

Report

Inverse association between autoimmunity and elevated IgE among childhood vitiligo

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Abstract

Background Multiple factors contribute to the pathogenesis of childhood vitiligo. The characteristics in a different population under modified environmental factors need further reevaluation. The present study aimed to reevaluate the clinical and laboratory features in consequent children vitiligo patients.

Materials and methods We retrospectively reviewed consequent children vitiligo patients who visited Children's Hospital of Fudan University (National Children's Medical Center of China). The prevalence rate of thyroid dysfunction, circulating autoantibodies, serum IgE, and associated factors were analyzed.

Results A total of 244 consequent vitiligo patients were included, of which 20 children had personal autoimmune history. Two hundred and nineteen of the 244 patients took a thyroid function test, and the abnormal rate was only 3.7% (8/219). The elevated IgE rate was 31.7% (52/157), the antinuclear antibody (ANA) positive rate was 9.8% (12/123), and the extractable nuclear antigens (ENA) positive rate was 4.4% (4/91), respectively. The elevated IgE was significantly associated with atopic disease history and male gender. Of note, personal autoimmune history showed a significant inverse association with elevated IgE.

Conclusions Thyroid dysfunction rate was low among the consequent children vitiligo patients. Personal autoimmune history was inversely associated with elevated IgE. Various clinical characteristics and pathogenesis might contribute to different long-term outcomes of vitiligo.

Introduction

Vitiligo is among the first recognized skin diseases, characterized by the destruction of melanocytes resulting in milky-white macules or patches.^{1,2} The estimated overall prevalence was 0.06–2.28% and 0.0–2.16% in children.³ The etiology of vitiligo is multifactorial.⁴ Several hypotheses propose that the pathogenesis of vitiligo involves genetic, autoimmune, and environmental factors. The overall distribution of the onset age was bimodal,⁵ with half of the patients developing vitiligo during the first and second decades. Early onset and late-onset subgroups presented various features. Childhood vitiligo could be a distinct entity. However, the characteristics of childhood vitiligo have not been studied adequately.

Several studies reported the association between vitiligo and autoimmune disease as well as increased autoantibodies. Among these, thyroid disease is the most studied with a varied prevalence.^{6–9} Although a high thyroid dysfunction rate was observed in childhood vitiligo and thyroid testing was recommended, a Korean study reported that only 5.9% were diagnosed with thyroid disease, with no difference between the vitiligo and control groups.¹⁰ It is supposed that autoimmune diseases have a high prevalence in Western societies and low in Asian countries. Another study from China reported 43.4% thyroid function abnormalities,¹¹ which could be related to different stages and types of vitiligo, diverse population, altered environment, and selection bias. The contradictions need further careful reevaluation.

In addition to autoimmunity, atopy has been assumed to be involved in the pathogenesis of vitiligo.^{12,13} Zhang et al. reported asthma prevalence in familial vitiligo probands.¹⁴ Also, the role of atopy is known in alopecia areata. Similarly, the predisposing background in vitiligo is not limited to autoimmunity, especially in prepubertal onset type.¹⁵ The pro-inflammatory status might predispose toward melanocyte destruction. Furthermore, Ying et al. reported vitiligo onset age exhibited remarkable change, with a mean age increase from 14.7 to 31.8 years in the past decades, suggesting altered environmental triggers.¹⁶

Due to inconsistent data, potentially altered environment triggers, and updated hypotheses, we conducted this study to re-evaluate the demographic and clinical features of childhood vitiligo in China. The prevalence rate of thyroid dysfunction, circulating antibodies, IgE level, and associated factors were evaluated.

Materials and methods

Study participants

Children's Hospital of Fudan University, Shanghai (National Children's Medical Center), is the largest children's hospital in east China. In this retrospective study, we reviewed the clinical chart of the consequent patients who visited the Vitiligo Clinic from September 2019 to April 2021. Routinely, a comprehensive evaluation and thyroid function tests are conducted for each patient. Patients <18 years old were included in this study. The diagnosis was made by an experienced dermatologist, using Wood's lamp, after exclusion of other differential diagnoses. The variables collected were sex, age at onset, age at visit, disease duration, potential triggers, site of onset, and vitiligo type. Autoimmune disease history, atopic disease history, and family history were also evaluated. Atopic diseases included atopic dermatitis, allergic conjunctivitis, allergic rhinitis, and asthma. Segmental vitiligo (SV) was classified as unilateral lesions that totally or partially match a cutaneous segment, while others were classified as nonsegmental vitiligo (NSV).¹⁷

Laboratory methods

Free triiodothyronine T3 (FT3), free thyroxine T4 (FT4), thyroid-stimulating hormone (TSH), thyroglobulin antibody (Tg-Ab), and thyroid peroxidase antibody (TPO-Ab) administered to patients routinely were recorded. Thyroid dysfunction is defined as any thyroid parameter beyond the reference range. The levels of the antinuclear antibody (ANA), extractable nuclear antigens (ENA), and serum IgE were also recorded. ENA test assessed the levels of Jo-1, Scl-70, Sm, SSA, SSB, ribonucleoprotein (RNP), antinucleosome antibody (ANuA), anti-dsDNA, proliferating cell nuclear antigen (PCNA), and antihistone antibodies (AHA).

Statistical methods

The data were input into Microsoft Excel. Descriptive statistics were presented for the demographic and clinical data.

Frequencies and percentages were used to describe qualitative variables, whereas means and standard deviations were used for continuous data. Univariate regression analyses were performed to test for evidence of association. The odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were also presented, and $p < 0.05$ indicated statistical significance. Statistical Package for Social Sciences (SPSS23; SPSS Inc., IL, USA) was used for data analyses.

Ethics statement

The study was approved by the Ethics Committee of Fudan Children's Hospital. Written informed consent was not required because of the retrospective design. Patient information was anonymous, and the study adhered to the principles of the Declaration of Helsinki.

Results

Study population

A total of 244 cases of childhood vitiligo were included from August 2019 to April 2021. The demographic characteristics of the study population are shown in Table 1. The cohort consisted of 135 boys (55.3%) and 109 girls (44.7%), with a male to female ratio of 1.24:1. The average age of disease onset was 5.3 ± 3.3 years, and the average enrollment age was 6.9 ± 3.4 years. The boys and girls had similar onset ages. The duration of the disease at the time of presentation varied from 1 month to 11 years. The onset age of most patients (64.8%, 158/244) was before 6 years.

Furthermore, 33/228 (13.5%) patients were classified as segmental vitiligo (SV), and 211 (86.5%) were NSV. No significant

Table 1 Demographic characteristics of childhood vitiligo ($N = 244$)

Characteristics	% (No.)
Sex	
Male	55.3% (135/244)
Female	44.7% (109/244)
Onset age	
≤6 years	64.8% (158/244)
>6 years	35.2% (86/244)
Duration	
≤1 year	54.9% (134/244)
>1 year	45.1% (110/244)
Personal autoimmune history	
Yes	8.2% (20/244)
No	91.8% (224/244)
Family vitiligo history	
Yes	13.9% (34/244)
No	86.1% (210/244)
Type	
SV	13.5% (33/244)
NSV	86.5% (211/244)

difference was observed in the sex ratio between SV and NSV. The age of onset was similar between SV (5.4 ± 2.7) and NSV (5.3 ± 3.4) years. The most affected site of onset was the head/face (51.3%), followed by the trunk (27.6%), upper limbs (8.3%), lower limbs (9.6%), and mucosae (3.1%). Halo nevus was diagnosed in 17/244 (7.0%) of the patients.

Further, 34/244 (13.9%) patients had a family history of vitiligo. The family history of other autoimmune diseases was recorded in 17/244 (7.0%) patients. The mean age of onset was similar between those with and without family vitiligo history.

Concomitant disease

About 73/244 (30.0%) patients had at least one atopic disorder, including atopic dermatitis (31/244, 12.7%), allergic rhinitis (50/244, 20.5%), allergic conjunctivitis (15/244, 6.1%), and asthma (16/244, 6.6%), and 20/244 (8.2%) vitiligo patients had a personal history of autoimmune diseases; among these, eight had concomitant thyroid disease, and four had alopecia areata. The frequency of concomitant diseases is presented in Table 2. Surgery or trauma was reported by 19/244 (7.8%) patients, and emotional stress (such as caretaker change, excessive homework, moving to another place, and hyperkinesia) was reported by 26/244 (10.7%) patients as the potential trigger.

Abnormal laboratory results

Among the 244 consequent vitiligo patients, 219 (89.8%) had undergone thyroid function testing. Surprisingly, only 8/219 (3.7%) had abnormal thyroid function (Table 3), and 5/8 patients had elevated FT3 and/or FT4, one had decreased FT3 and FT4, and the remaining two were subclinical thyroid dysfunction cases (one decreased and one elevated TSH). Among 123 patients who underwent ANA screening, 12 (9.8%) were ANA-positive cases, one had abnormal thyroid function, one was diagnosed with IgA disease, and six had family vitiligo or other autoimmune disease history. Among the 91 patients tested for ENA, only four (4.4%) were ENA-positive, including AMA-, Jo-1-, Sm-, and

Table 2 Concomitant disease in childhood vitiligo

Concomitant disease	% (No.)
Any atopic disease	30.7% (73/244)
Atopic dermatitis	12.7% (31/244)
Allergic rhinitis	20.5% (50/244)
Allergic conjunctivitis	6.1% (15/244)
Asthma	6.6% (16/244)
Autoimmune disease	8.2% (20/244)
Thyroid disease	3.3% (8/244)
Pericious anemia	0.4% (1/244)
Alopecia areata	1.6% (4/244)
Scleroderma	0.4% (1/244)
IgA nephropathy	0.4% (1/244)
Thrombocytopenic purpura	0.8% (2/244)
Dermatomyositis	0.4% (1/244)
Rheumatoid arthritis	0.4% (1/244)

Table 3 Abnormal laboratory results

	% (No.)
Thyroid function testing	
Abnormal thyroid function	3.7% (8/219)
Normal thyroid function	96.3% (211/219)
Serum IgE	
Elevated serum IgE	31.7% (52/157)
Normal serum IgE	68.3% (105/157)
Extractable nuclear antigens (ENA)	
Jo-1	1.1% (1/91)
Scl-70	0% (0/91)
AMA	1.1% (1/91)
Sm	1.1% (1/91)
SSA	1.1% (1/91)
SSB	0% (0/91)
Ribonucleoprotein (RNP)	0% (0/91)
Antinucleosome antibody (ANuA)	0% (0/91)
Anti-dsDNA	0% (0/91)
Proliferating Cell Nuclear Antigen (PCNA)	0% (0/91)
Antihistone antibodies (AHA)	0% (0/91)
Antinuclear antibody (ANA)	
ANA positive	9.8% (12/123)
ANA negative	90.2% (111/123)

SSA-positive, respectively. Also, one of the ENA-positive patients had halo nevus.

Of the 157 patients who were subjected to the IgE test, 52 (31.7%) had elevated IgE levels. The onset age of patients with elevated IgE was similar (5.4 ± 3.3) compared to those with normal IgE (5.32 ± 3.1).

Factors associated with elevated IgE

Elevated IgE was significantly associated with atopic disease history (OR = 2.79, 95% CI: 1.40–5.54) and male gender (OR = 4.26, 95% CI: 1.98–9.18) (Table 4). Interestingly, 5/9 (55.6%) diaper vitiligo patients had elevated IgE. The average IgE level was higher in boys than girls (196.5 ± 335.5 and 64.9 ± 81.0 kU/L).

Furthermore, 1/17 (5.9%) of those with personal autoimmune history had elevated IgE. Personal autoimmune history showed a significant inverse association with elevated IgE (OR = 0.11, 95% CI 0.01–0.85) (Table 4). Among patients with abnormal thyroid function, positive ANA, and family vitiligo history, the elevated IgE rate was 0%, 10.0%, and 16.7%, respectively. A consistent inverse association trend was implied between autoimmune and atopy conditions although not significantly. The association with onset age, disease duration, and vitiligo type were not significant.

Discussion

Although parents tend to pay more attention to cosmetic issues for girls, and one of the features of autoimmune diseases is the female predominance,^{18,19} our study consisted of more boys

Table 4 Univariate analysis of factors associated with elevated IgE

Variable	Freq %	Univariate OR (95%CI)
Sex		
Male	41.2%	4.26 (1.98–9.18)**
Female	20.0%	1
Onset age		
≤6 years	33.7%	1.07 (0.53–2.17)
>6 years	32.1%	1
Duration		
≤1 year	38.2%	1.56 (0.80–3.04)
>1 year	28.4%	1
Type		
SV	23.1%	0.56 (0.21–1.48)
NSV	35.1%	1
Family vitiligo history		
Yes	16.7%	0.37 (0.10–1.33)
No	35.3%	1
Atopic disease		
Yes	47.5%	2.79 (1.40–5.54)**
No	24.5%	1
Autoimmune disease		
Yes	5.9%	0.11 (0.01–0.85)*
No	36.4%	1
Antinuclear antibody (ANA)		
Yes	10.0%	0.26 (0.03–2.14)
No	30.1%	1

CI, confidence interval; OR, odds ratio.

* $p < 0.05$.** $p < 0.01$.

than girls. This ratio was also slightly higher than the sex ratio at birth in China.²⁰ The elevated IgE was significantly associated with boys in our study, which might imply that increased atopy conditions are involved in childhood vitiligo.

The median disease duration was short, indicating that vitiligo parents prefer an early diagnosis and treatment. The average age of onset (5.3 years) in our study was younger than that reported previously (range 7.3–10.1 years).^{10,21,22} These trends were also observed in our childhood alopecia areata patients (unpublished data), which might be attributed to the changes in lifestyle and environmental triggers. Vitiligo consists of early onset and late-onset groups, with a bimodal distribution of onset age. Recently, Jin et al. reported remarkable changes in the late-onset groups, with mean onset age increased more than twofold in the past decades.¹⁶ Jin et al. proposed that the shift of vitiligo onset could be attributed to altered environmental triggers. Conversely, our study identified a forward trend. Lifestyle change and emotional stress might contribute to the early onset of vitiligo.^{23,24} Some children start to recite words and calculate at the early age of 3 or 4 years old, giving rise to anxiety in both patients and children. On the other hand, recent reports indicated that allergy is also involved in vitiligo. The increased atopic condition could also be attributed to the early disease onset.²⁵

Elevated IgE was significantly associated with atopic disease history and male gender. Atopic and autoimmune conditions could influence vitiligo from a different direction. Female patients might be connected to autoimmune diseases; therefore, male patients might be inclined toward the atopic condition. However, a large sample size and long-term data are required to substantiate these findings.

In the current cohort, 73 (30.7%) patients had atopic disease history, and 31.7% had elevated IgE. Marti et al. showed that 17.97% of vitiligo patients had elevated IgE, and 25.78% had an atopic condition. In developing countries, a high prevalence of elevated IgE is associated with a high prevalence of parasitic infections.²⁶ The elevated IgE level was significantly associated with atopic disease history and negatively associated with personal autoimmune history. This finding was consistent with the study by Marti et al., which also showed that elevated IgE indicates low autoimmunity.²⁷ The current sample size might not be sufficiently large, and the positive rate of the variables is not high, which could influence the power of statistics. Interestingly, inverse trends are noted between several autoimmune conditions and elevated IgE; for example, none of the eight abnormal thyroid function patients had elevated IgE. Thus, the presence of IgE might be a protective factor for the development of other chronic autoimmune conditions. Nonetheless, due to the low number of cases, these hypotheses need to be further verified with large sample size. Previous studies demonstrated a low prevalence of atopy in Th1-mediated autoimmune diseases, such as type 1 diabetes and rheumatoid arthritis.^{28,29} Th1 and Th2 diseases could be mutually exclusive. Khoryati et al. indicated that IgE downregulated IFN- α secretion through decreased expression of TLR-9 and IRF-7, involved in chronic inflammatory conditions and vitiligo.³⁰ Vitiligo is a typical multifactorial disease mediated by various factors. Furthermore, there is the possibility that the autoimmune or atopic conditions might influence the long-term outcome of the disease.

In contrast to a previous report, our study demonstrated a low prevalence (3.7%) of thyroid dysfunction in consequent vitiligo children. Previous data showed that thyroid dysfunction prevalence varied from 5.9% to 43.4%,^{10,11} which could be attributed to the following reasons: First, Western countries might have a higher frequency of autoimmune diseases, including thyroid dysfunction, than Asian patients. A Korean study showed a low thyroid dysfunction rate (5.9%). Second, the age of onset was young and the duration was short; hence, patients might not have thyroid dysfunction in the early phase but could develop later. Third, many patients had elevated IgE, which was inversely associated with the autoimmune condition. Furthermore, selection bias is critical. Although up to 43.4% of the vitiligo children showed thyroid dysfunction in a Chinese report, the patients were not included consequently. Investigators did not mention how to select these patients and the proportion of those who underwent thyroid tests. Children from different areas of China visited the tertiary hospital, and the severe and

resistant cases or those with suspicious clinical symptoms were prone to take thyroid function tests, thereby resulting in a high dysfunction rate. Strikingly, nearly 90% of our patients had taken the thyroid test, and thus selection bias was probable. Therefore, the current data could provide some useful information about the clinical characteristics of childhood vitiligo.

Nevertheless, the present study had several limitations. In this retrospective study, data were collected from a single center, and the sample size was small. The strengths of the study were as follows: First, our hospital is the National Children's Center, and patients originated from different areas of China. Second, the patients were included consecutively, and the thyroid function test rate was high. Third, a comprehensive review is routine for all the patients in our clinic, and complete data are provided. Although we are a tertiary hospital, the included patients were mainly mild to moderate cases. Thus, this study provided some important evidence on childhood vitiligo.

Conclusion

The present study showed a low thyroid abnormal rate in the consequent vitiligo children. Personal autoimmune history was inversely associated with elevated IgE. Different factors contributed to the etiology of vitiligo. Various clinical characteristics and pathogenesis might contribute to different long-term outcomes of vitiligo.

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Author Contributions

Ting Dai and Liuhui Wang take responsibility for the integrity of the work as a whole, from inception to published article. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data: Ting Dai, Yao Wu, Fulun Li. Drafting the article or revising it critically for important intellectual content: Ting Dai, Wei Song. Final approval of the version to be published: All authors. The authors thank the patients included in this study. We thank all our colleagues who helped to manage these patients.

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