

# Halo Nevi Association in Nonsegmental Vitiligo Affects Age at Onset and Depigmentation Pattern

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**Objective:** To compare factors associated with halo nevi with nonsegmental vitiligo (NSV) vs NSV alone.

**Design:** Prospective observational study in 553 patients with a confirmed diagnosis of NSV attending a vitiligo clinic between January 1, 2006, and July 1, 2010.

**Setting:** Vitiligo Clinic at the Department of Dermatology, University Hospital Center of Bordeaux, Bordeaux, France.

**Patients:** The Vitiligo European Task Force questionnaire was informed for each patient attending the clinic with a confirmed diagnosis of NSV after the exclusion of other forms of vitiligo (focal, mucosal, and not classifiable). Thyroid function and antithyroid antibodies were screened if not obtained in the previous year.

**Main Outcome Measures:** Extent of disease and markers of autoimmunity or autoinflammation.

**Results:** Of the 553 patients, 130 had halo nevi–NSV and 423 had NSV. Family history of premature hair graying (odds ratio, 1.74;  $P < .01$ ) was positively associated with halo nevi–NSV by univariate analysis. Using multivariate analysis, age at onset younger than 18 years, phototype, total body area, localization on the trunk, involvement of hands and feet, and total staging were found to be independent factors. Age at onset younger than 18 years; phototypes I, II, and III; trunk involvement; and staging were positively associated with halo nevi–NSV, whereas this association was negative for total affected area and involvement of hands and feet.

**Conclusions:** Halo nevi association in NSV affects age at onset and depigmentation pattern and has a stronger link with familial premature hair graying, suggesting that premature hair graying may involve, at least partly, an autoimmune pathway.

*Arch Dermatol.* 2012;148(4):497-502

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**A** HALO NEVUS (HN) IS USUALLY an acquired melanocytic nevus, which can be a junctional, dermal, or compound nevus, surrounded by a white depigmented circle. Congenital nevi may also present a halo phenomenon. During its clinical course, an HN may progress up to complete clearing of the nevus. In 1916, Sutton<sup>1</sup> described this entity under the name “leukoderma acquisitum centrifugum,” and later, the term *Sutton nevus* was used among dermatologists. In 1964, Frank and Cohen<sup>2</sup> used the term *halo nevus* regarding the white depigmented circle surrounding the nevus. Both terms, *halo nevus* and *Sutton nevus*, are currently used to refer to this clinical entity. The prevalence of HNs in the white general population is 1%,<sup>3,4</sup> and HNs usually appear in childhood or early adulthood. In HNs, the diameter of the depigmented circle varies from less than 1 mm to several centimeters.<sup>5</sup> The size of the nevus itself is also

highly variable and ranges from a few millimeters to several centimeters. The clinical aspects of the HN may vary greatly according to the stage of the depigmenting process. In addition, in an individual with multiple HNs, different stages can be observed for the halos and the nevi.<sup>6</sup>

The link between vitiligo and HN has been studied because of its striking clinical association. Some researchers have proposed that HN could be a risk factor for vitiligo<sup>7</sup> and, furthermore, that HN could be a clinical sign of vitiligo. However, some cases of extensive vitiligo clearly spare melanocytic nevi.<sup>6</sup> In this context, whether nonsegmental vitiligo associated with HN (HN-NSV) is different from NSV not associated with HNs was previously investigated by only 1 other group. In this study, van Geel et al<sup>8</sup> described the prognostic value and clinical significance of HNs in their patients with vitiligo.

We herein present the result of a prospective observational study aimed at identifying weighted factors associated with

## METHODS

We conducted an observational study in the setting of a prospective cohort of patients attending the Vitiligo Clinic at the Department of Dermatology, University Hospital Center of Bordeaux, Bordeaux, France, between January 1, 2006, and July 1, 2010. The study was approved by the local ethics committee of the University Hospital of Bordeaux, France. All the patients with a diagnosis of NSV were enrolled in the present study. Nonsegmental vitiligo was defined as an acquired progressive bilateral hypomelanosis according to the Vitiligo European Task Force (VETF) definition.<sup>8</sup> Mixed vitiligo, that is, the association of a characteristic segmental involvement associated usually in a second step with the onset of bilateral vitiligo patches,<sup>9</sup> and other forms of vitiligo (segmental, focal, mucosal, and not classifiable) were excluded. The VETF questionnaires were completed for each patient attending the clinic at the first visit.<sup>8</sup> The VETF form provides a wide range of demographic and clinical information, including sex, age, age at onset of leukoderma, phototype, site of involvement and distribution patterns, Koebner phenomenon (defined as depigmentation on scars), presence of HNs, family history of vitiligo, personal or family history of chronic autoimmune/autoinflammatory diseases (autoimmune thyroiditis, atopic dermatitis, psoriasis, rheumatoid arthritis, type 1 diabetes mellitus, alopecia areata, sarcoidosis, systemic lupus erythematosus, Addison disease, and Crohn disease), family history of premature hair graying (PHG) (>50% white hair before age 40 years) with family trees if needed, emotional stress at onset, and response to treatment, if any. Finally, staging and spreading were assessed as recommended by the VETF group after natural light and Wood lamp examination.<sup>9</sup> This evaluation individually assesses 5 body regions (head and neck, trunk, upper and lower extremities, hands, and feet) for (1) extent of disease (affected body surface, percentage scored 0% to 100%), (2) stage of disease (staging) (normal pigmentation/incomplete depigmentation/complete depigmentation/complete depigmentation plus partial leukotrichia/complete depigmentation plus complete leukotrichia) (scored 0-4), and (3) disease progression (spreading) (regressive is scored -1; stable, or 0; progressive, 1). A total score for staging and spreading was determined, with values ranging from 0 to 16 for staging and from -5 to 5 for spreading.

Descriptive characteristics were first assessed according to the presence vs absence of HNs. Basic summary statistics, such as proportions, means, and standard deviations, were used to characterize population attributes. To identify factors associated with HN-associated NSV and NSV without a history of HN, comparisons between groups were conducted by univariate and multivariate unconditional logistic regression. All potential predictors of HN-NSV and NSV were first assessed individually, and odds ratios (ORs), corresponding 95% CIs, and *P* values were computed. The OR significance was determined by Wald test  $\chi^2$ , and predictors with *P* < .20 were subsequently assessed using multivariate analysis with a forward stepwise selection procedure. Possible interactions and multicollinearity were examined; when 2 or more potential factors risk were highly correlated, the predictor that was known as being more clinically important was selected for entry. Finally, the goodness of fit of the final model was assessed by using the logistic regression diagnostics procedure. *P* ≤ .05 was considered statistically significant. The Hosmer-Lemeshow test was performed to test the adequation of the model. Statistical analyses were performed using a commercially available software program (SAS, version 9.1.3; SAS Institute, Inc, Cary, North Carolina).

## RESULTS

### PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

A total of 553 patients were included: 189 males and 364 females (male to female ratio, 1 to 2). Of the 553 patients, 130 had associated HNs (23.5%) and 423 had no HNs (76.5%). The mean (SD) age of patients at inclusion was 32.15 (18.46) years (age range, 1-74 years), whereas the mean (SD) age at onset of vitiligo was 22.46 (16.09) years (age range, 0.25-73 years). Moreover, patients with HN-NSV had a significantly lower mean (SD) age at onset of disease (15.02 [13.08] years). The descriptive characteristics of patients with HN-NSV and NSV alone are given in **Table 1**.

### UNIVARIATE ANALYSIS

Results of univariate logistic regression of HN-NSV vs NSV for patient characteristics are given in **Table 2**. There was no significant statistical difference for items such as sex and pruritus preceding onset, which may relate to inflammation or autoimmunity. Patients with NSV tended to more frequently have a history of thyroid disease (OR, 1.61, *P* = .07), although there was no significant difference for the presence of antithyroid antibodies between HN-NSV and NSV.

Patients with HN-NSV were more likely to have disease onset before age 18 years (OR, 3.46; *P* < .001). Family history of PHG (OR, 1.74; *P* < .01) was positively associated with HN-NSV, whereas patients with NSV alone had greater surface involvement compared with those with HN-NSV (OR, 1.03; *P* < .01). In addition, trunk involvement was positively associated with HN-NSV (OR, 3.05; *P* < .001), as opposed to acral involvement (ie, hands and feet), which tends to be more frequent in patients with NSV compared with patients with HN-NSV (OR, 1.53; *P* < .07). Moreover, although there was no significant difference in family history of vitiligo between HN-NSV and NSV, a familial background of autoimmune diseases was more frequent in patients with HN-NSV compared with those with NSV (OR, 1.98; *P* = .02). In addition, Fitzpatrick phototypes I, II, and III were more frequent in patients with HN-NSV than in those with NSV (OR, 2.65; *P* < .001). We found HNs to be present in 22 of 97 patients (23%) with phototypes I and II, 91 of 343 (27%) with phototype III, 5 of 34 (15%) with phototype IV, and 9 of 84 (11%) with phototypes V and VI.

### MULTIVARIATE ANALYSIS

When conducting multivariate analysis, age at onset younger than 18 years, phototype, total body area, localization on the trunk, involvement of hands and feet, and total staging were all found to be independent factors, namely, age at onset younger than 18 years; phototypes I, II, and III; trunk involvement; and staging were positively associated with HN-NSV, whereas this association was negative for total affected area and involvement of hands and feet (**Table 3**).

**Table 1. Repartition of Individual Features of 553 Patients With Halo Nevi–Associated Nonsegmental Vitiligo vs Nonsegmental Vitiligo Alone**

Feature	Halo Nevus		
	No (n=423)	Yes (n=130)	Total (N=553) <sup>a</sup>
Sex, No. (%)			
Male	150 (35.5)	39 (30.2)	<b>189</b> (34.2)
Female	273 (64.5)	90 (69.8)	<b>363</b> (65.8)
Disease activity in the past 6 mo progressive, No. (%)			
Progressive stable or regressive	286 (69.1)	96 (73.8)	<b>382</b> (70.2)
Stable/regressive	128 (30.9)	34 (26.2)	<b>162</b> (29.8)
Previous episode of repigmentation, No. (%)			
No	180 (44.6)	57 (44.9)	<b>237</b> (44.6)
Yes	224 (55.4)	70 (55.1)	<b>294</b> (55.4)
Depigmentation on scars (Koebner phenomenon), No. (%)			
No	204 (51.6)	74 (58.3)	<b>278</b> (53.3)
Yes	191 (48.4)	53 (41.7)	<b>244</b> (46.7)
Stress as onset factor, No. (%)			
No	176 (43.7)	65 (52.4)	<b>241</b> (45.7)
Yes	227 (56.3)	59 (47.6)	<b>286</b> (54.3)
Pruritus before hypopigmentation, No. (%)			
No	314 (78.3)	101 (80.2)	<b>415</b> (78.7)
Yes	87 (21.7)	25 (19.8)	<b>112</b> (21.3)
Thyroid disease, No. (%)			
No	285 (75.6)	100 (83.3)	<b>385</b> (77.5)
Yes	92 (24.4)	20 (16.7)	<b>112</b> (22.5)
Family history of autoimmune disease, No. (%)			
No	225 (53.2)	55 (42.3)	<b>280</b> (50.6)
Yes	198 (46.8)	75 (57.7)	<b>273</b> (49.4)
Family history of vitiligo, No. (%)			
No	275 (66.6)	85 (66.9)	<b>360</b> (66.7)
Yes	138 (33.4)	42 (33.1)	<b>180</b> (33.3)
Presence of antithyroid antibodies, No. (%)			
No	185 (62.7)	68 (66.7)	<b>253</b> (63.7)
Yes	110 (37.3)	34 (33.3)	<b>144</b> (36.3)
Personal history of autoimmune disease, No. (%)			
No	257 (60.8)	82 (63.1)	<b>339</b> (61.3)
Yes	166 (39.2)	48 (36.9)	<b>214</b> (38.7)
Family history of premature hair graying, No. (%)			
No	280 (69.5)	71 (56.3)	<b>351</b> (66.4)
Yes	123 (30.5)	55 (43.7)	<b>178</b> (33.6)
Phototype, No. (%)			
I-III	317 (75.3)	113 (89.0)	<b>430</b> (78.5)
IV-VI	104 (24.7)	14 (11.0)	<b>118</b> (21.5)
Head and neck, No. (%)			
No	68 (17.0)	25 (19.8)	<b>93</b> (17.7)
Yes	332 (83.0)	101 (80.2)	<b>433</b> (82.3)
Hands and feet, No. (%)			
No	85 (21.2)	37 (29.1)	<b>122</b> (23.1)
Yes	316 (78.8)	90 (70.9)	<b>406</b> (76.9)
Trunk, No. (%)			
No	157 (39.1)	22 (17.3)	<b>179</b> (33.8)
Yes	245 (60.9)	105 (82.7)	<b>350</b> (66.2)
Limbs, No. (%)			
No	98 (24.4)	25 (19.7)	<b>123</b> (23.3)
Yes	303 (75.6)	102 (80.3)	<b>405</b> (76.7)
Genitals, No. (%)			
No	205 (52.0)	70 (55.6)	<b>275</b> (52.9)
Yes	189 (48.0)	56 (44.4)	<b>245</b> (47.1)
Age at visit, mean (SD), y	35.57 (17.68)		
Age at onset, mean (SD), y	24.79 (16.25)	21.05 (16.54)	32.15 (18.46)
Total affected area, mean (SD)	8.27 (12.34)	15.02 (13.08)	22.46 (16.09)
Staging, mean (SD)	4.99 (2.86)	5.54 (7.92)	7.60 (11.48)
Spreading, mean (SD)	1.26 (1.98)	6.09 (2.70)	5.26 (2.86)

<sup>a</sup>Due to possible missing data, the sum of each variable did not always match the total number of patients in the column totals (N=553).

**Table 2. Univariate Logistic Regression for Halo Nevus Occurrence in a Population of Nonsegmental Vitiligo**

Feature	Halo Nevus (Yes/No)		
	OR (95% CI)	Patients, No. <sup>a</sup>	P Value (Wald Test)
Sex (M/F)	1.268 (0.829-1.940)	552	.27
Disease activity in the past 6 mo (yes/no)	0.791 (0.508-1.233)	544	.30
Previous episode of repigmentation (yes/no)	0.987 (0.661-1.474)	531	.95
Depigmentation on scars (Koebner phenomenon)	0.765 (0.511-1.146)	522	.19
Stress as onset factor (yes/no)	0.704 (0.470-1.054)	527	.09
Pruritus before depigmentation (yes/no)	0.893 (0.543-1.470)	527	.65
Thyroid disease (yes/no)	0.620 (0.363-1.057)	497	.07
Presence of antithyroid antibodies (yes/no)	0.841 (0.523-1.352)	397	.47
Personal history of autoimmune disease (yes/no)	0.906 (0.604-1.360)	553	.63
Family history of premature hair graying (yes/no)	1.764 (1.169-2.660)	529	<.01
Family history of vitiligo (yes/no)	0.985 (0.645-1.502)	540	.94
Family history of autoimmune disease (yes/no)	1.550 (1.042-2.305)	553	.03
Phototype (I, II, III/IV, V, VI)	2.648 (1.456-4.815)	548	<.001
Head and neck (yes/no)	0.827 (0.497-1.377)	526	.47
Hands and feet (yes/no)	0.654 (0.417-1.028)	528	.07
Trunk (yes/no)	3.058 (1.852-5.049)	529	<.001
Limbs (yes/no)	1.320 (0.806-2.161)	528	.26
Genitals (yes/no)	0.868 (0.580-1.299)	520	.49
Age at visit (<18 y/≥18 y)	6.641 (4.329-10.189)	553	<.001
Age at onset (<18 y/≥18 y)	3.458 (2.265-5.280)	547	<.001
Total affected area (for a 1% increase step)	0.973 (0.951-0.996)	510	.02
Staging (≤3/>3)	2.682 (1.607-4.478)	520	<.001
Spreading (<0/≥0)	1.458 (0.941-2.259)	502	.09

Abbreviation: OR, odds ratio.

<sup>a</sup>Due to possible missing data, the sum of each variable did not always match the total number of patients reported in this column (N=553).**Table 3. Multivariate Logistic Regression for Halo Nevus Occurrence in a Population of Nonsegmental Vitiligo (n = 494)**

Feature	Halo Nevus (Yes/No)	
	OR (95% CI)	P Value
Age at onset (≥18 y/<18 y)	0.39 (0.24-0.63)	<.001
Phototype (I, II, III/IV, V, VI)	0.26 (0.13-0.52)	<.001
Total affected area (for a 1% decrease step)	1.05 (1.02-1.08)	<.001
Trunk (no/yes)	0.37 (0.21-0.66)	<.001
Staging (≤3/>3)	0.38 (0.20-0.71)	<.01
Hands and feet (no/yes)	1.89 (1.08-3.32)	.02

Abbreviation: OR, odds ratio.

**COMMENT**

Compared with segmental vitiligo, NSV is more often associated with an autoimmune background. We recently showed<sup>10</sup> that some clinical items collected in the VETF assessment form, namely, pruritus before depigmentation, HNs, and thyroid autoantibodies, which may relate to the autoimmune/autoinflammatory diathesis, are strongly linked to NSV together with a positive familial background of vitiligo and autoimmune diseases. Specifically, HN is a clinical marker of cellular immune response against abnormal melanocytic cells, nevocytes, which may indirectly pertain to the process targeting normal melanocytes in vitiligo. Nonsegmental vitiligo is clinically heterogeneous in terms of clinical presentation and outcomes. Whether HN-NSV has distinct clinical fea-

tures and prognosis needs to be confirmed because the relationship between HN and NSV has not been studied so far using weighted factors for HN-NSV vs NSV in isolation, although the prognostic value and clinical significance of HNs were investigated in 1 other study so far.<sup>8</sup> The present study shows that HN-NSV is associated with distinctive clinical features when performing multivariate analysis in a carefully studied monocentric cohort.

As suggested by the results of an earlier study,<sup>11</sup> body surface area involvement was lower in HN-NSV. We also found trunk (the most common site of HNs) to be more frequently involved in HN-NSV than in NSV alone. On the contrary, involvement of the hands and feet was negatively associated with HN-NSV. These findings are in line with a recently published study<sup>12</sup> that describes in a subset of patients with HN discrete depigmentations at a close distance from HNs. According to the investigators,<sup>12</sup> this collateral damage may result from skin immunosurveillance, with clinical consequences on the evolution pattern of this subset of patients.

In another recently published study, van Geel et al<sup>8</sup> found that the first sign of leukoderma, whether vitiligo or HNs, was earlier in patients with HN-NSV vs those with NSV. Similarly, we found an earlier age at NSV onset in patients with HN. This finding should be reconsidered based on a recent genome-wide association study in which the 2 disease subtypes, that is, NSV and HN-NSV, have not been differentiated. The major histocompatibility complex class II region, in contrast with the major histocompatibility complex class I region (which is associated with NSV susceptibility per se), is associated

with NSV age at onset in white individuals.<sup>13</sup> Moreover, de Vijlder et al<sup>11</sup> also noticed a negative association between certain HLA class II subtypes in HN-NSV compared with in NSV alone.

In the univariate analysis, we also found that patients with HN-NSV have a more frequent familial background of autoimmunity, although there was no significant difference for personal history of autoimmunity. This latter finding is similarly directed or partially overlapping with a previous study that found personal background of autoimmunity to be more frequent in patients with NSV vs those with HN-NSV or HN alone.<sup>8</sup> Concerning the familial background of autoimmunity, the reliability of a family history for autoimmune disease is low, and its value can be questionable. However, the latter study<sup>8</sup> was performed on a smaller sample and was restricted to some statistical analysis ( $\chi^2$  test, Mann-Whitney test, and the Kruskal-Wallis test for comparison between >2 different groups).

We also found HNs to be more often present in fair-skinned patients (phototypes I, II, and III) vs dark-skinned patients (phototypes IV, V, and VI). Skin phototype is mainly driven by the balance between eumelanin and pheomelanin. Pheomelanin is prominent in fair phototypes, whereas eumelanin is the major component in dark-skinned individuals. The finding that HN-NSV is more frequent in lighter skin phototypes might be related to the fact that dark-skinned individuals tend to develop fewer melanocytic nevi.<sup>14-16</sup> An additional hypothesis is that pheomelanin is prone to generate more UV-related stress responses and immunogenicity, leading to HNs. Indeed, these 2 types of melanin react differently in response to UV: eumelanin acts as a photoprotective antioxidant and pheomelanin exhibits phototoxic pro-oxidant behavior.<sup>17-21</sup> If pheomelanin and eumelanin are present in all skin phototypes, the ratio of pheomelanin to total melanin is higher in patients with lighter phototypes (ie, phototypes I, II, and III), and the induction of cyclobutane pyrimidine dimers and 6-4 photoproducts is inversely correlated with the phototype of origin of cultured melanocytes.<sup>19,22</sup> Consequently, this may affect melanocyte survival and the possible release of melanocytic immunogenic proteins.

Moreover, we found that a family history of PHG was positively associated with HN-NSV. Premature hair graying is an inherited trait. Specifically, hair graying is probably linked to an early reduction in tyrosinase activity in hair bulbar melanocytes associated with inappropriate melanocyte-cortical keratinocyte interactions and defective migration of melanocytes to the follicular papilla of the hair bulb.<sup>23,24</sup> An autoimmune/autoinflammatory cause is usually not considered for PHG. However, the positive association between HN-NSV and PHG should be reexamined based on genome-wide association study data, which found a susceptibility variant for NSV in the tyrosinase gene (*TYR*) in white Europeans. The major (*Arg*) allele of single-nucleotide polymorphism rs1126809, a common nonsynonymous (*Arg402Gln*) polymorphism, is associated with NSV in white Europeans. In contrast, the minor (*Gln*) allele, which is protective with respect to NSV, is associated with susceptibility to malignant melanoma in the same population. The *TYRArg402Gln*

polymorphism thus represents an inverse relationship between NSV and malignant melanoma<sup>25</sup> and suggests that the susceptibility variants govern normal immunosurveillance against the melanocytic system. A subset of PHG might, thus, be reconsidered as an immune process targeting inappropriately specifically the hair follicle melanocytic compartment. To what extent the higher propensity to target the hair follicle in HN-NSV (because the higher staging scores found in the NSV subset in this study are related to leukotrichia) is associated with this positive family history of PHG is intriguing. Premature leukotrichia/canities is not a usual feature in patients with NSV, suggesting that the vitiligo immune responses may target differentiated melanocytes rather than amelanotic follicular precursors. Furthermore, the finding of a positive association of PHG with HN-NSV suggests searching for PHG in the context of risk of melanoma.

Based on these results, we hypothesize that HN-NSV and NSV can be considered of inflammatory/autoimmune origin but with possible differences in the recognition pattern of melanocytic antigens (hair follicle compartment/interfollicular compartment, the former being more involved in HN-NSV than in NSV in isolation) and possibly in the circulation pattern of skin lymphocytes in charge of the immune surveillance of the various skin territories. The argument for the latter point is that HNs are mostly situated in nonacral areas and that vitiligo lesions in this setting have a more central distribution. In the context of a possible stronger natural cutaneous immunosurveillance, HN-NSV might be initiated by an immune response first directed against nevocellular targets with a collateral damage of surrounding melanocytes belonging to the same territory of circulation, as hypothesized for segmental vitiligo.<sup>26</sup> Moreover, the strong link that we found between HN-NSV and PHG may suggest that the latter may involve an autoimmune process. Further epidemiologic studies more accurately accounting for the chronological order of HN-NSV or NSV-HN may be of interest for confirming the hypotheses.

**Accepted for Publication:** August 4, 2011.

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**Author Contributions:** Drs Ezzedine and Taieb had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Ezzedine and Diallo. *Acquisition of data:* Ezzedine, Léauté-Labrèze, Seneschal, Mossalayi, AlGhamdi, Prey, Bouchtnei, Cario-André, Boralevi, Jouary, and Taieb. *Analysis and interpretation of data:* Ezzedine and Diallo. *Drafting of the manuscript:* Ezzedine and Diallo. *Critical revision of the manuscript for important intellectual content:* Ezzedine, Diallo, Léauté-Labrèze, Seneschal, Mossalayi, AlGhamdi, Prey, Bouchtnei, Cario-André, Boralevi, Jouary, and Taieb. *Statistical analysis:* Ezzedine and Diallo.

**Financial Disclosure:** None reported.

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