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ASSOCIATION BETWEEN EXPOSURE TO ENVIRONMENTAL RISKS AND ATOPIC DERMATITIS IN CHILDREN

ASSOCIAÇÃO ENTRE A EXPOSIÇÃO A RISCOS AMBIENTAIS E DERMATITE ATÓPICA EM CRIANÇAS

ASOCIACIÓN ENTRE LA EXPOSICIÓN A RIESGOS AMBIENTALES Y LA DERMATITIS ATÓPICA EN NIÑOS

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ABSTRACT

Atopic dermatitis (AD) affects up to 20% of children and is influenced by genetic, immunological, and environmental factors. It is not fully known the impact of the environment on this dermatosis, the type of exposure to which children are more exposed to, or the factors can cause or worsen the disease. The objective of this study is to evaluate the environmental exposures most associated with atopic dermatitis in children with the disease. So, we conducted a case-control study, evaluating two groups of age-matched children, aged 1 to 12 years, through anamnesis focused on environmental aspects. Environmental factors were compared in both groups seeking associations between environmental risks and atopic dermatitis. A total of 93 children were evaluated: 44 from the AD group and 49 in the control group. The two groups were similar in the main demographic variables. Children with AD live closer to gas stations (OR 9.7 - 95% CI 2.3-39.6; p = 0.02), have more frequent visible mold indoors (OR 7.2 - 95% CI 2.2-22.9; p <0.01.) and reported less pest control at home in the last 12 months (OR 0.12 - 95% CI 0.02-0.58; p <0.01). There was no statistically significant difference regarding the proximity to factories, automotive service centers, heavy traffic, crops with pesticides, open sewage, and waste recycling near home. The study was not designed to assess the temporality and cause-effect relationship between risk factors and the main outcome, but suggests associations between often overlooked environmental variables and atopic dermatitis. The results showed that patients with atopic dermatitis live closer to gas stations, have more contact with mold and less frequent pest control at home.

KEYWORDS

Environmental Health ; dermatitis, atopic ; eczema ; environmental pollutants

RESUMO

A dermatite atópica (DA) afeta até 20% das crianças e é influenciada por fatores genéticos, imunológicos e ambientais. Não se sabe ao certo o impacto do ambiente sobre essa dermatose, o tipo de exposição ao qual as crianças estão mais próximas ou quais fatores podem causar ou agravar a doença. O objetivo deste estudo é avaliar as exposições ambientais mais associadas à dermatite atópica em crianças acometidas pela doença. Para isso, realizamos um estudo caso-controle, no qual avaliamos dois grupos de crianças pareadas por idade, de 1 a 12 anos, por meio de anamnese focada em aspectos ambientais. Os fatores ambientais foram comparados nos dois grupos buscando associações entre riscos ambientais e dermatite atópica. Foram avaliadas 93 crianças, sendo 44 do grupo DA e 49 do grupo controle. Os dois grupos apresentaram semelhanças nas principais variáveis demográficas. Crianças com DA vivem mais perto de postos de gasolina (OR 9,7 - IC 95% 2,3-39,6; p = 0,02), têm mais frequentemente mofo visível dentro de casa (OR 7,2 - IC 95% 2,2-22,9; p < 0,01) e relataram menos controle de pragas em casa nos últimos 12 meses. (OR 0,12 - IC 95% 0,02-0,58; p < 0,01). Não houve diferença estatisticamente significativa em relação à proximidade de fábricas, centros de serviços automotivos, tráfego pesado, plantio com pesticidas, esgoto a céu aberto e reciclagem de resíduos perto da casa. O estudo não foi projetado para avaliar a temporalidade e a relação de causa e efeito entre os fatores de risco e o desfecho principal, mas sugere associações entre variáveis ambientais geralmente negligenciadas e DA. Os resultados mostraram que os pacientes com DA vivem mais perto de postos de gasolina, têm mais contato com mofo e controle de pragas menos frequente em casa.

PALAVRAS-CHAVE

Saúde Ambiental; Dermatite Atópica; Eczema ; Poluentes Ambientais

RESUMEN

La dermatitis atópica (DA) afecta hasta al 20% de los niños y está influenciada por factores genéticos, inmunológicos y ambientales. No se conoce completamente el impacto del medio ambiente en esta dermatosis, el tipo de exposición al que los niños están más próximos o qué factores pueden causar o empeorar la enfermedad. El objetivo de este estudio es evaluar las exposiciones ambientales más

asociadas con la DA en niños con la enfermedad. Para ello, realizamos un estudio de casos y controles evaluando dos grupos de niños emparejados por edad, de 1 a 12 años, mediante anamnesis centrada en aspectos ambientales. Se compararon los factores ambientales en ambos grupos, buscando asociaciones entre los riesgos ambientales y la DA. Se evaluó a un total de 93 niños, 44 del grupo de DA y 49 del grupo control. Los grupos presentaron similitudes en variables demográficas clave. Los niños con DA viven más cerca de gasolineras (OR 9,7 - IC 95% 2,3-39,6; p = 0,02), tienen moho visible más frecuente en interiores (OR 7,2 - IC 95% 2,2-22,9; p <0,01) y reportaron menos control de plagas en casa en los últimos 12 meses. (OR 0,12 - IC 95% 0,02-0,58; p <0,01). No hubo diferencia estadísticamente significativa con respecto a la proximidad a fábricas, centros de servicio automotriz, tráfico pesado, cultivos con pesticidas, alcantarillado abierto y reciclaje cerca del hogar. El estudio no fue diseñado para evaluar la temporalidad y la relación causal entre los factores de riesgo y el resultado principal, pero sugiere asociaciones entre variables ambientales a menudo pasadas por alto y la DA. Los resultados mostraron que los pacientes con DA viven más cerca de gasolineras, tienen más contacto con moho y un control de plagas menos frecuente en casa.

PALABRAS-CLAVE

Salud ambiental; Dermatitis atópica; Eccema; Contaminantes ambientales

1 INTRODUCTION

Atopic dermatitis (AD) is a chronic, recurrent inflammatory disease characterized by eczematous, pruritic lesions and is frequently associated with other atopic diseases, such as asthma and allergic rhinitis. AD affects around 20% of all children and 3% of adults and is influenced by genetic, immunological, and environmental factors. It is due to a defect in the skin barrier with secondary inflammation (WOLLENBERG *et al.*, 2020). As a chronic condition, AD causes a series of limitations that negatively impact children's quality of life, such as worsening sleep quality, reducing the ability to concentrate, and, consequently, worsening school performance. In addition, it can cause situations of psychological distress due to stigmatization and bullying (NERI *et al.*, 2023). One of the most obscure aspects concerning AD is its increasing incidence in recent decades, which followed the increase in atopic diseases in general (SHIN *et al.*, 2023). In addition to this increase, studies show a reduction in the prevalence of AD in rural populations when compared to urban populations, which seems to reinforce the so-called "hygiene theory". This theory postulates that less exposure to antigens (use of vaccines, antibiotics, antiparasitic agents, and improvement in general hygiene and sanitation conditions) leads the immune system to deregulation and hyperactivation, with a predominance of the Th2 lymphocyte response, leading to an allergic response (KREMPSKI *et al.*, 2020). The other plausible possibility for this increase in prevalence is the exposure to environmental pollutants in urban settin-

gs, such as exposure to air pollution, industrialized products, chemical, and solid waste (HENDRICKS *et al.*, 2020; STEFANOVIC *et al.*, 2021).

Health professionals in many countries, especially developing countries, lack training in clinical recognition, management, and prevention of diseases linked to the environment. Few doctors routinely obtain information about the home, school, or playground as part of demographic and social history (WHO, 2009). Conducting an anamnesis that assesses environmental exposures is a way in which health professionals can recognize, assess, control, and prevent diseases related to the environment in children (WHO, 2009). Pediatric Environmental Anamnesis is a tool recommended by the World Health Organization (WHO), which assesses the possible environmental risk factors that the child is exposed to. It does not have the role of confirming or unequivocally determining environmental exposures but providing an idea of which exposures are relevant in an environment, and which should be addressed through confirmatory methods in subsequent studies. To date, there are no studies in the literature that used this anamnesis proposal to specifically assess children with AD. Several studies suggest the relationship between AD and environmental risk factors, but to our knowledge, no Brazilian study has evaluated which specific exposures are associated with AD in children.

This research aims to investigate the association between AD and environmental risk factors in an industrialized city in southern Brazil, identifying potential pollutants related to the disease that can be explored causally in future studies and looked after by clinicians involved in children's health.

2 METHODS

2.1 STUDY DESIGN

Case-control study.

2.2 STUDY POPULATION

The sample had as inclusion criteria children between 1 and 12 years of age, diagnosed with AD evaluated by a dermatologist according to the current criteria of the American Academy of Dermatology (EICHENFIELD *et al.*, 2014). The allocation criteria for the children were based on the order of arrival at the service, once the diagnosis was confirmed. The control group was formed by children without dermatological alterations who are routinely monitored by the pediatric service at the same outpatient clinic or in basic health units from which the children are referred. Pairing between groups was made by gender and age. In selecting the control group, an age interval of plus or minus one year was considered for the corresponding case. The exclusion criterion for all groups was children brought by guardians who were unable to provide information about the child's last months of life.

2.3 SAMPLE CALCULATION

In a small pilot study, we estimated that around 70% of children with AD would have some environmental exposure, while 40% of children in the control group would report positive environmental

exposure. With a statistical power of 80%, an alpha error of 5%, the sample size found was 33 children in each group. Given the study's originality and the fact that the estimates are based on a small pilot sample, and predicting 10% losses, we have added 20% more participants, with a minimum of 40 in each group.

2.4 PROCEDURES

Children with AD were seen in a medical consultation at the dermatology outpatient clinic. The children and parents were subjected to an environmental anamnesis on environmental risk factors to which the child is or has been exposed. The questionnaires were administered by previously trained team members. Since this is a prospective tool intended solely for tracking major environmental aggressions, the WHO's proposed anamnesis does not aim to accurately determine exposure. Recall bias was assumed to be symmetrical in both groups. The children in the control group were submitted to 3 questions to exclude eczema based on standardized criteria established by the ISAAC study (SILVERBERG *et al.*, 2021). The study was approved by the Ethics and Research Committee of the University, with CAAE nº 07651619.7.0000.5341. An informed consent form was obtained from parents or guardians after clarification about the study. Children assessed as having sufficient understanding were also asked to fill out a form of consent.

2.5 VARIABLES

Current environmental exposure: residence or school located close to factories/industries, gas stations, heavy traffic, recycling of garbage, plantations with pesticides, and auto service centers. Due to the unavailability of georeferenced data and the exploratory nature of this study, proximity to the pollution source was assessed based on self-reported residence within a two-block radius. Given the characteristics of the local urban layout, this criterion corresponds approximately to a mean distance of 100 meters from the source, a threshold commonly used to define close-range exposure to air pollutants (ZHOU; LEVY, 2007; MEDINA-RAMÓN *et al.*, 2008). In addition, they were asked about problems in prenatal care, family income, exposure to smoking, and mother's schooling. Environmental exposure was defined as a positive response to any of the questions, as there is not any single marker or score available in literature that can encompass solely all environmental exposures a child can receive.

2.6 DEFINITION OF ATOPIC DERMATITIS

The diagnosis of AD was clinical, according to the American Academy of Dermatology criteria (EICHENFIELD *et al.*, 2014). AD was defined by the presence of relapsing pruritus and eczema that could be reinforced by the early age of onset, atopy, and xerosis.

2.7 STATISTICAL ANALYSIS

Descriptive statistics included absolute and relative frequencies for categorical variables that were compared between groups (AD or not) using Chi-squared tests. Fisher's exact test was used when there was an expected count of less than 5 in 25% or more cells. Continuous variables were expressed as mean ± standard deviation (SD), or as median and interquartile range (IQR) according

to distributional assumptions and compared using a t-test. Univariable and multivariable logistic regression were used within the generalized estimating equations (GEE). The dependent variable was the AD (absent or present). Covariates with a P value <0.20 in the univariable model were considered for inclusion in the multivariable analysis. Then, a backward selection of variables was performed by progressively removing the least relevant ones, as indicated by the model. The process continues until none of the remaining variables can be removed without significantly affecting the model's fitness. The smallest Akaike Information Criterion (AIC) indicated the best fit of final model. The null hypothesis was assessed at a level of statistical significance of P<0.05. All the analyses were performed using R for Windows, version 4.2.2.

3 RESULTS

Ninety-three children were evaluated, 44 from the group with AD and 49 from the control group. Table 1 shows the general characteristics of the groups. There was no statistically significant difference between groups in the main demographic variables. AD has been shown to affect predominantly young children, which demonstrates the early onset of AD in our population.

Table 1 - Characteristics of children in both groups (with atopic dermatitis and controls).

Variables	Atopic Dermatitis (n=44)	Controls (n=49)	*p*
Age, months*	68 (36)	72 (43)	0,60
Male (%)	22 (50)	23 (47)	0,70
Birth weight , grams*	2967 (577)	3081 (660)	0,40
Gestational age, weeks**	39 (38-40)	39 (38-40)	0,09
Number of brothers/Sisters	1 (1)	1 (1)	0,50
Wheezing or asthma ever in life n (%)	29 (78)	15 (33)	<0,01
Family income (in R$/month)**	2250 (1425 – 3000)	1600 (990 – 2000)	0,20
Maternal education < 9 years n (%)	32 (86)	34 (74)	0,20
Time living on site (in months)**	28 (12 – 57)	48 (12-72)	0,50

*mean (±SD); **median (IQ_{25-75}); SD: standard deviation; R$: Brazilian currency;
Source: Research data

The group of children with AD also had more reports of asthma or wheezing, reassuring the atopic characterization of the group, which presented twice as many children with wheezing and asthma than

in the control group. In the global assessment, all children had at least one environmental risk factor among those investigated, characterizing a high environmental burden on the evaluated communities.

In the univariate analysis, patients with AD had more gas stations close to home (p <0.01), more mold or visible fungi indoors (p <0.01), and less pest control at home in the last 12 months (p = 0.02) compared to the control group. (Table 2) Children with AD attended more daycare than controls (p = 0.01). There was no difference between groups regarding factories, auto service centers, heavy traffic, crops with pesticides, open sewage, and waste recycling close to home. It was not possible to analyze the relation with pesticides because it is an urban population without direct exposure to pesticides. There was also no difference between the renovation of the house in the last 12 months and the use of repellents. Breastfeeding for 6 months was similar between groups and maternal smoking during pregnancy was more frequent in the control group, despite not being statistically significant (p = 0.06). Control group patients reported more frequent smoke odor at home (p = 0.02).

Table 2 - Environmental risk factors for atopic dermatitis

Variables	Atopic Dermatitis n=44(%)	Controls n=49(%)	*p*
Attended day care anytime	29(65)	24(49)	0,01
Breastfeeding for 6 months	24(54)	22(45)	0,10
Maternal smoking during pregnancy	1 (2)	7 (14)	0,06
Animals currently in the house	27 (61)	31 (63)	0,60
Current smoking in the house	13 (30)	19 (39)	0,60
Factories close home	15 (34)	17 (35)	0,70
Auto service center close to home	18 (41)	13 (27)	0,06
Gas station close home	16 (36)	3 (6)	<0,01
Vegetable garden, crop, or orchard close home	7 (16)	6 (12)	0,40
Home renovation in the last 12 months	8 (18)	16 (33)	0,20
Pest control in the home in the last 12 months	3 (7)	13 (27)	0,02
Use of repellents/poison at home at least twice a week	12 (27)	18 (37)	0,50
Heavy traffic close home	28 (64)	29 (59)	0,20
Open sewage close home	5 (11)	7 (14)	0,80
Waste recycling close home	4 (9)	9 (18)	0,20
Frequent odor of smoke at home	10 (23)	24 (49)	0,02
Mold or visible fungi indoors	22 (50)	13 (27)	<0,01

Environmental exposure at school was also assessed, but the effects of all investigated variables (the same ones concerning home) were not as relevant as those of home exposure. After variables adjustment it was found that only residence near gas stations and the presence of visible mold in the household remained as predictive variables for AD, while recent pest control was a protective factor (Table 3). According to this study, patients with AD are 9.7 times (CI 95% 2.38 - 39.69) more likely to live near a gas station than controls and 7.23 times (CI 95% 2.2 - 22.9) more likely to have mold at home. There was no association of AD with current smoking at home and pets in the house.

Table 3 - Simple and adjusted logistic regression of the main environmental factors associated with atopic dermatitis.

Variables	OR un-adjusted (IC95%)	OR adjusted (IC95%)	*p* (Wald test)
Male	0,89 (0,38-2,08)	1,28 (0,4-3.8)	0,60
Open sewage close home	0,86 (0,25-2,96)	0,98 (0,21-4,51)	0,90
Current smoking in the house	0,76 (0,32-1,8)	0,53 (0,17-1,64)	0,20
Mold or visible fungi in the house	3,87 (1.57-9,53)	7,23 (2.2-22,9)	<0,01
Domestic animals	1,27 (0,51-3,19)	1,14 (0,38-3,4)	0,80
Pest control in the home in the last 12 months	0,22 (0,06-0,8)	0,12 (0,02-0,58)	<0,01
Gas station close home	7,65(2.29-25,56)	9,71 (2,38-39,69)	0,02

4 DISCUSSION

In our study, children with AD were more likely to live near a gas station, had more mold inside their homes, and reported less pest control at home in the last 12 months than a control group. So far, the relationships in literature between AD and certain environments are conflicting, probably due to the difficult characterization of multiple exposure factors over time. However, we have not found in the literature a study that used an extensive anamnesis in children with AD.

The baseline characteristics were similar between the 2 groups, which reinforces the importance of the results obtained. Since some environmental factors may take time to manifest noticeable symptoms, attention was taken to ensure that participants had lived in their current residences long enough for potential effects to emerge. Both groups had significant time residing in the same location, with averages greater than two years of residence. Therefore, the control group was not lacking in exposure time, which supports the interpretation that any greater effects observed in the exposed group are likely due to the exposure itself.

This study found a strong association between living near gas stations and clinical AD. To our knowledge, no study in the literature has shown this relationship. It is known that there are occupational diseases related to work at gas stations (TONGSANTIA *et al.*, 2021), but there is no reference in the literature to these effects in children. It is known that benzene, one of the main components of gasoline, penetrates the skin barrier through direct contact in its liquid form or its gaseous (volatile) form (DU *et al.*, 2024; FRASCH; BARBERO, 2018). However, there is no data on the relationship between proximity to these products and the effect on children's skin. Some studies suggest the possible relationship of compounds derived from the burning of fuels with the development of atopy (KIM, 2015; SÖZENER *et al.*, 2020) but, apparently, no study has evaluated the exposure to these fuels before burning, such as proximity to gas stations, for example, and the relationship with AD. It also remains unclear whether these associations result from direct skin damage or from the persistent activation of systemic inflammation. A study conducted in Japan analyzed skin biopsies from 75 patients with atopic dermatitis (AD) and found a correlation between disease severity and damage associated with reactive oxygen species (ROS)—which can originate from volatile organic compounds (VOCs) released by fuel combustion. These findings support the hypothesis that ROS generated by environmental exposures may contribute to oxidative protein damage in the *stratum corneum* (NIWA *et al.*, 2003).

We also have found an association between visible mold at home and AD, which has been shown in other studies. Skin reactions have been described after exposure to molds, such as xerosis, pruritus, and dermatitis, but it was not clear whether these reactions could be interpreted as immunological reactions to indoor mold (HURRAß *et al.*, 2017). A Japanese study found a relationship between AD and visible mold (UKAWA *et al.*, 2013). Another study, conducted with children in Puerto Rico, found an association between mold inside the home and an increased risk of AD with skin tests reactive to aeroallergens (YANG *et al.*, 2019).

In our study, children with AD reported less pest control at home in the past 12 months than children in the control group. There is little data in the literature on the relationship between insecticide use and atopy. There is only one African study that showed a relationship between the use of insecticides and an increased prevalence of allergic diseases (MEHANNA *et al.*, 2018). Miyake *et al.* found no relationship between the concentration of organochlorines in breast milk and the prevalence of atopic diseases in adult Japanese women (MIYAKE *et al.*, 2011). There are no specific studies on the relationship between insecticides and AD. In contrast, there is evidence that allergens from some insects, such as the cockroach, can induce eczema in contact tests in patients with AD (AMIN; ELKADY, 2023). In addition, there is evidence that children with AD have more specific IgE to cockroach antigens (DONOHUE *et al.*, 2008). Perhaps this may explain the lower prevalence of AD in children whose homes were cleaned the previous year. Although the use of repellents and insecticides has not reached statistical significance, the percentages of use were different in the two groups, and there was probably insufficient data for confirmation. This pattern, if better studied, could confirm the above hypothesis.

Children who attended preschool activities had more AD than the others. Although there is no consensus among previous studies, some evidence of this relationship has been raised previously. One of the main studies on this association, led in Germany, which evaluated more than three thou-

sand children prospectively, identified that attending daycare in the first two years of life was the only risk factor to explain the regional differences in the prevalence and incidence of eczema (CRAMER *et al.*, 2011). This could be explained by increased exposure to allergens and microorganisms in children with compromised skin barrier. In addition, it is possible that cofactors, such as stress, may mediate this relationship. Several studies report an association between stress and daycare and between stress and the development of eczema (CRAMER *et al.*, 2011).

Our study was not designed to assess the temporality and cause-and-effect relationship between risk factors and the main outcome. It is interesting, though, as it suggests associations between usually overlooked environmental variables and AD. Another limitation is the simultaneous evaluation of many variables, due to the large number of environmental exposures to which one is susceptible and its interactions, but this is a known limitation intrinsic to the field of environmental science. Even the use of biomarkers is of limited power, as it fails to depict the whole group of environmental exposures. Biomarkers in environmental health are used to detect exposure to specific pollutants, but these need to be identified locally as relevant before they can be measured; otherwise, they will present false negatives, which in turn can lead to improper environmental safety. Another limitation of this study is that there is no standardized instrument that covers all environmental exposures, which is impossible given the complexity of exposures, their continuity, and interactions. There is no single score that characterizes "environmental exposure" and, therefore, there is no specific instrument that fully and unequivocally assesses the degree of total exposure from the environment.

This may be one of the first studies that applied Pediatric Environmental Anamnesis in the dermatological consultation of children with AD, exploring the association between environmental risk factors and dermatitis. We chose to define environmental exposure as the positive response to at least one of the questions asked by the team in the anamnesis. This alone may not be sufficient to unambiguously characterize exposure to a pollutant. However, this is an inherent limitation in the field of environmental health study, where exposures often do not leave persistent and measurable biomarkers, in addition to often participating in a pool of synergistic and concomitant pollutants that can potentially cause harm. Thus, in environmental health, associations are often assumed, rather than determining causalities. This study does the same by raising hypotheses and possible associations, but it has no power to determine causality. However, the results point to the need for greater public health policy attention to tracking and monitoring environmental risk situations. Similarly, further studies are needed to clarify the relationships between AD and environmental agents using exposure quantification methods, such as biomarkers, and longitudinal studies capable of detecting temporality and, therefore, causal relationships.

5 CONCLUSIONS

There is a strong association between living near a gas station and AD in children. Similarly, the presence of mold and less use of home insecticides also seem to be associated with the disease. Most

of these relations are described here for the first time, and hopefully this study will help to calculate more robust sample sizes in next studies. Finally, clinicians should address environmental risk factors more thoroughly when evaluating a child with AD.

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