



Favorable hymenoptera sting reactions during childhood may have enabled transmission of responsible allergic genotype into generations

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Summary Allergic reactions caused by hymenoptera venoms represent a major medical problem for certain groups of population. In addition to different anaphylaxis reactions, less frequent fatal cases have been recorded in Europe and USA. It has been observed that generally, following the initial anaphylaxis reaction to the venom of such insects, milder and less frequent successive reactions occur in children than in adults, though the latter are less frequently stung. Such findings could be explained by the fact that mainly children may have the advantage of self-restraining the aggravation of further reactions due to the ability of a higher plasticity of immune and non-immune protective mechanisms or the ability of adjustment of regulatory autonomous vital systems, activated after a prior allergic reaction. Hypothetically such ability has enabled most of those individuals to reach at least major age and frequently have their successors. This way the genetic lines carrying the respective allergic phenotype might have been transmitted generation after generation, although the prior allergic generations lacked modern treatment of anaphylactic reactions.

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Hymenoptera represent an insects order, where together with other species, bees and wasps are included [1–5]. While stinging, their venom may cause quite dramatic allergic reactions in sensitized persons [4–6]. In some cases, incidents of stinging by hymenoptera may be fatal [5,7,8]. According to findings reported by a number of authors, anaphylactic reactions caused by the hymenoptera venom may affect 0.4–5% of the population, while their mortality rate may reach 0.09–0.45 deaths per million inhabitants annually

[2–5,9–14]. However, the researches show that reactions caused by the hymenoptera venom are less frequent in children than in adults (prevalence rates 0.15–0.8%), though children are much more stung [7,14–21]. The general clinical progress of allergy caused by the hymenoptera is also much more benign in children than in adults [22–25]. After the first sensitization and experience of a threatening or lack of allergy there exist the possibility that such an anaphylactic reaction reappears or be more serious. A number of studies carried out by Golden, Reisman, Valentine, etc. show that if no treatment by specific immune-therapy is undertaken, the possibility of repetition of

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reactions in allergic persons goes up to 40–80% in adults and 9–40% of cases in children, especially including those occurring following prior moderate or severe reactions [10,14,17,24,26–28]. According to Björnsson et al., the progression of age is considered to be an independent factor of sensitization risk [12]. Furthermore, while in adults which are allergic to hymenoptera venom, when they are re-stung, vital respiratory or cardiovascular systems endanger to be affected up to the loss of conscience more frequently than in children, the latter are more frequently than adults affected by skin reactions [10,24,29]. According to Lockett and Chipps, in all systemic reactions to hymenoptera venom children are affected in 60% by solely cutaneous reactions as against respiratory and cardiovascular reactions, which are present in 70% of cases in adults [30,31]. Therefore, some authors such as Valentine, Reisman or Eckes are of the opinion that since children face low risk of repetition of anaphylactic reactions, they generally do not need vaccination but in cases of serious reactions [18,24,27]. This way, the immunotherapy in children with mild allergic reactions to hymenoptera venom may be considered unnecessary [24].

It is believed that epidemiologic differences between children and adults regarding the progress of anaphylactic reactions to hymenoptera venom are not casual. The findings collected until now do not allow us to formulate a medical-scientific opinion on eventual reasons of such epidemiologic differences between these group-ages. Actually it is difficult to take a position on the matter. It means that there is not described a clear profile of an immune, other system or phys-pathological mechanism suggesting the answer to the introduction of an antigenic factor into human body, provided it depending on the group-age of the subject.

Under these circumstances, it may be ascertained that such observations might eventually confirm the presence of a more favorable clinical course of allergies deriving from stinging of hymenoptera, in children in particular, also because of yet unclear self-restraining mechanisms [27].

In this context an eventual explanation could be that children, although initially might not have an adequate immune response, at their very early age do have adequate immunity because of their high plasticity. Such ability would increase chances in later exposures for a more favorable response to antigens in question. Referring to the New Oxford Dictionary by “plasticity” should be understood the adaptability of an organism to changes in its environment or differences between its various habitats. In this case the immune system, following

the memorization of the antigen found in the repertory of its immune response, would ensure a response as adequate as possible and with minimal side effects. In fact, the eventual immune changes observed in such patients as response to repeated exposures to hymenoptera venom, differing individuals provided with a satisfactory tolerance from those lacking such an ability, result exclusively from researches in patients treated with specific immunotherapy.

Consequently, their value in the case of the above-mentioned epidemiological changes is quite limited. Furthermore, Freye and Litwin have reported in a work that allergic families to hymenoptera venom are distinguished from the other part of the population by frequency of occurrence of allergic reactions [32]. This genetic mosaic may affect both the level of expression of immune and non-immune physiological factors [33,34]. A number of different mediators are included in this category. According to Ponvert et al., a high plasmatic level of RANTES has been observed in allergic children indicating side effects during specific immunotherapy with wasp venom [33]. This cytokine produced by lymphocytes T, eosinophils, etc. has a chemotactic effect and activates inflammatory cells such as eosinophils or basophils. Qualitative changes of immune components between allergic and non-allergic persons stung several times by hymenoptera have been observed as well at the level of both specific IgE and responses of IgG subclasses, which are more emphatic in case of lack of allergy or successful desensitization [35,36]. Thus, Müller et al. have proved in his research that lack of IgG response to particular components of bee venom is correlated with repeated reactions during specific immunotherapy [37]. Though IgG₄ levels have gradually increased in a few days, values in those patients did not reach the levels of the beekeepers that were not allergic. The latter had high values even in relation to IgG₂ subclass, while patients with side reactions that could still manage to withstand immunotherapy with bee venom in doses 60–80 µg (common maintenance dose goes up to 100 µg), had higher plasmatic levels of IgG₁ subclasses [37]. As demonstrated by the same research, the only patient interrupting completely the immunotherapy with the bee venom did not show any increase of plasmatic values of the latter, while IgG₃ values were insignificant in both patients and beekeepers [37]. Later findings have linked the presence of allergy from hymenoptera venom with the domination of cytokine profile TH₂ against that of TH₁ or immune tolerance of respective antigens with the

induction of regulatory cells CD4⁺/CD25⁺ through pertinent cytokines [36,38,39]. Thus, a high level of IL-10 at the age of 12 months has been found in non-atopic children, while its low values in atopic children have caused the lack of inhibition of inflammatory processes [40]. In a research in experimental animals on models of allergy from wasp venom, Winkler et al. reported also that an increase of the level of messenger RNA for transforming growth factor beta (TGF- β) and IL-10, proved that immuno-suppression following the intranasal application of the recombinant antigen Ves v 5 has been mediated by regulatory mechanisms [41]. However, even recently recognized mechanisms regarding such mediators, have only at a certain degree explained the course of action of specific immunotherapy, but did not help to explain the nature of the origin of demographic differences between various group-ages. Differences in anti-corporal or mediatory profiles between groups of patients are mentioned here because the injections of the maintenance doses of specific immunotherapy are considered as a test of charge and the initial responses of the patient would also have a resemblance with the response to natural stings. This conclusion is justifiable since at the beginning of the treatment with specific immunotherapy in those patients there is no dealing with remodeling of the immune response. In fact, such differences most of which are presented in this discussion, do not answer the question how and why during evolution various models of respective profiles have played a positive or negative role, but at least they show that different groups of patients do have such differences, not yet clearly identified, in relation to the prognosis of the illness.

Another mechanism would explain also, not directly, the changes occurring in response to the repeated exposure to hymenoptera venom, which differentiate individuals provided with the ability to have a satisfactory progress, from those who do not have it. It would consist in the ability of autonomic systems to adapt to the repeated impact of harmful stimuli in order to ensure a permanent stability of vegetative vital systems, such as cardiovascular and respiratory ones. Unfortunately, also in this case the data come from researches made mainly in patients treated with specific immunotherapy of hymenoptera venom. In this framework, in confronting stinging or maintenance therapeutic doses, avoiding affection by anaphylaxis in the cardiovascular system, the presence of high levels of rennin and of angiotensin I and angiotensin II from the beginning of treatment by hymenoptera venom is important rather than

catecholamines one [34,42]. This fact has an additional value as well. In this respect, at the beginning of the treatment with specific immunotherapy the plasmatic level of these mediators affects the presence or lack of side reactions, at a time when yet no change in the level of immune response of the patient has occurred. And further on, the specific immunotherapy itself induces an increase of the plasmatic level of these mediators, while their high level has been accompanied by the lack of occurrence of side reactions, even in the initial phase of specific immunotherapy [34,43]. Furthermore, their level correlates inversely rather with the degree of affection of cardiovascular system, which is not the case with the results of skin tests or value of specific IgE. Such peptides in this case are found in basophile leucocytes [44]. These findings suggest that angiotensins may affect leucocytes as mediator or stimulate modulation of other mediators. A low level of them after the exposure to hymenoptera venom in allergic persons may be connected with the presence of an insufficient adaptation of the cardiovascular system to such stimuli [44]. The mentioned findings eventually suggest that the role of mechanisms in question is more important than the role immune mechanisms in confronting a casual hymenoptera sting in the most appropriate way.

In addition to the plastic abilities ensuring adequate adaptability expressed mainly in young ages, in mechanisms of adaptive differences between age groups eventually there should be included the presence of phys-pathological changes or defects in adults as result of their ageing. Aver has ascertained in this framework that in addition to other things histamine is a potent coronary vasoconstrictor and can induce rhythm or conduction disturbances [45,46]. Furthermore, Pomerance has stated that mast cells are known to be enriched in areas of atheromatous plaque and to be especially prominent in the adventitia of the coronary arteries [46,47]. According to Wasserman, the fact that mast cells are increased in the coronary arteries of patients with coronary disease, suggests that anaphylaxis in older patients or the patients with known coronary disease may be especially unfortunate both from the view of tolerance of hypotension and hypoxia, but also because of the potential for severe cardiac anaphylaxis [46]. On the contrary, in the case of children, the normal clinical course of stinging does not have a negative effect for children, because they have vital systems intact of changes and diseases of older ages.

The analysis of the above-mentioned epidemiological data leads to the conclusion that cognition of mechanisms ensuring a more favourable clinical

course of allergy from hymenoptera venom in young individuals, comparing to adults, is still very limited and almost completely tangential.

On the other hand, the reasons and importance of the presence of a particular profile of changes in relation also to age has not been a subject of discussions in the respective periodical press. Based on these facts, it may be suggested that the above-mentioned changes eventually may have their origin in the evolution of human species itself. The evolution of responses of different anti-corporal profiles, such as those of IgG, IgA, or IgE, efficient to a spectrum of definite organisms or products according to environmental situation, has created and inherited the presence of respective different genotypic and phenotypic lines. This may be valid also for other structural and functional, immune and non-immune adaptive mechanisms, which at present circumstances can still be activated. In circumstances of a natural evolution in front of factors to which the exposure was permanent, a more adequate response has been established. In cases where the exposure has been relatively casual (in the case of hymenoptera also because of the successful avoidance of repeated stinging, in order to avoid at least the experience of painful episodes), the specific response frequently depended on the profile favoured by inheritance or environmental factors, which were more evidently exposed. Consequently, the response to hymenoptera venom in different persons has been adequate but sometimes not adequate and the lack of modern treatment might have caused death because of the anaphylactic reaction. In the framework of this selection during millennia of prehistoric life, there was mostly assured the survival of genotypic and phenotypic lines successfully adapted to the environment. Therefore, with the passing of time maybe there was a reduction of prevalence of the allergy to hymenoptera venom.

On the other hand, after repeated stinging of hymenoptera venom maybe temporary there were created lines with sufficient adaptability to ensure the survival only for the period of childhood or youth. It might have happened because of the ever more casual exposure to stinging as result as well of preventive measures by conscious or consciousness-raising individuals and of the experience of painful stinging at earlier periods of life of every individual, allergic or non-allergic to hymenoptera venom. This behavior of various individuals during passing years might have led to the loss of individual adaptability, even without experiencing unexpected fatal reactions following the stinging by hymenoptera at later periods of life. However, in

such cases the grown individuals have often left their successors thus ensuring transmission of respective genetic and phenotypic lines. It is not excluded also that from these lines might have derived such genetic and phenotypic lines, which could ensure adaptability, heritable only during childhood or early youth of individuals of their origin. Therefore, the existence of successors of those lines (at least when they did survive), might have allowed the continuous existence of allergic sub-categories of population – allergic to hymenoptera venom up to present generations, which today represent in general a small fraction of population.

It is understandable that the role of evolution rules is actually minimized due to the modern medical achievements ensuring the safety of life quality for each subject, regardless disposable genotypic or phenotypic mosaic.

In conclusion, it should be claimed that even low frequency of stinging during major age has ensured in the past a natural survival for persons with sufficient adaptability only during the period of childhood or early youth, up to older ages. The changes related to plasticity of immune and non-immune abilities or to genotypic and phenotypic profile of different adaptive mechanisms between such individuals and those with adequate adaptability expressed during the entire life, are on the contrary, maybe the reason for milder and less frequent experiences of anaphylactic responses during childhood in comparison with further periods of life.

The expression of almost adequate responses to hymenoptera venom only by some definite lines of subgroups of population during childhood and earlier youth have possibly enabled the transmission of genetic lines carrying respective allergic phenotype up to modern times. Further comparing genetic and physiological studies are needed to prove this hypothesis with the view of studying individual characteristics related to hypersensitivity to hymenoptera sting, disease prognosis and the age of such individuals. The further knowledge of regulatory immune and non-immune mechanisms involved in these processes may lead to the providing and application of more successful methods in treating and preventing allergies to hymenoptera venom and consequently to the relief of frequency of occurrence of these threatening diseases to life.

References

- [1] Chinery M. A field guide to the insects of Britain and Northern Europe. London: William Collins; 1984.
- [2] Fernandez J, Blanca M, Soriano V, Sanchez J, Juarez C. Epidemiological study of the prevalence of allergic

- reactions to Hymenoptera in a rural population in the Mediterranean area. *Clin Exp Allergy* 1999;29:1069–74.
- [3] Mingomataj E, Priftanji A, Qirko E, Dinh QT, Fischer A, Peiser C, et al. Specific immunotherapy in Albanian patients with anaphylaxis to hymenoptera venoms. *BMC Dermatol* 2002;2:11–6.
 - [4] Mingomataj E, Ohri D, Dhimitri V, Priftanji A, Qirko E, Pani L, et al. Hymenoptera sting anaphylactic reactions in the Mediterranean population of Albania. *J Invest Allergol Clin Immunol* 2003;13(4):272–7.
 - [5] Przybilla B, Ruff F, Fuchs T, Pfeiffer C, Rakoski J, Stolz W. Insektengiftallergie. *Allergo J* 2004;13:186–90.
 - [6] Mosbech H. Hymenoptera immunotherapy. *Allergy* 1997;52:1–3.
 - [7] Barnard JH. Studies of 400 Hymenoptera sting deaths in the United States. *J Allergy Clin Immunol* 1973;52:259–64.
 - [8] Mosbech H. Deaths caused by wasp and bee stings in Denmark 1960–80. *Allergy* 1983;38:195–200.
 - [9] Settipane GA, Boyd GR. Prevalence of Bee sting allergy in 4992 boy scouts. *Acta Allergol* 1970;25:286–91.
 - [10] Reisman RE. Stinging insect allergy. *Med Clin North Am* 1992;76(4):883–94.
 - [11] Charpin D, Birnbaum J, Vervloet D. Epidemiology of Hymenoptera allergy. *Clin Exp Allergy* 1994;24:1010–5.
 - [12] Björnsson E, Janson C, Plaschke P, Norrman E, Sjöberg O. Venom allergy in adult Swedes: a population study. *Allergy* 1995;50:800–5.
 - [13] Grigoreas Ch, Galatas ID, Kiamouris Ch, Papaioannou D. Insect-venom allergy in Greek adults. *Allergy* 1997;52:51–7.
 - [14] Golden DBK, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Outcomes of Allergy to Insect Stings in Children, with and without Venom Immunotherapy. *N Engl J Med* 2004;351:668–74.
 - [15] Abrishami MH, Boyd GK, Settipane GA. Prevalence of bee sting allergy in 2010 girl scouts. *Acta Allergol* 1971;26:117–20.
 - [16] Settipane GA, Newstead GJ, Boyd GK. Frequency of Hymenoptera allergy in atopic and normal population. *J Allergy Clin Immunol* 1972;50:146–50.
 - [17] Novembre E, Cianferoni A, Bernardini R, Mugnaini L, Caffarelli C, Cavagni G, et al. Anaphylaxis in children: clinical and allergologic features. *Pediatrics* 1998;101:8–15.
 - [18] Rance F, Abbal M, Bremont F, Dutau G. Allergy to hymenoptera venoms in children. *Arch Pediatr* 1996;6(Suppl. 1):555–60S.
 - [19] Leopold W, Saner H. Probleme der Insektengiftallergie im Kindesalter. *Allerg Immunol* 1991;37:31–5.
 - [20] Lantner R, Reisman RE. Clinical and immunologic features and subsequent course of patients with severe insect-sting anaphylaxis. *J Allergy Clin Immunol* 1989;84:900–6.
 - [21] Reisman RE. Current concepts: insect stings. *N Engl J Med* 1994;331:523–7.
 - [22] Schuberth KC, Lichtenstein LM, Kagey-Sobotka A, Szklo M, Kwiterovich KA, Valentine MD. Epidemiologic study of insect allergy in children: II. Effect of accidental stings in allergic children. *J Pediatr* 1983;102:361–5.
 - [23] Graft DF, Schuberth KC, Kagey-Sobotka A, et al. A prospective study of the natural history of large local reactions after hymenoptera stings in children. *J Pediatr* 1984;104:664–8.
 - [24] Valentine MD, Schuberth KC, Kagey-Sobotka A, Graft DF, Kwiterovich KA, Szklo M, et al. The value of immunotherapy with venom in children with allergy to insect stings. *N Engl J Med* 1990;323:1601–3.
 - [25] Forster J, Kühr J, Hauk P, Schwab O, Urbanek R. Stichproaktionen bei Kindern mit Insektengiftallergien. *Allergologie* 1996;19(7):330–3.
 - [26] Eckes A, Forster J, Urbanek R. Langzeitbeobachtung von nicht-hyposensibilisierten Kindern mit Insektengift-Allergie. *Allergologie* 1990;13(Suppl. 1):S58–9.
 - [27] Reisman RE. Natural history of insect sting allergy: relationship of severity of symptoms of initial sting anaphylaxis to re-sting reactions. *J Allergy Clin Immunol* 1992;90(3 Pt. 1):335–9.
 - [28] Golden DB. Insect sting allergy and venom immunotherapy: a model and a mystery. *J Allergy Clin Immunol* 2005;115(3):439–48.
 - [29] Schultze-Werninghaus C, Wahn U, Niggemann B. Evaluation of the risk of anaphylactic reactions by wasp venom-extract challenges in children. *Pediatr Allergy Immunol* 1999;10(2):133–7.
 - [30] Chipps BE, Valentine MD, Kagey-Sobotka A, Schuberth KC, Lichtenstein LM. Diagnosis and treatment of anaphylactic reactions to Hymenoptera stings in children. *J Pediatr* 1980;97:177–84.
 - [31] Lockey RF, Turkeltaub PC, Baird-Warren IA, et al. The Hymenoptera venom study I, 1979–1982: demographics and history-sting data. *J Allergy Clin Immunol* 1988;82:370–81.
 - [32] Freye HB, Litwin CM. Hymenoptera sensitivity occurring in families. *Allergy Proc* 1994;15(2):69–71.
 - [33] Ponvert C, Le Corvoisier C, Weill B, Bloch E, Paupe J, Scheinmann P. Kinetics of plasma cytokine levels in children hyposensitized with wasp venom. *Cytokine* 2001;15(4):229–31.
 - [34] Hermann K, Ring J. Association between the renin angiotensin system and anaphylaxis. *Adv Exp Med Biol* 1995;377:299–309.
 - [35] Wyss M, Wüthrich B, Jacobsen L. IgG₄-Antikörper während einer Desensibilisierung mit Aluminiumhydroxid – adsorbenten Hymenopterengiftextrakten. *Allergologie* 1990 (Suppl. 1):S39–43.
 - [36] Akdis CA, Blaser K. Mechanisms of allergen-specific immunotherapy. *Allergy* 2000;55:522–30.
 - [37] Müller UR, Morris T, Bischof M, Friedli H, Skarvil F. Combined active and passive immunotherapy in honey-bee-sting allergy. *J Allergy Clin Immunol* 1986;78:115–22.
 - [38] Romagnani S. Type 1 T helper and type 2 T helper cells: functions, regulation and role in protection and disease. *Int J Clin Lab Res* 1991;21:152–8.
 - [39] Akoum I, Tsicopoulos A, Vorng H, Wallaert B, Dessaint JP, Joseph M, et al. Venom immunotherapy modulates interleukin-4 and interferon- γ messenger RNA expression of peripheral T lymphocytes. *Immunology* 1996;87:593–8.
 - [40] Van der Velden VH, Laan MP, Baert MR, de Waal Malefyt R, Neijens HJ, et al. Selective development of a strong Th2 cytokine profile in high-risk children who develop atopy: risk factors and regulatory role of IFN-gamma, IL-4 and IL-10. *Clin Exp Allergy* 2001;31(7):997–1006.
 - [41] Winkler B, Bolwig C, Seppala U, Spangfort MD, Ebner C, Wiedermann U. Allergen-specific immunosuppression by mucosal treatment with recombinant Ves v 5, a major allergen of *Vespula vulgaris* venom, in a murine model of wasp venom allergy. *Immunology* 2003;110(3):376–85.
 - [42] Hauk P, Otto J, Schwab KO, Kaufmehl K, Urbanek R, Eichler EG, et al. Anaphylactic reactions to bee-sting challenges in allergic children are not modified by endogenous catecholamines. *Pediatr Res* 1995;38(6):998–1002.

- [43] Hermann K, von Eschenbach CE, von Tschirschnitz M, Ring J. Plasma concentrations of arginine vasopressin, oxytocin and angiotensin in patients with hymenoptera venom anaphylaxis. *Regul Peptides* 1993;49(1):1–7.
- [44] Hermann K, Ring J. Angiotensin und Insektengift-Anaphylaxie. *Allergologie* 1990;13(Suppl. 1):S47–8.
- [45] Aver J, Lewis PA. Physiology of immediate reaction of anaphylaxis in guinea pig. *J Exp Med* 1910;12:151.
- [46] Wasserman SI. The heart in anaphylaxis. *J Allergy Clin Immunol* 1986;77:681–6.
- [47] Pomerance A. Periarterial mast cells in coronary atheroma and thrombosis. *J Pathol Bacteriol* 1958;76:55.

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