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ORIGINAL ARTICLE

The initial manifestations and final diagnosis of patients with high and low titers of antinuclear antibodies after 6 months of follow-up

Kun-Yi Wang [a,b], Yao-Hsu Yang [a], Ya-Hui Chuang [c], Pei-Jung Chan [d], Hsin-Hui Yu [a], Jyh-Hong Lee [a], Li-Chieh Wang [a], Bor-Luen Chiang [a,*]

[a] *Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan*
[b] *Department of Pediatrics, Taitung Christian Hospital, Taitung, Taiwan*
[c] *Department of Clinical Laboratory Sciences and Medical Biotechnology, National Taiwan University, Taipei, Taiwan*
[d] *Department of Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan*

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Background: The antinuclear antibody (ANA) test is the most commonly used test to screen for autoimmune diseases. However, only a limited numbers of studies have addressed the characteristics of patients positive for ANA. In this study, we aimed to clarify the relationship between initial presentations, ANA titer, and final diagnoses.
Methods: Patients who visited National Taiwan University Hospital and received a first ANA test were enrolled and then followed for a further 6 months. The symptoms and signs at the time of ANA testing, ANA titers, and the final diagnoses were recorded and analyzed.
Results: A total of 355 patients were positive for ANA. Joint pain was the most common initial presentation at the time of ANA testing. Compared with the patients with low ANA titers ($<$1:640), those with high ANA titers ($\geq$1:640) were more susceptible to autoimmune diseases. More importantly, of the patients with initial presentations of joint pain, fever, abnormal urinalysis, or skin rash/skin tightness, autoimmune diseases were more frequently diagnosed in those with high ANA titers than with low ANA titers ($p < 0.05$). In addition, both anti-double strand DNA antibodies and anti-extractable nuclear antibodies were more commonly detected in patients with high ANA titers.

* Corresponding author. Department of Pediatrics, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 10002, Taiwan.
E-mail address: gicmbor@ntu.edu.tw (B.-L. Chiang).

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Conclusions: A high ANA titer seems to be a useful biomarker for the diagnosis of autoimmune diseases, especially for patients presenting with joint pain, fever, abnormal urinalysis, or skin rash/skin tightness.

Introduction

Autoantibodies directed against nuclear and cytoplasmic components of tissue cells have been known to play an important role in autoimmune diseases for several decades.[1,2] The methods used to detect antinuclear antibodies (ANAs) evolved from the lupus erythematosus cell phenomenon into indirect immunofluorescence assay and enzyme-linked immunosorbent assay. At present, the ANA test is the most commonly used autoantibody test and also one of the most over ordered tests in the clinical laboratory.[3] Many clinicians use the ANA test to screen for autoimmune diseases, including systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), systemic sclerosis (SSc), and mixed connective tissue disease. However, ANA can be detected not only in autoimmune diseases but also in other medical conditions, such as liver disease, malignancy, chronic infections, and thyroid disease.[3]

Although many studies have reported the distribution of various ANA titers, patterns, and associated diseases, there are only limited data available on the relationship between initial presentations, different ANA titers, and final diagnoses. In addition, Vaile et al.[4] concluded that setting a higher ANA titer cutoff point (1:640) is of limited benefit to predict autoimmune disease. The purpose of our study is to clarify the relationship between initial presentations, ANA titers, and final diagnoses and combined with initial presentations, to determine whether the patients with high ANA titers are more susceptible to autoimmune diseases.

Material and methods

From September 2007 to March 2008, the patients who visited National Taiwan University Hospital and received a first ANA test were enrolled. ANA were detected by immunofluorescence assay techniques using human epithelial tumor cell lines, HEp-2 cells as substrate, and an immunoglobulin G-specific conjugate to reveal ANA binding. Because more than 30% of normal individuals have been found to have low ANA titers,[5] the patients with negative or positive results at a titer of 1:40 were excluded. In our laboratory, an ANA titer of 1:640 is defined as a "high titer" because of a 0.5% prevalence of positives in normal individuals. Therefore, we divided the patients into a high titer group ($\geq$1:640) and low titer group ($<$1:640). The initial symptoms and signs on presentation were recorded and divided into 14 categories (shown in Table 1). Tests for anti-extractable nuclear antigen (anti-ENA) or anti-double strand DNA (anti-dsDNA) were also performed subsequently in some patients. The patients positive for ANA were followed for a further 6 months. The final diagnoses were then classified into three major categories (shown in Table 2); autoimmune diseases, nonautoimmune diseases, and not confirmed. Systemic autoimmune diseases and organ-specific autoimmune diseases were categorized together as autoimmune diseases. The nonautoimmune diseases were subdivided into seven categories.

All statistical analyses were performed using SPSS software version 15.0. (SPSS Inc., Chicago, IL, USA). Differences between groups in categorical variables were examined

Table 1 The initial presentations of patients positive for ANA test

Initial presentations	Total (n = 355), n (%)	Adult (n = 320), n (%)	Child (n = 35), n (%)
Hematologic problems	35 (9.9)	32 (10)	3 (8.6)
Abnormal urinalysis findings	12 (3.4)	10 (3.1)	2 (5.7)
Liver function impairment	36 (10.1)	34 (10.6)	2 (5.7)
Joint pain	132 (37.2)	116 (36.4)	16 (45.7)
Muscle weakness/myalgia	7 (2.0)	5 (1.6)	2 (5.7)
Oral lesions	23 (6.5)	22 (6.9)	1 (2.9)
Raynaud's phenomenon	14 (3.9)	13 (4.1)	1 (2.9)
Skin presentations[a]	51 (14.4)	38 (11.9)	13 (37.1)
Sicca syndrome	44 (12.4)	44 (13.8)	0 (0)
Lymphadenopathy	7 (2.0)	6 (1.9)	1 (2.9)
Cardiopulmonary s/s	17 (4.8)	17 (5.3)	0 (0)
Neuropsychologic problems	21 (5.9)	20 (6.3)	1 (2.9)
Fever	28 (7.9)	24 (7.5)	4 (11.4)
Others	9 (2.5)	9 (2.8)	0 (0)

[a] Skin presentations included skin rash or skin tightness.
ANA = antinuclear antibody; s/s = symptoms/signs.