nose or the mouth [14, 40]. To assure their penetration into the host and latter their reproduction or development, these parasites need to affront or avoid the reactive (including allergic) response of the host (like the cough, airway obstruction and airway hyper-responsiveness) due to induction of immuno-modulatory network [11-14, 70].

CONCLUSIONS

Based on the current knowledge, it could be concluded that parasites attempt to manipulate the host behavior for its own benefit in different ways, altering its (epi)genetic, biochemical, immunologic or physiologic functions as well as altering its behavior and activity [11-14, 42, 43, 62, 65, 71, 72]. Both protozoan and cestode/nematode parasites may induce the Th1/Th2 switch in order to assure better possibilities to survive in the hostile organisms, but among them helminths are the superior IgE inducers [10-14, 21, 24]. In this framework, could be postulated that the higher parasitic burden, the more efficient seems to be the parasite-related manipulation [14, 18]. Acting as immune manipulators during infection, parasitic allergens and their cytokines can induce the IgE synthesis or at least the IgG4 one, to avoid the antiparasitic role of complement system [14, 25, 34-36]. On the other hand, urticaria induction due to IgE-mediated mast cell degranulation seems to be an active parasitic effect that can provide the parasitic migration into tissues [42, 43, 73]. Usually, urticaria can be induced by multicellular or enteric parasites such as A*nisakis simplex*, *larva migrans and currents*, *Giardia lamblia or cercarial dermatitis*, but even protozoan blood parasites may induce urticarial reactions during unusual migration through a compact tissue [5, 15, 16, 19-21, 32, 41-43, 74-77]. Because the parasitic migration may be related to certain life cycle stages, also the parasites-related urticaria/dermatitis occurrence and its resolving after antiparasitic therapy could not necessarily agree with epidemiologic data [4, 38, 43, 44, 78, 79]. Apart from the involvement of humoral mechanism such as complement system and antibody response, the active role of parasite in the urticaria-associated migration and accomplishing of life cycle can be manifested by eosinophil attraction [56, 80]. In this framework, eosinophils act not only as innate immune cells, but also as perforators of biologic barriers [47, 48]. Recent studies of the structure, content, and activities of the eosinophil have shown that it has potent toxic proteins with the potential to mediate tissue damage after its disruption [54, 80]. Specifically, deposition of eosinophil granule proteins outside of eosinophils has been observed in pathologies associated by elevated serum IgE levels, such as in urticarial

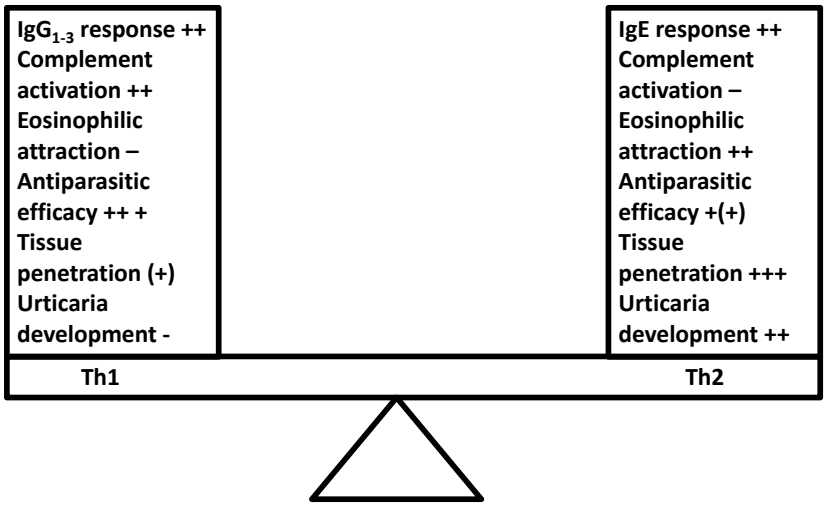

Fig. (1). Th1 vs. Th2 response during parasitoses and the urticaria development: Although both responses provide antiparasitic effects, the Th1 seems to be superior to the Th2 response. Maybe the Th2 (and urticaria) induction is a host-response, chosen by the parasite that is associated with better survival and hostile tissue dispersion/penetration. The eosinophil chemotaxis and the avoidance of complement-dependent mechanisms are also targets of parasite-induced host immune modulation that can improve its development and survival possibilities within hostile organism.

and angioedematous disorders [80]. The tissue penetration is preceded by parasitic induction of different molecules that mediate its adherence with hostile cellular barriers. Thus, the specific IgE response during *Giardia*-related urticaria is also associated with expression of soluble adhesion molecules in the hostile serum, such as intercellular or vascular adhesion molecules ICAM-1 and VCAM-1, as well as IL-6 [77, 81]. Therefore, this symptom seems to be related with enteric epithelial inoculation of the parasite, but not to the enteric lumenal presence.

In summary, these findings indicate that skin allergy may be associated with certain stages of the parasites' life cycle or with host tissue location, but not necessarily only with parasites presence in the hostile organism. As compared to Th1, the Th2 response (including the IgE production), the eosinophilic infiltration and the complement inhibition could assure better conditions for the development of some parasites (see the Fig. **1**) [21, 24, 35, 41, 56]. The ambiguity of the host immune response during parasitoses remains a puzzle, but much evidence stresses the fact that the sum effect of the deviated host reactivity could be the creation of a favorable environment for the parasite migration and survival within hostile organism [30]. The combination of these suggestions could be a plausible explanation for the epidemiological association's paradox between low rate of urticaria development and frequent IgE response during parasitoses [7]. In this context, the timing of urticaria occurrence seems to rely with parasites-induced tissue migration and the penetration of hostile biologic barriers. Nevertheless, further studies focused on the monitoring of experimental parasitic development, on dispersion/penetration through the host tissue, and on the association of parasitic life stages with urticarial development are necessary.

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