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Pediatric Patients with Vitiligo in Eastern China: Abnormalities in 145 Cases Based on Thyroid Function Tests and Immunological Findings

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Statistical Analysis C
Data Interpretation D
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Background: The aim of this study was to evaluate abnormalities in thyroid function according to tests and the humoral immune systems of patients from Eastern China with pediatric vitiligo.

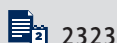
Material/Methods: A total of 145 pediatric patients with vitiligo were investigated in this study, along with 59 children without autoimmune diseases as controls. Laboratory tests of thyroid function were conducted, and these tests examined free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), thyroglobulin antibody (TG-Ab), thyroid peroxidase antibody (TPO-Ab), antinuclear antibodies (ANAs), immunoglobulins (IgA, IgM, and IgG), and complements (C3 and C4).

Results: A total of 63 patients (43.4%), including 39 boys (44.3%) and 24 girls (42.1%), displayed abnormalities in thyroid function according to the tests. This finding indicated that patients with vitiligo differed significantly from those in the control group ($P < 0.001$), particularly in terms of FT3 and TSH abnormalities ($P < 0.05$). However, these groups did not deviate significantly with respect to FT4, Tg-Ab, and TPO-Ab abnormalities ($P > 0.05$). Thirteen patients (8.9%) and 1 (1.7%) control were positive for ANA. All 12 specific antibodies were detected in 8 patients. Anti-SSA/Ro-60 and anti-SSA/Ro-52 were the most prevalent antibodies, followed by anti-dsDNA and then by anti-SmD1 and CENB-P. The serum levels of IgA and IgG decreased more significantly in the vitiligo group than in the control group ($P < 0.001$). However, no significant difference was observed in terms of IgM levels ($P > 0.05$). C4 serum levels also decreased more significantly in the vitiligo group than in the control group ($P = 0.035$).

Conclusions: Results suggest that the incidence of abnormalities in the thyroid functions of children and adolescents is significantly higher in those with vitiligo than that in those in the control group. In addition, immunological dysfunction is common in the vitiligo group.

MeSH Keywords: **Antibodies, Antinuclear • Immunoglobulins • Thyroid Function Tests • Vitiligo**

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Background

Vitiligo is a hypomelanotic, autoimmune skin disease caused by the loss of functional melanocytes from the skin. This disease strikes an estimated 0.5–2% of the general population [1]. It can affect individuals of any age, given that 50% of cases occur before the age of 20 years and 25% are diagnosed before the age of 10 years [2,3]. Although vitiligo is not considered to be extremely serious, individuals with this disease, especially children and adolescents, may have high stress, low self-esteem, and difficulty at work and school [4].

To date, the pathogenesis of vitiligo remains unclear. Three major theories have been proposed to explain it [5–10]. One of the most popular theories considers vitiligo as an autoimmune disease because much evidence confirms the role of autoimmunity in vitiligo [5,6]. Some studies reported that the melanocytes could be damaged by a toxin released from the nerve endings or that they produced [7]. Furthermore, some possible etiological factors were proposed to be involved in the depigmentation process, such as the deficiency of melanocyte growth factors and structure or function of melanocytes [8–10].

However, none of these theories can explain the onset of vitiligo alone, possibly because many factors are involved in its pathogenesis. Research has indicated that the onset of vitiligo is associated with the immune function, particularly humoral immunity [11,12]. In fact, the presence of organ-specific autoantibodies and its complements in the sera of vitiligo patients facilitate this onset of this disease [13].

Several studies have suggested that vitiligo is frequently associated with many other autoimmune diseases, including thyroid disease, alopecia areata, systemic lupus erythematosus (SLE), psoriasis, and diabetes mellitus type 1. Vitiligo commonly coexists with such diseases in a maximum of 20% of cases [14–16]. Therefore, the aim of the present study was to investigate the association between vitiligo and thyroid disease in 145 patients aged younger than 17 years and to examine the immunologic serum parameters, such as antinuclear antibodies [ANAs], complements, and immunoglobulins, which suggest immune and autoimmune activity.

Material and Methods

Patients and controls

Vitiligo patients ($n=145$) younger than 17 years old were sampled from May 2012 to December 2014. The diagnosis by several expert dermatologists was based on the history and physical examination, including Wood's light assessment [17]. Furthermore, these individuals were all patients of

the Outpatient Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union. This study was approved by Ethics Committee of the Chinese Academy of Medical Sciences and Peking Union. All patients included in this study signed an informed consent. This institute is the most important center of dermatology in Nanjing City. The patients mainly resided in Jiangsu Province and Anhui Province in Eastern China. Moreover, 59 individuals (29 male and 30 female adolescents) without autoimmune diseases were sampled as controls.

Sample collection and processing

Serum samples were obtained from these patients and from the controls. The samples were centrifuged at 5000 rpm under 4°C for 10 min. All sera were then frozen at –20°C no more than 3 days until required.

Thyroid function tests

The tests of thyroid function included free triiodothyronine (FT3) (reference range: 3.8–6.0 pmol/L), free thyroxine (FT4) (reference range: 7.9–17.2 pmol/L), thyroid-stimulating hormone (TSH) (reference range: 0.2–4.0 nmol/L), thyroglobulin antibody (Tg-Ab) (reference range: 0–4 IU/ml), and thyroid peroxidase antibody (TPO-Ab) (reference range: 0–9 IU/ml). The levels were determined through chemiluminescence (Beckman Coulter Unicel Dxl800, CA, USA).

ANAs detection

Fluoro Hepana Test kits (MBL, Nagoya, Japan) were used to detect ANAs. The cells proliferated in HEp-2 and were then fixed on slides. During the first stage of this test, serum was added to the cells at a titer of 1:20. The cells were then washed 3 times with phosphate-buffered saline after 30 min of incubation. Fluorescein-iso-thio-cyanate-conjugated, anti-human immunoglobulin from goats was added to each well on the slide. Finally, the samples were assessed with a fluorescent microscope after incubation and washing. The line immunoassay (Human, Magdeburg, Germany) is an indirect membrane-based enzyme immunoassay that is used to qualitatively measure IgG-class antibodies against nucleosomes, dsDNA, histones, SmD1, U1-snRNP, SS-A/Ro60KD, SS-A/ Ro52KD, SS-B/La, Scl70, CENP-B, Jo1, and P0. The test strips were first inserted into the incubation tray, and samples diluted at a titer of 1:100 were then added. Subsequently, the anti-human-IgG conjugate was incorporated after 60 min of incubation and washed 3 times. Finally, the test strips were assessed after a stop solution was added.

Table 1. Age distribution of the patients with vitiligo and of the controls.

Age group (year old)	Vitiligo group (n,%)	Control group (n,%)
2–5 (preschool age)	13 (8.97)	6 (10.34)
6–11 (school age)	68 (46.90)	22 (37.93)
12–17 (adolescents)	64 (44.14)	30 (51.72)

Table 2. Level of thyroid function abnormality as per tests conducted on the pediatric patients with vitiligo and on the controls.

Tests	Vitiligo group		Total	Control group		Total
	Male (n,%)	Female (n,%)		Male (n,%)	Female (n,%)	
FT3	28 (31.28)	12 (21.05)	40 (27.59)**	1 (3.23)	2 (7.14)	3 (5.08)
FT4	4 (5.26)	3 (4.55)	7 (4.83)	1 (3.23)	1 (3.57)	2 (3.39)
TSH	13 (14.77)	5 (8.77)	18 (12.41)*	2 (6.45)	0 (0.00)	2 (3.39)
Tg-Ab	5 (8.77)	3 (3.41)	8 (5.22)	2 (6.45)	1 (3.57)	3 (5.22)
TPO-Ab	4 (4.55)	6 (10.53)	10 (6.90)	1 (3.23)	2 (7.14)	3 (5.22)

* P<0.01; ** P<0.05.

Immunoglobulins (IgA, IgM, and IgG) and complements (C3 and C4)

The levels of IgA, IgM, and IgG were determined with immunoturbidimetry (Beckman Coulter Unicel AU680, CA, USA), along with those of the complements (C3 and C4). The levels of the immunoglobulins were compared with the reference ranges (IgA: 0.7–4.29 g/L, IgM: 0.29–3.4 g/L, and IgG: 8–17 g/L). The C3 and C4 levels were compared with the normal ranges (C3: 0.78–2.1 g/L; C4: 0.17–0.4 g/L).

Statistical analysis

Chi-square tests and Fisher's exact probability were used to identify the differences between the 2 groups in terms of FT3, TSH, FT4, Tg-Ab, and TPO-Ab abnormalities. Moreover, a t test was performed to compare the immunological parameters of the patients (P<0.05 indicated statistical significance). These statistical analyses were conducted with SPSS 13.0 (SPSS Inc., Chicago, USA).

Results

Characteristics of patients

A total of 145 pediatric patients with vitiligo were enrolled in the study. Their ages ranged between 2 and 17 years.

Eighty-eight (60.7%) patients were male and 57 (39.3%) were female (male: female=1.54:1). Twenty-nine (49.1%) controls were male and 30 (50.9%) were female (male: female=1:1.03). The mean age of the patients was 10.73±3.73 years. Thirteen (8.9%) patients were aged between 2 and 5 years; 68 (46.9%) patients were between 6 and 11 years; and 64 (45.2%) patients were between 12 and 17 years. The mean age of the controls was 11.07±4.08 years. The 2 groups did not differ significantly in terms of age (P=0.57) (Table 1).

Thyroid function tests

Of the 63 patients (43.4%) with thyroid diseases, 39 (44.3%) were male and 24 (42.1%) were female. No significant difference was observed in terms of sex (P=0.285). Of the controls diagnosed with abnormal thyroid function according to tests and with thyroid autoantibodies, 4 (13.8%) were male and 4 (13.3%) were female. The 2 groups differed significantly in statistical comparison of the number of the times they took the thyroid function test (P<0.001).

A total of 40 (27.6%) patients and 3 (5.1%) controls were diagnosed with FT3 abnormality. The difference between the 2 groups was statistically significant (P<0.05). TSH abnormality was significantly higher in patients than in the controls (P<0.01). We also found 7, 8, and 10 patients with FT4, Tg-Ab, and TPO-Ab abnormalities, respectively, which was higher than in the control group, but the difference was not significant

Table 3. The frequency of twelve specific antibodies in different groups.

Test item	Vitiligo group		Control group		P value
	Positive (n)	Positive rate (%)	Positive (n)	Positive rate (%)	
ANA	13	8.9	1	1.7	0.072
Nucleosomes	0	0	0	0	–
dsDNA	2	1.4	0	0	1.000
Histones	0	0	0	0	–
SmD1	1	0.7	0	0	1.000
U1-snRNP	0	0	0	0	–
SS-A/Ro60KD	3	2.1	1	1.7	1.000
SS-A/Ro52KD	0	0	0	0	–
SS-B/La	3	2.1	0	0	0.558
Sc1-70	0	0	0	0	–
CENP-B	1	0.7	0	0	1.000
Jo1	0	0	0	0	–
P0	0	0	0	0	–

Table 4. Comparison of the levels of immunological parameters.

Variable	Vitiligo group (n=145)	Control group (n=59)	t	P value
IgG	8.67±2.20	10.35±1.98	5.08	<0.001
IgA	1.09±0.47	1.51±0.76	4.77	<0.001
IgM	1.59±0.59	1.57±0.51	0.16	0.871
C3	1.09±0.18	1.11±0.23	0.92	0.358
C4	0.19±0.06	0.21±0.06	2.17	0.031

Values are expressed as mean ±SD.

($P>0.05$) (Table 2), and the positivity of these 2 antibodies together was present in a total of 7 (4.8%) patients.

Of the 40 patients in whom thyroid function tests and/or thyroid antibodies were abnormal, 6 (4.1%) had a high TSH level and normal FT3 and FT4 levels and were evaluated as having subclinical hypothyroidism, and 4 (2.8%) patients had high FT3 and FT4 and low TSH levels with TPO-Ab and TG-Ab activity were evaluated as having hypothyroidism and autoimmune thyroiditis.

ANAs detection

Thirteen patients (8.9%) and 1 (1.7%) control were positive for ANAs. Nonetheless, the rates of ANAs positivity were not statistically significant ($P=0.072$). Five patients exhibited ANA titers $>1:40$, and 8 patients displayed ANA titers $>1:80$. All 12

specific antibodies were detected in 8 out of 13 patients with ANA titers $>1:40$; anti-SSA/Ro-60 and anti-SSA/Ro-52 (2.1%) were the most prevalent antibodies, followed by anti-dsDNA (1.4%) and then by anti-SmD1 and CENP-P (0.7%) (Table 3).

Levels of immunological parameters IgA, IgM, IgG, C3, and C4

The serum levels of IgA and IgG decreased more significantly in the vitiligo group than in the control group ($P<0.001$). However, the 2 groups did not differ significantly in terms of IgM levels ($P>0.05$). Nine (6.2%) patients had a decrease in C3 serum level, but none of the controls had this result ($P=0.114$). Moreover, the serum levels of C4 decreased in 51 patients (35.2%). This percentage was significantly higher than that in the control group ($P=0.035$) (Table 4).

Discussion

Vitiligo is a relatively common skin problem in children and adolescents, especially in China. Although the cause of this disease is unclear, the autoimmune hypothesis is supported by clinical examinations of human and animal models [18–20]. Thus far, only a few studies have compared the humoral immune system factors of children with vitiligo with those of normal children in China. In the current study, we examined 145 pediatric vitiligo patients who are aged below 17 years and reside in Eastern China to evaluate the coexistence of autoimmune diseases within their immune systems.

The results of the survey conducted by Wang et al. in 6 Chinese cities showed that the number of girls with vitiligo is higher than that of boys. However, our data differ from those considered in the report by Wang et al. in that we obtained similar numbers of male and female patients [21]. As with the Wang et al. study, however, 46.9% of children with vitiligo were aged between 6 and 10 years in our research [22].

Vitiligo is commonly associated with other autoimmune diseases, especially autoimmune thyroid diseases such as irido-choroidal vitiligo [23]. Afsar et al. [24] reported that 25.3% of children experienced thyroid dysfunction. Specifically, 2.5% were diagnosed with hypothyroidism and 6.3% with euthyroidism. In our study, we also noted a high prevalence of thyroid dysfunction in 43.4% of the children with vitiligo. This dysfunction was particularly evident in the elevated FT3 and TSH levels. The prevalence of subclinical hypothyroidism was higher (4.1%) than that in <2% in the pediatric age. Although subclinical hypothyroidism is a laboratory diagnosis with no significant findings or symptoms in patients, studies have demonstrated the development of overt hypothyroidism at a rate of 5–20% per year, especially in autoimmune thyroiditis [24,25]. Kroon et al. [17] indicated that the presence of TG-Ab and TPO-Ab may serve as an immunological marker for the screening of autoimmune thyroid diseases prior to clinical diagnosis in adults. These 2 antibodies can also be used to perform a pre-diagnosis of the children and adolescents in our study, given that TG-Ab and TPO-Ab levels were high in 9.5% of the patients. This prevalence was higher than that reported in studies conducted in the Netherlands. Furthermore, the prevalence of these antibodies increased with age in our study, but only in females [26]. Thus, dermatologists must perform a follow-up checkup on and monitor the thyroid function parameters of pediatric patients with vitiligo.

Aside from thyroid disease, other autoimmune diseases are also associated with vitiligo. The presence of positive autoantibodies in the sera, especially high titers of ANA, is important in the diagnosis of autoimmune disease. In our study, we determined that 13 patients (8.9%) were positive for ANA. However, the

titers were low and ranged from 1:40 to 1:80. Moreover, the relationship between vitiligo and ANA was not statistically significant. These results agree with those of Farrokhi et al. [12]. In addition, all 12 specific antibodies were detected in 8 patients, which differed from the control group. Anti-SSA/Ro-60 and anti-SSA/Ro-52 (2.1%) were the most prevalent antibodies, followed by anti-dsDNA (1.4%) and then by anti-SmD1 and CENB-P (0.7%). This finding varied from that of a study conducted on the general population in China [26]. Furthermore, ANA and the 12 specific antibodies may not serve as the markers for pediatric vitiligo in our investigation.

In the present study, IgG and IgA levels decreased in one-third of the patients. This proportion was significantly higher than that of the control group. Moreover, IgM level increased insignificantly in pediatric patients with vitiligo in comparison with that observed in the controls. The findings presented by Ali et al. [27] agreed with our findings in that IgG and IgA levels decreased more significantly in 30 patients ($P < 0.05$) than in the controls. However, the change in IgM level was not significant. C4 levels also decreased in one-fifth of the patients. Similarly, this proportion was significantly higher than that of the control group. C3 levels were also lower in patients than in the controls. However, this difference was not statistically significant. Farrokhi et al. [12] determined that C3 and C4 levels decreased in 14 patients (25.5%). This proportion was significantly higher than that in the control group ($P < 0.001$). Moreover, Venneker et al. [28] analyzed the functional activities of C4 in 42 patients with vitiligo and indicated that 7 of them exhibited C4 deficiency. This prevalence was higher than that in the control group. These significant differences in the lowered levels of immunoglobulins and complements suggested that the onset of vitiligo in pediatric patients may be strongly correlated with humoral immunity. This finding is well-supported by previous reports that the antibodies acting against melanocyte antigens in sera damaged melanocytes through the classical pathway of complement activation and antibody-dependent cellular cytotoxicity [29]. Recently, studies reported that vitiligo patients might have common variable immunodeficiency (CVID) as well as other autoimmune disorders [30,31]. However, whether CVID is the reason why immunological dysfunction is common in the vitiligo group is still unknown. As a consequence, we need follow the CVID outcome of these participants for several years to determine the association between vitiligo and immunological dysfunction. Basic research to explore the mechanism of thyroid and immunological effect on vitiligo cells [32] *in vitro* is also important.

Conclusions

Our data indicated a high prevalence of thyroid dysfunction and humoral immunity disorders in children with vitiligo from

eastern China. These findings focus attention on the risk and symptoms of thyroid disease and lead us to consider the importance of the immune system in the pathogenesis of vitiligo.

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