

INVESTIGATIVE REPORT

Vitiligo in North-eastern China: An Association between Mucosal and Acrofacial Lesions

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Vitiligo is a mucocutaneous pigmentary disorder with worldwide distribution. Little is known about the clinical profile of vitiligo in North-eastern China. Accordingly, we reviewed 692 vitiligo out-patients from seven government hospitals in North-eastern China via a questionnaire in a multi-centre study conducted between June 2007 and June 2008, and hence characterized the epidemiology of vitiligo in North-eastern China. The mean \pm standard deviation age of onset was 23.69 ± 13.83 years (range < 1–77 years). No gender preponderance was seen. The back was the most common site of involvement (39.6%). Vitiligo vulgaris was the predominant form (53.5%). Mucosal lesions were associated with lesions on the feet (odds ratio (OR)=3.177, $p<0.001$), hands (OR=2.228, $p<0.01$), face (OR=2.028, $p<0.05$) and neck (OR=0.454, $p<0.05$); but were not associated with chest, abdomen, waist, arms, legs or scalp lesions. Mucosal vitiligo is probably a special form of acrofacial vitiligo. Key words: vitiligo; epidemiology; Chinese.

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Vitiligo involves a progressive loss of melanocytes from the epidermis and hair follicles, making the integument and sometimes hairs milky-white in appearance (1, 2). There has been considerable controversy regarding the aetiology and pathogenesis of vitiligo (3–5), though most investigators now consider generalized vitiligo to be an autoimmune disease. Owing to close resemblance in histopathological characteristics, vitiligo has been likened to hair greying, in which pigment loss in hair follicles results from marked reduction in melanogenically-active melanocytes in the hair bulb of grey anagen hair follicles (6). Premature hair greying may be associated, among other diseases, with vitiligo (7), although the relationship between premature hair greying and vitiliginous leukotrichia has not been studied. The relationship between premature hair greying and a family history of premature hair greying in vitiligo patients has also not been well studied.

China has a population so diverse that the clinical and epidemiological data obtained from one region of the country may not accurately represent another region. The Han ethnic group, which comprises more than 90% of the Chinese population, has been the focus of many epidemiological studies conducted in China, whereas little attention has been paid to regional variations in the clinical profile of vitiligo elsewhere in China. North-eastern China, for example, has a population of approximately 90 million people, but to the best of our knowledge, no clinico-epidemiological data on vitiligo in this region are available. Accordingly, in the present study, we obtained clinico-epidemiological data on this disease in North-eastern China, compared it with those obtained in other parts of the world, and thus established a reference base for this important region of the world.

PATIENTS AND METHODS

A total of 692 vitiligo out-patients from seven government hospitals in North-eastern China were reviewed via a questionnaire in a multi-centre study conducted between June 2007 and June 2008. A confirmed clinical diagnosis of vitiligo was required for a patient to be included in this study. Patients with other forms of leukoderma were excluded. The same general questionnaire form was used for all patients in all the centres, and training was provided to all the assessors prior to the study. The questionnaire itself queried information that included patient's name, age, sex, address, telephone number, marital status, self-described ethnic group, age of disease onset, family history of vitiligo and family or personal history of thyroid disease and other autoimmune diseases, such as alopecia areata, rheumatoid arthritis, diabetes, and pernicious anaemia. Distribution of the patient's lesions and extent of disease, disease stage and duration, level of activity, and previous episodes of repigmentation were also recorded. Follow-up telephone interviews were used to complete missing or inconsistent items. Questionnaires with missing or inconsistent items that could not be corrected by telephone interviews were excluded.

We grouped the patients into six vitiligo types: vulgaris, acrofacial, focal, segmental, universal, and mixed: in accordance with the standard working classification of clinical types of vitiligo. Onset age was defined as the age at which the first white spot was observed by the patient and confirmed by a dermatologist as vitiligo.

To improve reliability and data accuracy, 249 patients seen in one of the centres (No. 1 Hospital of China Medical University) were further analysed for premature hair greying, vitiliginous leukotrichia, Koebner's phenomenon, halo phenomenon, and other risk factors during the same study period. These patients were interviewed by the same assessor using a longer version of the questionnaire, which included the items in the

general questionnaire mentioned above and, additionally special questions concerning premature hair greying, vitiliginous leukotrichia, etc.

Premature hair greying was defined as hair greying before age 25 years or, alternatively, a self-report that the subject's hair had turned more than 50% grey before age 40 years (6–8). We carefully examined our patients to exclude those with hair greying on lesional skin, especially for vitiligo involving scalp skin, which we regarded strictly as vitiliginous leukotrichia. We also excluded the occasional few grey hairs that may develop in children.

Statistical analysis of the results was carried out using the Statistics Package for Social Sciences (SPSS, version 13.0) for Windows. Statistical analyses, such as frequencies, cross tabs and non-parametric tests, were performed, and a level of $p < 0.05$ (two-tailed) was considered statistically significant.

RESULTS

General information

The mean \pm SD age of the patients at the time of study was 26.90 ± 14.80 years and the age range 3–77 years. Overall, 93.8% ($n = 649$) of study cases were of the Han ethnic group, while non-Han Chinese comprised 6.2% ($n = 43$) of cases. A total of 268 (38.7%) of visits were new cases (first diagnosis) and 424 were old cases, of which 315 (45.5%) presented due to a persistent disease and 109 (15.8%) due to relapse after a previous disease-free period.

In 50.6% ($n = 350$) of cases lesions were still expanding or spreading at the time of the visit (progressive course), 44.8% ($n = 310$) of cases had stable lesions, and 4.6% ($n = 32$) of cases reported lesions that were decreasing in number or size (regressive course). The mean disease duration was 30.58 ± 55.38 months for those in progressive stage, 42.52 ± 95.03 months for those in stable stage and 28.91 ± 44.78 months for those in regressive stage. The overall mean disease duration was 35.85 ± 75.58 months (range 1 month–50 years).

Onset age, site and vitiligo types

The earliest age of disease onset was before the patient's first birthday, and the latest was at age 77 years mean 23.69 ± 13.83 years and median 21 years. The mean onset age was 22.82 ± 13.08 years (median 20, range <1–76) for male patients and 24.68 ± 14.61 years (median 22, range 2–77) for female patients. Male patients ($n = 369$; 53.3%) slightly outnumbered female patients ($n = 323$; 46.7%); this difference was not statistically significant. Overall, vitiligo vulgaris was the predominant type (53.5%), followed by focal (32.5%), acrofacial (6.8%), mixed (6.0%), universal (2.7%), and segmental (0.7%) types. Both sexes had equal chances of acquiring any of the types mentioned above ($p = 0.227$, Fig. 1).

The most common site of disease involvement was the back (39.6%). Other commonly involved sites were the face (35.3%), chest (32.8%), legs (32.2%), abdomen

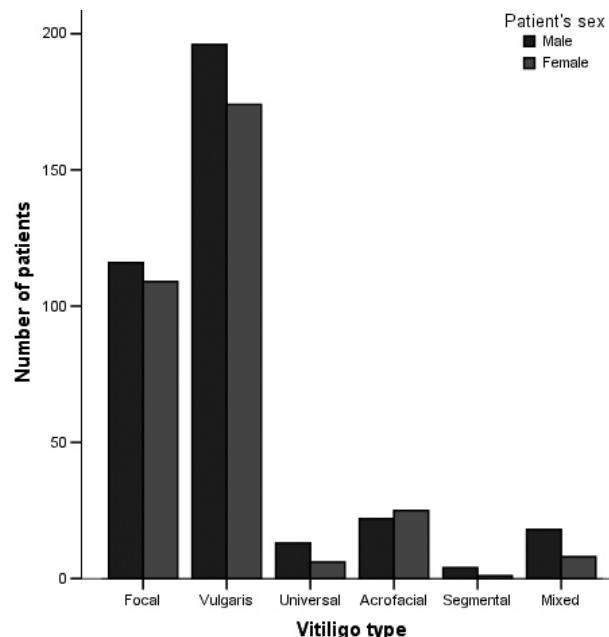


Fig. 1. Distribution of vitiligo types by gender in North-eastern China.

(31.9%), neck (31.4%), hands (29.2), arms (27.5%), waist (22.0%), feet (15.0%), scalp (11.3%) and oral, nasal and genital mucosae (8.8%).

We found that mucosal involvement was associated with involvement of the feet ($OR = 3.177$, $\chi^2 = 16.519$, $p < 0.001$), hands ($OR = 2.228$, $\chi^2 = 9.038$, $p < 0.01$), face ($OR = 2.028$, $\chi^2 = 7.095$, $p < 0.01$), and neck ($OR = 0.454$, $\chi^2 = 5.519$, $p < 0.05$). Mucosal involvement was not associated with involvement of the chest, abdomen, back, waist, arms, legs or scalp (Table I). As for the neck, which is not part of acrofacial vitiligo, the OR value of 0.454 shows that lesions on the neck were protective for mucosal vitiligo. Considered together, these results suggest that "mucosal vitiligo", as proposed by some authors, may be a special form of acrofacial vitiligo.

Table I. Association of mucosal vitiligo with vitiligo involving other sites, in North-eastern China

Sites involved (cross-tabulated)	OR value	Pearson χ^2	Significance (2-tailed)
Mucosa * Scalp	1.821	2.896	0.089
Mucosa * Face	2.028	7.095	0.008
Mucosa * Neck	0.454	5.519	0.019
Mucosa * Chest	0.644	2.047	0.153
Mucosa * Back	0.613	2.846	0.092
Mucosa * Abdomen	0.961	0.019	0.890
Mucosa * Waist	0.675	1.212	0.272
Mucosa * Arm	1.207	0.421	0.517
Mucosa * Leg	1.304	0.920	0.338
Mucosa * Hand	2.228	9.038	0.003
Mucosa * Foot	3.177	16.519	0.000

OR: odds ratio

Table II. Frequencies of first-, second- and multiple-degree relatives with vitiligo in North-eastern China

Relative	Frequency n (%)
First-degree relative	17 (44.7)
Second-degree relative	16 (42.1)
Multiple-degree (first- and second-degree) relatives	5 (13.2)
Total	38 (100)

Family history and precipitating factors

Thirty-eight patients (5.5%) had a family history of vitiligo. The frequencies of the first-, second- and multiple degree relatives are shown in Table II. Twenty-six patients (3.8%) had other autoimmune diseases, with hyperthyroidism (22.2%), rheumatoid arthritis (18.5%) and alopecia areata (14.8%) being the most common.

Of the 249 cases reported, 8.0% ($n=20$) had a rash prior to vitiligo onset and 23.3% ($n=58$) had vitiligo at a site of significant physical trauma or operation either prior to the onset of the disease or during the course of the disease (Koebner's phenomenon). 8.4% ($n=21$) had vitiligo around a naevus (halo phenomenon).

Premature hair greying and leukotrichia

Sixty-six patients (26.5%) of the 249 cases had premature hair greying, with 97.0% of those showing greying of scalp hair. The remainder of the patients (3.0%) showed greying of other body hairs, such as eyebrows, eyelashes, beard and moustache.

The mean onset age of premature hair greying was 15.50 ± 5.41 years (range 3–24, median 17). Male subjects slightly outnumbered the females (41 males, 25 females), but this difference was not statistically significant ($p=0.455$). Most of the patients with premature hair greying were those with vitiligo vulgaris ($n=33$), followed by focal ($n=24$), acrofacial ($n=5$), mixed ($n=3$) and universal ($n=1$) vitiligo.

This distribution mirrors the distribution of vitiligo types in general.

Forty patients (16.1%) of the 249 cases reported one or more other family members with premature hair greying. The odds of having a family history of premature hair greying were more than four times greater among those who had premature hair greying than for those who did not, and the difference was statistically significant ($OR=4.028, \chi^2=16.530, p<0.001$). Our results show that vitiligo patients with a family history of premature greying are more likely to develop premature greying themselves. However, no comparison with the general population was made, and, due to greater awareness of pigmentary phenomena among individuals who themselves have vitiligo and/or premature greying, it remains unclear whether this represents a true familial tendency of premature greying among these patients or

biased reporting of relatives with premature greying among these patients.

Seventy-three (29.3%) cases reported white hairs on vitiliginous sites (vitiliginous leukotrichia). There was no statistical significance in showing vitiliginous leukotrichia between male and female subjects (38 males, 35 females, $p=0.208$). Most patients who showed vitiliginous leukotrichia were those with vitiligo vulgaris ($n=36$), followed by focal ($n=26$), acrofacial ($n=5$), mixed ($n=3$), and universal ($n=3$) vitiligo. Again, this distribution mirrors the distribution of vitiligo types in general.

We found a significant difference in vitiliginous leukotrichia between patients in the progressive stage ($n=51$) and those in the stable stage ($n=20, p<0.01$). The difference in vitiliginous leukotrichia between progressive and regressive stage ($n=2, p=0.095$), or stable ($n=20$) and regressive stage ($n=2, p=0.571$) were not statistically significant. Vitiliginous leukotrichia was not associated with disease duration (data not shown).

The odds of having premature hair greying were more than four times greater for those who had vitiliginous leukotrichia than for those who did not ($OR=4.735, \chi^2=27.582, p<0.001$).

The odds of having a rash prior to the onset of vitiligo were more than three times greater for those who had vitiliginous leukotrichia than for those who did not ($OR=3.292, \chi^2=6.922, p<0.05$).

DISCUSSION

Most of the clinical results obtained in this study are similar to those reported in other parts of China and elsewhere in the world. Vitiligo vulgaris was the most common type in our study, and this agrees well with the results obtained in Tunisia, India, Turkey and other parts of China (9–11, 14). Lack of sexual preponderance has also been reported in India, Tunisia, Turkey, Denmark and other parts of China (10–12, 14, 15). While our study shows the back to be the most common site of involvement at onset, other studies have shown the face, head and neck, lower limbs and upper limbs to be the most common sites of involvement at onset (9–11, 14). Our results show a family history of vitiligo in 5.5% of patients, lower than those reported in other studies (11.1–30%) (9, 10, 12, 16). Vitiliginous leukotrichia has been reported worldwide at a range of 9–47.3% (9–11, 17). We observed leukotrichia in 29.3% of subjects, which falls within this range.

Reports on association of vitiligo with other autoimmune diseases vary widely depending on the patient populations studied. Age of patients at the time of study, the number of autoimmune diseases analysed, as well as the patient's ability to distinguish different forms of autoimmune diseases also affect the accuracy of the frequencies reported. Association of vitiligo with other

autoimmune diseases has been reported at frequencies ranging from 4.76% to 7.6% in China in both adult and childhood vitiligo (12, other references in Chinese). Frequencies as low as 1.3% in childhood vitiligo, and up to 43% in a Romanian population isolate have been reported elsewhere in the world (18, 19). Our results show low frequency (3.8%) of autoimmune diseases in this population, though we cannot rule out the possibility of under-reporting.

Despite the possible confounding bias from race, we included both Han and non-Han Chinese in our study in order to construct a representative model of this disease based on geographical locality rather than race. The Han ethnic group comprises more than 90% of the Chinese population, and this was reflected in our study in which 93.8% of patients belonged to this group.

Our study found significant association between mucosal and acrofacial forms of vitiligo, suggesting that mucosal vitiligo may be a form of acrofacial vitiligo.

We also bring to the attention of dermatologists the need for a universal definition of premature hair greying with consideration of both onset and rate of progression of hair greying. There is no current universal definition of premature hair greying. Rosen et al. (7) defined premature hair greying as hair turning more than 50% grey before age 40 years. In another study, Orr-Walker et al. (8) defined premature hair greying, *a priori*, as the majority (>70%) hair greying before age 40 years. According to other authors, hair is said to grey prematurely if it occurs before age 20 years in whites, before 25 in Asians, and before 30 in Africans (6). The average age of onset of hair greying is mid-30s for Caucasians, late-30s for Asians and mid-40s for Africans; and a simple rule of thumb suggests that by 50 years of age, 50% of people have 50% grey hair (Keough & Walsh, 1965) (6).

Our definition of premature hair greying was established for the purpose of this study only, bearing in mind that both onset and rate of progression are important in defining hair greying. However, though we included a self-report that the subject's hair had turned more than 50% grey before age 40 years in the definition, all subjects that reported premature hair greying did so due to meeting the first part of our definition (i.e. they had hair greying before age 25 years).

There are a few shortcomings in our definition. Hair greying before age 25 years lacks visible parameters required to make it comparable to self-report that hair had turned more than 50% grey before age 40 years. Previous studies have not quantified the extent of involvement of hair greying before age 25 years for it to be regarded as premature. Although we excluded the occasional few grey hairs that develop in children, these could represent a true onset of greying and thus could have a significant impact on the interpretation of our results.

We found that vitiligo patients with a family history of premature hair greying are more likely to show premature hair greying than those without a family history of premature hair greying. However, while premature hair greying is believed to tend to run in families, we found little published evidence to support this or to document its inheritance in the general population, thus limiting the opportunity to compare our data from vitiligo patients with analogous data from controls.

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The authors declare no conflict of interest.

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