CIÊNCIAS DA SAÚDE

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(Organizadores)

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APRESENTAÇÃO

A obra "*As Ciências da Saúde*" aborda uma série de livros de publicação da Atena Editora, em seus 15 capítulos do volume I, apresenta a importância da farmacovigilância com o desenvolvimento de estudos relacionados com biomoléculas ativas na melhoria da qualidade de vida de pacientes, numa perspectiva farmacológica por meio do desenvolvimento e utilização de novas terapias farmacêuticas.

A farmacovigilância se relaciona em todos os aspectos com a utilização de medicamentos, desde seu desenvolvimento com estudos preliminares e laboratoriais a sua utilização empírica ou cientifica, sendo assim, trata-se da ciência que desempenha atividades relativas à identificação, avaliação, compreensão e prevenção de efeitos adversos ou quaisquer problemas relacionados ao uso de medicamentos. Desta forma, cabe a ela identificar, avaliar e monitorar a ocorrência dos eventos adversos relacionados ao uso dos medicamentos comercializados no mercado brasileiro, com o objetivo de garantir que os benefícios relacionados ao uso desses produtos sejam maiores que os riscos por eles causados.

Atualmente, o desenvolvimento de medicamentos no Brasil se baseia majoritariamente na utilização de produtos naturais. As plantas fornecem uma gama de compostos bioativos que podem ser utilizados das mais diversas formas em medicamentos, possuindo, assim, ações antifúngicas, antibacterianas, antioxidantes, antidiabéticas, entre outros.

A união entre o desenvolvimento e a utilização de medicamentos compõe um viés gigante para o cuidado com o paciente, uma vez que medicamentos, se utilizados de forma incorreta, tem elevado potencial de causar mal.

Colaborando com tais descobertas este volume I é dedicado aos pesquisadores na área da saúde que buscam um melhor entendimento sobre o desenvolvimento e uso de moléculas bioativas. Trazendo artigos que abordam a avaliação da atividade de diversos compostos biologicamente ativos de plantas; do ácido gálico sobre a formação de biofilme por *Candida albicans;* da radiopacidade de cimentos de ionômero de vidro indicados para tratamento restaurador atraumático; da eficiência da síntese de nanopartículas de prata em extrato de *Beta vulgaris* para aplicação em têxteis com atividade antimicrobiana; e a análise do uso de medicamentos já produzidos e os danos causados por eles, bem como a automedicação.

Ademais, esperamos que este livro possa mudar a perspectiva do leitor sobre o uso inadequado de medicamentos, colaborando e instigando pesquisadores a conhecer o desenvolvimento de novas drogas e impacto social e econômico do seu uso pela sociedade.

Nayara Araújo Cardoso
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SUMÁRIO

CAPÍTULO 11

USE OF PATCH TEST TO DETERMINE THE PREVALENCE OF NICKEL ALLERGY IN CHILDREN AGED 5–12 YEARS

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ABSTRACT: Nickel causes contact allergies in a large segment of the population, and several studies have investigated etiological factors in the development of nickel sensitivity. This sensitivity has important implications for dentistry, as several dental materials contain nickel. The aim of our study was to use patch test to determine the prevalence of nickel allergy in children aged 5–12 years. The sample comprised 87 individuals who were screened for dental care at the Dentistry Clinics I and II of the Dentistry Course of the Federal University of Santa Maria. The study showed that 41.4% of participants reacted positively on the nickel sensitivity patch test, of those exhibiting positive responses, 27.8% were males and 72.2% were females. The prevalence of nickel allergy was evaluated only in children aged 5–12 years. There was a high prevalence (41.4%) of cutaneous sensitivity to nickel among children aged 5–12 years; the prevalence is higher among females.

KEYWORDS: Contact dermatitis. Nickel. Pediatric dentistry. Prevalence.

INTRODUCTION

Nickel is one of the main causes of allergic contact dermatitis in the general population because it is widespread in the environment and is used in a wide variety of products[1,2]. Nickel is present in garments, footwear, costume jewelry, watches, piercings, and orthodontic appliances; in addition, air pollutants in certain geographical areas contain nickel[3].

Contact with nickel by sensitized people induces an immune response that results in a skin condition called allergic contact dermatitis; this condition ranges from mild to more serious symptoms such as erythema, exudation, papules, peeling and bubbles[4]. According to Rietschel and Fowler (2000), clinical findings or the evolution of the allergic reaction are often not sufficient to obtain a conclusive diagnosis[5]. Nevertheless, the patch test remains an efficient method for diagnosing nickel allergy. The use of metal orthodontic appliances is associated with some hypersensitivity reactions caused by ionic releases[6].

The frequency of nickel allergy increases concomitantly to the addition of perforations for inserts of props and exposures to the metal. Thus, the frequency of contact dermatitis by nickel is more in females. The difference is explained by the higher occurrence of perforated ears, piercings and greater exposure to jewelry, when compared to male subjects[7].

There has been a substantial increase in the prevalence of contact allergies among children. It is believed that this increased frequency is influenced by current lifestyles (including fashion and clothing) that are increasing exposure to allergens at younger ages. After sensitization, it is advisable to avoid contact; however, many children report difficulties in following this directive[7, 8].

The results of this study may contribute to discussions on the behavioral and treatment strategies that may be adopted when nickel allergy is observed in patients who require dental or orthodontic treatment. The main objective of this study is to identify the prevalence of nickel allergy.

SUBJECTS AND METHODS

Study design

A longitudinal observational study was conducted at the Pediatric Dentistry Clinic of the Federal University of Santa Maria (UFSM), Santa Maria, RS, Brazil, from March to September 2017. All patients underwent anamnesis and assessment of both the Visible Plaque Index (VPI) and the Gingival Bleeding Index (GBI). The protocol was approved by the Human Research Ethics Committee of UFSM (registration number CAAE: 58487116.5.0000.5346). All patients and their caregivers were provided various written materials detailing the nature of the study: the terms of free and informed consent, free and informed consent forms, and confidentiality forms. Confidentiality of the interviewees was maintained during analysis and dissemination of the results.

Study population

The study included 87 children aged 5–12 years who presented for dental consultation at the Pediatric Dentistry Clinic of the UFSM and whose parents consented to their participation in the study. Children who had used or were using any active or

passive orthodontic appliances and those who had used steroidal anti-inflammatory drugs within 30 days prior to the test were excluded.

Sample calculation

The present study aimed to test the null hypothesis that the correlation in the population is 0.00. Significance was set at 0.05, and two-sided tests were conducted. Based on the sample size of 87 participants, the study had a power of 80%, assuming a population correlation of 0.29—the smallest correlation that could be detected.

Patch tests

Patch tests are used to identify the etiologic agent(s) in allergic contact dermatitis. This is a scientific method of investigation with well-defined and established rules that are constantly reviewed and updated[4].

Patients included in the study were tested for sensitization to 5% nickel sulfate (IMUNO CENTER, Rio de Janeiro, Brazil) and solid petroleum jelly. The substances were applied to each patient's dorsal region at two points 10 cm apart and were secured with adhesive tape (Finn Chambers® AQUA, Phoenix, AZ, USA). The test was left in place for 48 hours, with patients instructed not to make sudden movements or to rub the region of the test adhesive. In the event of allergic reaction beyond the expected level, patients were instructed to remove the test and call for the responsible investigator.

Immediately after removal of the test, a circular depression in the skin confirmed the occlusion and validity of the test. Evaluation of the reaction to the contact test was conducted 48 hours after the test with a reading rule, waiting at least 20 min after removal of the tape. Subsequent readings occurred at 72 h and 7 d after test contact. The protocol used in the placement, removal and reading of patch tests were described by Lazarini *et al.*[4]. The results of the test were evaluated using the International Contact Dermatitis Research Group (ICDRG) criteria: - = negative reaction (without skin changes); + = weak reaction (erythema and infiltration, non-vesicular; ++ = strong (vesicular) reaction; +++ = extreme reaction (bullous or ulcerated); ?+ = doubtful reaction (erythema without infiltration; IR = irritative reaction[9, 10]. Tests areas of each patient were photographed at application, 48 h, 72 h and 7 d using a Canon EOS Digital Rebel® camera.

Statistical analysis

Data were analyzed using SPSS 20.0 software. Participants comprised 87 individuals aged 5–12 years.

An exploratory analysis of the data was performed, and normality was verified using Kolmogorov-Smirnov and Shapiro-Wilk tests. Spearman's correlation was used because the data were non-normal.

RESULTS

Eighty-seven individuals were tested, all of whom completed the study. Two participants missed the one-sided test and were followed to the end of the study, but refused to repeat the test. Of the 87 participants, 38 (43.7%) were male and 49 (56.3%) were female; the mean age was 8.56 ± 1.99 years. The mean VPI score was 20.77 ± 17.92 (range: 0–71), and the mean GBI was 8.80 ± 12.18 (range: 0–57). Thirty-six of the subjects (41.4%) reacted positively to nickel (including doubtful reactions). Of these, 10 (27.8%) were male and 26 (72.2%) were female. Among female subjects who presented with allergy, 12 girls used earrings and jewelry; only one male participant used these items. The frequencies of nickel allergy at 48 h, 72 h and 7 d are presented in Tables 1, 2 and 3, respectively.

48 h		
Score	Frequency	Percentage
-	51	58.6
+	8	9.2
++	8	9.2
+++	0	0
?+	20	23.0
IR	0	0
Total	87	100.0

Table 1. Frequency and percentage of nickel allergy at 48 h

Note: (-) negative reaction; (+) weak reaction; (++) strong reaction; (+++) extreme reaction; (?+) doubtful reaction; (IR) irritative reaction

72 h		
Reaction score	Frequency	Percentage
-	69	79.3
+	5	5.7
++	10	11.5
+++	0	0
?+	3	3.4
IR	0	0
Total	87	100.0

Table 2. Frequency and percentage of nickel allergy at 72 h

Note: (-) negative reaction; (+) weak reaction; (++) strong reaction; (+++) extreme reaction; (?+) doubtful reaction; (IR) irritative reaction

7 d		
Reaction score	Frequency	Percentage
-	75	86.2
+	9	10.3
++	2	2.3
+++	0	0
?+	1	1.1
IR	0	0
Total	87	100.0

Table 3. Frequency and percentage of nickel allergy at 7 d

Note: (-) negative reaction; (+) weak reaction; (++) strong reaction; (+++) extreme reaction; (?+) doubtful reaction; (IR) irritative reaction

In evaluating the dichotomous correlations of sex, age, 48 h, 72 h, 7 d, previous contact, allergy, medication and surgery, there was a statistically significant correlation (-0.235) the presence of allergy in girls at 72 h, independent of the severity of the reaction. There were also statistically significant correlations between girls and other types of allergy (-0.471), between day 2 and day 3 (0.550) and between day 2 and day 7 (0.408).

DISCUSSION

VPI and GBI indexes are parameters used to determine the hygiene and oral health conditions of a population. The positive correlation between these two indices is widely recognized and was also statistically significant in our study (0.598). This positive correlation can be interpreted as an indication of poor oral hygiene in the children evaluated. Despite this finding, it was not possible to correlate these indices (VPI and GBI) with the allergic reactions seen at the periods evaluated.

In our study, 41.4% of children (n = 87) aged 5–12 years exhibited an allergy to 5% nickel sulfate. In 1963, Marcussen in Denmark performed the first contact test in a group of children. A total of 191 children aged 0–10 years were evaluated, with 29% exhibiting positive responses to 5% nickel sulfate at 48 h[11].

In 1991, Barros *et al.* performed a contact test in 562 children aged 5–14 years from four Portuguese schools; the 48-h reading revealed five (0.98%) reactions to nickel, three (0.53%) to cobalt and one (0.18%) to chromium, a lower result than was found in our study[12]. In 1996, Stables *et al.* evaluated 92 children aged 3–14 years and observed 10 (10.9%) positive reactions to nickel at 48 and 96 h[13]. In 2010, Brandão *et al.* evaluated 144 children aged 0–12 years; 20.1% of those presented a reaction to 5% nickel sulfate, 4.9% to 0.5% potassium dichromate and 9.7% to 1% cobalt chloride at 48 and 96 h[8]. Belloni Fortina *et al.* (2015) demonstrated that 16.87% of the children tested were allergic to 1% nickel sulfate in a population of 6708 children aged 1–16 years at the 48- and 96-h readings[14]. In 2017, Zafrir *et al.* evaluated 343 Israelis aged

1–18 years who had clinically suspected allergy[15]. At the 48- and 72-h readings, 12.5% reacted positively to nickel sulfate, 5.2% to potassium dichromate and 5.2% to cobalt chloride.

Zafrir *et al.* found that 20.8% of the individuals with nickel allergy were females and 1.4% were males[15]. Brandão *et al.* showed that 69% of children with nickel allergy were females with pierced ears[8]. In the present study, the majority of individuals—67.6% (25/37)—who exhibited a reaction to nickel were females, and 12 of those used earrings. These results indicate a weak correlation between female sex and allergic reaction at 72 h after sensitization. Some researchers have shown that nickel sensitization is associated with increased frequency of perforated ears and increased jewelry exposure, and the frequency of nickel allergy increases concurrently with increasing numbers of metal exposures[7]. According to Brandão *et al.,* the only factor associated with the nickel reaction in his investigation was the presence of a pierced ear[8]. After sensitization, it is advisable to avoid contact with the allergen, but children and adolescents report difficulty in following this guideline[7, 8].

The images obtained from 20 subjects (23% of the sample) at 48 h showed allergic reactions that were classified as doubtful due to the absence of characteristics for groups 0, 1, 2 and 3. However, these observed allergic reactions may have been triggered by products used in this study, including nickel sulfate, vaseline and adhesive.

It has been shown that 5% nickel sulfate can produce irritating reactions in children. However, Brandão *et al.* observed only three of these reactions (2.1% of children tested)[8]. This finding is similar to those reported by several authors and our own study in which irritant reactions to nickel were not observed at this concentration in children[13, 16]. No serious side effects were detected, and the contact test was safe in the study population.

In 2004, Menezes *et al.* evaluated the hypersensitivity of nickel sulfate used in orthodontic practice and showed statistically significant positive reactions in 21.1% of the 38 patients; there were no differences between reactions before and after orthodontic appliance placement[17]. Studies have shown that the use of metal orthodontic appliances may be associated with some hypersensitivity reactions due to ionic release. There may be a risk of sensitizing patients to nickel through long-term exposure to devices containing nickel, as occurs in routine orthodontic therapy[6]. Although levels of metal ions have been detected in some studies after orthodontic appliance placement, they are not sufficient to cause alarm; however, more studies are needed to clarify these issues[18].

Assessment of patch test results is the most difficult aspect of the procedure, as it depends on the researcher's skill, experience and curiosity. Limitations of this study include assessment of the results and the size of the sample used. There are currently a limited number of studies on this subject. The results of this study may contribute to new lines of research, using larger sample sizes and different evaluation time points.

The issue of allergic contact dermatitis caused by nickel is relevant today because

children are using earrings, costume jewelry, clothing accessories, orthodontic appliances, cell phones, tablets and video games that contain nickel metal alloys, which may be the possible etiological agent for these allergies.

The prevalence of contact sensitivity to nickel in this study population was 41.4%, with 72.2% of females and 27.8% of males demonstrating sensitivity. There is a high prevalence of cutaneous sensitivity to nickel among children aged 5–12 years, and this sensitivity is more prevalent in females.

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