Original Article

Factors Associated with Development of Vitiligo in Patients with Halo Nevus

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Abstract

Background: Halo nevus (HN) has been shown to be associated with vitiligo, but no standard signs are currently available to identify HN patients at risk of vitiligo, and the relevant data obtained in previous studies are somewhat conflicting. This study aimed to identify factors affecting the presence of vitiligo in HN patients.

Methods: We performed a retrospective study on consecutive patients with HN at the First Affiliated Hospital of Sun Yat-sen University between January 2011 and December 2016. Detailed demographic and clinical data were collected to identify the factors associated with the presence of vitiligo in this cohort of patients using uni- and multi-variate logistic regression analyses.

Results: A total of 212 HN patients were included, 101 of whom had vitiligo-associated HN (HNV). Univariate analysis indicated that a personal history of thyroid diseases was positively associated with HNV (odds ratio [*OR*] = 10.761, *P* = 0.025), while the onset age of HN was negatively associated with HNV (*OR* = 0.537, *P* = 0.026). Multivariate analysis demonstrated that the Koebner phenomenon (KP; *OR* = 10.632, *P* < 0.0001), multiple HN (*OR* = 3.918, *P* < 0.0001), and a familial history of vitiligo (*OR* = 3.222, *P* = 0.014) were independent factors associated with HNV.

Conclusions: HN without vitiligo has clinical features distinct from HN associated with vitiligo. HN patients with KP, multiple lesions, or familial history of vitiligo are more likely to develop vitiligo and therefore should be monitored for clinical signs of such accompanied conditions.

Key words: Koebner Phenomenon; Nevus; Halo; Risk Factors; Vitiligo

Introduction

Halo nevus (HN) usually occurs as a depigmented halo around a melanocytic nevus.[1,2] Although the pathogenesis of HN remains unclear, the lesion-infiltrating $CD8^+$ T-lymphocytes are regarded as having a key role in the immune-mediated melanocytic degeneration in this condition.[3-5] HN has been shown to be associated with many autoimmune diseases, of which vitiligo is the most closely related.[2,6] Currently, no standard signs are available to identify HN patients at risk of vitiligo, and the relevant data obtained in previous studies are somewhat conflicting.[7-9] This study aimed to identify factors affecting the presence of vitiligo in HN patients using uni- and multi-variate analyses.

Methods

Ethical approval

This study was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sen University (No. 188). All patients provided written informed consent.

Patients

This was a retrospective study on patients with HN at the Department of Dermatology, the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) between January 2011 and December 2016. Patients diagnosed as HN based on their history, typical clinical manifestations, and evaluation of Wood's light were invited to participate in

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this study. Patients with doubtful diagnoses were excluded as follows: (1) depigmentation around the nevus without a symmetric halo and regression of central nevus, which cannot exclude the possibility of vitiligo involving a nevus; and (2) symmetric round or ellipsoid depigmentation without documented photographs or written record of the previous presence of a central nevomelanocytic nevus. Based on the clinical presentation, patients were classified into two different subgroups: patients with HN only (HNO) and patients with vitiligo-associated HN (HNV).

Data evaluation

Information was collected through an interview, which included a wide range of demographic and clinical data such as age, gender, age of onset of HN, the number of HN, site of involvement, presence of Koebner phenomenon (KP), a family history of HN and premature hair greying (>50% white hair before the age of 40 years),[10,11] personal and family history of melanoma, vitiligo, autoimmune thyroid diseases, and other (nonthyroidal and nonvitiligo) autoimmune diseases (including diabetes mellitus type 1, psoriasis, alopecia areata, rheumatoid arthritis, systemic lupus erythematosus, allergic purpura, inflammatory bowel disease, and Addison's disease). Data regarding triggering and/or precipitating factors for HN, including psychological stress, sleep deficiency (<7 h/night), illness, physical trauma (sunburn and mechanical factors including friction, scratching, squeezing, cryotherapy, and laser), chemical factors (topical cautery, systemic administration, and exposure to toxic or harmful substances), and sex hormone changes (pregnancy, menopause, and puberty), were also collected. HN patients would be photographed whenever possible.

Serum thyroid-stimulating hormone (TSH), anti-thyroglobulin, and anti-thyroperoxidase antibodies were measured at the time of enrollment, at the discretion of the patient's dermatologist. This was mainly based on the patient's clinical symptoms, such as weight loss, heart palpitations, weakness, insomnia, goiter, and exophthalmos.

Statistical analysis

All statistical analyses were performed using SPSS 16.0 software package (SPSS, Chicago, IL, USA). Numerical variables were analyzed using the independent samples *t*-test or the Mann-Whitney *U*-test when data did not follow a normal distribution. Categorical variables between groups were compared using the Chi-square test or Fisher's exact test. For all tests, statistical significance was set at a value of $P < 0.05$.

To identify the factors affecting the presence of vitiligo in HN patients, various variables were compared between the HNO and HNV groups by uni- and multi-variate unconditional logistic regression analyses. All potential predictors of HNO and HNV were initially assessed by univariate analysis, with odds ratios (*OR*s), the corresponding 95% confidence intervals (*CI*s), and *P* values calculated. Predictors with a value of $P < 0.2$ were entered into multivariate analysis with a forward step-wise selection procedure, with possible interactions and multicollinearity examined. The goodness-of-fit of the final model was assessed using the logistic regression procedure. A value of $P < 0.05$ was considered statistically significant. The Hosmer-Lemeshow test was used to confirm the adequacy of the model.

Results

Demographic and clinical characteristics

This study enrolled 212 patients with a total of 309 with HN, including 111 with HNO and 101 with HNV. Table 1 shows the demographic and clinical characteristics of the patients. Of the 212 patients, 104 were male and 108 were female, with a male-to-female ratio of 0.96:1. Mean age of the patients at inclusion was 21.5 ± 12.0 years (range,

Table 1: Clinical characteristics of patients with HNO and patients with HNV

Characteristics	HNO (n = 111)	HNV (n = 101)
Sex (male/female), *n*	54/57	50/51
Age at onset of HN (years), mean ± SD	21.6 ± 12.6	17.8 ± 11.1
Duration of disease		
≤3 years	98 (88.3)	86 (85.1)
>3 years	13 (11.7)	15 (14.9)
Self-reported provoking factors for HN (n = 201)*	26 (24.5)	14 (14.7)
KP (n = 203)*†	2 (1.9)	19 (19.8)
Multiple HN	15 (13.5)	41 (40.6)
Pruritus preceding HN development (n = 201)	14 (13.3)	17 (17.7)
Accompanied lesional leukotrichia (n = 210)	55 (50.0)	57 (57.0)
Personal history of nonvitiligo autoimmune diseases		
Thyroid diseases	1 (0.9)	9 (8.9)
Alopecia areata	0	5 (5.0)
Allergic purpura	0	1 (1.0)
Family history of premature hair greying (n = 206)*‡	27 (25.0)	33 (33.7)
Family history of HN (n = 209)*	1 (0.9)	2 (2.0)
Family history of autoimmune diseases		
Vitiligo (n = 211)*	8 (7.3)	26 (25.7)
Autoimmune thyroid diseases (n = 208)*	9 (8.3)	13 (13.1)
Psoriasis (n = 209)*	1 (0.9)	1 (1.0)
Alopecia areata (n = 209)*	0	1 (1.0)
Systemic lupus erythematosus (n = 209)*	1 (0.9)	1 (1.0)
Rheumatoid arthritis (n = 209)*	0	1 (1.0)
Ankylosing spondylitis (n = 209)*	0	1 (1.0)

Data are shown as *n* (%) or otherwise noted. *Variance in the number of patients among different characteristics is due to missing data. †KP was defined as historical depigmentation at sites of friction/trauma. ‡The family history included relatives of three generations. HN: Halo nevus; KP: Koebner phenomenon; HNO: Halo nevus only; HNV: Vitiligo-associated halo nevus; SD: Standard deviation.

4–59 years), whereas mean age at onset of HN was 19.8 ± 12.0 years (range, 3–57 years). HNV patients had a significantly lower mean age at onset of HN (17.8 ± 11.1 years) than patients with HNO (21.6 ± 12.6 years). Approximately a quarter (26.4%, 56/212) of patients had multiple HN. Mild pruritus proceeding flares of halo formation developed in 15.4% (31/201) of patients, and the presence of KP was observed in 10.3% (21/203) of patients. Associated autoimmune diseases (AADs), including vitiligo (47.6%, 101/212), autoimmune thyroid diseases (4.7%, 10/211), alopecia areata (2.4%, 5/211), and anaphylactoid purpura (0.5%, 1/211), were present in 48.3% (102/211) of patients, with 6.2% (13/211) having more than one associated disease. Vitiligo (16.1%, 34/211) was the most common self-reported autoimmune family history, followed by thyroid diseases (10.6%, 22/208), other nonthyroidal autoimmune diseases (3.4%, 7/209), and HN (1.4%, 3/209). No patients had a family history of melanoma.

Stress (45.0%, 18/40) and physical factors (40.0%, 16/40) were the most mentioned triggering factors for HN, followed by sleep loss (32.5%, 13/40) and chemical factors (5.0%, 2/40). No significant difference was found regarding the presence of a provoking factor for the onset of HN between the HNO and HNV groups ($P = 0.083$).

Laboratory examinations were performed in 43.4% (92/212) of the patients, including 54 (48.7%) of the 111 HNO patients and 38 (37.6%) of the 101 HNV patients. Thyroid abnormalities were found in 14 (36.8%) of the 38 patients with HNV (36.8%) versus 9 of the 54 patients with HNO (16.7%) ($P = 0.028$). TSH abnormalities were found in 4 (10.5%) of the 38 HNV patients while none of the 54 HNO patients ($P = 0.026$). Three newly diagnosed cases were identified as overt and subclinical thyroid dysfunction.

Univariate analysis

Table 2 shows the results of univariate logistic regression analysis of the demographic and clinical characteristics between HNO and HNV patients. Although there was no significant difference in the distribution of sex, duration of disease (>3 years/≤3 years), presence of pruritus preceding the onset of HN, accompanied lesional leukotrichia, or family history of premature hair greying between the two groups, patients with HNV showed a trend toward a positive family history of premature hair greying.

KP and multiple HN were significantly more frequently observed in HNV patients than those in HNO patients ($OR = 11.221$, $P < 0.0001$ and $OR = 4.373$, $P < 0.0001$, respectively). There was also a significant difference in the presence of personal history of nonvitiligo autoimmune diseases between patients with HNO and those with HNV ($OR = 16.102$, $P = 0.008$). Patients with HNV were more likely to have a positive family history of vitiligo ($OR = 4.420$, $P = 0.001$).

Table 3 shows the location of HN lesions in our patient cohort. The most commonly involved site in HN was the head and neck, accounting for 58.6% (181/309) of all lesions and affecting 91 HNO patients and 58 HNV patients [Figure 1].

Table 2: Univariate analysis of factors affecting the presence of vitiligo in patients with HN

Variable	*OR* (95% *CI*)	*P*
Sex (male/female)	0.966 (0.564–1.657)	0.901
Age at onset of HN (>18 years/≤18 years)	0.537 (0.311–0.928)	0.026
Duration of disease (>3 years/≤3 years)	1.315 (0.592–2.918)	0.501
Self-reported provoking factors for HN (yes/no)	1.880 (0.916–3.861)	0.085
KP (yes/no)	11.221 (3.262–38.593)	<0.0001
Multiple HN (yes/no)	4.373 (2.230–8.578)	<0.0001
Preceding pruritus (yes/no)	0.767 (0.369–1.594)	0.477
Accompanied lesional leukotrichia (yes/no)	1.272 (0.740–2.186)	0.383
Personal history of nonvitiligo autoimmune diseases (yes/no)	16.102 (2.066–125.489)	0.008
Autoimmune thyroid diseases (yes/no)	10.761 (1.338–86.520)	0.025
Nonthyroid autoimmune diseases (yes/no)	NA	NA
Family history of premature hair greying (yes/no)	1.584 (0.869–2.885)	0.133
Family history of HN (yes/no)	2.268 (0.203–25.402)	0.506
Family history of autoimmune diseases (yes/no)	2.969 (1.553–5.678)	0.001
Vitiligo (yes/no)	4.420 (1.896–10.307)	0.001
Autoimmune thyroid diseases (yes/no)	1.693 (0.691–4.152)	0.250
Nonthyroid and nonvitiligo autoimmune diseases (yes/no)	1.860 (0.433–7.991)	0.404

NA: Not available; HN: Halo nevus; *OR*: Odd ratio; *CI*: Confidence interval; KP: Koebner phenomenon.

Table 3: Location of the lesions in the HNO and HNV groups, *n* (%)

Location	HNO ($n = 111$)	HNV ($n = 101$)
Head and neck	91 (82.0)	58 (57.4)
Trunk	25 (22.5)	55 (54.5)
Limbs	4 (3.6)	19 (18.8)
Hands and feet	0	0

HNO: Halo nevus only; HNV: Vitiligo-associated halo nevus.

Of the 91 HNO patients with the head and neck involved, eight also had other sites affected. Of the 58 HNV patients having the nevi on the head and neck, 22 had other sites involved. None of the lesions occurred on the hands or feet.

Multivariate analysis

As shown in Table 4, multivariate analysis demonstrated that KP, the number of HN (≥2), and a family history of vitiligo were independent factors associated with the presence of vitiligo in patients with HN.

Discussion

To date, there have been few data regarding the precipitating factors and concomitant autoimmune diseases in patients

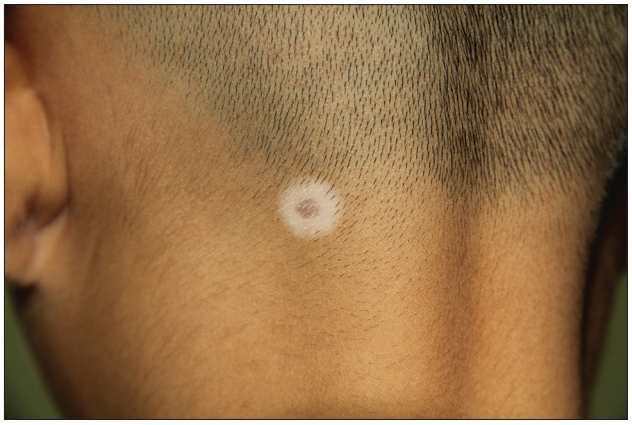

Figure 1: Halo nevus on the left occipital region of a patient.

Table 4: Multivariate logistic regression analysis of factors affecting the presence of vitiligo in patients with HN (*n* = 199)

Variable	*OR* (95% *CI*)	*P*
KP	10.632 (2.964–38.137)	<0.0001
Multiple HN (≥2)	3.918 (1.869–8.215)	<0.0001
Family history of vitiligo	3.222 (1.264–8.212)	0.014

HN: Halo nevus; *OR*: Odds ratio; *CI*: Confidence interval; KP: Koebner phenomenon.

with HN, especially Asian populations due to the lower incidence of HN in this region.[12] Few studies have been performed to identify the risk factors for the development of vitiligo in HN patients. To fill this research gap, the present study explored the association between HN and vitiligo, using uni- and multi-variate logistic regression analyses.

The exact etiology and pathogenesis of HN remain obscure, although the involvement of $CD8^+$ cytotoxic T-cell activity in the destruction of both nevus melanocytes and adjacent epidermal melanocytes seems evident.[3,5] However, the precipitating factors and antigens that trigger the immune reaction in HN are currently unknown.[13] Regarding patient-reported triggering factors, our results agree with previous studies that reported stress as the most common triggering factor for HN.[9] Stress can promote the production of pro-inflammatory cytokines (interleukin [IL]-6, IL-1, and tumor necrosis factor [TNF]-α) to lead to pro-inflammatory status, which may result in a widespread enhancement of the immune responses and inflammatory activity in susceptible individuals,[14] thus increasing the possibility of intolerance to self-antigens. Furthermore, another common patient-mentioned provoking factor for HN was physical trauma (including scratching and friction), which could injure the nevus cells and cause the release of some covert autoantigens by nevomelanocytes and the subsequent inflammatory infiltration. These antigens can trigger the activation of the innate/adaptive immune systems, further injuring the melanocytes. Based on these findings on patient-reported provoking factors, we surmise that environmental stress, which can lead to chronic systemic inflammation, and local irritation, which can activate the innate immune system, may be two significant synergistic causative factors to precipitate or aggravate HN in individuals with genetic susceptibility.

Consistent with the findings by Van Geel *et al*.[9] and Zhang *et al*.,[8] we found that the average onset of HN was significantly lower in HNV patients than that in HNO patients. This finding suggests that earlier onset age of HN might be associated with a higher risk of developing vitiligo. Interestingly, another research focusing on pre- and post-pubertal onset of vitiligo suggested that a greater genetic component can be found in prepubertal than in postpubertal onset vitiligo.[10] Collectively, we speculate that earlier onset of HN may be associated with a more powerful genetic constituent of autoimmunity targeting nevoid melanocytes.

As to the location of HN, previous studies in the Caucasian population suggested that HN usually affects the trunk.[1,7] In the present study, the head and neck was found to be the most commonly involved site, followed by the trunk. This finding is similar to another study on Asians.[15] This discrepancy between Caucasians and Asians is probably due to the fact that discoloration is more easily visible in Asians, who have darker skin than Caucasians. Especially, when the lesions are located on the areas that are easily perceived, the patients are more likely to seek medical treatment.

HN can be single or multiple, with multiple lesions occurring in 20–50% of patients. In our series, 26.4% of patients demonstrated multiple lesions, the majority (73.2%) of which had concomitant vitiligo. A positive association between multiple HN and vitiligo remained after adjusting for all other confounding factors in the multivariate analysis. Multiple involvement might be related to the presence of nevomelanocyte-specific T-cells homing to the skin and/or circulating autoantibodies targeting nevomelanocytes in the blood circulation,[3,16] either of which may destroy the same antigens shared between nevomelanocytes and adjacent epidermal melanocytes. Similar to our results, a long-term follow-up study on pediatric patients from Italy[7] and a study from China[8] also indicated that multiple rather than single HN is more frequently associated with vitiligo, although another study suggested that the presence of ≥3 HN apparently lowers the risk of developing vitiligo.[9] Future studies with greater sample sizes and longer follow-up periods are needed to address this discrepancy.

In contrast to other chronic skin conditions such as psoriasis,[17] HN was not epidemiologically linked to inflammation due to the lack of prominent signs of erythema and edema. However, our finding showed that 16.2% of patients with HN reported mild pruritus preceding flares of depigmentation, suggesting that HN might be related to the intense inflammatory infiltrate around the central nevus.

In terms of KP, our multivariate logistic regression model indicated that the presence of KP in HN patients is highly suggestive of an increased risk of developing vitiligo. KP is often considered a sign of more active or extensive condition.

Immunological, neural, and vascular mechanisms as well as oxidative stress have been suggested to play a role in the etiology and pathogenesis of KP.[18,19] Various reports suggested that multiple contributing factors, including disease severity,[18] skin injury,[19] and emotional stress,[20] may trigger KP. These are all nonspecific stimuli, which generally induce inflammatory reactions, promote the release of common inflammatory factors (e.g., TNF-α, IL-6, and heat shock proteins), and initiate the specific immune attacks targeting melanocytes through multiple integrated mechanisms, based on the proposed two-step hypothesis of the KP in vitiligo.[19] As indicated by our previous research[21] and Mooney *et al*.'s[22] histopathological study, intradermal nevi, usually elevated from the skin surface, are the predominant histological subtype of central nevi. Therefore, it is recommended that genetically susceptible individuals should avoid any physical-mechanical challenge such as scratching or friction on melanocytic nevi, which might lead to the risk of KP and subsequent specific immune targeting of melanocytes.

AADs, especially thyroid diseases, were significantly more frequently observed in HNV patients compared with HNO patients. Since vitiligo is closely associated with autoimmune thyroid diseases epidemiologically, immunologically, and genetically,[23-26] we recommend assessing thyroid dysfunction and autoantibodies in patients with HN to estimate the risk of future vitiligo. HN patients with abnormal thyroid test results, which highly suggest an increased risk of vitiligo, should be monitored closely and given education to avoid environmental triggers such as sunburn, stress, and physical irritation. As all our patients did not undergo laboratory investigations, we failed to investigate laboratory thyroid parameters in our multivariate analysis.

Given several significant differences found between HNO and HNV patients in our study and the proof from other epidemiological and experimental studies that strongly supports that HN and vitiligo are two distinct entities,[9,27-30] we agree with van Geel *et al*.'s[9] opinion that HN should be viewed as a distinct entity, namely, a disease predisposing toward vitiligo, not a sign of vitiligo. We consider that these two conditions might be the two ends of the spectrum, with HNO on one end ("mild end", local immune response) and vitiligo on the other end ("severe end", widespread autoimmunity).

This study has several limitations. Due to its retrospective nature, possible recall errors might have occurred. Furthermore, there was a selection bias toward more cases with vitiligo. In addition, only a portion of our patients underwent laboratory investigations.

In summary, the present study shows that HNO and HNV have distinctive clinical features. KP, multiple HN, and a family history of vitiligo are the risk factors for vitiligo in HN patients. HN patients with two or more involved nevi, KP, or familial background of vitiligo may carry an increased risk of developing vitiligo.

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Conflicts of interest

There are no conflicts of interest.

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