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SYSTEMIC NICKEL ALLERGY SYNDROME: NOSOLOGIC FRAMEWORK AND USEFULNESS OF DIET REGIMEN FOR DIAGNOSIS

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Systemic (gastrointestinal and skin) reactions to ingestion of nickel rich foods in patients with nickel allergic contact dermatitis characterize Systemic Nickel Allergy Syndrome (SNAS). The objective of the study was to describe the nosologic framework of the syndrome and to compare sensibility and specificity for SNAS diagnosis between two different low nickel diets - BraMa-Ni and the usually prescribed list of forbidden foods - along with patient adherence to diet. One hundred forty-five patients with suspected SNAS (by history and benefit from nickel dietary restrictions) were selected and orally challenged with nickel for a definite diagnosis. Specificity and sensibility of the diets were calculated in relation to the results of nickel challenges. The nosologic framework of SNAS was deduced from the clinical pictures of 98 patients with positive nickel challenge and characterized essentially by skin and gastrointestinal symptoms, whereas all other symptoms (dizziness, headache etc.) were never elicited by the oral nickel challenge. The specificity and sensibility of BraMa-Ni in detecting SNAS were significantly higher than the forbidden food list diet, with an excellent patient adherence. Therefore, BraMa-Ni diet can be prescribed for the treatment of the syndrome other than for the diagnosis, the gold standard of which remains the oral nickel challenge.

Nickel (Ni) is an ubiquitous highly sensitizing metal which can trigger allergic contact dermatitis (ACD) in about 10-20% of the worldwide population (1). Twenty percent of these ACD patients also experience urticaria and angioedema, flares, itching, cough, headache and gastrointestinal symptoms due to the ingestion of nickel-rich foods (2-4). This condition, firstly known as systemic contact dermatitis, has been named systemic nickel allergy syndrome (SNAS) which better describes both the involvement of organs other than the skin and the implied immunologic mechanism that not only involves ACD typical Th1 but also Th2 cytokines (5).

Few works have addressed the clinical nosology of this syndrome, being symptomatology described in case reports (6-8), in some therapeutic trials (4, 10), as a result of oral nickel challenges (9).

In patients with suspected SNAS, a low nickel diet reduces symptoms and is applicable as a

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diagnostic and therapeutic means. However, it is difficult to calculate the exact nickel content in food, and its daily intake changes from country to country (11). The estimated intake is higher in Western countries: in Italy it is about 300-400 μg/day (12), in the UK 120-210 μg/day (13), in the US 74-100 μg/day (14), in Finland 130 μg/day (15), in Canada 207-406 μg/day (16), in Denmark 900 μg/day (17). For this reason the WHO (18) and the European Union (19, 20) adopted resolutions to control the water Ni-content and to limit the manufacture and import of high-releasing nickel products intended for prolonged contact with skin.

SNAS can be diagnosed in patients with nickel ACD whose gastrointestinal and cutaneous symptoms ameliorate after a low nickel diet. However, given the difficulties in establishing the quantitative and qualitative composition of a low-nickel diet (20), the diagnosis should always be confirmed by a nickel oral challenge which induces symptom reappearance.

Only a few SNAS patients can reintroduce the forbidden foods after a long period of diet, whereas the majority of them has to maintain a low nickel diet for life. However, this regimen is difficult to follow not only because it affects the patient's quality of life, but also because nutritional characteristics of many nickel-containing foods (fibers, carbohydrate, essential elements and vitamin content, etc.) are important for human health. At present, the low nickel diet prescription only comprehends a list of forbidden foods without a healthy balanced diet plan. For this purpose, we developed a nutritionally balanced diet with low nickel content (BraMa-Ni), also providing a list of allowed foods and a number of appropriate recipes (22) to increase patients' compliance. This diet derives from BraMa (acronym of two authors Braga and Maccarinelli), a diet developed with purpose of minimizing the additive content and avoiding vasoactive amine foods (23).

The aim of the study was to describe the clinical characteristics of patients referring to the outpatient clinics of four hospitals in Italy, three in the Abruzzo region and one in the Lombardy region. The authors also verified the reliability of the diagnostic potential of the BraMa-Ni diet. Moreover, the patients' acceptance and adherence to the BraMa-Ni versus the classical list of forbidden foods were evaluated.

MATERIALS AND METHODS

Three hundred sixty-three patients suffering from nickel ACD were interviewed using a questionnaire to verify the presence of symptoms linked to the ingestion of nickel-rich foods (Table I). One hundred forty-five subjects who reported symptoms of suspected SNAS were placed on a one-month low nickel diet: a list of forbidden foods (Table II) for 112 patients and the BraMa-Ni diet (Table III) for the remaining 33 patients (the BraMa-Ni diet being available in the last year of the study). Patients were asked to relate on a visual analogue scale (VAS - with 0 the worst and 10 the best) their clinical conditions before and after nickel restriction. Subjects who reported the disappearance or a reduction of symptoms by at least 70% after the diet were suspected as SNAS patients.

The low nickel balanced BraMa-Ni diet was calculated according to the recommended intake levels of nutrients (24) for an adult man and woman of normal weight, with a daily intake of 1932 kcal and 1733 kcal respectively and of about 50 μg/day of nickel (Table III).

At the end of the month of diet, all patients were asked to answer a satisfaction questionnaire for the prescribed diet restrictions indicating also their adherence to the diet regimen (total: 100%; once a week ingestion of nickel-rich foods: 75%; twice a week ingestion of nickel-rich foods: 50%; daily ingestion of a nickel-rich foods: 25%; complete non adherence to the diet: 0%).

A single-blind nickel oral challenge was performed after a month of diet on all 145 patients by administering increasing doses of nickel (1.25, 2.5 and 3.75 capsules made by Lofarma SpA, Milan, Italy) until reappearance of SNAS symptoms. Each dose was administered with a one-week interval.

In all patients, IgE mediated food allergy was excluded as the cause of SNAS symptoms by cutaneous and serum allergological tests. Clinical data from the questionnaires and symptoms induced by the oral nickel challenge were evaluated for statistics.

Statistics: Quantitative data were assessed using descriptive analysis. Pearson Chi-square was applied to compare adherence and acceptance of the two diet regimens; sensitivity and specificity were assessed according to known formulas by SPSS software.

RESULTS

Among the 145 subjects with suspected SNAS, 60 (41.4%) patients (16 following the BraMa-Ni diet and 44 using a list of forbidden foods) reported

a complete remission of symptoms after the diets: 27 (18.6%) patients (2 treated by BraMa-Ni diet and 25 by a list of forbidden foods) ameliorated by at least 70% in respect to the basal VAS; and 58 (40%) patients (15 treated by BraMa-Ni diet and 43 by list of forbidden foods) had no improvement or less than 70% of the basal VAS. The acceptance and the adherence to the diets are reported in Fig. 1. Patients receiving only the list of forbidden foods found difficulties in following the diet regimen. In fact, only 26.8% of them carefully observed the prescription; on the contrary, all patients except one, followed the BraMa-Ni regimen.

After a month of diet all 145 patients were orally challenged (single-blind) with nickel. Ninety-eight of them (79 females and 19 males, mean age 38+/-12 years) were diagnosed with SNAS. Ninety-six patients reacted to the oral administration of 1.25 μg of nickel, one to 2.50 μg and one to 3.75 μg (the last two with partial improvement after the forbidden food diet) with skin or gastrointestinal symptoms.

The group of patients with positive nickel challenge was composed of 56 out of the 60 who completely ameliorated after the diet (16 BraMa-Ni and 40 forbidden food diet), 17 out of the 27 who partially (70%) ameliorated after diet (1 BraMa-Ni and 16 forbidden food diet) and 25 out of the 58 who had no improvement with the diet regimens (1 BraMa-Ni and 24 forbidden food diet). It is worthy of note that the 25 patients who were positive to

Table I. *Questionnaire for patients with suspect of SNAS.*

If you are affected by nickel allergic contact dermatitis please answer the following questions:				
Data of appearance of eczematous lesions in contact with metals				
Data of ACD diagnosis by patch test				
Severity of eczema (1 the lowest and 10 the highest)				
Grade of positivity of patch test as expressed by doctors (+,++,+++)				
Do you suffer from one or more of the following conditions induced or exacerbated by the ingestion of foods such as tomato, cacao, green tea, mushrooms, or other (please describe)…….. ……				
Symptoms	Description	Yes	No	Data of appearance
Urticaria				
Angioedema				
Eczema in regions not in contact with metals				
Vomit				
Diarrhea				
Meteorism				
Gastric acidity				
Other gastrointestinal symptoms (please describe)				
Other symptoms (Please describe)				
……				
……				
……				
……				
Are symptoms induced by:				
Single meal				
Repeated ingestion of the same foods				

Table II. *List of forbidden nickel-rich foods.*

FORBIDDEN FOOD		
Almond	Flounder and plaice	Peanut
Apricot	Fresh and dried fig	Pear
Artichoke	Hazelnut	Pea
Asparagus	Herring	Plum/prune
Avocado	Lentil	Potato
Baking powder	Lettuce	Raisin
Bean and French bean	Lobster	Rhubarb
Broccoli	Margarine	Shellfish
Buckwheat and maize	Mushroom	Spinach
Canned beverage	Mussel	Tea
Canned foods	Nut	Tomato
Carrot	Oat	Yeast
Cauliflower and cabbage	Onion	Walnut
Chocolate and cocoa	Oyster	Whole wheat flour
Stored or cooked food in iron container		
Ni-containing vitamin/mineral supplements		

nickel challenge and had no improvement after the diet related that they followed the diet regimen by 50% or less.

In relation to the oral nickel challenge, the low nickel diet specificity in detecting SNAS was 70.2% and sensitivity 74.4%. However, comparing the two diet regimens, the BraMa-Ni showed a specificity of 93.3% and a sensitivity of 94.4% compared to a specificity of 44.2% and a sensitivity of 51.1% of the forbidden food diet.

Table IV shows the details of symptoms reported in history by SNAS patients: all were affected by nickel ACD and the majority reported cutaneous (90%) and gastrointestinal symptoms (88%). Symptoms reported by SNAS patients included urticaria, angioedema, eczema in an area without direct nickel contact, meteorism, gastric acidity, abdominal colic, diarrhea, vomit and acidity to the throat. Gastrointestinal symptoms appeared in 63 patients (59 of whom also reported cutaneous symptoms) after the ingestion of a single nickel-rich meal, while a repeated ingestion of dietary nickel induced gut symptoms in 25 subjects and skin symptoms in 31 (Table IV).

Thirty patients also reported cough, dyspnea, headache, chronic fatigue and dizziness always associated to gastrointestinal symptoms. Sixty-two patients with gastrointestinal symptoms were also lactose intolerant. Before being classified as SNAS, patients were diagnosed with gastritis (30 pts) and/or gastro-esophageal reflux (33 pts) and/or hepato-biliary diseases (22 pts).

Tables V and VI show symptoms elicited by the oral nickel challenge. All had a flare-up of ACD lesions and 10 only had cutaneous symptoms. Meteorism was the most characteristic gastrointestinal symptom observed in all challenged patients. The other symptoms (cough, dyspnea, headache, chronic fatigue, dizziness) reported by patients as linked to dietary nickel ingestion were never elicited by oral nickel challenges.

Two patients also had atopic dermatitis, 29 had respiratory allergy to pollens and/or mites (8 asthma and 21 rhinitis) and 4 had allergy to latex and were also sensitive to latex cross-reactive fruits.

DISCUSSION

Since the 1970s, several authors (25) have reported that some nickel ACD patients had

Table III. *Low nickel (50 μg/die) balanced BraMa-Ni diet for adult man or woman of normal weight.*

	Food	Male	Female
Breakfast	Semi-skimmed milk with low lactose content	250 mg	250 mg
	00 flour bread	60 gr	40 gr
Snack	White yogurt	125 gr	No
Lunch	Rice with a teaspoon of olive oil	80 gr	80 gr
	Zucchini	50 gr	50 gr
	Chicken (or lean meat)	130 gr	130 gr
	Lettuce	100 gr	100 gr
	00 flour bread	60 gr	60 gr
	Apple	150 gr	150 gr
Dinner	Pasta or rice in vegetable broth	30 gr	30 gr
	Jam (or cow ricotta 80 gr)	50 gr	40 gr
	Peppers (or zucchini, eggplant, endive)	150 gr	150 gr
	00 flour bread	60 gr	60 gr
	Apple or (300 gr of peach or pineapple)	200 gr	200 gr
	3 spoons of oil/day	30 gr	30 gr

Nutritional Analysis: Diet for adult men: 1932 kcal, Proteins: 16.28%, Lipids: 27.71%, Saturated fatty acids: 5.66%, Carbohydrates: 55.89%. Diet for adult women: 1733 kcal, Proteins: 15.83%, Lipids: 26.22%, Saturated fatty acids: 8.33%, Carbohydrates: 57.84 %.

eczematous manifestations in skin sites not in contact with the metal after ingestion of nickel-rich foods - a condition named "systemic contact dermatitis". The histopathology of the flare-up eczema appeared to be similar to the skin reactions of ACD. This clinical picture was initially attributed to an abnormal absorption/secretion of nickel. However, studies demonstrated that there were no differences in nickel absorption and elimination between healthy subjects and nickel ACD patients both reacting and not reacting to the nickel oral challenge (26,27). However, many nickel ACD patients also presented with extra-cutaneous manifestations, mainly gastrointestinal, thus justifying the denomination of "systemic nickel allergy syndrome" (5). Immunological studies demonstrated that SNAS is characterized by an involvement of a complex cytokine network with production and release of Th2 other than Th1 cytokines, typical of a type IV immune reaction. In particular, it has been reported that some nickel ACD patients reacting with systemic symptoms (cutaneous and gastrointestinal) to a 10 mg nickel oral challenge, had IL-5 serum levels increased by 57% in respect to the basal values; whereas, no significant changes were observed in healthy people and in ACD patients without systemic symptoms after the same nickel treatment (27). The data were later confirmed (4, 28, 29) showing a parallel IL-4 production by nickel-stimulated PBMC from SNAS patients. Immunohistochemistry of intestinal biopsies, taken after 10 mg nickel oral challenge in SNAS patients, demonstrated an infiltration of CD4+ cells in the duodenal lamina propria and in the epithelium with a strong reduction of epithelial CD8+ lymphocytes, due to apoptosis induced by the strong antigen challenge (2). Both CD4+ and CD8+ lymphocytes decreased in blood (2, 30).

In the present study, we compared clinical manifestations of SNAS by history with those induced by oral nickel challenge in order to better define the nosology of the syndrome.

Forty percent of all 361 enrolled ACD patients reported a history of systemic symptoms linked to the ingestion of nickel-rich foods. However, only 67% (98) of them (27% of all patients) had a positive oral nickel challenge, and in no cases the not better

Table IV. *Symptoms by history of 98 SNAS patients.*

	ACD	Cutaneous symptoms	Gastrointestinal symptoms	Respiratory symptoms	Headache	Other
Years from appearance	15±7	10±4	7±6	2±2	6±3	2±1
Number of patients	98	90	88	7	15	8
Linked to a single Ni rich meal		59	63	3	5	0
Repeated ingestion of Ni rich meals		31	25	4	10	8

Cutaneous symptoms: urticaria, angioedema, eczema in region without direct contact with nickel. Gastrointestinal symptoms: meteorism, gastric acidity, abdominal colic, diarrhea, vomit, acidity to the throat. Respiratory symptoms: cough, dyspnea. Other: dizziness, chronic fatigue.

Table V. *Cutaneous symptoms of 98 SNAS patients after nickel oral challenge.*

Symptom	Ni-ACD Flare-up	Positive Ni-PT flare-up	Widespread eczema	Urticaria	Angioedema
Total	98	67	64	42	34
Associated to (n)	All	All of the followings	Urticaria (8)	WE (8)	WE (4)
Associated to (n)			Angioedema (4)	Angioedema (20)	Urticaria (20)
Associated to (n)			Urticaria and angioedema (10)	WE and angioedema (10)	WE and urticaria (10)

WE: widespread eczema; ACD: Allergic contact dermatitis; PT: Patch test.

defined symptoms of headache, dizziness, chronic fatigue, cough and dyspnea were induced by nickel oral challenge. Similar data are also reported after higher (10 mg) nickel doses (26, 27, 31). Likely, these symptoms are related to the generic state of discomfort rather than specifically to ingested nickel; therefore, only cutaneous and gastrointestinal symptoms clinically characterize SNAS. In SNAS patients systemic symptoms followed a clinically evident nickel ACD of about 5±3 years, irrespective of the severity of eczematous lesions and of the positivity degree of nickel patch tests.

Skin and gut manifestations appeared almost always combined, except for 10 patients showing ACD flare-up and widespread eczema, and 8 patients with meteorism and dyspepsia. The majority of patients (73%) reported that systemic symptoms followed the ingestion of a single nickel-rich food, whereas the remaining patients needed a higher nickel intake to elicit symptoms. In agreement, almost all SNAS patients reacted to an oral challenge with the lowest nickel dose. Many authors criticize the

Table VI. *Gastrointestinal symptoms of 98 SNAS patients, after nickel oral challenge.*

Symptom	Meteorism	Dyspepsia	Colic	Gastric acidity	Vomit	Diarrhea	Throat acidity
Total	88	88	65	33	12	22	16
Associated to (n)	All	All	Gastric acidity (17)	Colic (17)	Colic (12)	Colic (22)	
Associated to (n)			Gastric and throat acidity (7)	Colic and throat acidity (7)			Colic and gastric acidity (7)
Associated to (n)			Vomit (12)	Throat acidity (9)			Gastric acidity (9)
Associated to (n)			Diarrhea (22)				

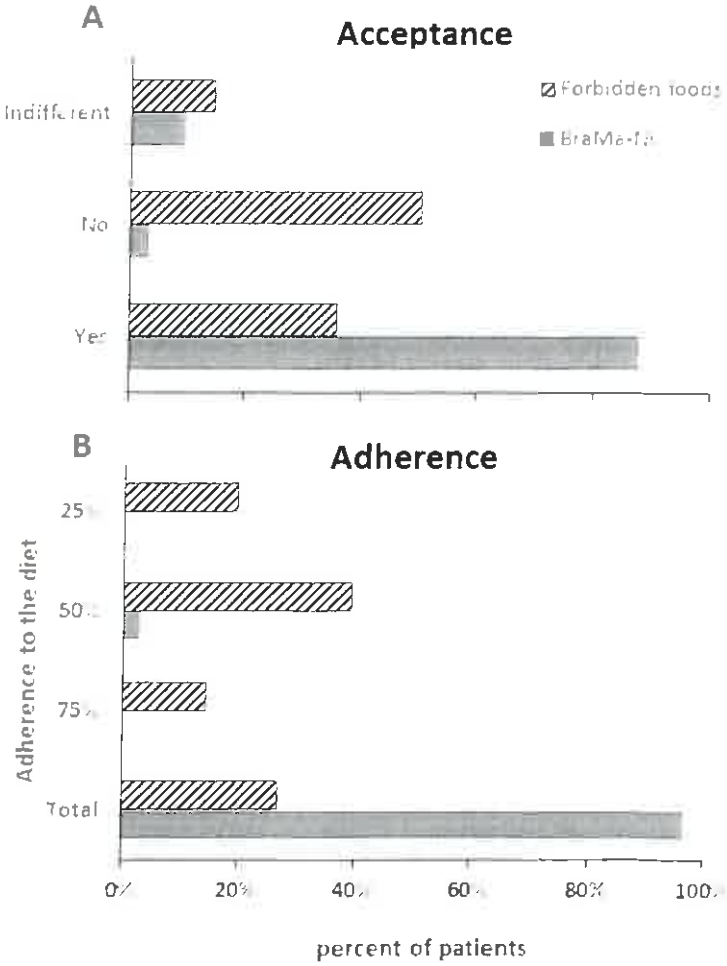

Fig. 1. *Percentage of patients in relation to the levels of acceptance (A) and adherence (B) to the two diet regimens (forbidden food list and BraMa-Ni diet). Both parameters were significantly better for patients placed on BraMa-Ni diet compared to those following the forbidden food diet (Pearson Chi-square test: p=0.001 for both).*

usefulness of this test considering that the 1.25 mg dose is higher than that of a single nickel-rich meal. In any case, the authors who studied the dose-response dependency of oral exposure to nickel in sensitive subjects found a high sensitivity and specificity of the nickel oral challenge (9). Increasing symptoms were noted in SNAS patients orally challenged with nickel doses ranging from 0.3 to 4 mg, while none of the healthy controls reacted.

The most frequent manifestation of SNAS was the flare-up of previous ACD eczematous lesions reported by all patients, followed by a flare-up of a previously positive nickel patch test. Such symptoms were variably associated with eczema in regions not in contact with the metal or with urticaria and angioedema. In all cases patients reported meteorism and dyspepsia combined with colic, gastric acidity, vomit, diarrhea or throat acidity; only 8 patients out of 98 experienced gut symptoms without skin manifestations. In agreement with other authors (32), we found a high percentage of SNAS patient suffering from lactose intolerance. It can be hypothesized that in SNAS patients the nickel induced pro-inflammatory status could temporarily impair the brush border enzymatic functions, resulting in hypolactasia.

Allergen avoidance is the most effective treatment for allergic diseases and a nickel low diet is actually effective in SNAS patients. It is not easy for patients to balance levels of nutrients in the usually prescribed elimination diet composed by a list of forbidden foods. Moreover, if maintained for a long time, this diet can provoke a nutritional deficiency because of the elimination of many vegetables which makes the diet perceived as tasteless and difficult to adhere to. For this reason many patients abandon the diet, leading to a relapse of SNAS symptoms.

In the present study, we evaluated the diagnostic efficiency of BraMa-Ni which can be used for the treatment of the syndrome and which is suitable to be followed for life. The BraMa-Ni diet is balanced according to recommended intake levels of nutrients (RDAs) (25), and its nickel content is about 50 µg, much lower than the daily nickel intake in Western countries (13-18). The patients' acceptance of the BraMa-Ni diet is excellent (87.8% of positive judgment in the questionnaire), significantly higher than that observed in the group who received the list of forbidden foods (35.7%) (Pearson *Chi*-square: $p=0.001$). Consequently, the adherence was almost complete (96.9%), also favored by the enclosed recipes. In fact, only one male subject of the 33 patients who received the BraMa-Ni diet partially complied with the suggested regimen. The complete adherence to the forbidden food diet was on the contrary low (26.8%), and the majority of patients deviated from the diet once a week or even daily. This explains the differences in sensitivity and sensibility in detecting SNAS between the two diet regimens. At present, all patients with SNAS are following the BraMa-Ni diet with a complete remission of symptoms.

In the present manuscript we demonstrate that the clinical picture of SNAS is characterized essentially by gastrointestinal and cutaneous symptoms in a subject with a previous Ni-ACD. On the contrary, headache, dizziness, chronic fatigue, cough and dyspnea that are frequently attributed by patients to nickel ingestion are not part of the syndrome, as they were never induced by nickel oral challenges.

There is an ongoing discussion about the causal relationship between ingested nickel and systemic reactions (21), however, results of nickel oral challenges also reported in other studies (2, 4, 9, 28) have clearly demonstrated this relationship. The main problem remains that of defining the nickel dose able to elicit symptoms: the amount of nickel administered in oral challenges is significantly greater than that ingested during a normal meal. However, the majority of patients report symptoms following repeated ingestion of nickel-rich foods and not after a single nickel-rich meal. Therefore, there is the need to carefully study nickel metabolism not only after a single challenge (31), but also in real life to observe the possible accumulation of the metal in the body in SNAS patients compared to healthy subjects and ACD patients. In any case, patients who are positive to a nickel oral challenge report that restriction of dietary nickel is associated to a significant amelioration (frequently disappearance) of SNAS symptoms. BraMa-Ni, being the unique diet scheme balanced in nutrients, should be preferred to the list of forbidden food at present prescribed.

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