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Prevalence and factors associated with sensitivity to methylisothiazolinone in individuals with suspected allergic contact dermatitis: A cross-sectional study

Prevalencia y factores asociados con la sensibilidad a la metilisotiazolinona en individuos con sospecha de dermatitis alérgica por contacto: un estudio transversal

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Abstract

Objectives: To evaluate the prevalence of methylisothiazolinone (MI) sensitivity and associated factors in individuals with suspected allergic contact dermatitis.

Methods: Cross-sectional study based on patch tests, including methylisothiazolinone 0.2%, in 286 participants with suspected allergic contact dermatitis, in Brasília/DF, Brazil, between March/2020 and March/2022.

Results: 13.6% of participants were diagnosed with allergic contact dermatitis and sensitive to MI. The mean age was 43.7 years, and the majority were women (71,8%). The average duration of the disease was 60 months. The most common location was hands (76.9%) and upper limbs (33.3%). In 97.4%, allergy to methylisothiazolinone was considered of current relevance. In the multivariate model, being domestic/household increased the chance of presenting sensitivity to MI by 4.2 (95% CI= 1.36 - 13.5). Presenting lesions in several places of the body was also significantly associated (OR=2.84; CI 95%=1.17 - 6.86) to be sensitive to the test substance.

Conclusion: The findings confirm the epidemic of allergy to methylisothiazolinone. They reinforce the need for the inclusion of this isolated substance in the Brazilian baseline series. We emphasize the need for regulations on the use of methylisothiazolinone in industrial products and household detergents, as is done for cosmetics. Studies in other centers are needed to confirm these results.

Keywords: Prevalence; Methylisothiazolinone; Allergic contact dermatitis; Allergy; Epidemiology; Detergents; Industrial products.

Resumen

Objetivo: Evaluar la prevalencia de sensibilidad a la metilisotiazolinona y los factores asociados en individuos con sospecha de dermatitis alérgica por contacto.

Métodos: Estudio transversal, llevado a cabo en pacientes con sospecha de dermatitis alérgica por contacto, a quienes se aplicaron pruebas de parche, incluida la metilisotiazolinona al 0.2%, atendidos en Brasilia/DF, Brasil, entre marzo de 2020 y marzo de 2022.

Resultados: Se registraron 286 pacientes con dermatitis alérgica por contacto. El 13.6% de los participantes fueron diagnosticados con dermatitis alérgica de contacto y sensibles a metilisotiazolinona. La edad media fue de 43.7 años y la mayoría fueron mujeres (71.8%). La duración media de la enfermedad fue de 60 meses. La localización más frecuente fueron las manos (76.9%) y los miembros superiores (33.3%). En el 97.4% la alergia a la metilisotiazolinona se consideró de relevancia actual. En el modelo multivariante, ser ama de casa incrementó la probabilidad de padecer sensibilidad

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a la metilisotiazolinona en 4.2% de los casos (IC95%: 1.36 – 13.5). Manifestar lesiones en diferentes sitios anatómicos también tuvo asociación significativa (OR: 2.84; IC95%: 1.17 – 6.86) de tener sensibilidad a la sustancia de ensayo.

Conclusión: Los hallazgos confirman la epidemia de alergia a la metilisotiazolinona. Refuerzan la necesidad de inclusión de esta sustancia aislada en las series de referencia brasileñas. Es importante reglamentar el uso de metilisotiazolinona en productos industriales y detergentes domésticos, como se hace con los cosméticos; por tanto, se requieren estudios adicionales, en otros centros, para confirmar estos resultados.

Palabras clave: Prevalencia; Metilisotiazolinona; Dermatitis por contacto; Alergia; Epidemiología; Detergentes; Productos industriales.

INTRODUCTION

Isothiazolinone derivatives are widely used as preservatives or biocides in industrial and domestic products, and many are contained in personal care products.[1] The list of products that contain them ranges from occupational use products, such as water-based paints or glues, to children's toys (slimes).[2] The compound mixture of methylchloroisothiazolinone (MCI) and methylisothiazolinone (MI) in a 3:1 ratio caused an epidemic of allergic contact dermatitis (ACD) in the 1980s. More recently, using MI (CAS No. 2682-20-4) as a preservative isolated in cosmetics has resulted in dramatic levels of sensitization in several parts of the world.[3]

In 2013, MI was named "allergen of the year" by the American Contact Dermatitis Society and was then added to the European baseline series. Subsequently, European legislation banned the use of MI in leave-on products and limited its use to a maximum of 15 ppm in rinse-off products.[2] It was only in 2021 that Brazilian legislation followed international restrictions; however, companies were given time to adapt, meaning that the effects of these limitations may take a while to be felt.[4] It is worth noting that the introduction of similar legislative measures around the world led to a decrease in the prevalence of non-occupational ACD due to MI, mainly from cosmetic products. However, no impact was observed on occupational allergy due to the absence of legal restrictions on the use of isothiazolinones in industrial products.[2]

Since MI constitutes only 25% of the total material tested with MCI/MI, a mixture of preservatives in a fixed combination (3:1), the prevalence of hypersensitivity to MI cannot be accurately determined by routine MCI/MI testing in the baseline series.[5] For example, a previous study on MCI/MI did not detect 27.3% of MI allergy.[6] For this reason, the inclusion of MI in the baseline series has been recommended, using MI 2,000 ppm (0.2%) in an aqueous vehicle.[7]

There are hardly any studies on MI sensitization in Brazil. The Brazilian baseline series not contain MI and, since its creation, 0.5% aqueous MI/MCI has been tested, a concentration well above the 0.02% or 0.01% used in other countries.[8] Concern has already been raised regarding the possibility of an epidemic of MI allergy in our country, alerting specialists to the need for clinical research on this issue and how to correctly diagnosis this allergy.[9]

The objective of this study was: to demonstrate the importance of MI in the etiology of ACD, by evaluating the profile of sensitization (frequency, clinical, and demographic characteristics) to this substance.

METHODS

This is a cross-sectional study conducted on individuals from a single center, based on patch tests carried out on consecutive patients using the Latin American series, for clinical suspicion of ACD, at the Allergy and Dermatology Outpatient Unit of the Hospital Regional da Asa Norte, in Brasília, DF, Brazil, between March 2020 and March 2022.

The study included individuals treated with a diagnostic hypothesis of ACD or other types of chronic eczema that did not respond to usual treatment. Individuals were excluded if they presented the following: severe or generalized active dermatitis, dermatitis in the dorsal region, use of systemic immunosuppressants in the three weeks before the test, use of topical corticosteroid or calcineurin inhibitor on the back up to one week before the test, exposure to solar radiation up to two weeks before the test, and individuals who were pregnant or breastfeeding, or less than 18 years old.

After clarification and signing a term of free, informed consent, participants who were indicated for the patch test were submitted to clinical-epidemiological evaluation. Next, the patch test was applied using Alergochamber® hypoallergenic adhesive tapes (Neoflex Biotecnologia Ltda). The test substances were manipulated, following their CAS number, by the company IPI ASAC BRASIL, as recommended by the *Colegio Ibero-Latinoamericano de Dermatología* (LA-1000 Chemotechnique®, Sweden).

The attachment site (back) was thoroughly cleaned and degreased with an ether/alcohol solution (Hoffmann® Liqueur). Allergens were removed at 48 hours and readings were taken at 48 (D2) and 96 hours (D4). Readings were performed according to the consensus of the International Contact Dermatitis Research Group (ICDRG).[10] Positive reactions were scored as +, ++ or +++ and irritating or dubious reactions were considered negative.

The prevalence of sensitivity to MI was calculated as the proportion of positive patch tests for the substance in relation to all patch-tested participants. Comparison of clinical and epidemiological characteristics between sexes was performed using the Chi-square test or Fischer's exact test. Crude and adjusted logistic regression analyses were used to determine the relation between the variables under study.

In both analyzes (crude and adjusted), odds ratios (OR) and respective confidence intervals (95%CI) were calculated, at a significance level of 5%. The statistical method used in the multivariate models followed a backward stepwise elimination procedure. Initially, all explanatory variables that presented $p < 0.20$ in the bivariate analysis were incorporated into the multivariate models. The study complied with all the provisions contained in CNS Resolution no. 466/2012 and was approved by the Research Ethics Committee of the State Secretariat of Health for the Federal District (report 3.711.423).

RESULTS

In total, 286 individuals were tested with the Latin American baseline series. A diagnosis of ACD was confirmed for 158 (55.2%). There was a predominance of white (70.6%)

women (79.4%) aged between 18 and 50 years old (67.1%). Participant's mean age was 43.1 years old (range: 18-89) and the median age was 42 years old.

Regarding education, 46.5% reported having completed higher education and the most frequent occupations were in the administrative sector/civil servants (26.9%), students (15.4%), homemakers/domestic workers (11.2%), and health professionals (9.1%).

Regarding disease duration, 63.6% reported a duration of up to 24 months, with a mean of 40.8 months; 52.8% reported family history of allergy and the majority (65.7%) presented lesions in several locations on their body.

The variables presented a significant distribution ($p < 0.05$): occupation, having a hobby, lesions in several locations, disease lasting 25 months or more, and of current relevance. **Table 1**

Table 1. Distribution of sensitivity frequencies for methylisothiazolinone in the results of patch tests carried out on individuals treated at the Allergy and Dermatology Outpatient Unit at the Hospital Regional da Asa Norte, March 2020 to March 2022.

Variable	Sensitivity to methylisothiazolinone		p value*
	Yes n (%)	No n (%)	
Sex			
Female	28 (12.3)	199 (87.7)	0.208
Male	11 (18.6)	48 (81.4)	
Age			
Up to 39 years old	16 (12.7)	110 (87.3)	0.682
40 years old and over	23 (14.4)	137 (85.6)	
Ethnicity			
White	26 (12.9)	176 (87.1)	0.559
Non-White	13 (15.5)	71 (84.5)	
Higher education			
Yes	23 (13.1)	152 (86.9)	0.760
No	16 (14.4)	95 (85.6)	
Occupation			
Administration/Civil servant	16 (20.8)	61 (79.2)	0.035
Student	3 (6.8)	41 (93.2)	
Homemaker/Domestic worker	7 (21.9)	25 (78.1)	
Others	13 (9.8)	120 (90.2)	

...continuation table 1.

Hobby / pastime			
Yes	18 (20.9)	68 (79.1)	0.018
No	21 (10.5)	179 (89.5)	
Occupational connection			
Yes	10 (20.4)	39 (79.6)	0.129
No	29 (12.2)	208 (87.8)	
Family history of allergy			
Yes	21 (13.9)	130 (86.1)	0.888
No	18 (13.3)	117 (86.7)	
Personal history of allergy			
Yes	18 (11.2)	143 (88.8)	0.170
No	21 (16.8)	104 (83.2)	
Lesion location			
Single location	8 (8.2)	90 (91.8)	0.051
Several locations	31 (16.5)	157 (83.5)	
Disease duration			
Up to 24 months	13 (7.1)	169 (92.9)	0.000
25 months or over	26 (25.0)	78 (75.0)	
Current relevance			
Yes	38 (27.0)	103 (73.0)	0.000
No	1 (0.7)	144 (99.3)	

* test or Fisher's exact test.

Sensitivity to MI was verified in 39 patients (13.6%), predominantly white (66.7%) women (71.8%) aged between 31 and 50 years old (56.4%), who had completed higher education (48.7%), and held an administrative position/civil servant (41%). Most had a personal history of allergies, with rhinitis being the most common disease. Furthermore, personal and family history of atopy was verified in 46.1% of participants, with rhinitis being the most common in personal history, and ACD and rhinitis being the most prevalent diseases in the families of those allergic to MI.

In 74.4% of the sensitized patients, no occupational connection was identified for sensitivity to MI; therefore, it seems reasonable to conclude that the allergy is due to contact with household, personal care, and cosmetic products. A significant majority had lesions in several areas of the body (79.5%). The lesions were most frequently located on the hands, upper limbs, and face. **Figure 1**

Among sensitized patients, ACD (84.6%) was the most frequently determined clinical diagnosis. Current relevance of sensitivity was seen in almost all cases (97.4%).

Patients sensitized to MI showed concomitant sensitization with 25 other substances, the most frequent concomitant allergen was nickel sulfate (28.2%), followed by fragrance mix I (23.1%), and methyldibromo glutaronitrile (23.1%). **Figure 2**

In the multivariate analysis, among homemakers/domestic workers the chance of being sensitive to MI was 4.2 higher in relation to other occupations (OR = 4.23; 95%CI = 1.36-13.5). Professionals who worked in the administrative sector/civil servants also presented a higher chance of sensitivity to MI (OR = 2.45; 95%CI = 1.07-5.61).

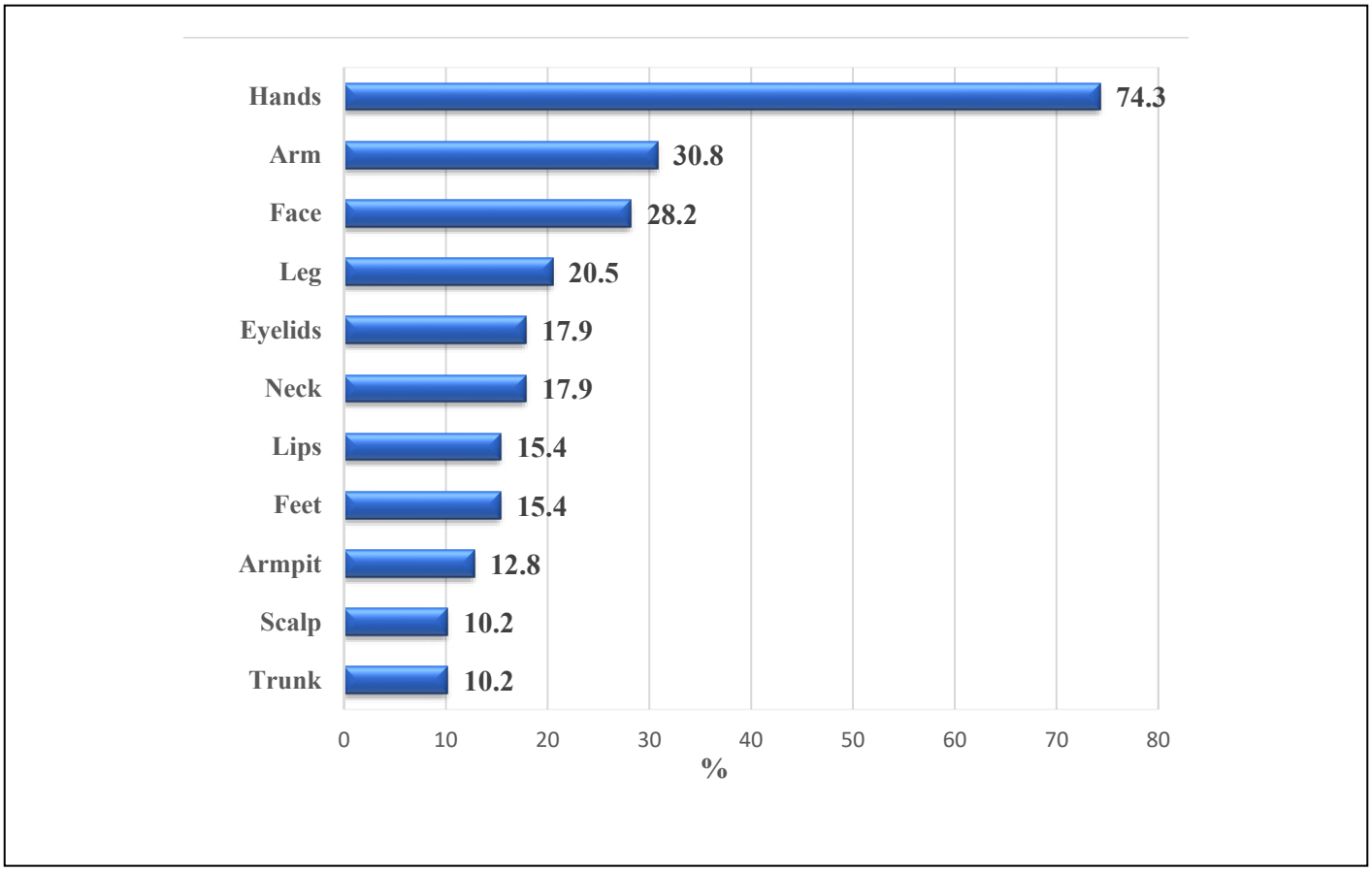
Having a hobby was associated with a greater chance of sensitivity to the substance. Regarding the type of activity carried out as a hobby, the following were mentioned: acrylic painting, crafts, fishing, washing dishes, gardening, animal husbandry, diving, and physical activity, among others. Another factor that increased the chance of the individual being sensitive to MI was presenting lesions in several areas of the body (OR = 2.84; 95%CI = 1.17-6.86). **Table 2**

DISCUSSION

To our knowledge, this is the first study involving prospective collection to investigate the prevalence of contact allergy to MI in Brazil. We believe that a single researcher conducting all the stages of all exams is important for reducing the variability observed when several examiners are involved.

The results obtained in this work agree with studies on ACD and MI. A study conducted by the ICDRG in countries on different continents showed contact sensitization to MI of 7.3%, with frequencies ranging from 0.8% to 10.9%.[11] The group from Massachusetts General Hospital analyzed the rate of sensitization to MI and determined a rate of 10%.[12] For the period 2019-20, the North American Contact Dermatitis Group (NACDG) obtained a higher positivity rate of 13.8% for MI.[13] Another group using the Mayo Clinic baseline series verified that MI was the substance with the second-highest rate of positive reaction (13.6%), surpassed only by nickel sulfate.[14] It is worth noting that a prospective study with a similar methodology diagnosed contact allergy to MI in 13.2% of participants,[15] values very similar to those obtained here (13.6%).

The prevalence of positivity for the MCI/MI association was considered low (1%). In contrast, MI showed a significant percentage of +++ reactions, including intense reactions in patients with a negative test for MCI/MI. This is explained by the classic dose-response, where the concentration of MI when tested at 0.2% is 80 times greater than the concentration of MI when MCI/MI is tested at 0.01%. The current level of allergy to the isothiazolinone group is probably driven by the increasing action of MI as a primary sensitizer.[16]



* Location of the lesion: The same person could present a lesion in more than one body site.

Figure 1. Distribution of location of the lesion in participants sensitive to methylisothiazolinone treated at the Allergy and Dermatology Outpatient Unit at the Hospital Regional da Asa Norte, March 2020 to March 2022.

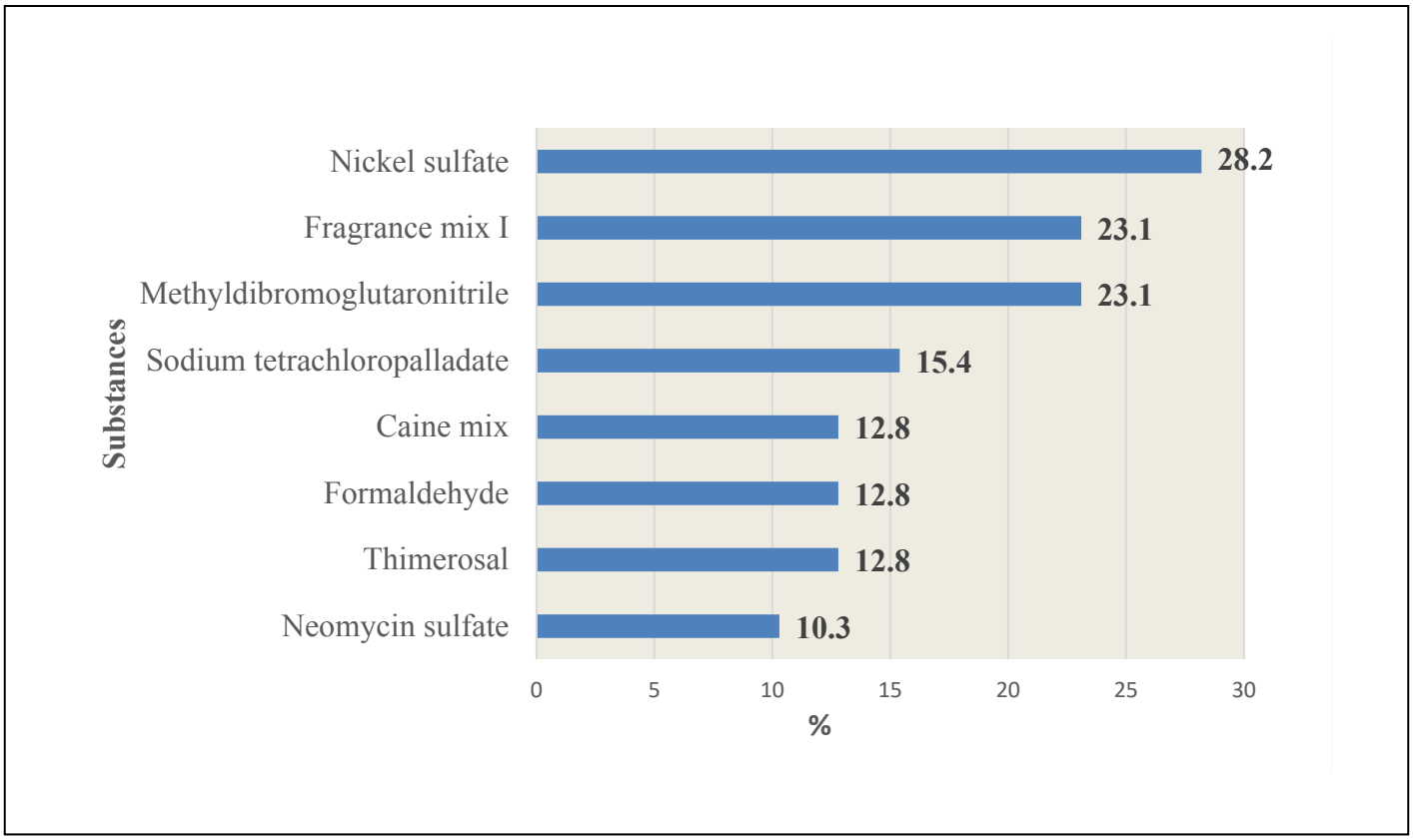


Figure 2. Distribution of positive reactions concomitant with methylisothiazolinone sensitivity in individuals treated at the Allergy and Dermatology Outpatient Unit at the Hospital Regional da Asa Norte, March 2020 to March 2022.

Table 2. Logistic regression analysis for sensitivity to methylisothiazolinone in participants treated at the Allergy and Dermatology Outpatient Unit at the Hospital Regional da Asa Norte, March 2020 to March 2022.

Variable	Sensitivity to methylisothiazolinone			
	n (%)	OR*	95%CI	p value
Sex				
Female	28 (12.3)	0.562	0.24 - 1.31	0.185
Male	11 (18.6)	1		
Occupation				
Administration/ Civil servant	16 (20.8)	2.450	1.07 - 5.61	0.034
Student	3 (6.8)	0.87	0.22 - 3.37	0.841
Homemaker/Domestic worker	7 (21.9)	4.231	1.36 - 13.5	0.013
Others	13 (9.8)	1		

...continuation table 2.

Hobby / pastime				
Yes	18 (20.9)	2.45	1.14 - 5.26	0.021
No	21 (10.5)	1		
Lesion location				
Single location	31 (16.5)	2.84	1.17 - 6.86	0.02
Several locations	8 (8.2)	1		
Disease duration				
In months	-	1	1.00 - 1.01	0.023

* Model adjusted by backward stepwise technique.

Numerous studies on sensitization to isothiazolinones report a clear preponderance in women and a high percentage of patients over 40 years of age.[2,7] Similarly, this study shows a much higher prevalence in women (72.0%); however, this was not significant compared with distribution by sex in the non-sensitized group. Furthermore, we also observed a higher prevalence in those over 40 years of age, with a mean age of 43.7 years old. A recent Thai study showed similar data to that obtained here, with a predominance of women (76.1%) and a mean age of 42.7 years old.[17] In Brazil, a report shows that among the positive results for MCI/MI, 93.1% were women.[18]

Atopic dermatitis has been suggested as a risk factor for sensitization to this preservative.[2] However, this finding was not confirmed in our study, in which there was a preponderance of a clinical diagnosis of isolated ACD. A personal history of atopy was observed in 46.1%, which is higher compared with another study in which such data was observed in 36.6% of participants.[19]

The majority of individuals showed no occupational connection (74.4%), a figure close to the 80% obtained in another study.[2] Non-occupational ACD is more common among women, mainly due to the daily use of cosmetics and other personal care products.[7] In adults, MI ACD mainly affects the face (particularly the eyelids) and hands due to handling chemicals, such as paints or household detergents. Airborne pattern is another possibility involving the face and neck.[1] In this study, a predominance of hands, upper limbs and the face was observed. In another report, the anatomical site most frequently involved was the hands (33.3%), followed by the face, including the eyelids (26.5%), and generalized involvement (14.8%).[19] As for MCI/MI alone, a Brazilian study indicated that the hands were the most affected site, followed by the face and neck.[18]

Regarding sources of sensitization, it is believed that cosmetics have been of special importance. Other leave-on products have also been implicated, including wet wipes. Detergents containing MI can cause ACD, either via direct contact or airborne.[1] It has been reported that 93% of different paints contained MI in varying concentrations,[20] an occurrence that has recently been corroborated.[21] This work did not evaluate suspected sources of exposure, however significant current relevance (97.4%) was verified solely by observing the products that participants brought in for evaluation at the time of examination. In countries where measures restricting the use of this preservative have been implemented for some time, a change in clinical relevance in the genesis of this contact allergy has been noted, with a decrease in leave-on cosmetics and a relative increase in the contribution of rinse-off personal use substances and household products that still contain MI.[22]

Polysensitization may be an important factor among patients allergic to MI.[19] Confirmation of data from the literature was achieved through observation of concomitant sensitization to 24 other elements in the series. The concomitance of positive tests for different substances, such as preservatives, for example, may occur due to simultaneous exposure to different materials containing these elements.[18] We were unable to assess the possibility of cross-reactivity with other isothiazolinones,[22] such as benzisothiazolinone and octylisothiazolinone, because these substances are not available in Brazil.

One limitation of this study was that it was conducted during the COVID-19 pandemic, which led to a reduction in attendance at outpatient clinics, thus reducing the number of participants tested.

CONCLUSIONS

Briefly, this work reinforces the importance of MI as an etiological agent of ACD in our country, since the data confirm the allergy epidemic to this preservative. We highlight the pressing need to add this isolated substance

to the Brazilian baseline series. Finally, we believe that regulations concerning the use of MI in industrial products and household detergents are essential, as established for cosmetics. Studies in other centers are required to further confirm these results.

Conflicts of interest

There was no conflict of interest.

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