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ORIGINAL ARTICLE

Risk factors and treatment responses in patients with vitiligo in Japan—A retrospective large-scale study

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Abstract Vitiligo is a refractory skin disease. To investigate the risk factors and treatment responses of patients with vitiligo in Japan, we recorded and analyzed the details of 713 vitiligo patients (comorbidity, treatment responses, family history, age, and sex) who visited the dermatology clinic of the Nagoya City University Hospital, Nagoya, Japan between January 2004 and August 2010 (mean age, 35.2 years; 302 men, 411 women) using logistic regression analysis. The results are expressed as odds ratios (OR) with 95% confidence interval (CI). Patients were diagnosed with vitiligo [$n = 644$; 338 generalized type (47.4%), 170 segmental type (23.8%), and 136 localized type (19.1%)], nevus depigmentosus ($n = 53$, 7.4%), halo nevus ($n = 14$, 2.0%), and hypomelanosis of Ito ($n = 2$, 0.3%). For generalized and localized types, none of the analyzed factors were statistically significant. For the segmental type, antinuclear antibody (OR = 1.005; 95% CI, 1.00–1.01; $p < 0.05$) and onset age < 14 years were the significant factors in patients between 15 years and 29 years (OR = 0.246; 95% CI, 0.113–0.538; $p < 0.001$), 30–54 years (OR = 0.0419; 95% CI, 0.0133–0.132; $p < 0.001$), and >55 years (OR = 0.0171; 95% CI, 0.00333–0.0879; $p < 0.001$). The treatment response rates for narrow-band UV-B, topical vitamin D_3, and punch graft (1 mm minigraft) were, respectively, as follows: (1) generalized type: 46.3%, 21.1%, and 38.9%; (2) segmental type: 20.3%, 29.0%, and 77.3%; and (3) localized type: 29.2%, 54.8%, and 73.3%. We report the comorbidities and efficacy rates of these treatments. The response data for these treatments, in particular, would be of assistance to the previous explanations, because there were only a few reports

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on the response data for these treatments. The appropriate treatment should be selected depending on the type of vitiligo.

Introduction

Vitiligo is a refractory skin disease in which risk factors and treatment modalities are not yet established. There are three clinical types of vitiligo: (1) generalized type, which spreads widely over the body; (2) segmental type, which spreads along the course of a nerve; and (3) localized type, which is unclassifiable and can develop into either generalized or segmental type in the future [1]. The efficacy of treatment was different for each type [2]. Some large-scale studies were conducted in Brazilian and Chinese populations [3,4]. In these studies, the risk factors of vitiligo included thyroid dysfunction and type 1 diabetes mellitus. In Japan, Narita et al [5] reported on the comorbidities and family history 133 vitiligo patients. Zaima and Koga [1], meanwhile, conducted a long-term follow-up of about 44 localized vitiligo cases. In this study, the data of >700 patients were collected and analyzed, although there was no such large-scale study in Japan. To investigate the risk factors and treatment responses of patients with vitiligo in Japan, we analyzed the data of vitiligo patients who visited our dermatology clinic (Nagoya City University Hospital, Nagoya, Japan).

Patients and methods

A total of 713 patients of Japanese origin with a chief complaint of depigmentation (mean age, 35.2 years; 302 men, 411 women) were recruited for the study. Of these, 69 patients were excluded because they were diagnosed to have other depigmented diseases [nevus depigmentosus ($n = 53$, 7.4%), halo nevus ($n = 14$, 2.0%), and hypomelanosis of Ito ($n = 2$, 0.3%)]. Therefore, we analyzed the details of 644 vitiligo patients [generalized type, 338 (47.4%); segmental type, 170 (23.8%); localized type, 136 (19.1%)], including their background, comorbidities, treatment responses, family history, age, and sex (Table1). Furthermore, multivariable logistic regression analysis comparing segmental vitiligo against other types was performed. As an evaluation for narrow-band UV-B therapy and topical vitamin D_3 therapy, when the pigmentation was found in the treatment area, the case was evaluated as effective; if not, the case was considered not effective. The accumulative dose of narrow-band UV-B was between 5.5 J/cm^2 and 25 J/cm^2. The 1-mm minigraft therapy was one of the surgical treatment options for vitiligo. The skin donor site was the abdomen, and full-thickness grafts were obtained using a 1-mm punch (Kai Industry, Seki, Japan) following the administration of local anesthesia or full anesthesia. Using the 1-mm punch, holes were made in the vitiligo lesions with 3–5 mm between them. After hemostasis, the grafts were implanted into the holes. Overall, 3–200 grafts were done for each case. In the 1-mm minigraft therapy, when the stable pigmentation was found around the transplanted point, that case was evaluated as effective; if not, that case was evaluated as not effective. We determined the effect of topical therapy after 6 months and that of narrow-band UV-B after 30 irradiations. The effect of 1-mm minigraft therapy was determined after 1 month. A total of 323 cases (head and neck, 148 cases; body, 144 cases; extremities, 31 cases) treated using at least one of these methods were analyzed based on their location. All treatment methods were explained to the patients, who then made their own choice. Patients who had vitiligos with large surface areas tended to select narrow-band UV-B. By contrast, patients with small vitiligo lesions tended to choose topical therapy. Surgical treatment was mostly selected by patients who were unresponsive to less invasive therapies. Statistical analyses were performed using the Pharmaco Analyst II software (Human Life, Tokyo, Japan) and Excel (Microsoft, Redmond, WA, USA).

Results

Table 2 shows the comorbidities of each type of vitiligo. Overall, 7.69% of patients with generalized-type vitiligos experienced complications (i.e., thyroid dysfunction), as compared to only 0.59% for those with the segmental type ($p < 0.01$, Chi-square test). Furthermore, 3.55% of patients with generalized-type vitiligos were complicated with carcinoma, as compared to only 0.59% for those with the

Table 1 Patients' profile.[a]

Type (cases)	Men/women (cases)	Age of onset (y)	Disease duration (y)
Generalized (338)	154/184	38.45 ± 22.38	7.080 ± 9.996
Segmental (170)	77/95	11.09 ± 12.03	3.360 ± 6.243
Localized (136)	50/84	32.71 ± 24.53	3.836 ± 8.078

[a] A total of 644 vitiligo patients who visited Nagoya City University hospital between April 2004 and August 2010 were analyzed in this study. There was a significant difference between generalized type and segmental type.

Table 2 Comorbidities.

Type (cases)	Carcinoma cases (%)	Atopic dermatitis cases (%)	Alopecia cases (%)	Uticaria cases (%)	Thyroid dysfunction cases (%)
Generalized (338)	12 (3.55)*	13 (3.85)	4 (1.18)	3 (0.89)	26 (7.69)
Segmental (170)	1 (0.59)	3 (1.76)	1 (0.59)	1 (0.59)	1 (0.59)**
Localized (136)	0 (0)	3 (2.21)	0 (0)	0 (0)	8 (5.88)

7.69% of generalized type vitiligo patients had thyroid dysfunction. In contrast, 0.59% of segmental type vitiligo patients had it (*$p<0.05$, **$p<0.01$, Chai-square test).
Also 3.55% of patients were complicated with Carcinoma, whereas were only 0.59% with the segmental type (*$p<0.05$, **$p<0.01$, Chi-square test).

Table 3 Family history.[a]

Type (no. of cases)	Family history cases (%)
Generalized (338)	12 (3.55)
Segmental (170)	1 (0.59)
Localized (136)	2 (0.59)

[a] Overall, 3.55% of generalized type vilitigo patients had a family history of their condition. By contrast, few patients who had segmental and localized types of vitiligo had it. There was no significant difference in each group (Chi-square test).

segmental type ($p < 0.05$, Chi-square test). In addition, 3.55% of generalized type had a family history of their condition, as compared to only 0.59% of segmental type (Table 3) . However, this difference was not statistically significant.

Multivariable logistic regression analysis was performed for each type of vitiligo against other types. For generalized and localized types, none of the analyzed factors were statistically significant. For the segmental type, antinuclear antibody (ANA) [odds ratio (OR) = 1.005; 95% confidence interval (CI), 1.00—1.01; $p < 0.05$] and onset age < 14 years were significant factors in patients who were 15—29 years old (OR = 0.246; 95% CI, 0.113—0.538; $p < 0.001$), 30—54 years old (OR = 0.0419; 95% CI, 0.0133—0.132; $p < 0.001$), and >55 years (OR = 0.0171; 95% CI, 0.00333—0.0879; $p < 0.001$) (Table 4). The individuals whose condition was complicated by thyroid dysfunction were older than the others (Fig. 1). The data on the treatment response of each type of vitiligo are shown in Fig. 2. Narrow-band UV-B was significantly effective for the generalized type and the localized type ($p < 0.05$, Chi-square test). The treatment response rate was 46.3% for the generalized type, 20.3% for the segmental type, and 29.2% for the localized type. The 1-mm minigraft was significantly effective for the segmental type and the localized type ($p < 0.01$, Chi-square test). The treatment response rate was 38.9% for the generalized type, 77.3% for the segmental type, and 73.3% for the localized type. Topical vitamin D_3 therapy was significantly effective for the localized type ($p < 0.05$, Chi-square test). The treatment response rate was 21.1% for the generalized type, 29.0% for the segmental type, and 54.8% for the localized type. Vitiligo lesions located in the head, neck, and body were treated more effectively than those located in the extremities (**$p < 0.01$, Chi-square test; Table 5).

Discussion

Pathophysiologically, the detailed mechanisms of vitiligos remain unclear. In the generalized type, there were many reports relating to autoimmune diseases such as thyroid dysfunction, type 1 diabetes mellitus, Addison disease, and alopecia areata [6]. The antimelanocyte antibodies that destroyed melanocytes were identified in many patients in the 1990s [7]. Jin et al [8] highlighted *NALP1* gene polymorphism in vitiligo patients using the single-nucleotide polymorphism method [8]. They reported that generalized

Table 4 Logistic regression.[a]

Characteristic		Odds ratio	95% confidence interval	p
Age (664 cases)	15—29 y	0.246	0.103—0.538	<0.001**
	30—54 y	0.042	0.113—0.132	<0.001**
	>55 y	0.017	0.003—0.088	<0.001**
Sex (664 cases)	Men	0.657	0.335—1.291	0.223
ANA (336 cases)	10 units	1.005	1.001—1.010	0.039*
TSH (344 cases)	1 unit	1.001	0.724—1.385	0.994
FT3 (340 cases)	1 unit	1.114	0.744—1.735	0.554
FT4 (340 cases)	1 unit	0.988	0.868—1.124	0.853
Having a carcinoma (664 cases)		0.312	0.026—3.767	0.595
Having a thyroid dysfunction (664 cases)		0.076	0.003—2.167	0.131

[a] Multivariable logistic regression was performed in segmental vitiligo against other types of vitiligo. Age (younger) and antinuclear antibodies (higher) were risk factors of the segmental type in vitiligo vulgaris (*$p<0.05$, **$p<0.01$). The breakdown of the number of cases is as follows: <14 years old, 169 cases; 15—29 years old, 129 cases; 30—54 years old, 157 cases; and >55 years old, 189 cases.

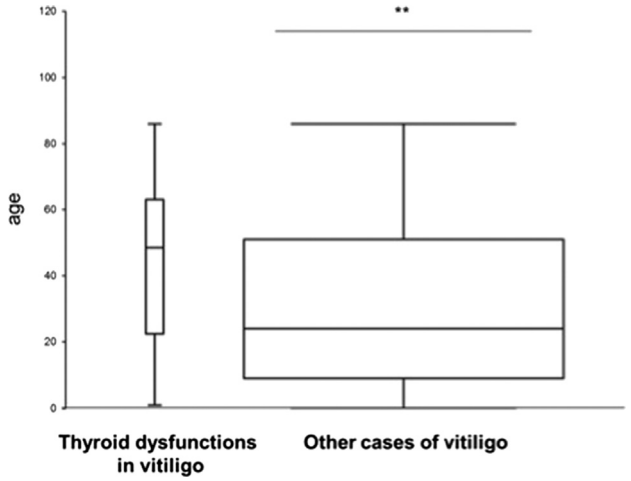

Figure 1. Analysis between age and thyroid dysfunction. Patients with thyroid dysfunction were older than the other vitiligo patients. This is one of the reasons why no significant difference was found in the logistic regression analysis.

vitiligo was correlated with thyroid disease, autoimmune diabetes, and rheumatism in a statistically significant level. It was well known that CD8-positive T cells damaged melanocytes directly [9]. Lili et al [10] reported that an imbalance between CD8-positive T cells and regulatory T cell existed in patients with vitiligo [10]. In vitiligo, Th17 positive cells infiltrated the upper dermis, suggesting that cytokines associated with Th17 such as IL-1α, TNF-α, and IL17 A play a role in the dysregulation of melanocytes [11]. In addition, nitrogen monoxide and hydrogen peroxide as oxidant stress increased in vitiligo lesions [12]. By contrast, antioxidants such as catalase, ubiquinol, and vitamin E decreased in lesions. The failure of the autonomic balance of the lesion contributed to the risk of segmental vitiligo [13].

We conducted a large retrospective study in Japan. Unexpectedly, thyroid disease and malignant tumor did not prove to be related to any type of vitiligo in terms of complications. Younger age of onset and higher ANA were noted in segmental vitiligo, as compared with generalized vitiligo. ANA became positive in healthy controls at a constant rate. Overall, 8.3% of healthy adults had a titer of $>$1:160. By contrast, in children, 15.6% had a titer of $>$1:160. One of the reasons for the high titer of ANA might be attributed to the population of children in our segmental cases [14,15]. Age of onset occurred later in patients who had thyroid disease compared with those who did not have this condition, a factor that might have played a role in the result of the multivariable logistic regression analysis. Narrow-band UV-B was effective for generalized vitiligos. There are many reports about the use of narrow-band UV-B for vitiligo, although its mechanism of action has not been made clear [16,17]. Dong et al [18] reported that narrow-band UV-B differentiated hair follicle-derived neural crest stem cells into melanocyte lineage. By contrast, 1-mm minigraft therapy was effective for segmental and localized vitiligos, suggesting that the mechanism was different between segmental vitiligo and generalized vitiligo [19].

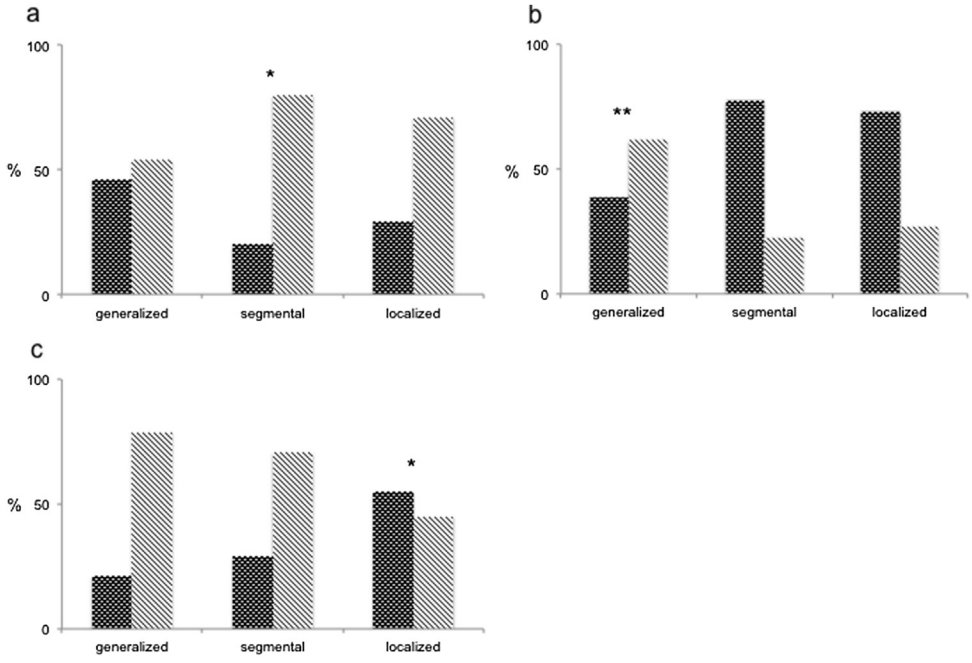

Figure 2. Treatment response. The dark bar denotes effective cases and sickly gray bar denotes not effective cases. As an evaluation for narrow-band UV-B therapy and topical vitamin D_3 therapy, when the pigmentation was found in the treatment area, that case was evaluated as effective; if not, that case was deemed not effective. For the 1-mm minigraft therapy, when the stable pigmentation was found around the transplanted point, that case was evaluated as effective; if not, that case was evaluated as not effective. (A) Narrow-band UV-B had a good outcome in generalized and localized types (*$p < 0.05$, Chi-square test). (B) The 1-mm minigraft, by contrast, had a good outcome in segmental and localized types (**$p < 0.01$, Chi-square test). (C) Topical vitamin D_3 elicited a good response in localized type (*$p < 0.05$, Chi-square test).

Table 5 Successful cases and location—vitiligo cases located in the head, neck, and body were more effectively treated than those located in extremities.

Location (cases)	Successful cases (%)
Head and neck (148)	59.5
Body (144)	56.9
Extremity (31)	22.6*

*$p < 0.01$, Chi-square test.

Surgical treatment should be selected for cases where the Koebner phenomenon does not occur, and no progress has been made for more than a year [2]. Topical vitamin D therapy was effective for localized vitiligos. Goktas et al [20] reported that the combined approach of narrow-band UV-B and topical vitamin D therapy was effective for generalized vitiligos [20]. The combination of narrow-band UV-B and topical vitamin D therapy decreased the number of Langerhans cells and increased regulatory T cells, suggesting that this combination therapy induced immune suppression [21]. Based on the results, narrow-band UV-B is recommended for the generalized type of vitiligo, and 1-mm minigraft is recommended for the segmental and localized types. For some cases, especially localized types, it may be appropriate to use topical vitamin D_3 therapy. Age of onset and some laboratory findings can be helpful when making a diagnosis and selecting an appropriate therapy. As time goes on, the accumulation of data from case reports and large-scale analyses is expected to lead to the discovery of a better therapy. For this retrospective study, however, no clear criterion has been established for the choice of treatment. Therefore, a prospective study is necessary to assess the efficacy of each specific treatment.

In conclusion, we reported on the comorbidities and effective treatment rates of a large-scale study for vitiligo patients. In particular, the response data for these treatments will be helpful to previous explanations because there have only been very few reports about the response data for such treatments. The appropriate treatment should be selected depending on the type of vitiligo.

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