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ORIGINAL ARTICLE

Immunization and Bacterial Pathogens in the Oropharynx as Risk Factors for Alopecia Areata

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KEYWORDS
Alopecia areata;
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Abstract
Introduction: Alopecia areata is an autoimmune inflammatory disease affecting the hair follicles. Researchers are currently interested in whether the presence of bacterial pathogens and/or a history of immunization can trigger an autoimmune response in patients who are genetically predisposed.
Objective: This study aimed to determine whether there is an association between the development of alopecia areata and throat carriage of bacterial pathogens or a history of immunization.
Material and methods: Sixty-five men and women with alopecia areata and 65 control patients with other skin diseases were studied at the Dr Ladislao de la Pascua Dermatology Clinic between September 2008 and February 2009. The patients ranged in age from 18 to 59 years. Patients with scalp diseases were excluded from the control group. In all cases, the patient was questioned about immunizations received in the previous 6 months, and a throat swab was cultured.
Results: A history of immunization (odds ratio [OR], 3.3; 1.6% confidence interval [CI], 1.6-6.7; *P*=.001), the presence of bacterial pathogens in the oropharynx (OR, 2.6; 95% CI, 1.1-6.2; *P*=.033), and being a carrier of Streptococcus pyogenes (OR, 2.1; 95% CI, 1.7-2.5; *P*=.042) were risk factors for alopecia areata. *Klebsiella pneumoniae*, *S pyogenes*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Serratia marcescens* and *Escherichia coli* were isolated from cultures.
Conclusions: This is the first study to show an association between alopecia areata and throat carriage of bacterial pathogens or history of immunization, as risk factors for development of the disease. Given the characteristics of our study population, the association appears valid for patients with less than 25% hair loss and a course of disease under 1 year.

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PALABRAS CLAVE
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Estado de portador
de *S. pyogenes*

Inmunizaciones y bacterias patógenas en la faringe como factores de riesgo para alopecia areata

Resumen

Introducción: La alopecia areata es una enfermedad inflamatoria autoinmune que afecta al pelo. Actualmente se estudia si las bacterias patógenas y las inmunizaciones son inductores de la respuesta autoinmune en pacientes con susceptibilidad genética.

Objetivo: El objetivo de este estudio fue determinar si las bacterias patógenas en la faringe y el antecedente de haber recibido inmunizaciones están asociados a la enfermedad.

Materiales y métodos: En el Centro Dermatológico «Dr. Ladislao de la Pascua», desde septiembre de 2008 a febrero de 2009, se estudiaron 65 pacientes con alopecia areata y 65 controles con otras dermatosis, excluyendo las del cuero cabelludo. Se incluyeron pacientes de 18 a 59 años de edad y de ambos sexos. A todos se les interrogó sobre inmunizaciones recibidas 6 meses antes y se les realizó un cultivo de exudado faríngeo.

Resultados: Haber recibido inmunizaciones, la presencia de bacterias patógenas en la faringe y ser portador de *S. pyogenes* se comportaron como factores de riesgo para la alopecia areata, con una razón de probabilidades de 3,3 (IC 95% 1,6-6,7; p = 0,001), 2,6 (IC 95%: 1,1-6,2; p = 0,033) y 2,1 (IC 95% 1,7-2,5; p = 0,042), respectivamente. Las bacterias aisladas fueron *Klebiella penumoniae, Streptococcus pyogenes, Pseudomonas aeruginosa, Streptococcus pneumoniae, Serratia marcescens* y *Escherichia coli*.

Conclusiones: Este es el primer estudio que apoya los hallazgos de estado de portador de bacterias patógenas en la faringe y la aplicación de inmunizaciones como factores de riesgo para desarrollar alopecia areata. Por las características de nuestra población, esta asociación es válida para los pacientes con menos del 25% de pérdida de pelo y con una evolución inferior a un año.

Introduction

Alopecia areata is an autoimmune inflammatory disease in which the immune system attacks hair follicles and nail plates.[1,2] An incidence of 20.2 cases per 100 000 person-years and a prevalence of 1.7% have been reported[3]; in Mexico, the prevalence is 0.57%. We treated 460 patients with alopecia areata in 2007 at the Dr Ladislao de la Pascua Dermatology Clinic in Mexico; 257 were newly registered in that year.

The autoimmune attack against hair follicles in alopecia areata is mainly T-cell mediated.[4] Under normal circumstances, antigens are not recognized as either self or foreign in the immunologically privileged hair follicle. Multiple factors are now known to bring about immune privilege collapse, however. Genetic predisposition[5] and an association with psychiatric disorders[6] have both been implicated.

When infectious agents cause autoimmune diseases, the mechanisms responsible may be either antigen-specific or non–antigen-specific.[7] In the first category, antigens of a pathogen provoke a reaction, with superantigens or epitope (molecular) mimicry playing a role.[8] In the second, the pathogen creates an inflammatory environment characterized by increased self-antigen activity, expression of major histocompatibility complex molecules, release of cytokines, and overall activation of the immune system, particularly of T cells.[9]

Roles for various pathogens, mainly viruses, have been investigated. When investigators looked for a relation between cytomegalovirus and alopecia areata, no antigens were detected by Jackow et al[10] in humans, by McElwee et al[11] in C3H/HeJ mice, or by Ofdiani et al[12] in scalp biopsies using polymerase chain reaction. This last group of researchers also looked unsuccessfully for evidence of Epstein-Barr virus or herpesvirus in their patients. Similarly, although Rodríguez et al[13] calculated that 25% of patients in the US Alopecia Areata Registry linked the onset of their disease to environmental factors, they found no association between the patients' baldness and a history of either Epstein-Barr virus or infectious mononucleosis. Other infectious agents that have been studied are hepatitis C virus[14] and *Helicobacter pylori*[15]; once again, no connection was found in either case.

The pathogen that has most consistently been associated with triggering an autoimmune response is *Streptococcus pyogenes*.[15] This group A streptococcus bacterium is a gram-positive, catalase-negative, facultative anaerobe that measures 0.6 to 1.0 µm in diameter. The worldwide prevalence of airway carriage of *S pyogenes* is estimated to range from 15% to 20%.[17-19] This bacterium causes both suppurative and nonsuppurative infections. Diagnosis usually relies on bacterial culture, but it is also possible to detect specific antibodies or antigens.[20]

The possibility that carriage of oropharyngeal pathogens might induce an autoimmune reaction in alopecia areata has

not been studied. A carrier is defined as an individual from whom a bacterium that does not form part of the normal flora of the nose or throat is recovered in the absence of acute infection.[21] Normal nasal and oropharyngeal flora include α-hemolytic streptococci (*Streptococcus mutans, Streptococcus sanguis, Streptococcus salivarius*), and species of the genera *Actinomyces, Lactobacillus, Bacteroides, Fusobacterium, Peptococcus, Peptostreptococcus, Ruminococcus, Mycoplasma*, and *Candida*.[22]

An autoimmune response can also be triggered by a vaccine, particularly the recombinant hepatitis B vaccine, which contains viral antigens. Adults are currently being vaccinated against hepatitis A and B; measles, mumps and rubella (MMR); tetanus; chicken pox; pneumococcus; meningococcus; typhoid fever; yellow fever; cholera; and rabies. In Mexico, adults are only recommended the following vaccines: influenza (over the age of 60 years) pneumococcus (over the age of 60 years), tetanus, and diphtheria (booster every 10 years). The remaining vaccines have specific indications and the MMR vaccine is administered mainly to women of reproductive age and only during campaigns.[23]

Material and Methods

This cross-sectional comparative study was carried out at the Dr Ladislao de la Pascua Dermatology Clinic in Mexico City from September 2008 to February 2009.

Patients aged 18 to 59 years, of both sexes, were enrolled if clinically diagnosed with alopecia areata within the previous year.

Diagnosis was based on a finding of smooth, circular, shiny bald patches with so-called exclamation-point hairs around the edges or possibly repopulation by vellus hair. Additionally, the patches might also have felt edematous to the touch.

Two dermatologists performed independent examinations and patients were enrolled only if both agreed on a diagnosis of alopecia areata. The episode was considered active if repopulation with vellus hair was absent or covered less than 50% of the patch.

The control group was made up of patients of both sexes, aged 18 to 59 years, whose complaints were unrelated to alopecia areata.

Patients were excluded if alopecia areata was resolving, as shown by repopulation of at least 50% of the area with terminal hair on each of the bald patches, if there was a concurrent scalp disease that could have caused scarring alopecia (eg, lupus erythematosus, folliculitis decalvans, and follicular lichen planus), or if an antibiotic was being taken or had been taken within the past 4 weeks.

Control patients were excluded if they had scalp diseases, psoriasis, bacterial or autoimmune diseases, or were taking or had taken an antibiotic within the past 4 weeks.

The sample size was calculated to compare 2 proportions with a power level of 80% and an α level of .05, hypothesizing a difference of at least 20% and assuming a 20% prevalence of oropharyngeal bacterial pathogen carriage (consistent with the rate reported for *S pyogenes*). It was calculated that we needed to enroll 63.8 patients in each group. Patients were recruited for the study group consecutively. The control group was created by random sampling.

Procedures

The extension of scalp surface affected was determined with the Severity of Alopecia Tool (SALT).[24]

Throat carriage of bacterial pathogens was determined by taking a swab and culturing in a 5% blood-agar medium, incubating at 35°C for 72 hours. *S pyogenes* was identified with a bacitracin sensitivity test, a pyrrolidonyl arylamidase test, and detection of Lancefield group A antigen. Antibiograms were determined for all pathogens found. All samples were transported in Amies medium.

A vaccination history was taken during an interview with each patient, who was asked directly about immunizations during the 6 months before the onset of alopecia areata. Subjects in the control group were asked about the 6 months prior to the interview. Of concern were immunizations indicated for adults (against hepatitis A and B, MMR, tetanus, chicken pox, pneumococcus, influenza, typhoid fever, and yellow fever).

Patients were also asked directly about tonsillitis and sore throat in the 6 months before the onset of alopecia areata; subjects in the control group were asked about the 6 months prior to the interview. Additionally, the interviewer enquired about the following common clinical signs and symptoms: cough, sore throat that made swallowing difficult, fever, joint and muscle pain, loss of appetite, and headache. If a patient was diagnosed or treated by a physician for such complaints, this was also recorded as a positive finding.

In accordance with paragraph 17 of directives governing research on human subjects, this study was classified as involving minimal risk. The protocol for the study was registered with and approved by the corresponding research ethics committee and the patients gave their written informed consent (registry number 07-10).

Statistical Analysis

Quantitative variables are reported with measures of central tendency and dispersion and qualitative variables are expressed in percentages. The *t* and χ^2 tests, respectively, were used to compare quantitative or qualitative variables between groups. Risk factors were explored by calculating odds ratios (OR) and confidence intervals as well as statistical significance. SPSS software (version 17.0) was used for all analyses.

Results

Sixty-five patients were enrolled in each group. No statistically significant differences in mean age, sex distribution, place of origin, or education were found (Table 1). Seventy-four percent in each group were from Mexico City.

The distribution by type was as follows: 93.8%, plaque areata (40%, a single patch; 53.8%, multiple patches), and 6.2%, ophiasis or alopecia areata totalis or universalis.

SALT indices, reflecting the extension of baldness, classified 92.3% of the patients as S1 (<25%), 3.1% as S2 (25%-49%), 1.5% as S3 (50%-74%), and 3.1% as S5 (100%). Mean (SD) onset of alopecia areata was 3 (2.8) months before the interview.

The bivariate analysis identified a history of immunization, carriage of oropharyngeal bacterial pathogens, and isolation of *S pyogenes* as statistically significant risk factors; there was no significant difference in the frequency of sore throat or tonsillitis (Table 2).

Among the study group patients who reported having been vaccinated, 7.7% had received 2 immunizations and 3.1% had received 3; 31.1% of the control group had received 2 immunizations (Table 3).

Positive throat cultures were observed for 29.2% of the alopecia areata patients and 13.8% of the controls (Table 4).

Bacteria that are part of the normal oropharyngeal flora were identified as follows: *Staphylococcus aureus* was isolated for 47.7% of the study group and 43.1% of the controls; α-hemolytic streptococci for 30.8% and 40%, respectively; and *Candida* species for 23.1% and 26.2%, respectively.

Discussion

This is the first study to find an association between alopecia areata on the one hand and pharyngeal carriage of bacterial pathogens and a history of immunization on the other.

The distribution of alopecia areata between men (38.5%) and women (61.5%) was similar to the distribution reported by Safavi et al[3] (49% and 51%), García-Hernández et al[25](1:1.1), and Guzmán-Sánchez et al [26] (42.3% and 57.7%). The slight predominance of women in these studies and ours contrasts with the predominance of men (64.6%) reported by Sharma et al[27] in a northern Indian population. As other authors have not reported the other demographic variables we recorded, comparisons cannot be made; however, the variables were similarly distributed in our 2 study groups.

Regarding extension of disease, 95.4% of our patients had mild alopecia areata (SALT categories S1 and S2); only 4.6% had severe disease (categories S3-S5). This range of severity is different from that reported by Tosti et al,[28] who saw mild alopecia areata in 67% and severe disease in 33%. Our observations are similar, however, to those of Guzmán-Sánchez et al[26] in a Mexican population, where

Table 1 Patient Characteristics[a]

Characteristics	Patients With Alopecia Areata n = 65	Patients Without Alopecia Areata n = 65	*P*[b]
Mean (SD) Age, y	32.10	32.10	.659
Sex			
Male	25 (39)	27 (42)	.720
Female	40 (62)	38 (59)	
Marital status			
Single	32 (49)	41 (63)	.132
Married	33 (51)	24 (37)	
Place of origin			
Mexico City	48 (74)	48 (74)	.126
Mexico (the state)	6 (9)	6 (9)	
Other Mexican states	11 (17)	11 (17)	
Education completed			
Primary	15 (23)	11 (17)	.659
Secondary	18 (28)	18 (28)	
University preparatory studies	19 (29)	25 (38)	
University degree	13 (20)	11 (17)	
Occupation			
Homemaker	14 (21)	13 (20)	.210
Student	11 (17)	20 (31)	
Professional	11 (17)	5 (8)	
Office worker	9 (14)	11 (17)	
Services and sales	9 (14)	11 (17)	
Laborers and machine operators	9 (14)	3 (5)	
Agricultural	0	1 (1)	
Unemployed	2 (3)	1 (1)	

[a]Data are expressed as the number (%) of patients unless otherwise indicated.
[b]χ^2 test.

Table 2 Bivariate Analysis

Variable	Patients With Alopecia Areata n = 65	Patients Without Alopecia Areata n = 65	OR	95% CI	χ^2	*P*
History of immunization						
Yes	35	17	3.3	1.6-6.9	10.4	.001
No	30	48				
Bacterial pathogens in the oropharynx						
Yes	19	9	2.6	1.1-6.2	4.6	.033
No	46	56				
Carrier of *Streptococcus pyogenes*						
Yes	4	0	2.1	1.7-2.5	4.1	.042
No	61	65				
History of tonsillitis or sore throat						
Yes	33	31	1.1	0.6-2.3	0.1	.726
No	32	34				

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 3 History of Immunization by Group[a]

Vaccine	Patients With Alopecia Areata n = 35	Patients Without Alopecia Areata n = 17
Hepatitis B	5 (11.4)	1 (4.8)
Influenza	11 (25)	7 (33.3)
Tetanus	10 (22.7)	5 (23.8)
MMR	17 (38.6)	6 (28.6)
Chicken pox	1 (2.3)	2 (9.5)
Total[b]	44	21

Abbreviation: MMR, measles, mumps, and rubella.

[a]Data are expressed as the number (%) of patients receiving the vaccine.

[b]The total number of immunizations does not coincide with the total number of patients with a history of immunization because some subjects received more than 1 vaccine.

Table 4 Bacterial Pathogens Isolated, by Group[a]

Microorganism	Patients With Alopecia Areata n = 19	Patients Without Alopecia Areata n = 9
Klebsiella pneumoniae	9 (47.4)	6 (66.7)
Streptococcus pyogenes	4 (21.1)	0
Pseudomonas aeruginosa	3 (15.8)	0
Streptococcus pneumoniae	1 (5.3)	0
Serratia marcescens	1 (5.3)	1 (11.1)
Escherichia coli	1 (5.3)	2 (22.2)

[a]Data are expressed as the number (%) of patients receiving the vaccine.

most patients had mild disease and only a single case of alopecia areata universalis was found.

Thus, our study population did not have an even distribution in terms of disease severity or extension, as most patients had mild cases. Although all levels of disease severity were not present, the population we studied was nonetheless representative of observations in the Mexican population, where most cases have been categorized as S1 or S2 (the SALT scores for mild cases).[3]

The largest study of the role of infection in triggering alopecia areata was carried out by Guzmán-Sánchez et al,[26] who described 90 patients with alopecia areata at the Instituto Dermatológico de Jalisco Dr José Barba Rubio. Previous infection (tonsillitis, sinusitis, otitis, or dental abscesses) was identified in the medical histories of these patients, but some patients had had more than a single infection and the actual percentages of patients who had particular infections were not reported. This was not the case in our study, in which we found that 51% of patients with alopecia areata had a history of tonsillitis. Guzmán-Sánchez et al found that 56 patients had infections at the time of the study and that some had more than one. A limitation of our study is that we did not swab nasal fossa, the ear, and teeth as well as the throat in order to detect infections at other sites and perform cultures. If we had, the prevalence of bacterial pathogen carriage would have been higher. In their study, Guzmán-Sánchez et al mentioned that the frequency of infection in patients with alopecia areata was similar to the frequency in the general population, in agreement with our findings of similar percentages for tonsillitis in our 2 groups (51% of patients with alopecia areata and 48% of controls).

Pathogens capable of triggering an autoimmune response by means of superantigens or molecular mimicry include

bacteria (*S pyogenes* and *S aureus*), fungi (*Malassezia* species and *Candida albicans*), and viruses (human papillomavirus and retrovirus). Of all of these, however, *S pyogenes* is the most frequently implicated,[16] given that a reservoir of superantigens (toxins that activate T cells) accumulates when this bacterium is absorbed by epithelial cells in the tonsils. There they activate self-reactive T cells, which migrate to the skin, triggering an inflammatory cascade. The resulting tissue damage exposes the host's cryptic antigens (self-antigens to which immune tolerance has not been developed by previous exposure to T cells, which therefore recognize them as foreign).

A role for pharyngeal pathogens as inducers of an autoimmune response in alopecia areata has neither been demonstrated or confirmed by previous studies. However, we found that carriers of bacterial pathogens had a 1.6-fold higher risk of alopecia areata. Our patient sample was not large enough to allow us to estimate the degree of association more precisely, as indicated by the confidence intervals, although a relationship clearly exists.

The prevalence of *S pyogenes* carriage in our sample was lower than has been reported in the literature, where 15% to 20%[17-19] is the normal range; no patient in the control group carried this bacterium and only 4 patients with alopecia areata did (statistically significant difference). Higher rates are reported in the literature partly because studies that count asymptomatic carriers of *S pyogenes* are usually looking at pediatric populations and the prevalence of this species decreases with age.[29] However, the rate we observed was similar to the study of Raza et al[30] in 40 patients with plaque psoriasis; in that study, cultures demonstrated that 5 of the patients were carriers of *S pyogenes* whereas no control throat cultures grew that pathogen. Bacteria isolated from patients with alopecia areata in our study were *Klebsiella pneumoniae, S pyogenes, Pseudomonas aeruginosa*, and *Streptococcus pneumoniae;* the last 3 were not found in the control group. It is important to note that of this list, only *S pyogenes* has ever been linked to autoimmunity. Further study is therefore needed to establish whether there is or is not a causal relationship.

Another bacterium that can trigger an autoimmune response, by means of molecular mimicry, is *S aureus*. Its relevance has not been confirmed, however, because it commonly colonizes the throats of healthy individuals and in fact, in our study, *S aureus* was isolated in both groups in similar proportions: 48% of alopecia areata patients and 43% of controls harbored this pathogen. Other microorganisms that form part of the normal flora, such as α-hemolytic streptococci and yeasts of the *Candida* species were also present in similar proportions.

Immunization has been considered a cause of the rapid development of alopecia areata since the study of Wise et al,[31] who identified 60 cases of diffuse alopecia associated with vaccination in patients ranging in age from 2 months to 67 years. Of the 46 patients who received the recombinant hepatitis B vaccine, 84% had developed alopecia within a month. Anagen effluvium or telogen effluvium or both were initially suggested as the mechanism. However, this vaccine contains surface antigens of the hepatitis B virus, aluminum (as an adjuvant), mercury (thimerosal, as a preservative), and yeasts that work together synergistically to generate autoimmune responses.[32,33]

The association between the recombinant hepatitis B vaccine and autoimmune diseases was confirmed by Geier and Geier[34] in a case-control study that found that vaccinated individuals had greater risk of multiple sclerosis, optic neuritis, vasculitis, rheumatoid arthritis, lupus erythematosus, thrombocytopenia, and alopecia. For alopecia, the risk was 6-fold higher in the vaccinated group than in the general population.

The first study to suggest that vaccines and alopecia areata are related was that of Guzmán-Sánchez et al,[26] in which 66.6% of the patients had received some vaccine within 6 months of hair loss. This percentage was higher than the 54% we observed, but the percentage in our control group (26%) was lower still. A history of vaccination conferred a 2.3-fold higher risk for alopecia areata. We did not observe an association with a particular vaccine, although the most commonly administered ones were against MMR and tetanus. Only 6 patients (5 with alopecia areata and 1 control) had received the recombinant hepatitis B vaccine in our study; statistical significance was therefore not detected, though we note that this vaccine has been implicated in alopecia areata.

More recently, Sundberg et al[35] developed a model of alopecia areata triggered by the recombinant hepatitis B vaccine administered to C3H/HeJ mice. The vaccinated mice tended to suffer hair loss sooner than the control group; however, the difference was not statistically significant.

Given the characteristics of our study population, which was recruited from a dermatology referral clinic, the results may be extrapolated to patients whose disease process began less than a year earlier and who have plaque alopecia areata (a single patch or multiple patches) and less than 25% of the scalp affected. This is to say that both carriage of bacterial pathogens and a history of vaccination are risk factors for localized alopecia areata in the short term, supporting the theory that these factors may trigger an autoimmune response against the hair follicle.

Although our study design does not allow us to affirm there is a causal relationship between carriage of bacterial pathogens or a history of immunization on the one hand and alopecia areata on the other, it is possible to infer that both factors participate in triggering an autoimmune response. Our findings suggest that patients with alopecia areata should be evaluated more thoroughly to detect infectious agents or states. We do not recommend the suspension of immunizations, as they provide health benefits that surpass the possible adverse effect of alopecia areata, though the relationship should be studied fully.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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