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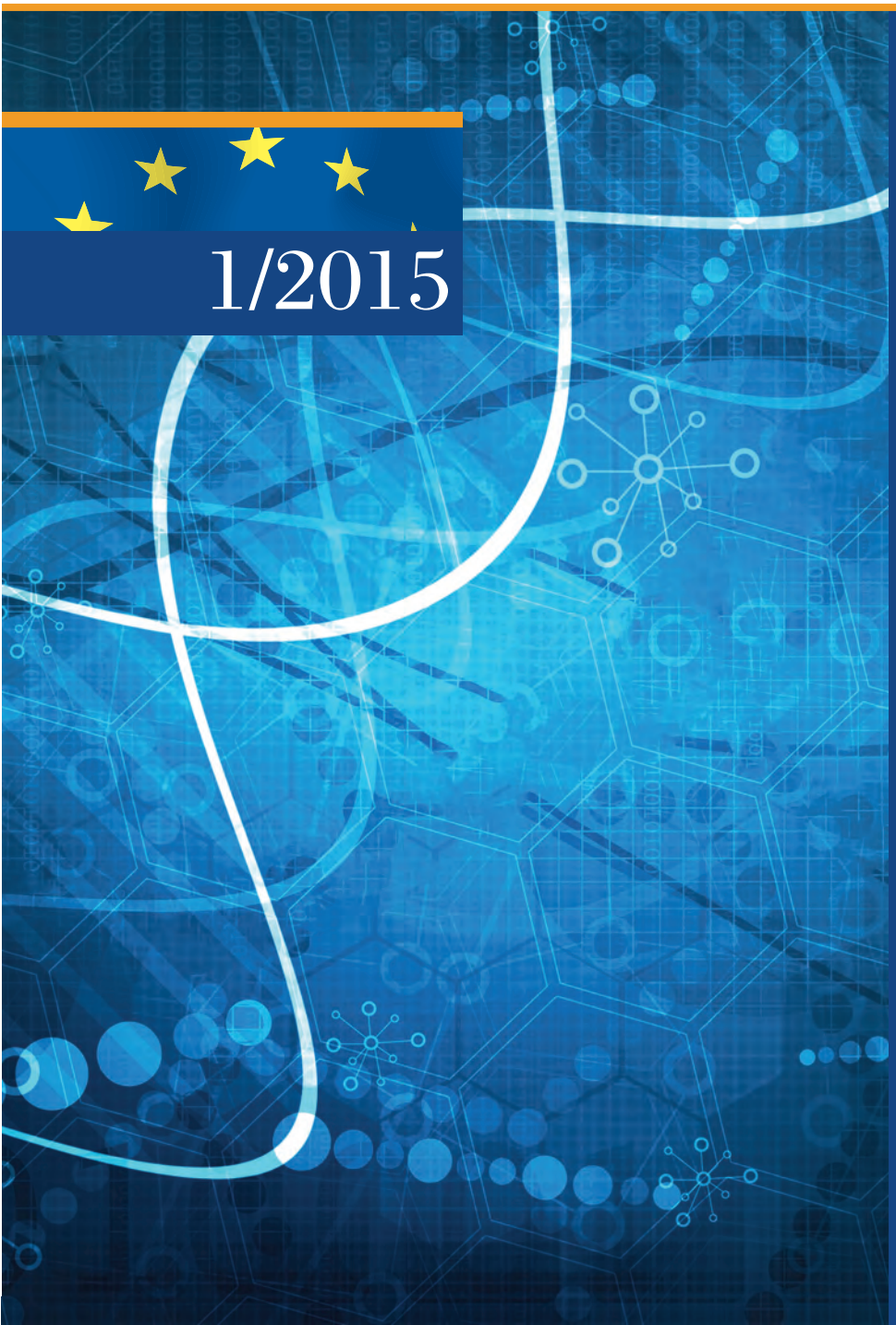

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Chiara Scelsi
c.scelsi@lswr.it
Tel. 02 88184.257

Production Manager
Walter Castiglione
w.castiglione@lswr.it
Tel. 02 88184.222

Sales & Marketing
Ludovico Baldessin
l.baldessin@lswr.it
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Traffic
Donatella Tardini
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Subscription
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N. Wyrzykowska, M. Czarnecka-Operacz, Z. Adamski

Long-term efficacy of allergen specific immunotherapy in atopic dermatitis patients in relation to quality of life

Key words
Atopic dermatitis; DLQI; allergen specific immunotherapy

Corresponding author
Nina Wyrzykowska
Department of Dermatology
Poznan University of Medical Sciences
49 Przybyszewskiego,
60-355 Poznan, Poland
E-mail: nina.wyrzykowska@gmail.com

Summary
Introduction. *Atopic dermatitis (AD) is an inflammatory, chronically relapsing and highly pruritic skin disorder that considerably effects patients' life. Dermatology Life Quality Index (DLQI) is often applied in clinical research in order to evaluate the impact of AD on daily performance of patients.* ***Aims.*** *The aim of the study was to evaluate the long-term effect of allergen specific immunotherapy (ASIT) on the quality of life in AD patients.* ***Materials and methods.*** *15 patients suffering from AD, allergic to house dust mites or grass pollen allergens, who were previously treated with ASIT participated in the study. Our treatment with allergy vaccinations was performed during the time period between 1995 and 2001. DLQI questionnaires have been filled by the patients before the treatment, after termination of ASIT and after 2 - 12 years of the observational period.* ***Results.*** *The statistical tests revealed a significant difference between the DLQI before ASIT was introduced and after termination of ASIT. Every answer except two (describing the influence of skin condition on preventing from working or studying and on sexual life) of these periods also disclosed statistically significant difference. As for the relation between the DLQI after ASIT and the actual one the tests revealed non significant difference, also regarding to every single answer of the questionnaire.* ***Conclusions****. In relation to improvement of quality of life in AD patients, this study confirms the effectiveness of ASIT and it discloses the persistence of its results in long-term aspect.*

Introduction

Atopic dermatitis (AD) is an inflammatory, chronically relapsing, and highly pruritic skin disorder. AD affects more than 10% of children and 2% of adults. In industrialized countries the prevalence has increased significantly in last years, it has doubled or even tripled. AD is often associated with other atopic diseases such as asthma or allergic rhinitis. The etiology of atopic dermatitis is complicated and it is based on defects concerning the immunologic system that leads to IgE-mediated sensitization and epithelial barrier dysfunction. Both dysfunctions result in inflammatory skin lesions that vary with age in localization and clinical manifestation. In each stage, itching that continues throughout the day and worsens at night causes sleep loss and considerably affects patient's and family unit's life (1). The successful treatment of atopic dermatitis is based on complex management: optimal moisturization, topical anti-inflammatory treatment (corticosteroids and calcineurin inhibitors), first-generation antihistamines to decrease the itch and sleeping disturbances and the adequate skin infections treatment. The patient education is still one of the most important tools to improve patients' health status. Other therapeutic options may be considered in severe cases, such as oral corticosteroids, ultraviolet phototherapy, cyclosporine A, azathioprine (2). Although optimistic researches reporting the benefit influence of allergen-specific immunotherapy (SIT) on atopic dermatitis patients have appeared (3,4,5), this method still remains contro-

versial. SIT as an only known casual allergy treatment involves complicated mechanisms that need further investigations. The evidences of SIT efficacy in atopic dermatitis were summarized by Comapalati et al and Bea et al (6,7).

Aims

The aim of the study was to evaluate the long-term effect of allergen specific immunotherapy (SIT) on the quality of life in AD patients.

Material and methods

Fifteen patients suffering from AD, allergic to house dust mites (n - 7), grass pollen allergens (n - 7) or house dust mites and grass pollen allergens (n - 1), who were previously treated with SIT, participated in the study. SIT was performed subcutaneously for five years for each allergen. In case of one patient treated with two types of allergen vaccines, SIT lasted for eight years in total. At the baseline patients presented moderate and/or severe AD, and clinical characteristics were one of the inclusion criteria for the treatment with allergen vaccinations. At the baseline patients were evaluated on the basis of W-AZS index (Severity and Extensiveness of skin Inflammation in Atopic Dermatitis Index) with the mean value of 102,6 points.
Depending on the type of airborne sensitization, patients were treated with allergen vaccinations of an appropriate composition (mites or grass pollen allergens extracts). In case of a patient with airborne sensitization to mite as well as grass pollen allergens, first the mite allergy vaccine has been introduced and thereafter SIT with the second vaccination (after one year of the treatment), composed of grass pollen allergens extract was started. For our study allergy vaccines, Novo-Helisen® Depot, Nexter - Allergopharma (Katowice, Poland and Reinbek, Germany) have been selected. SIT was performed according to the international European guidelines, and it was a perennial type of treatment. The starting dose was 0,05 ml of 50 TE/ml concentration, followed by injections administered every 7-14 days with increasing amount dosages, finally reaching the maintenance dose of 1 ml of 5000 TE/ml allergen concentration. Maintenance doses while reached in the course of treatment, were administered monthly.
The age of patients ranged from 5 to 46 years (mean age: 20,4) and the group was composed of 20% males and 80% females. Our treatment with allergy vaccinations was performed during the time period between 1995 and 2001. Dermatology Life Quality Index (DLQI) questionnaires have been filled by the patients before the treatment, after termination of SIT, and after 2 - 12 years of the observational period. DLQI is one of the most practical and easy measure that was developed in 1994 by the team at the Department of Dermatology, Cardiff University (**table 1**). This simple questionnaire for routine clinical is often used to describe the impact of the disease and its treatment on patient's lives. It was used in over 1000 publications and it is available in over 21 languages. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology. It is a questionnaire that consists of ten simple questions concerning symptoms and feelings, daily activities, leisure, work, and school, personal relationships and treatment (8). The score for each question is from 0 to 3 points, summed giving a range from 0 (no impact on life) to 30 points (maximum impairment of life quality).

Results

Friedman Test (Nonparametric Repeated Measures ANOVA) and Dunn's Multiple Comparisons Test were used to statistical analysis (**table 2**,**3**). Also the average DLQI results comparison is presented (**table 3**). It reveals the constant improvement of quality of life in the time course. We did not observe any statistical significant difference in DLQI results depending on presented type of allergy.

Before SIT and after SIT

The tests revealed significant difference between the DLQI before SIT was introduced and after termination of the treatment, what can be considered as an important factor of success of SIT in our AD patients. In case of all answers except two (describing the influence of skin condition on preventing from working or studying and on sexual life) the difference was statistically significant.

Before SIT and the present time point (now) (after 2 - 12 years of the observational period)

The quality of life before SIT was performed has been improved till today, although the statistical analysis only in some questions revealed significant improvement.

After SIT and the present time point (now) (after 2 - 12 years of the observational period)

As for the relation between the DLQI after SIT and the actual one the tests revealed non-significant difference also regarding to every single answer of the questionnaire.

Table 1 *- Dermatology Life Quality Index (DLQI).*

DERMATOLOGY LIFE QUALITY INDEX				
Hospital No: Name: Address:	Date: Diagnosis:		**DLQI** Score:	
The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ⇛ one box for each question.				
1. Over the last week, how **itchy**, **sore painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❑ ❑ ❑ ❑		
2. Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❑ ❑ ❑ ❑		
3. Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❑ ❑ ❑ ❑	Not relevant	❑
4. Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❑ ❑ ❑ ❑	Not relevant	❑
5. Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❑ ❑ ❑ ❑	Not relevant	❑
6. Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❑ ❑ ❑ ❑	Not relevant	❑
7. Over the last week, has your skin prevented you from **working** or **studying**? If "No", over the last week how much has your skin been a problem at **work** or **studying**?	Yes No A lot A little Not at all	❑ ❑ ❑ ❑ ❑	Not relevant	❑
8. Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❑ ❑ ❑ ❑	Not relevant	❑
9. Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❑ ❑ ❑ ❑	Not relevant	❑
10. Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❑ ❑ ❑ ❑	Not relevant	❑
Please check you have answered EVERY question. Thank you.				
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Table 2 *- The statistical analysis of DLQI questions before SIT, after SIT and now.*

Question		Before SIT and AFTER SIT	Before SIT and now	After SIT and now
1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	SIGNIFICANT	SIGNIFICANT	NON SIGNIFICANT
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	SIGNIFICANT	SIGNIFICANT	NON SIGNIFICANT
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	SIGNIFICANT	SIGNIFICANT	NON SIGNIFICANT
4.	Over the last week, how much has your skin influenced the clothes you wear?	SIGNIFICANT	SIGNIFICANT	NON SIGNIFICANT
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	SIGNIFICANT	SIGNIFICANT	NON SIGNIFICANT
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	SIGNIFICANT	NON SIGNIFICANT	NON SIGNIFICANT
7.	Over the last week, has your skin prevented you from **working** or **studying**? / Over the last week how much has your skin been a problem at **work** or **studying**?	NON SIGNIFICANT	NON SIGNIFICANT	NON SIGNIFICANT
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	SIGNIFICANT	NON SIGNIFICANT	NON SIGNIFICANT
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	NON SIGNIFICANT	NON SIGNIFICANT	NON SIGNIFICANT
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	SIGNIFICANT	SIGNIFICANT	NON SIGNIFICANT
DLQI – total score		SIGNIFICANT	SIGNIFICANT	NON SIGNIFICANT

Table 3 *- Average DLQI results (max. - 30 points).*

	Before SIT	After SIT	Now
Average DLQI result (points)	20,0	9,0	4,0

Discussion

Skin diseases such as AD can have a great impact on patients' lives in terms of psychological well-being, everyday activities and functioning in the society. Therefore, the quality of life improvement has become a major object to achieve in various clinical trials.

In this study we show that SIT has a long-term efficacy in AD patients. The initial average DLQI result has been reduced after SIT was completed (what reflects in statistical analysis as a significant difference) and after then the score still has a decreasing tendency, although it is of no statistical significance. Every single question of the DLQI questionnaire has been analysed separately in addition. We are able to show a significant improvement in case of six questions (except two, concerning preventing from working or studying and sexual life) before and after SIT was performed. Then, the value of quality of life obtained due to the treatment with allergy vaccination has become stabilized till today, although statistical analysis revealed no significant difference. On the basis of the comparison between DLQI score before SIT and now, we observe that in two of ten questions (concerning sport, relation with relatives and friends) the actual

score has been decreased; it was not that satisfying as after SIT, but anyhow not that distressing as before SIT. In case of other two questions, regarding preventing from working or studying and sexual life, we did not observe any influence of SIT on this part of the quality of life of our patients.

The long-term comparison of quality of life in AD patients who were treated with SIT has not been described so far. Besides, even the effectiveness of SIT in AD patients using the quality of life measures has been poorly described in the medical literature. Bae JM et al performed a systemic review of efficacy of allergen-specific immunotherapy for atopic dermatitis (7). Almost all of the trials mentioned in the review did not analyse the patient's quality of life as an important factor describing success of treatment.

Novak N et al showed a clinically important reduction of the total DLQI due to SIT in the trial, although it was not always statistically significant. The AD group obtained the following median DLQI score before -5.7, and after active treatment (SIT) -6.0 (5).

The long-term efficacy defined by quality of life measures was highlighted in articles dedicated to rhinoconjunctivitis. Stephen R. Durham performed a double-blind, placebo-controlled trial, that involved a group of two hundred thirty-eight participants with a clinical history of grass pollen-induced allergy, presenting symptoms interfering with usual daily activities or sleep. The significant decrease in days with severe symptoms, and the improved of quality of life in the active group, supported the clinical relevance of the primary efficacy end points, and emphasized the relevance of sublingual grass SIT treatment from the patient perspective (9).

Also Didier et al describes improvement in quality of life over the fourth pollen period in patients with rhinoconjunctivitis. Besides, it is highlighted that this improvement may be underestimated, due to the higher rescue medication use in placebo-treated group compared to the active group (10).

Conclusions

The current study was designed to assess whether SIT in AD patients displays a long-term efficacy in relation to quality of life. SIT has been shown to improve patients' well-being, not only just after SIT was performed, however it also has a beneficial sustained influence years after its termination.

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D. Ullrich[1], K. Ullrich[1], S. Mussler[2], S. Thum-Oltmer[2]

Vaccination during concurrent subcutaneous immunotherapy: safety of simultaneous application

[1]Otorhinolaryngological Medical Practice/Day Surgery, Wedemark, Germany
[2]Allergopharma GmbH & Co. KG, Reinbek, Germany

Key words

Vaccination against infectious diseases; allergen-specific subcutaneous immunotherapy; IgE-mediated allergy, simultaneous application

Corresponding author
Dieter Ullrich
Otorhinolaryngological Medical Practice/Day Surgery
Wedemarkstr. 83
30900 Wedemark, Germany
Phone: +49 5130 3737 87
Fax: +49 5130 3752 62
E-mail: Ullrich-Dieter@t-online.de

Summary

Background. *During subcutaneous immunotherapy (SCIT), injections should be separated from vaccinations against infectious diseases by at least 1 week, because it is assumed that adverse reactions can result from the additional activation of the immune system.* ***Material and Methods.*** *Data of a total of 875 individuals receiving SCIT and/or vaccination in one ENT-practice were included and analyzed retrospectively. 444 individuals had received vaccination against infectious diseases, 336 allergic patients received only SCIT. Moreover, 79 allergic patients had received vaccination and SCIT injections simultaneously on one day in different locations, while 16 patients inadvertently received SCIT injections within up to 4 days after vaccination. Some of the patients were observed for consecutive years receiving several vaccinations parallel to SCIT. Systemic reactions (SRs) during SCIT were classified according to the WAO (World Allergy Organization) grading.* ***Results.*** *Patients exclusively receiving vaccinations did not report any drug-related SR. One SR third grade and two SRs second grade occurred in 3 asthmatic patients exclusively receiving SCIT. The patients simultaneously receiving vaccination and SCIT did not have any SR. This was also the case for the subjects consecutively receiving parallel SCIT and vaccination for up to 5 years.* ***Conclusion.*** *The international guidelines for allergen-specific immunotherapy (SIT) recommend an intermission of at least one week between SCIT and the administration of vaccines. However, these findings demonstrate the possibility to shorten or abolish this interval without increasing the risk of SRs.*

Abbreviations

SCIT - subcutaneous immunotherapy
SR - systemic reaction
WAO - World Allergy Organization
SIT - allergen-specific immunotherapy
WHO - World Health Organization
FDA - Food and Drug Administration
DTP - diphtheria/tetanus/pertussis
EAACI - European Academy of Allergy and Clinical Immunology
MMR - measles/mumps/rubella
TBE - tick-borne encephalitis
ELISA - enzyme-linked immunosorbent assay
RAST - radioallergosorbent assay
SmPC - Summary of Product Characteristics

Introduction

The immune system is a complex interactive network with the capacity of protecting the host from a number of pathogens while keeping either a state of tolerance to self and innocuous non-self antigens or to develop an adaptive immunity against pathogens (1). IgE-mediated allergic diseases are immune tolerance-related and arise as a direct consequence of a dysregulated immune system. The innate and adaptive immune responses to environmental antigens lead to inflammatory reactions with a T-helper-2-type cell and allergen-specific IgE predominance (1).

Currently, allergen-specific immunotherapy remains the only curative approach by administering gradually increasing quan-

tities of an allergen product to an individual with IgE-mediated allergic diseases (2). It induces clinical and immunological tolerance, and thereby improves the quality of life in allergic patients. SIT has long-term efficacy and may prevent either disease progression of rhinitis into asthma and/or the onset of new allergic sensitizations (2).

In general, subcutaneous immunotherapy is started with an up-dosing phase until reaching the maintenance dose. The up-dosing phase may be conducted as conventional 'one injection per week', or alternatively as a clustered or rush regimen (2). In case of a perennial dosage scheme, the injection interval may be spread up to 8 weeks during the maintenance phase, depending on the manufacturers' recommendation. In case of larger intervals, the allergen doses have to be reduced or even SCIT has to be restarted. It is recommended to perform SCIT for 3 to 5 years.

Vaccination is the use of antigenic substances to prevent infectious diseases and/or ameliorate the outcome of infectious- and/or toxin-related diseases. As to the World Health Organization (WHO), "a vaccine is a biological preparation that improves immunity to a particular disease. It typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters."

In the beginning, vaccines like tetanus and diphtheria were administered separately. Having once established the value of each of these, it was proposed combining them, though there was the possibility of interaction between the immune responses (3,4). In the best case, association enriches the immune response which may enhance the protective efficacy. In the worse case, however, a vaccine in association with another displays poorer immunogenicity than the same vaccine administered alone (3). One of the first combination vaccines to be licensed by the Food and Drug Administration (FDA) was diphtheria/tetanus/pertussis (DTP) in the late 1940s (5). Today, the simultaneous vaccination and/or the use of combined vaccines is widely and successfully practiced.

Although SIT is often also called "allergen vaccination" there is a major difference to vaccination against infectious diseases. SIT is usually associated with therapeutic intervention in already sensitized individuals. In contrast, the vaccination against infectious diseases is administered to prevent a disease before its manifestation, and therefore it sensitizes the organism against infectious pathogens (6).

Nevertheless, since SCIT and vaccination for infectious diseases both influence the immune system, there are recommendations to separate the injections. As per the EAACI (European Academy of Allergy and Clinical Immunology) task force paper, "allergen injections should be separated from vaccinations by at least 1 week (2) because it is assumed that adverse reactions can result from the additional activation of the immune system" (7). Many manufacturers recommend interrupting subcutaneous immunotherapy for a total of 3 weeks in case of vaccination. This might be especially difficult during the up-dosing phase, when allergen injections are mainly administered in weekly intervals. Also during the maintenance phase, additional consultations cause inconvenience in patients who already perform a time-consuming SCIT. This raises the question whether it is possible and safe to administer both injections for SCIT and vaccination simultaneously, and if there is an increased risk in a case of simultaneous application. With this retrospective analysis the safety and feasibility of simultaneous SCIT and vaccination should be analyzed.

Material and methods

A total of 875 patients (about 23% children/adolescents up to 18 years of age) receiving SCIT and/or vaccination between 2007 and 2012 in one German otorhinolaryngological medical practice were included and analyzed retrospectively. For demographic data see **table 1**.

Table 1 *- Demographic data.*

Number of patients receiving	
Vaccination	444
SCIT	336
SCIT and vaccination simultaneously (total)	95
thereof intended	79
thereof accidentally	16
Sex	
Male	45%
Female	55%
Age	
Range	3-91 years
thereof children (< 18 years)	23%

444 individuals (age 3 to 91 years) had received at least one vaccination with influenza, pneumococcus, tetanus, tetanus / diphtheria, measles / mumps / rubella (MMR), hepatitis and/or tick-borne encephalitis (TBE).

SCIT was performed in patients with severe IgE-mediated allergic diseases (rhinitis and/or asthma) who showed respective allergen-related symptoms at exposure, a positive skin prick test, existence of specific IgE ≥ class 3 (ELISA, RAST) and a

Table 2 *- Number of patients receiving SCIT and vaccination simultaneously (n = 95).*

Number of patients receiving simultaneously	**Vaccination with**				
SCIT with	**Influenza**	**Pneumococcus**	**TBE**	**Hepatitis**	**Tetanus**
mite	25	3	-	-	-
early blooming trees	56	-	-	3	1
grasses	43	2	2	-	-
cat	2	1	-	1	-
lepidoglyphus	1	-	-	-	-
wasp	2	-	-	-	-
bee	1	-	-	-	-
dog	1	-	-	-	-

Patients receiving at least 2 SCIT preparations and 1 vaccine occur multiple. Patients receiving one SCIT preparation and at least 2 different vaccines occur multiple. Patients receiving 1 SCIT preparation and the same vaccine more than once occur once only. (TBE = tick borne encephalitis)

positive nasal provocation test. A total of 431 allergic patients (age 5 to 73 years) received SCIT. Of these, 336 patients were treated with SCIT only while 79 patients received vaccination and SCIT injections simultaneously on one day at different locations, e.g. into the left and right arm. Every patient was informed about that this procedure is not recommended by the manufacturer or the guidelines. This procedure was performed in all patients who agreed. No patient was excluded because of asthma. Additionally, 16 patients inadvertently received SCIT injections within up to 4 days after vaccination because they had not informed the physician about their previous vaccinations, that were administered in the practice of another physician. All patients were in the maintenance phase of SCIT.

Allergoids as well as unmodified depot preparations (Allergopharma GmbH & Co. KG, Reinbek, Germany; ALK-Abelló, Wedel, Germany) were used for SCIT, predominantly in a perennial application mode. **Table 2** shows the number of patients receiving vaccination and SCIT simultaneously as well as the type of vaccination and the allergen for SCIT.

Independent of the SCIT preparation, there was no dose reduction during the pollen season or when starting a new package. Allergen dose was only reduced in case of interruption of SCIT for more than 10 weeks. Some of the patients were observed for up to 5 consecutive years receiving several vaccinations during SCIT. Systemic reactions (SRs) were evaluated according to the WAO Subcutaneous Immunotherapy Systemic Reaction Grading System (8). Local adverse reactions like swelling, redness and itching were not documented. Patients got the physician's mobile phone number, to call him in case of delayed local or systemic reactions for up to 24 hours after the SCIT injection.

This survey was neither initiated nor sponsored by industry.

Results

Patients exclusively receiving vaccinations did not report any drug-related SR.

3 patients with allergic asthma receiving SCIT only showed one immediate SR each: One SR grade 3 (dyspnoea) and two grade 2 (shortness of breath, asthma) (**table 3**). Due to practice's competency of emergency treatment none of these patients was admitted to hospital and all recovered within 2 hours. No patient called the physician's mobile phone because of delayed local or systemic reactions. The 95 patients receiving SCIT and vaccination either simultaneously or within a maximum period of 4 days did not have any SR (**tables 3 and 4**). This was also the case for a subgroup of 36 of them who consecutively received SCIT and vaccination for up to 5 years. Additionally, none of the patients suffered of delayed SR.

Table 3 *- Number of patients receiving "SCIT" or "SCIT and vaccination simultaneously" at least once between 2007 and 2012 with systemic reactions (SRs) according to the WAO Subcutaneous Immunotherapy Systemic Reaction Grading System (5).*

	SCIT (n = 336)	**SCIT + vaccination simultaneously (n = 95)**
Patients with SR* grade 1 (n)	-	-
Patients with SR* grade 2 (n)	2	-
Patients with SR* grade 3 (n)	1	-
Patients with SR* grade 4 (n)	-	-

Table 4 *- Number of adults and children receiving inadvertent vaccination and SCIT within a time frame of at maximum 4 days (n = 16). There were no systemic reactions in any patient.*

	Adults	Children
Influenza	4	6
Tetanus / diphtheria	1	1
Pneumococcus	1	-
Measles / mumps / rubella	-	3

Discussion

Vaccination against infectious diseases and allergen-specific immunotherapy both influence the immune-system, however, the underlying immunological mechanisms are different. Vaccinations are administered to healthy people to induce protective immunity by stimulating the body's immune system to recognize the agent as foreign (9). They mediate the induction of high titer antibodies in serum or mucosal surfaces, which confer protection by blocking entry or limiting spread of bacteria, viruses and/or toxins (6).
In contrast, SIT is administered to individuals already suffering from allergic symptoms, to induce specific allergen tolerance by restoring normal immunity (10). Allergen tolerance is the adaption of the immune system characterized by a specific non-inflammatory reactivity to a given allergen, that in other circumstances would likely induce cell-mediated or humoral immunity leading to tissue inflammation and/or IgE production (10). Since both influence the immune system, it is recommended to separate the injections. For example, the EAACI task force paper recommends separating injections for SCIT and vaccinations by at least 1 week (2) because it is assumed that adverse reactions can result from the additional activation of the immune system (7). Many manufacturers recommend interrupting SCIT for a total of up to 3 weeks in case of vaccination, i.e. the interval between the last SCIT injection should be at least one week and SCIT should be continued 1 to 2 weeks after vaccination. Depending on the individual preparation the SCIT dose may also be reduced afterwards. This procedure is less convenient for the patients because it causes additional consultations during SCIT, which itself is time-consuming due to regular visits (up to 4-8 weekly intervals in the maintenance phase during a perennial application dosage scheme) for the recommended 3 to 5 years. Therefore, it would be most convenient if injections for SCIT and vaccination can be administered simultaneously. Moreover, conflicts between patient and doctor and/or medico-legal problems might occur in medical practice, in cases of inadvertent simultaneous and/or contemporary application of vaccination and SCIT. This might be true for real or putative adverse events after simultaneous or contemporary application.
In the present survey on hand, we investigated if there was an increased risk of SRs during simultaneous SCIT and vaccination compared to SCIT or vaccination alone.
There were systemic reactions in 0.7% (3/431) of patients receiving SCIT (with or without simultaneous vaccination) during the 5-years observational period. None of these patients was admitted to hospital and all recovered in the physician's practice within two hours. This is in the lower range of systemic reactions observed in studies performed in the daily practice, with (un-)modified SCIT preparations of different manufacturers showing systemic reaction in 0.8% up to 33% of patients (11-17).
In the trial on hand, no SR was observed in patients receiving vaccination against various infectious diseases. Amongst others, the "German Health Interview and Examination Survey for Children and Adolescents" investigated tolerability of vaccination in children aged 0 to 17 years between May 2003 and May 2006 (18). Data about adverse events during vaccination in 15,958 children and adolescents were evaluable. Parents of 332 (2.1%) children and adolescents reported adverse reactions after one or more vaccinations. Hence, the frequency of adverse events was rather lower than described in the respective Summary of Product Characteristics (SmPC).
In the survey on hand between 2007 and 2012 there was no systemic reaction when SCIT and vaccination were simultaneously administered to 79 subjects in different locations. Additional 16 patients were treated with SCIT and vaccination inadvertently within 4 days, since they had not informed their physician about the preceding vaccination. Since this retrospective evaluation was finished on October 15, 2012, twenty-three additional patients had received SCIT and vaccination simultaneously (17 adults and 3 children receiving SCIT and influenza vaccination, three adults either receiving SCIT and pneumococcus, tetanus / diphtheria or hepatitis A / B vaccination), without any SR confirming safety and feasibility of this procedure. As far as we know there is only one publication about simultaneous SIT and influenza vaccination which was described in 2003 (19). The 43-old woman developed symptoms of multiple sclerosis after SIT (19), but the authors did not offer any evidence of causal relationship and concluded that further studies are needed.
In total, the tolerability in this retrospective study during SCIT and/or vaccination against infectious diseases was slightly better than observed in other studies.

Conclusion

These results indicate that the recommended interval between injections of SCIT and vaccination against infectious diseases might be reduced without increasing the risk of SRs. Further data could be helpful to study the possibility to change the na-

tional and international recommendations respectively and to increase patients' convenience. In an optimum way, future research should focus on collecting data from each specific anti-infectious vaccination, because generalization, when discussing about safety, risks being misleading and dangerous. But until such data are available the present findings give according to the authors' opinion valuable evidences, that the risks of simultaneous vaccination and SCIT are considerably smaller than intended hitherto.

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P. Morais Silva[1], A.C. Costa[1], M. Lurdes Guerra[2], M. Pereira-Barbosa[1]

Hypereosinophilic syndrome due to ETV6/PDGFR-beta gene translocation - a diagnostic and therapeutic challenge

[1]Immunoallergology Department, Hospital de Santa Maria, Centro Hospitalar Lisboa-Norte, Lisbon, Portugal
[2]Hematology Department, Hospital de Santa Maria, Centro Hospitalar Lisboa-Norte, Lisbon, Portugal

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Corresponding author
Pedro Morais Silva
Serviço de Imunoalergologia
Hospital de Santa Maria
Avenida Professor Egas Moniz
1649-035 Lisboa, Portugal
Phone: +351 917 374 928
E-mail: pedrotiagosilva@gmail.com

Summary
Background. *Hypereosinophilic syndromes are characterized by sustained overproduction of eosinophils, leading to eosinophilic infiltration, mediator release and multi-organ damage.* ***Case report.*** *A 67 year old male was referred to our Department for investigation of a persistent mild-to-moderate eosinophilia, identified 10 years previously and unresponsive to corticosteroid treatment. No other alterations were present in his differential blood count and physical examination was unremarkable. Allergic, rheumatologic and iatrogenic causes of eosinophilia were excluded by clinical history, skin-prick tests and blood and stool analysis. Iliac crest bone marrow aspiration and biopsy were performed, revealing normal cellularity with an increased eosinophil count (6%). RT-PCR of the aspirate revealed the presence of transcripts of ETV6/PDGFR-beta t(5;12) gene fusion. Karyotype analysis was normal and no mutation in PDFGR-alpha was identified. There was no evidence in analytic or imaging studies of cardiac, skin, neurologic, pulmonary or splenic involvement. A skin biopsy showed no evidence of pathologic infiltration. Initially the patient was treated with a 100 mg daily dose of imatinib mesylate, a specific inhibitor of the tyrosine-kinase domain of PDGFR. Subsequently, the daily dosage was increased to 200 mg/day to obtain eosinophil count normalization. Currently, he is under monthly hematologic and hepatic function screening. No drug side effects have been reported.* ***Conclusion.*** *This patient was diagnosed with a rare myeloproliferative variant of hypereosinophilic syndrome due to a t(5;12) ETV6/PDGFR-beta translocation. Imatinib mesylate, previously used successfully in syndromes associated with PDFGR-alpha mutations, showed efficacy in the context of this mutation as well.*

Background

Eosinophilia remains relatively common in the Western world. Its etiology is not always clear: a broad variety of allergic, infectious, inflammatory, neoplastic, and idiopathic diseases are associated with increased blood and/or tissue eosinophilia and range in severity from self-limiting conditions to life-threatening disorders (1).

Persistently elevated levels of blood eosinophilia should prompt ongoing pursuit of the underlying etiology, and monitoring for organ-associated damage. Blood eosinophil values do not necessarily indicate the extent of eosinophil involvement in affected tissues, because these cells are primarily tissue-dwelling, being several hundredfold more abundant in tissues than in blood (2). Moreover, case-reports show that eosinophil-mediated damage occurred without elevation of peripheral blood eosinophils (3). Although accepted upper limits of normal blood eosinophil numbers vary somewhat, a value above 500 eosinophils/µl of blood is considered abnormal in the vast majority of cases (4). Traditionally, degrees of eosinophilia have been categorized as

mild (500-1500 cells/µl), moderate (1500-5000 cells/µl), and severe (> 5000 cells/µl). The term "hypereosinophilia" refers to eosinophil levels > 1500/µl, regardless of the underlying cause - primary, secondary or idiopathic.

A thorough investigation of a patient with eosinophilia requires consideration of their clinical history, physical examination, and information from laboratory and imaging studies. When a cause for secondary eosinophilia is not readily apparent, it is reasonable to make a working diagnosis of primary or idiopathic eosinophilia, and pursue specific diagnosis in this regard.

In primary eosinophilia, there is evidence of clonal expansion of eosinophils. It can accompany any of the myeloid malignancies defined by the World Health Organization (WHO) classification system for hematologic malignancies (5), usually acute leukemia or chronic myeloid disorders.

Idiopathic eosinophilia implies that both secondary and clonal eosinophilia have been ruled out as possible diagnoses. Hypereosinophilic syndrome (HES) is a subcategory of idiopathic eosinophilia and, as such, remains an exclusion diagnosis whose criteria have evolved over time, as more of its pathophysiology has been discovered, and additional investigative methods have been made available (6).

Classic criteria of 1) blood eosinophilia > 1500/µl for longer than 6 months, 2) lack of secondary causes of eosinophilia, and 3) presumptive signs and symptoms of eosinophilia-associated organ involvement have been largely abandoned as treatment options for these patients became available, with the aim of preventing tissue damage before it develops. Currently, patients with markedly increased blood eosinophilia and obvious tissue dysfunction should start the appropriate treatment before irreversible damage occurs, and no longer need to be observed for a six-month period (2).

According to the revised WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues (7), patients who meet HES criteria fall into 2 different categories:

1) myeloproliferative neoplasms including hypereosinophilic syndrome (M-HES) or chronic eosinophilic leukemia not otherwise specified (CEL-NOS); 2) myeloid and lymphoid neoplasms with eosinophilia and abnormalities of platelet-derived growth factor α (PDGFRA), platelet-derived growth factor β (PDGFRB), and fibroblast growth factor receptor 1 (FGFR1).

Unfortunately, in most cases, HES either presents with overlapping features, or fails to meet any of the above criteria. A 2005 international consensus workshop on HES treatment provided an alternative classification system, subdividing patients into six clinical subgroups:

1) myeloproliferative HES; 2) lymphocytic HES; 3) familial eosinophilia; 4) undefined HES (idiopathic HES with or without symptoms, including episodic variants); 5) overlap HES (eosinophilic disease restricted to a single organ system accompanied by peripheral eosinophilia) and 6) associated HES (eosinophilia in the setting of another diagnosis such as sarcoidosis or inflammatory bowel disease) (8).

Diagnostic evaluation relies on a combination of morphologic review of the blood and marrow, standard cytogenetics, fluorescent *in-situ* hybridization, flow cytometry and assessment of T-cell clonality, to detect histopathologic or clonal evidence for acute or chronic myeloid or lymphoproliferative disorders.

In this clinical case, we try to emphasize the most important diagnostic procedures associated with the investigation of a patient that presented with eosinophilia, and its treatment after diagnosis has been established.

Case presentation

A 67 year old male of Indian descent living in Lisbon, was referred to our out-patient clinic in September 2010. He had been recently diagnosed with persistent eosinophilia by his assistant nephrologist. Eosinophil counts ranged from 1500 to 2300/ml in several blood counts, with no evidence of other differential blood count abnormalities. The patient had a history of chronic renal disease, currently in NKF-KDOQI stage 4, with evidence of renal osteodystrophy associated with type 2 diabetes mellitus. He also had a history of nonallergic rhinitis and elevated, controlled blood pressure.

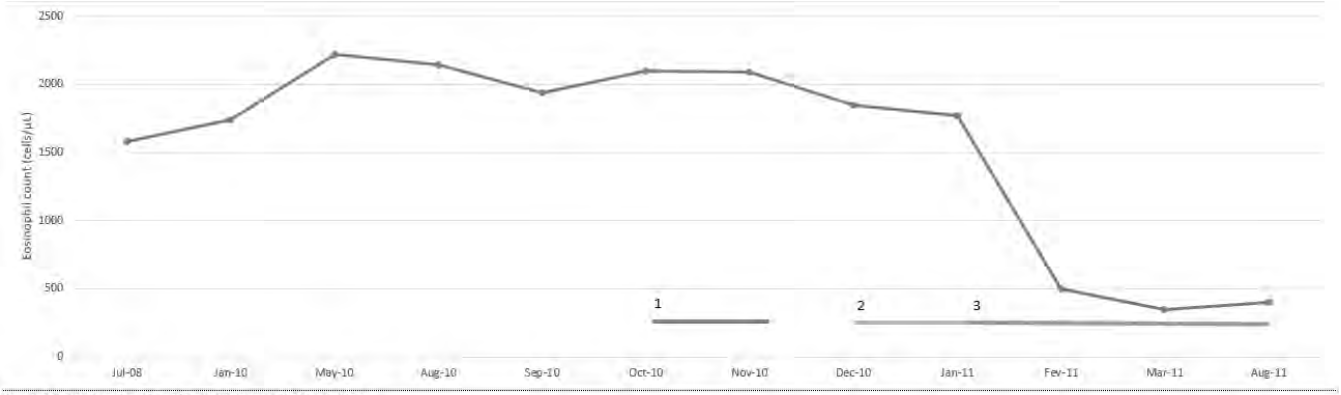
His medication list included nifedipine, furosemide, irbesartan, gliclazide, atorvastatine, clopidogrel, bisoprolol, and insulin. Although theoretically any medication may potentially be the cause of a hematologic alteration, none of the above are usually considered to be associated with hypereosinophilia.

A retrospective evaluation of past blood counts revealed that eosinophilia was present as early as May 2000 (age: 57 years) and similar, persistently elevated counts were identified over the following years. No records were available prior to the 2000. The evolution of eosinophil counts is presented in **figure 1**.

The patient had no symptoms directly attributable to eosinophilia. He denied recent or long-standing respiratory or gastrointestinal symptoms, as well as rheumatologic or constitutional symptoms, namely arthralgia, myalgia, fatigue or weight loss. He had no history of smoking or drug abuse, and did not consume alcohol regularly. He complained of occasional episodes of runny, itchy nose that were not associated with contact with potential allergens or specific seasons of the year. He had no history of exposure to toxic substances or pesticides. The patient lived in an urban setting, in conditions of good hygiene, with little contact with animals. He had not travelled abroad during the previous 10 years.

Physical examination was unspecific. He had dry and scaly skin on the trunk and inferior limbs. There were no changes in auscultation, or evidence of hepato/splenomegaly. Other blood count parameters were normal, including hemoglobin,

Figure 1 *- Evolution of eosinophil count between 2008 and 2011.*



Graph 1: Evolution of eosinophil count between 2008 and 2011.
Eosinophil values were unaltered after treatment with daily prednisolone 1mg/kg (1) and only a slight decrease was observed with a 100mg dose of imatinib mesialte (2). In contrast, a good response was obtained with a 200mg dose of imatinib mesilate (3).

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leukocyte and platelet count. A peripheral blood film showed normal eosinophils, red blood cells and platelets. There were no circulating blast cells. Routine laboratory testing, including serum tryptase, troponin, angiotensin-converting enzyme, immunoglobulin and vitamin B12 levels, were within the normal range. Total IgE value was 62 UI/ml. Eosinophil cationic protein values were elevated at 89 µg/l. Stool samples were collected on three different occasions, with no evidence of eggs and/or cysts. Specific blood antibodies for Schistosoma, Hidatide, Fasciola, Strongyloides, Echinococcus, Toxocara and Aspergillus, as well as anti-thyroid or anti-nuclear antibodies, were not detected. HIV 1/2 tests were negative. Skin prick tests were negative, both to an aeroallergen and a food allergen battery. An electrocardiogram, echocardiogram and pulmonary function tests were performed and were normal.

An iliac crest bone marrow aspiration and biopsy were performed, revealing normal cellularity with an increased eosinophil count (6%) without increased myeloblasts. Subsequent reverse transcription polymerase chain reaction (RT-PCR) of the aspirate revealed the presence of transcripts of a ETV6/PDGFRB t(5;12) gene fusion. Karyotype analysis was normal and no mutation in PDFGRA or Ph chromosome t(9;22) were identified.

Systemic glucocorticoid was chosen as the first line of therapy. Prior to referral, for a period of approximately 3 weeks, the patient had received a daily dose of 20mg prednisolone. A re-introduction of prednisolone was made, with a higher dose of 1 mg/kg daily. However, after 4 weeks, eosinophil values were unaltered.

Higher glucocorticoid doses and/or longer treatment regimens were considered, but dismissed, due to the patient's co-morbidities. Prednisolone was reduced and subsequently stopped, and an alternative steroid-sparing regimen planned.

The patient was started on imatinib mesylate, a specific inhibitor of the tyrosine-kinase domain of ABL, c-kit and PDGF-receptor genes, initially at a daily dose of 100 mg. A slight improvement was seen, although eosinophil levels were still above the desired threshold. The dose was increased to 200 mg, resulting in a marked reduction in the peripheral blood eosinophil count within three weeks.

During daily imatinib mesylate administration, regular evaluations of heart and liver function were performed and no alterations were observed. RT-PCR was performed on a new bone marrow aspirate obtained at beginning of 2014, and did not detect the presence of ETV6/PDGFRB t(5;12) transcripts (total treatment time: 37 months). Imatinib was subsequently stopped and the patient remains under clinical and analytical observation. Eosinophil levels have remained stable at less than 500 cells/µl during the follow-up period. No organ-specific alterations have so far become evident.

Discussion / Conclusions

The lack of other identified reasons for secondary eosinophilia, the presence of a mutation known to cause eosinophilia, and the good treatment response, all constitute strong arguments for the cause of the high eosinophil count in this patient being due to a specific, imatinib-responsive, mutation in the PDGFRB gene.

Hypereosinophilic syndromes associated with PDGFRB mutations seem to be less frequent than their PDGFRA counterparts (5,9).

The PDGF receptors belong to the receptor tyrosine kinase family, more precisely to the type III group, which also includes c-KIT, FLT3 and the macrophage-colony-stimulating factor receptor. Two highly homologous receptor genes have been cloned: PDGFRA and PDGFRB (10).

The first genetic alteration in PDGFRB receptors was reported in 1994 by Golub and Gilliland in patients with chronic myelomonocytic leukemia, as a result of a t(5;12) translocation, leading to the fusion of TEL (now renamed ETV6) with PDGFRB (11). This hybrid oncogene consists of the in-frame fusion of the N-terminal portion of the transcription repressor ETV6, including its pointed domain, with the kinase domain of PDGFRB (12). When introduced in mouse bone marrow cells, ETV6-PDGFRB induces a fatal myeloproliferative disorder. Noticeably, eosinophilia is not observed in this model, in contrast to the human disease (13).

The discovery that imatinib, a molecule approved for the treatment of BCR-ABL-positive chronic myelogenous leukemia, also blocks PDGF receptors when used at an even lower concentration, was a major breakthrough. Indeed, most patients with myeloproliferative neoplasms harbouring a PDGF receptor fusion respond well to low dose imatinib, despite rare resistant mutations having been described (14,15).

Previously described cases of ETV6-PDGFRB mutations have presented with more severe manifestations than those observed in this case (16,17,18); typically, they have featured myeloblast marrow infiltration and, thus, a chronic eosinophilic leukemia diagnosis.

A favourable response to imatinib mesylate was, in part, expected. The above-described cases had mostly good responses to this drug in doses ranging from 100 to 400 mg. A 2007 case series evaluated 12 patients (17) with BCR-ABL-negative chronic myeloproliferative disorders and reciprocal translocations involving PDGFRB, and receiving imatinib. Eleven had prompt responses featuring normalization of peripheral-blood cell counts and disappearance of eosinophilia, 10 with complete resolution of cytogenetic abnormalities and decrease or disappearance of fusion transcripts. Similarly good results were described in 4 patients in 2002 (19).

Despite the reassuring data, the prognosis for these patients is still, to a degree, uncertain. A French study of 40 patients in 1989, prior to the imatinib era, noted an 80% survival at five years and a 42% survival at 15 years (20). Several authors have reported slow progression towards full-blown T cell lymphoma (21). Malignant progression in such patients may be heralded by the appearance of cytogenetic changes (19). Drug-associated cardiomyopathy has also been reported as a rare complication of imatinib in patients being treated for CML, which should warrant additional attention in a patient with other significant co-morbidities.

In our case, the absence of findings associated with myeloproliferative disorders, such as elevated serum vitamin B12, abnormal leukocyte alkaline phosphatase scores, splenomegaly, cytogenetic abnormalities, myelofibrosis, and myeloid dysplasia, as indicated by the quarterly examinations performed, are likely a sign of a good prognosis. The absence of end-organ eosinophilic infiltration is also an important factor, and underlines the importance of an early intervention in idiopathic hypereosinophilic syndromes.

Monitoring of patients with HES must be individualized. This patient was assessed clinically every month at the beginning of treatment, and at increasing intervals when the disease stabilized. Monthly eosinophil counts were performed, coinciding with the provision of imatinib in our hospital. PCR testing for the ETV6-PDBFRB transcript was only repeated once, approximately 36 months after the beginning of treatment. Unfortunately, it is not possible to assess exactly when the transcripts became undetectable, but previous studies with variable doses of imatinib have shown cytogenetic transformation in as little as 9 months. Treatment has currently been stopped and the patient's eosinophil levels have remained whining the normal range during the 3 months post treatment cessation.

The patient is currently evaluated at regular intervals in our department. His disease showcases the complex interactions in the regulation of normal eosinophil genesis and the differing etiologies associated with similar genetic abnormalities.

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H. Haluk Akar[1], M. Akif Goktas[2], F. Tahan[1]

Grass pollen triggered anaphylaxis in an adolescent boy

[1]Erciyes University School of Medicine, Department of Pediatric Allergy, Kayseri, Turkey
[2]Erciyes University School of Medicine, Department of Pediatrics, Kayseri, Turkey

Key words
Anaphylaxis; grass pollen; adolescent

Summary
Anaphylaxis is a rapid onset serious allergic reaction which may be fatal. It is usually triggered by an agent such as a food, insect sting, or medication, through a mechanism involving immunoglobulin E (IgE) and the high-affinity IgE receptor on mast cells or basophils. Anaphylaxis has been rarely described which results from pollen antigen exposure. Here, we present unusual anaphylaxis, which results from inhaled pollen antigen in a 15-year-old boy.

Corresponding author
H. Haluk Akar
Erciyes University School of Medicine
Department of Pediatric Allergy
Kayseri, Turkey
E-mail: himmetakar@gmail.com
Phone: + 90 352 207 66 66 / 25 125
Fax: +90 352 437 58 25

Introduction

Anaphylaxis is a severe, acute and potentially life-threatening medical condition, caused by the systemic release of mediators from mast cells and basophils, often in response to an allergen (1,2). The incidence of patients with anaphylaxis presenting to emergency departments is estimated to be approximately 1/1000 to 4/1000 (3,4). Of these presentations, only one-third ends up having an identifiable trigger for the anaphylactic reaction. Food is the most common associated trigger, followed closely by hymenoptera (bee/wasp) stings and medications (5). Here, we present unusual anaphylaxis in an adolescent which inhaled grass pollen while wandering in local picnic area.

Case

A 15-year-old boy, who presented with pruritus, generalized urticaria, angioedema, cough and respiratory distress, was admitted to our pediatric emergency department on April 2013. It was learned that, almost one hour prior to admission, he went to a local picnic area with his family for wandering. Twenty minutes after entering the area, he suddenly experienced generalized itchy urticaria, angioedema, coughing and respiratory distress. One hour later, in physical examination in pediatric emergency department, generalized urticaria and angioedema on his lips and eyelids were observed. He also complained of nasal pruritus, sneezing, redness of eyes, coughing and dyspnea. The saturation of oxygen was 92%. We examined wheezing on auscultation. His blood pressure and heart rate were normal. The patient was treated with intramuscular adrenaline, oxygen and inhaled salbutamol. Antihistamine (pheniramine maleate) and methylprednisolone were administered. The patient symptoms were started on recovery with this treatment within one hour. Four hours after the treatment, the angioedema and the urticaria had completely disappeared. From the anamnesis, he

didn't eat anything in a few hours before the anaphylaxis. We couldn't find any insect's injury or bite on his skin. A few days later, prick test showed strong grass pollen allergy. Skin prick test was negative for common food allergens and aeroallergens, including Dermatophagoides Farinae, Dermatophagoides Pteronyssinus, Aspergillus, Cladosporium, Alternaria, Cockroach, Cat Dander. According to his father, plenty of grass was present in the local picnic area where the boy had been wandering. We didn't find any biochemical abnormality in blood tests. Eosinophil count was normal. Total IgE was 146 (0-100 IU/mL).

It was learned from the history, his family didn't have atopy and he had been suffering from allergic rhinoconjunctival symptoms especially in spring months. After that, adrenaline autoinjector was prescribed to the patient, and an emergency action plan was explained to the patient and his family. We have followed the patient up in terms of allergic rhinoconjunctivitis. It was examined that he had airway hyperreactivity with spirometer in his follow up.

Discussion

Most episodes of anaphylaxis are triggered through an immunologic mechanism involving IgE, which leads to mast cell and basophil activation and the subsequent release of inflammatory mediators such as histamine, leukotrienes, tryptase and prostaglandins. Although any substance has the potential to cause anaphylaxis, the most common causes of IgE-mediated anaphylaxis are: foods (especially, peanuts, tree nuts, shellfish and fish, cow's milk, eggs and wheat), insect stings and medications (most commonly penicillin). Exercise, non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, opiates, and radiocontrast agents can also cause anaphylaxis, but anaphylactic reactions to these agents often result from non-IgE-mediated mechanisms. In children, anaphylaxis is most often caused by foods, while venom- and drug-induced anaphylaxis is more common in adults. In other cases (idiopathic anaphylaxis), the cause of anaphylactic reactions is unknown (4,6-8). Also, we couldn't explain our patient anaphylaxis with known etiology causes. In our patient, anaphylactic episode was presumably triggered by exposition to grass pollen.

In the literature, similar critical allergic reactions caused by plants pollen have been reported (9). Similar anaphylactic reaction with grass pollen has been reported in a boy by Tsunoda et al (10). Anaphylaxis caused by the direct exposure of abraded skin to grass was reported in a patient with grass pollen allergy and a previous history of contact urticaria (11). Also, a case of anaphylaxis causing respiratory arrest after running in a wheat field (12) and a case of anaphylaxis while on an alpine slide (13) have been reported from different countries.

We would like to draw attention on grass pollens in anaphylaxis etiology as a rare triggering agent.

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M.A. Tosca[1], R. Olcese[1], G.A. Rossi[1], G. Ciprandi[2]

Severe biphasic anaphylaxis to bigarreau cherry in a child

[1]Pulmonary Disease and Allergy Unit, Istituto Giannina Gaslini, Genoa, Italy
[2]Medicine Department, IRCCS - Azienda Ospedaliera Universitaria San Martino, Genoa, Italy

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Corresponding author
Giorgio Ciprandi
Viale Benedetto XV 6, 16132 Genoa, Italy
Phone: + 39 10 35 33 8120
FAX: + 39 10 35 38 664
E-mail: gio.cip@libero.it

The cherry is the fruit of the cherry-tree belonging to *Rosaceae* family. There are two main cherry-trees: *Prunus avium* (the fruit is the sweet cherry, with two main varieties: wild cherry and bigarreau cherry) and *Prunus cerasus* (the fruit is the sour cherry). *Rosaceae* fruits may cause two allergic clinical patterns: i) oral allergy syndrome (OAS) sustained by sensitization to pathogenesis related proteins (PR-10) proteins family (Bet v1 homologous) or lipid transfer proteins (LTP) and ii) systemic reactions, including anaphylaxis, caused by LTP or thaumatin-like proteins (TLP) (1).

Four principle molecular allergens of the sweet cherry have been described (www.allergome.org). Pru av 1 is a Bet v 1-homologous protein (PR-10) with 67% homology with Bet v 1, a pan-allergen shared by many *Rosaceae* fruits. It is responsible of mild allergic reactions. Pru av 2 is a thaumatin-like protein, a common pan-allergen present in many fruits. Pru av 2 is the main protein in ripe cherry and shares high homology with TLP of grape and apple. It may cause also severe symptoms. Pru av 3 is a LTP, pan-allergen with high homology with peach and apricot and maize. Pru av 3 does not cross-react with PR-10. It is localized in the peel. LTP allergy may induce severe reactions. Pru av 4 is a profilin, a pan-allergen present in many pollens and fruits. Generally, it causes mild allergy.

Cherry allergy is rather rare and usually may induce mild symptoms, including OAS and gastrointestinal complaints, even though anaphylactic reaction may occur.

Anaphylaxis is a "severe; life-threatening, generalized or systemic hypersensitivity reaction" as reported by a systematic review on its epidemiology in Europe (2). The most quoted work definition was proposed by Sampson and colleagues: anaphylaxis is likely when any of 3 criteria are fulfilled: i) acute onset of an illness with involvement of skin/mucosal tissue and airway compromise or reduced blood pressure or associated symptoms; ii) 2 or more of the following after exposure to known allergen for the patient: history of severe allergic reaction, skin/mucosal tissue, airway compromise, reduced blood pressure, gastrointestinal symptoms (for food allergy); iii) hypotension after exposure to known allergen for the patient (3). Infants and teenagers have increased vulnerability to anaphylaxis (4). Food is the most important trigger in childhood (5). Food anaphylaxis typically occurs after ingestion, more rarely after skin contact or inhalation. Diagnosis is performed using validated criteria (3,4). Clinical diagnosis is based on consideration of presenting signs and symptoms and on excluding other sudden-onset multisystemic diseases. However, there is still no biomarker confirming the diagnosis. Clinical history and serum allergen-specific IgE and/or

skin prick test remain the cornerstone for diagnosing food allergy. Recently, molecular-based allergy diagnostics improved the work-up, as it allows defining the profile of proteins involved in anaphylactic reaction (7). Fortunately, only few foods, mainly including egg, milk, peanut, fish, soybean, wheat, are usually cause of anaphylaxis in children and adolescents. However, 6 cases of cherry anaphylaxis have been reported till now. The first description of cherry anaphylaxis was reported by Subiza and colleagues, but they did not detect serum specific IgE either to cherry or to other *Rosaceae* fruits (8). Escribano and collagues reported an adult case (36 years) with cherry anaphylaxis and hay fever (sensitization to grasses, olive tree, and mugwort): he had a negative prick-prick test for cherry, but high serum specific IgE to cherry (8 kU/L) and also to other *Rosaceae* fruits (9). Vieira et al. described a case referring cherry anaphylaxis occurred 20 years before (at 11 years): she had sensitization to plane and mugwort pollens, serum specific IgE were positive for LTP proteins, such as Pru p 3 (35.2 kU_A/L) and Cor a 8 (14.0 kU_A/L), but both prick test and serum specific IgE measurement were negative for cherry (10). Bianchi and colleagues reported a child (12 years) with food-dependent exercise-induced anaphylaxis, who experienced two episodes: the first after eating peach with peel, the second after eating some cherries (11). Prick-prick test was positive for cherry and peach (and also for other *Rosaceae* fruits), but serum specific IgE were negative for both raw peach and cherry extracts, as well as for LTP and PR-10 proteins (11). A survey on the incidence of anaphylaxis in Alcorcon (Spain) reported 1 case of cherry anaphylaxis, but without details (12). Another survey on Piemonte Region (Italy) reported 1 adult case of cherry anaphylaxis (13). It is to note that all these subjects lived in Spain or Italy: this fact is not surprising, as it is well known that LTP syndrome has some peculiarities, such as geographical distribution (Mediterranean basin), being frequently symptomless, symptoms occurrence needing co-factors, absence of pollen allergy favoring severe reactions (1).

Case Description

A 5 year-old boy living in southern Piemonte (Italy) in a rural area, without any relevant illness, experienced two distinct anaphylaxis episodes, both immediately after eating bigarreau cherries. The first episode occurred in May 2012; (few minutes after eating some cherries picked from the tree) he presented ocular hyperemia, swelling of eyelids and auricles, breathlessness, syncope, and sphincter release. He was rapidly moved to local Emergency Room, where he was treated with adrenaline, corticosteroids, and antihistamines. Symptoms disappeared within few hours. Thereafter, he enjoyed good health.
Exactly one year later (in May 2013), he experienced a second episode immediately after eating half bigarreau cherry. Initially, he presented wheezing, perioral and glottis angioedema, and drowsiness. At local ER, he was treated with the same medications; clinical remission was quickly achieved. However, breathlessness and fainting appeared after 4 hours, adequate treatment was administered and recovery occurred.
He was visited at Centro Malattie Allergiche of Istituto Giannina Gaslini (Genoa, Italy) for thorough assessment and management.

Skin tests

They were not performed for the risk of severe reactions. In fact, we previously reported a case of anaphylaxis after prick-by-prick with pine nut in a child with previous severe anaphylaxis to pesto, sauce containing pine nut (14).

Serum specific measurement

ImmunoCAP and ISAC tests (Thermofisher, Milan, Italy) were performed. ImmunoCAP showed a mono-sensitization to the raw cherry extract (11.3 kU_A/L). ISAC test showed positivity for 2 proteins families: i) LTP, such as Pru p 3 (1.7 ISU), Jug r 3 (1.3 ISU), and Ole e 7 (0.8 ISU); and ii) thaumatin-like protein, such as Act d 2 (0.9 ISU) and Alt a 1 (0.7 ISU), which is an acid glycoprotein that interacts with PR5, a TLP (15).

Food challenge

Oral food challenge was not obviously performed for ethical reasons. However, it is noteworthy that the child tolerated wild cherry, also after these two anaphylactic episodes.

Management

Adrenaline autoinjector was prescribed for severe symptom occurrence, antihistamine and steroid for milder complaints.

Discussion

Diagnosis of food anaphylaxis is based on validated criteria (2,3,4), such as: i) suggestive clinical history, ii) allergen-specific IgE detection for the suspected food, and iii) symptoms consistent with sensitization, i.e. the demonstration of a cause/effect dependence between ingestion of sensitizing food allergen and occurrence of anaphylaxis clinical features (*post hoc ergo propter hoc*). According to this work-up, we made the diagnosis of bigarreau cherry anaphylaxis.
Our findings are consistent with the remark that cherry anaphylaxis is prerogative for the Mediterranean area (1). The cases reported in literature occurred only in Spain and Italy (8-16).
In addition, our case presented sensitization to two molecular protein families, such as LTP and TLP, peculiar for severe hyperreactivity. It was also remarkable that there was no pollen sen-

sitization, and molecular allergy diagnostics confirmed absence of sensitization to PR-10 and profilins. These findings confirm the assumption that LTP syndrome is severe and characterized by sensitization to pan-allergens, mainly Pru p 3 that is the genuine allergen for peach, namely a *Rosaceae* fruit. TLP is another proteins family involved in food allergy (17).

Anyway, the most important outcome of the present case are its peculiar characteristics: i) sensitization to dangerous proteins (LTP and TLP), ii) biphasic anaphylaxis at the second episode, iii) tolerance of different cherry variety, iv) precocious age of onset.

These aspects underline the concept that pediatric anaphylaxis is a complex and complicated disorder, that should be carefully investigated and managed, and deserves adequate attention as it requires specific and in-depth competence.

The main limitation of the present experience is that information about the molecular profile of wild and bigarreau cherry is lacking. In addition, the parents will be advised to perform an immunoblotting to define the IgE profile to bigarreau and wild cherry proteins.

In conclusion, the present case report that cherry allergy may be also life threatening and adequate workup is mandatory.

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A. Goldenberg[1], S.E. Jacob[2]

Update on Systemic Nickel Allergy Syndrome and Diet

[1]School of Medicine, University of California, San Diego, USA
[2]Department of Dermatology, Loma Linda University, Loma Linda, California, USA

Key words

Allergic contact dermatitis; diet; nickel; systemic

Abbreviations

ACD - allergic contact dermatitis
SCD - systemic contact dermatitis
SNAS - systemic nickel allergy syndrome

Corresponding author
Sharon E. Jacob
Department of Dermatology
Loma Linda University,
Faculty Medical Offices
11370 Anderson Street, Suite 2600
Loma Linda, CA 92354, USA
E-mail: sjacob@contactderm.net
Phone: +1 909 558 2890
Fax: +1 858 966 7476

Dear editor,

We read with interest the Pizzutelli article on the relationship of systemic nickel hypersensitivity and diet, and find this an extremely immunologically complex and fascinating subject (1). We attempt to further elaborate on the differentiation of systemic nickel allergy syndrome (SNAS) and systemic contact dermatitis (SCD), as well as update the readers on recent developments in dietary nickel avoidance literature.

SCD, first described by Jadassohn in 1895, is a subset of allergic contact dermatitis (ACD) in which dermatitis is elicited from allergen exposure via routes other than trans-cutaneous contact (2) (see **table 1**). Cases have been reported to mercury, sulfonamide antibiotics, cinnamon oil, potassium dichromate, and thiamine, among others, and specifically to balsam of Peru, chromium and nickel following oral exposure (3,4). Nickel is the culprit behind systemic nickel allergy syndrome (SNAS) (3), which is reported to present with a multitude of symptoms, most commonly studied of which is vesicular hand eczema; however, SNAS can also present with generalized systemic (eg: fibromyalgia, headache), respiratory, generalized cutaneous and gastrointestinal symptoms (3).

Table 1 *- Routes of Systemic Exposure for SCD.*

Oral
Intravenous /Endovascular/ Subcutaneous/Intradermal/ Intramuscular
Intranasal/pulmonary inhalation
Subconjunctival
Dental
Intrauterine
Arthroplastic

Pizzutelli reported that the "therapeutic low-nickel diet is controversial" for the many manifestations of SNAS. While we agree that there is little data to suggest dietary impact of a low nickel diet on the respiratory and neurologic signs and symptoms, avoidance diets have been consistently studied for their preventive effect on cutaneous and gastrointestinal manifestations of SNAS (3, 5-8). In 1989, Veien proposed elimination diets as beneficial to decrease chances of repeat dermatitis (4), and corroborating this Jensen et al. demonstrated a dose-response between nickel-ingestion and dermatitis flares in 2003 (9). As nickel-elimination diets are commonly criticized for their adherence difficulty and variability, Mislankar et al. proposed a simplified point-based nickel-limitation diet for patients trying to limit daily intake and avoid systemic flares (10) (see **table 2**). The point-based nickel diet assigns individual foods point values that correspond to nickel content, and patients are instructed to limit the total point value to 15 per day (equivalent to 150 μg). This system is algorithmic and reproducible, making it a prime tool for patients, and clinical investigations.

***Table 2** - Foods with > 100 μg / serving of nickel [10*].*

Sunflower seeds
Cereal, oat ring
Beans (lima, pinto, refried, chili, with pork, canned)
Chocolate cake with icing

*Serving sizes based on average American portion consumption

SNAS pathophysiology involves both Th2 (typically associated with atopic dermatitis (AD)-related response) and Th1 (typically associated with the ACD-related response), and is thus complex in nature. It is plausible that expressed features may vary depending on the predominating immunologic milieu. While Th2 response to nickel dominates initially, respiratory symptoms such as rhinitis and asthma as well as cutaneous manifestations similar to AD would be expected (11,12). However, chronic exposure to nickel leads to a change in T cell expression with a reported Th1 secondary predominance and possibly predisposing to ACD, similar to the immunologic pathophysiology seen in chronic AD patients (13). Such immunologic response is seen clinically in non-atopic nickel allergic patients who develop indistinguishable-from-AD dermatitis after chronic continuous exposure to cutaneous nickel, a presentation known as "chemical atopic dermatitis" (13).

Di Gioacchino et al. assessed the effect of oral nickel desensitization in SNAS patients with both cutaneous and extra-cutaneous manifestations (gastrointestinal, cough, headache) (14). Notably, no cough or headache patients received the nickel oral challenge, but since they were enrolled, they were included in the analysis under "intention to treat". Patients who were both nickel-patch test and nickel-oral challenge positive were randomized into three groups receiving different doses of oral nickel for a year. When the dietary nickel was progressively reintroduced, the highest nickel-dosed group showed statistically significant control of cutaneous and gastrointestinal manifestations of SNAS, as assessed by subjective symptoms and individual visual analogic scale ratings (14). The development of oral nickel tolerance was theorized to be due to a proliferation of nickel-specific T regulatory lymphocytes (a distinct T cell promoted by IL-10 and which functions to inhibit general T cell responses) (14). These results suggest that chronic exposure to sensitizing allergens can lead to an immunologic loss of a "danger" signal, possibly via T cell class switching, summing to a gain of control over systemic response triggers.

In summary, although dietary avoidance and desensitization techniques utilizing oral nickel are not appropriate for all patients with contact sensitization to nickel, it is not controversial that it may be extremely helpful in a subset of patients with SNAS.

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S. Pizzutelli

Reply to: Update on Systemic Nickel Allergy Syndrome and Diet

Pediatric Allergology, Frosinone General Hospital, Frosinone, Italy

Corresponding author:
E-mail: sipizzut@tin.it

Dear editor,

I am glad to reply to Goldenberg and Jacob's observations, whom I thank for the kind attention given to my article.
As a preliminary consideration, I wish to reiterate that my paper discussed exclusively the exposure to nickel via food; it didn't discuss the other routes of systemic exposure. It distinguished allergic contact dermatitis (ACD) from systemic nickel allergy syndrome (SNAS) and, within the SNAS, systemic contact dermatitis (SCD, which has only cutaneous signs and symptoms) from extra-cutaneous (i.e. gastrointestinal, respiratory, neurological, etc.) signs and symptoms (see **table 1**) (1).
In what follows, I will discuss: diagnostic steps for nickel pathology (Section 1); and some possible differences in the management of the three forms of nickel pathology discussed (Section 2).

1. Diagnostic steps for nickel pathology

According to some authors, the following events would prove a relationship between the three forms of nickel pathology (ACD, SCD and extra-cutaneous SNAS) and nickel food intake (2):
a. Improvement of eczema or of other symptoms with a low-nickel diet,
b. Relapse or worsening with nickel oral challenge (NOC);
c. Management with low-nickel oral hyposensitization treatment (NiOHT).

Table 1 - *SNAS.*

1. Cutaneous symptoms (SCD: Systemic Contact Dermatitis)
   - involvement of areas previously exposed to metal with flare-ups of previous eczematous lesions and patch test;
   - involvement of areas not previously exposed in the form of:
     - pompholyx;
     - baboon syndrome;
     - maculopapular exanthema;
     - flexural eczema;
     - urticaria;
     - itching;
     - vasculitis-like lesions.
2. Extra-cutaneous symptoms
   - gastrointestinal symptoms (abdominal pain, diarrhoea, vomiting, swelling, heartburn, nausea, constipation, etc.);
   - respiratory symptoms (rhinitis and asthma);
   - neurological symptoms (headache);
   - general symptoms (fever, fibromyalgia, joint pain, chronic-fatigue syndrome, etc.).

The first two events are the two essential steps for the diagnosis of all allergies and food intolerances (diagnostic elimination diet and oral provocation test or challenge). As there is no specific laboratory test for the diagnosis of SNAS caused by nickel in food (both cutaneous and extra-cutaneous) the oral challenge is the diagnostic golden standard (3,4). Any other tests, such as the patch, are indicative but are not considered diagnostic.
In the following paragraphs I will discuss each event with respect to nickel pathology.

a. Elimination diet

As underlined by Sharma himself, the effectiveness and reliability of the elimination diet in nickel pathology is sensitively reduced by the following factors (5):

- Strictly speaking, the elimination diet doesn't exist, because nickel is ubiquitous and cannot be eliminated from the diet.
- The nickel content of every single meal and therefore the daily intake of the metal are impossible to know. Nickel content in the same food varies sensibly because it is strongly influenced by nickel concentration in soil, which varies from place to place up to 100 times (5-500 µg/ gram), depending on the type of soil, the use of synthetic fertilizers and pesticides, soil contamination by industrial effluents and urban wastes etc. There are variations even in different batches of the same food in the same place. Variability factors of nickel content in the same food include: the season (more nickel in spring and autumn, less in midsummer); the part of the plant (more nickel in leaves than in stems and roots; more nickel in old leaves than in young leaves); etc. (5).
- The low-nickel diets suggested in literature differ from each other, sometimes substantially (1). This is also the case of the diets recently developed by Braga and Mislankar, notwithstanding their greater desirability and easier management (6,7).

Sharma notes that, because of the variability of nickel content in foods and, therefore, of its daily intake also in subjects following a low-nickel diet, the benefits gained from a particular low-nickel diet may not be uniform in all seasons and in every patient. The benefits gained from one type of low-nickel diet by one group of patients in one place may not be observed by another group in a different place (5). In a 2011 Italian study, 62,5% of subjects diagnosed as SNAS-affected did not respond to a six-month low-nickel diet (8).
According to the 2009 guidelines of the British Association of Dermatologists, there is only some evidence of the benefit of low-nickel diets in nickel-sensitive patients (Quality of evidence IV; Strength of recommendation C) (9).
The problems inherent in the low-nickel diets are schematically summarised in **table 2** (1,5,10).
As the low-nickel diet is manifestly unable to determine all the hypothetically affected subjects, it cannot be considered as a reliable diagnostic tool. Consequently, all the scientific studies on subjects affected by SCD or SNAS, for which the patients were selected after a positive response to a low-nickel diet, must be considered methodologically weak and deprived of the necessary accuracy.
In the diagnostic iter of food allergies and intolerances the exclusion diet is followed by the evaluation of the improvement caused by such exclusion. However, such evaluations are contradictory. On one hand, Sharma underlines that one cannot expect the dermatitis to disappear completely during the diet, as the diet is only likely to lead to fewer and milder flare-ups (5,11). On the other hand, many studies, including recent ones, declare the complete resolution of the cutaneous pathology after the diet (12,13,14). Even greater problems in the interpretation of the results of the diet can be noted with respect to the extracutaneous SNAS and, above all, the neurological and gastrointestinal symptoms, which are subjectively reported by the patient and cannot be objectively evaluated by the physician.

Table 2 *- Problems and perplexities about the low-nickel diet.*

a. Complete elimination of nickel from the diet is impossible (nickel is ubiquitous).
b. Nickel content in the same type of food varies from place to place, season to season, even widely.
c. Therefore, the food nickel intake of a person following a restriction diet cannot be determined with certainty.
d. The beneficial effect of a low-nickel diet is not guaranteed. It is not uniformly seen in all patients being prescribed such a diet for nickel dermatitis (Sharma).
e. Opinions vary about the nickel content which would determine the threshold of a low-nickel diet.
f. The low-nickel diets suggested in scholarly articles vary widely under several respect. In particular, there is no unanimity about allowed and forbidden foods:
   - In the 7 low-nickel diets considered, only cocoa, chocolate, peas and canned foods are always forbidden;
   - Six out of 7 diets forbid hazelnuts and peanuts;
   - Five out of 7 diets proscribe beans, lentils, shellfish, tea, spinach;
   - Tomatoes, fish, vegetables are allowed in some diets, not allowed in others.
   - Although having low nickel content, beer, red wine, herrings, mackerel, tuna, raw tomatoes, onions, carrots, apples, citrus fruits and their juices are forbidden in some diets because considered to worsen nickel eczema;
g. Opinions vary about inox steel pans and kitchen tools, which are not universally prohibited.
h. Using tap water is prohibited in some diets, prohibited under some conditions (first water of the morning) or allowed in others.
i. Although nickel allergy is life long, it is not clear how long a low-nickel allergy should last.

b. Nickel Oral Challenge (NOC)

The NOC after a low-nickel diet should allow to evaluate the reappearance (or new appearance) of symptoms connected to the intake of suitable quantities of food nickel. The NOC, however, does not reproduce natural exposure, either in terms of quantity of nickel intake or in terms of distribution during the day and various meals.
In many studies, the doses given in the challenge were much higher than the amount of nickel taken progressively throughout the day in a regular diet (15,16). In a study, patients sensitized to nickel seem to react to doses of 4 mg (about 10 times the contents of a normal diet) significantly more than to placebo, but not as frequently to doses of a normal diet (0.3 mg) or to a diet rich in nickel (1.0 mg), unless these doses are added to the usual food exposure (17). In the more recent Sicilian study the administered doses are elevated to 1,25-3,75 mg (18).
A dose of 4 mg of nickel corresponds to the assumption in one time of more than 3 Kg of milk chocolate or of nearly 10 Kg of beans (19). This form of intake may lead to differences in absorption and biokinetics of the element (20). One cannot exclude a dose-dependent toxic effect (21,22,23).

c. Nickel Oral Hyposensitizing Treatment (NiOHT)

The nickel oral hyposensitizing treatment (NiOHT), predominantly discussed in Italian studies (12,24,25,26,27), was out of the scope of my precedent work. These studies, however, present the limitations mentioned above with respect to sample selection, based on an unreliable low-nickel diet and a NOC far away from natural exposure. Therefore they cannot be used to demonstrate the relationship between food nickel and symptoms of SNAS.
Additionally, NiOHT results with respect to cutaneous manifestations, which are objective and objectively appraisable, would not reach statistical significance, while such significance would be reached with respect to gastrointestinal symptoms (above all meteorism, but also abdominal pains, gastric acidity etc.), which are all subjective symptoms, reported by the patient and not objectively appraisable (12).
In conclusion, diagnostic difficulties and limitations in the clinical studies, resulting in non univocal results, do not allow me to reconsider the perplexities about food nickel allergy expressed in my previous paper.

2. Possible differences in the management of ACD, SCD and extracutaneous SNAS

The three types of nickel pathology discussed here (ACD, SCD and extracutaneous SNAS) may present some differences (**table 3**).

Table 3 *- Evidence of relationship with nickel and utility of diet in clinical manifestations of nickel allergy.*

Clinical form relationship with nickel		**Evidence diet utility**	
ACD		YES	NO
SNAS	Cutaneous manifestations (Systemic contact dermatitis: **SCD**) - flare-up - pompholyx, - baboon syndrome - maculopapular exanthema - flexural eczema - urticaria - itching - vasculitis-like lesions	??	??
	Extracutaneous manifestations • Gastrointestinal - heartburn - abdominal pain - nausea - vomiting - meteorism - constipation - abdominal distension	NO	NO
	• Respiratory - rhinitis - asthma	YES	NO
	• Other - headache - chronic-fatigue sindrome - arthralgia - fibromyalgia - fever	NO	NO

ACD

The relationship of ACD with cutaneous contact with nickel is undisputed; however, the symptoms are not affected by high or protracted oral nickel intake. Therefore, although dietary restrictions are commonly imposed on many patients, a low-nickel diet has no utility in localised ACD (6,28).
Additionally, there is no substantial support for the purported "preventive" effect of low-nickel diet on cutaneous and gastrointestinal symptoms of the SNAS, either in recent literature or in the studies quoted by Goldenberg and Jacob. On the contrary, according to Röhrl and Stenberg, a vegetarian diet, by definition at high-nickel diet, is not associated with an increased preva-

lence of hand eczema, frequent manifestation of SCD, in sensitized individuals (29).

SCD

Because of the weakness of the diagnostic methods and the lack of their standardization, different authors report widely varying prevalence of SCD manifestations. Sharma considers SCD to be a rare pathology, affecting a few patients (5,11); a Sicilian statistic study, on the other hand, maintains that SCD affects 3% of a population not selected for nickel sensitization (18); according to a recent report, SCD affects 20-30% of Ni-Patch positives (3).
There seems to be some evidence of the relationship between food nickel and flare-ups in the site of previous injuries and previous patch tests, as well as of the relationship between food nickel and vesicular eczema of the hands (pompholyx), but only for very high doses (up to 10 times the amount that is deemed present in a normal diet). Lower doses do not cause more reactions than placebo (30). According to Hindsen, the flare-up induced by nickel in previous patch tests appears to be linked not only with the dose, but also with the intensity of the previous reaction and its proximity in time (31).
Admittedly, Jensen's meta-analysis of 17 clinical trials, quoted by Goldberg and Jacob, affirms that 1% of nickel allergic patients may have a systemic reaction to the nickel contained in a normal diet (0.22 mg or 0.35 mg or 0.55 mg) and 10% may react when exposed to quantity of food nickel between 0.55 and 0.89 mg (a quantity which could be reached by having a diet rich in high-nickel foods, drinking nickel-contaminated water from pipes and taps and/or drinking on an empty stomach a large amount of high metal content water). However, the authors themselves have pointed out that the subjects included in the studies and tested are not representative of the general population, as they are a selected sample of nickel allergic individuals, with symptoms that were so strong or so persistent to lead them to consult specialized dermatologists (16). One per cent of a population selected among nickel allergic individuals according to the severity of their symptoms would appear in line with what reported by Sharma about the rarity of the pathology (5,11).
The most recent studies, which are numerically modest and often case reports, do not offer elements of novelty and explanation (14,32,33). On the contrary, they are affected by the same, effectively inevitable, methodological errors that affected previous studies.
The perplexities already expressed subsist also with respect to the low-nickel diets recently designed for both the diagnostic avoidance phase and the therapeutic phase, despite the excellent work by Braga and Mislankar to suggest more desirable, acceptable and easily applicable low-nickel diets (6,7).
Based on the considerations above, I cannot but confirm that the treatment with low-nickel diet, because of its evident limits, could be hypothetically suggested only for highly selected patients, i.e. for patients with wide and chronic manifestations of allergic dermatitis and nickel contact sensitization when topical avoidance does not appear sufficient, and a clear dependence between diet and clinical manifestations is shown. A low-nickel diet should not be a routine prescription or a first-step approach, as underlined in Matiz and Jacob's study (14).
However, for the same reasons explained above, the opinions about the use of a low-nickel diet, even in the limited cases suggested here, cannot be unanimous. In this sense, I reported that the therapeutic use of a low-nickel diet is controversial, i.e. debated and not unanimously shared. Unfortunately, this is still the case in the light of recent studies in literature.

Extracutaneous SNAS

With respect to extracutaneous SNAS, the most recent medical studies do not add much to what I reported in my previous paper. Nowadays, these studies appear to give less prominence to headache, dizziness and respiratory phenomena among the symptoms potentially due to food nickel (3,12), while gastrointestinal symptoms would be dominant (18). The Sicilian study reports that 5% of a sample of patients not selected for nickel sensitization are affected by gastrointestinal troubles due to food nickel.
Moreover, recent medical studies are few in number. The majority of them is of Italian production and many of them have been published in the same scientific magazine. A big part of them considers the existence of gastrointestinal troubles induced by nickel in foods to be acquired and verified as fact. Quotations very often refer back to other quotations; sometimes the bibliographical reference is entirely missing or lack the support of a clear evidence (12,25,26,27,34,35,36,37).
According to some of these studies, SNAS would even show itself with isolated gastrointestinal symptoms, in the absence of correlated cutaneous manifestations or of patch positiveness (18). This would allow to formulate an hypothesis of gastrointestinal troubles due to nickel on the basis of an exclusively anamnestic approach.
However, such symptoms (in particular meteorism, appearing to be dominant (18), but including also abdominal pain, nausea, constipation, heartburn, vomit, diarrhea) are numerically limited, not specific and not always objectively assessed. They are shared by the greatest part of gastrointestinal illnesses: infectious, inflammatory, due to enzymatic deficit, neoplastic, at times even psychosomatic. In similar cases, identical symptoms are often attributed to not celiac gluten-sensitivity or to food intolerance, two conditions that share with nickel allergy the difficulty of a supported diagnosis. Lactose intolerance due to lactase deficit as well can show the same symptoms as gastrointestinal SNAS. One risks considering lactose intolerant patients

(breath test positive) who are casually positive to the nickel patch test to be affected by gastrointestinal SNAS (38).
To add a further confusing element, in all these pathologies gastrointestinal symptoms are not always objectively appraisable and often lack objective parameters to assess their improvement in the elimination diet and their worsening or the relapse in the provocation test. Meteorism, flatulence, heartburn, nausea and so on are subjective symptoms and they could sometimes have a strong psychosomatic component.

Conclusions

In conclusion:
1. While SCD caused by food nickel might exist, the quality of the evidence is modest, the diagnostic tools are not orthodox and a possible diet has many limitations. Therefore, the prescription of a low-nickel diet is quite empirical and dictated by individual evaluations and its effectiveness, in any case, very uncertain and inconstant.
2. Extracutaneous SNAS caused by food nickel is much more doubtful, particularly the gastrointestinal type. In this case, besides the limits of the diagnostic iter described here, common to the whole suspicious nickel pathology, there are additional factors of doubt: the subjectivity of the symptoms, their not infrequent psychogenic component and the overlapping with gluten-sensitivity, food intolerances, and lactose intolerance.

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