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SHORT COMMUNICATION

# Clinical characteristics of children with positive anti-SSA/SSB antibodies

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**Abstract** This study aimed to characterize the manifestations of clinical symptoms and signs, primary rheumatic diseases, and other autoantibodies in pediatric patients with positive anti-SSA and/or anti-SSB antibodies. Subjects under age 18 with positive anti-SSA and/or anti-SSB antibodies were screened and enrolled in a tertiary hospital in Taiwan. Data were collected via medical records, including age, gender, onset of the primary rheumatic disease, clinical symptoms and signs, and the medication used. Schirmer test for Sjögren's syndrome (SS) screening was performed in all enrolled patients. Among twenty enrolled subjects, seventeen of them had systemic lupus erythematosus; four of them were diagnosed as SS with positive Schirmer test. In addition to antinuclear antibodies and anti-DNA antibodies, other common autoantibodies were anti-RNP antibodies (50 %) and anti-Sm antibodies (30 %). The most common symptoms were arthritis (60 %) followed by malar rash (40 %). In conclusion, we observed that a low proportion of childhood SS (4/20) exists in our patients with positive SSA and/or anti-SSB antibodies. It is suggested that clinicians should focus more on the clinical symptoms in these patients, rather than undertaking invasive diagnostic interventions to rule out Sjögren's syndrome.

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## Introduction

Antibodies to SSA(Ro) and SSB(La) are two kinds of human autoantibodies that have been correlated with autoimmune diseases. In adult patients, they have been found to be associated with a variety of primary rheumatic diseases such as systemic lupus erythematous (SLE), Sjögren's syndrome (SS), rheumatic arthritis (RA), systemic sclerosis and dermatomyositis, malignancy, fibromyalgia, spondyloarthropathy, polymyalgia rheumatica, polyneuritis, sensitivity hemisyndrome, mothers of children with neonatal lupus, lymphocytic infiltration of the skin, and hepatitis C virus infection [1, 2]. Furthermore, the prevalence of isolated anti-SSA antibodies has been reported to approximately 0.5 % [3].

Anti-SSA and anti-SSB antibodies are found in 60–90 % of adult patients with SS [4]. SS is a chronic autoimmune disease characterized by xerosis of the exocrine glands, and in particular the lacrimal and salivary glands. In some patients, more extensive xerosis may involve the skin, respiratory tract, or urogenital tract. Furthermore, abnormalities of systemic, hematological, and immunological features have been found in SS [5]. To date, no evidence of a relationship between anti-SSA/anti-SSB antibodies and SS in pediatric patients has been found. In addition, to the best of our knowledge, there have not been any studies regarding an association between anti-SSA/anti-SSB antibody and other autoantibodies.

The aim of this study was to describe the manifestations of clinical symptoms and signs, primary rheumatic diseases, and other autoantibodies in pediatric patients with positive anti-SSA and/or anti-SSB antibodies.

## Methods

From December 2006 to December 2011, subjects under age 18 with positive anti-SSA and/or anti-SSB antibodies were screened and enrolled at the Division of Pediatric Rheumatology, Department of Pediatrics, National Taiwan University Hospital. Data were collected via medical records, including age, gender, onset of the primary rheumatic disease, clinical symptoms and signs, and the medication used. All of the enrolled subjects (positive anti-SSA and/or anti-SSB) received a Schirmer's test instead of invasive parotid sialography or salivary scintigraphy. Self-reported questionnaires for eye and oral symptoms were also performed. Laboratory data associated with their primary rheumatic disease were collected, including anti-SSA, anti-SSB, anti-DNA, anti-Sm, anti-RNP, anti-scl70, and anti-Jo-1.

## Results

Twenty patients with positive anti-SSA and/or anti-SSB antibodies were enrolled, including three boys and seventeen girls. The median age was 13.9 years (range 10–18 years). The average onset age of primary rheumatic disease was 11.2 years (range 2–18 years). The primary rheumatic diseases included SLE (16/20), vasculitis (1/20), autoimmune lymphoproliferative syndrome (1/20), mucosa-associated lymphoid tissue lymphoma (1/20), and Sjögren's syndrome (4/20). The medications used were non-steroid anti-inflammatory drugs (6/20), hydroxyquinine (20/20), azathioprine (8/20), methotrexate (2/20), steroids (14/20), and other immunosuppressive drugs (mycophenolate mofetil, 4/20; cyclosporine, 7/20; methotrexate, 2/20). All of the baseline characteristics of these patients are summarized in Table 1.

**Table 1** Baseline characteristics and primary disease in our patients

| No. | Age | Sex | Onset age | Rheumatology disease | Current medication |
|---|---|---|---|---|---|
| 1 | 17 | F | 17 | SLE | PLA, STE, AZA |
| 2 | 12 | F | 10 | SLE | PLA, MMF |
| 3 | 18 | F | 14 | SLE | PLA, STE, CYC |
| 4 | 10 | M | 2 | ALPS, SS, SLE | PLA, STE, AZA, MMF |
| 5 | 14 | M | 12 | SLE | PLA, STE, CYC |
| 6 | 17 | F | 8 | SLE | PLA, STE, CYC, MMF |
| 7 | 15 | F | 12 | SLE | PLA, STE, MTX, CYC |
| 8 | 14 | F | 11 | SLE | PLA, STE, AZA |
| 9 | 14 | M | 11 | SLE | PLA, STE, CYC, MTX, NSA |
| 10 | 14 | F | 14 | SLE | PLA, STE, NSA |
| 11 | 18 | F | 14 | SLE, SS | PLA |
| 12 | 11 | F | 3 | Vasculitis | PLA, AZA, NSA |
| 13 | 17 | F | 17 | SLE | PLA, STE, AZA |
| 14 | 19 | F | 12 | SLE | PLA, STE, MMF |
| 15 | 17 | F | 17 | SLE | PLA, STE, AZA |
| 16 | 14 | F | 12 | MALT lymphoma | PLA, MMF, NSA |
| 17 | 14 | F | 14 | SLE | PLA, STE, NSA |
| 18 | 11 | F | 11 | SLE | PLA, STE, CYC |
| 19 | 7 | F | 4 | SS | PLA, AZA, NSA |
| 20 | 10 | F | 8 | SLE, SS | PLA, STE, AZA |

*SLE* systemic lupus erythematous, *ALPS*, autoimmune lymphoproliferative syndrome, *SS* Sjogren syndrome, *MALT* Mucosa-associated lymphoid tissue, *PLA* Plaquenil (hydroxychloroquine), *STE* steroid, *AZA* azathioprine, *MMF* mycophenolate mofetil, *CYC* cyclosporine, *MTX* methotrexate, *NSA* (*NSAID*) non-steroid anti-inflammatory drug

According to the results of the self-report questionnaire, eight patients had eye symptoms (8/20, 40 %), and ten had oral symptoms (10/20, 50 %). In addition to questionnaire, all of them received Schirmer's test. Only four patients were documented as dry eye by this test.

The immunological profiles for the primary rheumatic disease are summarized in Table 2. The positive rate of antinuclear antibodies (ANA) was 19/20 (95 %), and positive rate of anti-DNA was 17/20 (85 %). All of the twenty patients had anti-SSA antibodies (20/20, 100 %), and seven had anti-SSB antibodies (7/20, 35 %). Other autoantibodies found in the patients, including anti-Sm (6/20, 30 %) and anti- RNP (10/20, 50 %); however, anti-scl70 and anti-Jo-1 antibodies were not found in any patient.

The symptoms during follow-up are shown in Table 3. The two most common symptoms were arthritis (12/20, 60 %) and malar rash (8/20, 40 %). Other symptoms including discoid rash, photosensitivity, skin purpura, oral ulcers, and enthesitis were present and associated with their primary rheumatic disease.

There were three special cases of note in our study. The first one, case number 12, had had vasculitis since 3 years of age, and several attacks of parotitis were noted once or twice per year. She was our only one case with primary rheumatic disease as vasculitis. The second case of note was a male patient, case number 4, who had had autoimmune lymphoproliferative disease (ALPS) since 2 years of age. The initial presentations were general lymphadenopathy, hepatomegaly, skin rash, serositis, and thrombocytopenia. Despite evidence of genetic defect as Type III or Type IV ALPS, he was diagnosed with ALPS by clinical symptoms and signs. Episodes of pleuritis and appendicitis had also occurred, which may have been the consequence of using immunosuppressants, including steroids, azathioprine, and mycophenolate mofetil.

**Table 2** Laboratory data associated with primary rheumatic disease

| No. | Rheumatology disease | Anti-SSA | | Anti-SSB | ANA (1:X) | Anti-DNA | Anti-Sm | Anti-RNP | Anti-scl70 | Anti-Jo-1 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | SLE | + | + | | +(2560) | 526 | + | + | − | − |
| 2 | SLE | + | − | | +(1280) | 1190 | − | + | − | − |
| 3 | SLE | + | + | | +(320) | 647 | + | + | − | − |
| 4 | ALPS, SS, SLE | + | − | | +(320) | 400 | + | + | − | − |
| 5 | SLE | + | − | | +(40) | 248 | − | − | − | − |
| 6 | SLE | + | + | | +(2560) | 1400 | − | + | − | − |
| 7 | SLE | + | + | | +(2560) | 822 | + | + | − | − |
| 8 | SLE | + | − | | +(40) | 539 | − | − | − | − |
| 9 | SLE | + | − | | +(320) | 755 | − | + | − | − |
| 10 | SLE | + | − | | +(2560) | <87.5 | − | − | − | − |
| 11 | SLE, SS | + | − | | +(320) | 1240 | − | − | − | − |
| 12 | Vasculitis | + | + | | +(1280) | NA | − | − | − | − |
| 13 | SLE | + | − | | +(320) | 941 | − | − | − | − |
| 14 | SLE | + | − | | +(40) | 402 | + | + | − | − |
| 15 | SLE | + | − | | +(640) | 1000 | + | + | − | − |
| 16 | MALT lymphoma | + | − | | +(1280) | <87.5 | − | − | − | − |
| 17 | SLE | + | + | | +(320) | 197 | − | − | − | − |
| 18 | SLE | + | + | | +(1280) | 1130 | − | − | − | − |
| 19 | SS | + | − | | 0 | <87.5 | − | − | − | − |
| 20 | SLE, SS | + | − | | +(320) | 178 | − | + | − | − |

*SLE* systemic lupus erythematous, *ALPS* autoimmune lymphoproliferative syndrome, *SS* Sjogren syndrome, *MALT* Mucosa-associated lymphoid tissue, *NA* not applicable

**Table 3** Other related symptom and signs

| Symptoms | Case number (%) |
|---|---|
| Malar rash | 8 (40) |
| Discoid rash | 3 (15) |
| Skin purpura | 6 (30) |
| Photosensitivity | 1 (5) |
| Oral ulcers | 4 (20) |
| Arthritis | 12 (60) |
| Enthesitis | 1 (5) |
| Serositis | 3 (15) |
| Renal involvement | 5 (25) |
| Neurological disorder | 2 (10) |
| Hematological disorder | 4 (20) |
| Alopecia | 3 (15) |
| Gastrointestinal symptoms | 5 (25) |
| Abdominal pain | 2 |
| Appendicitis | 1 |
| Hepatitis | 1 |
| Gastroesophageal reflux | 1 |
| Others | 2 (10) |
| Precocious puberty | 1 |
| Past history of Kawasaki disease | 1 |

The third patient, case number 18, was the only case associated with malignancy. Mucosa-associated lymphoid tissue lymphoma originating from the thymus was diagnosed when she was 11 years old. After surgical excision and chemotherapy, she had been disease free for 3 years. However, occasional vasculitis over bilateral legs was noted. Although she had several high-risk factors for Sjögren's syndrome, including positive anti-SSA, anti-SSB antibodies, and mucosa-associated lymphoid tissue lymphoma, no clinical symptoms or signs compatible with Sjögren's syndrome were found.

## Discussion

This is the first study to describe the clinical characteristics of pediatric patients with anti-SSA and/or anti-SSB antibodies. The target antigens of anti-SSA and anti-SSB antibodies are 60 KD Ro (Ro 60, one subgroup of anti-SSA antibody) and 48 KD La (La 48, one subgroup of anti-SSB antibody) nucleocytoplasmic ribonucleoprotein [6, 7]. In addition, the 52 KD Ro (Ro 52, one subgroup of anti-SSA antibody) protein is another target in mothers whose children have congenital heart block (CHB) [8]. Because more

than 75 % of the sera from mothers whose children have CHB contain the antibody to 52 KD Ro [9], anti-Ro 52 is used clinically for predicting the risk of CHB. Anti-SSA antibody is also associated with other connective tissue disease, such as SLE, that mainly affected patients' risk of SS [10]. In our study, we did not screen the subtypes of anti-SSA and anti-SSB antibody because our patients did not have problems such as congenital heart block. In addition, the method to differentiate subtypes of anti-SSA and anti-SSB is not available in our laboratory.

In adult group, anti-SSA and anti-SSB antibodies are highly correlated with SS. Such autoantibodies were abundant in one study in the Netherlands, which revealed that anti-SSA and/or anti-SSB antibodies were 80 % in adults with SS [11]. In other study, anti-SSA and anti-SSB are found in 60–90 % of adult patients with SS [4]. In our study, pediatric patients with anti-SSA and/or anti-SSB have low risk of having SS (4/20). On the other hand, long-term follow-up is necessary to observe if these patients will or not be attacked by SS in the future.

Our study is remarkable in that anti-ENA, anti-SSA, anti-SSB, anti-Sm, anti- RNP, anti-scl70, and anti-Jo1 antibodies were all investigated in our patients. In these antibodies, anti-scl70 and anti-Jo1 antibodies are highly correlated with systemic sclerosis [12] and dermatomyositis [13, 14]. These two antibodies were not found in our study that might be due to relatively low case number in the study. In addition, anti-Sm antibodies are specific to SLE [15], and that was also compatible with our data in Table 2. Six patients who had anti-Sm antibody were diagnosed as SLE, except case number 4 was also diagnosed with ALPS.

The most common symptoms and signs in our study were arthritis and malar rash, which are common signs in connective tissue diseases, and especially in SLE. The diagnostic criteria of SLE were revised in 1997 [16], and most of the clinical signs and symptoms found in our study are included in these criteria. Interestingly, case number 20 had a main diagnosis of SS with other presentations of abdominal pain, neurological disorder (headache), precocious puberty (under hormone therapy), and a history of Kawasaki disease.

There are several limitations to this study. First, the case number was small. Second, patients with anti-SSA and/or anti-SSB antibodies without rheumatoid disorders were not enrolled in this study as a control group, so we cannot know the true prevalence of anti-SSA and/or anti-SSB antibodies in whole population. Finally, long-term follow-up is needed to see if these patients have more symptoms or other diseases in the future.

In conclusion, we observed that a low proportion of childhood SS (4/20) exists in our patients with positive SSA and/or anti-SSB antibodies. Arthritis and malar rash were the two most common symptoms and signs. It is suggested that we should focus more on the clinical symptoms of SS in patients with anti-SSA and/or anti-SSB antibodies, rather than undertaking invasive diagnostic interventions to rule out Sjögren's syndrome.

## References


1. Bartunkova J, Sediva A, Vencovsky J, Tesar V (1999) Primary Sjogren's syndrome in children and adolescents: proposal for diagnostic criteria. Clin Exp Rheumatol 17:381–386
2. Peene I, Meheus L, De Keyser S, Humbel R, Veys EM, De Keyser F (2002) Anti-Ro52 reactivity is an independent and additional serum marker in connective tissue disease. Ann Rheum Dis 61:929–933
3. Langguth DM, Morris S, Clifford L, Wilson RJ, Neil J, Hogan PG et al (2007) Specific testing for "isolated" anti-52 kDa SSA/Ro antibodies during standard anti-extractable nuclear antigen testing is of limited clinical value. J Clin Pathol 60:670–673
4. Ramos-Casals M, Solans R, Rosas J, Camps MT, Gil A, Del Pino-Montes J et al (2008) Primary Sjogren syndrome in Spain: clinical and immunologic expression in 1010 patients. Medicine (Baltimore) 87:210–219
5. Houghton K, Malleson P, Cabral D, Petty R, Tucker L (2005) Primary Sjogren's syndrome in children and adolescents: are proposed diagnostic criteria applicable? J Rheumatol 32: 2225–2232
6. Ben-Chetrit E, Gandy BJ, Tan EM, Sullivan KF (1989) Isolation and characterization of a cDNA clone encoding the 60-kD component of the human SS-A/Ro ribonucleoprotein autoantigen. J Clin Invest 83:1284–1292
7. Chan EK, Francoeur AM, Tan EM (1986) Epitopes, structural domains, and asymmetry of amino acid residues in SS-B/La nuclear protein. J Immunol 136:3744–3749
8. Ben-Chetrit E, Chan EK, Sullivan KF, Tan EM (1988) A 52-kD protein is a novel component of the SS-A/Ro antigenic particle. J Exp Med 167:1560–1571
9. Buyon JP, Waltuck J, Caldwell K, Crawford B, Slade SG, Copel J et al (1994) Relationship between maternal and neonatal levels of antibodies to 48 kDa SSB(La), 52 kDa SSA(Ro), and 60 kDa SSA(Ro) in pregnancies complicated by congenital heart block. J Rheumatol 21:1943–1950
10. Yao Q, Altman RD, Wang X (2012) Systemic lupus erythematosus with Sjogren syndrome compared to systemic lupus erythematosus alone: a meta-analysis. J Clin Rheumatol 18:28–32
11. ter Borg EJ, Risselada AP, Kelder JC (2011) Relation of systemic autoantibodies to the number of extraglandular manifestations in primary Sjogren's Syndrome: a retrospective analysis of 65 patients in the Netherlands. Semin Arthritis Rheum 40: 547–551
12. Volpe A, Ruzzenente O, Caramaschi P, Pieropan S, Tinazzi I, Carletto A et al (2009) Clinical associations of anti-CENP-B and anti-Scl70 antibody levels measured by multiplexed fluorescent microsphere immunoassay in systemic sclerosis. Rheumatol Int 29:1073–1079
13. Sugie K, Tonomura Y, Ueno S (2012) Characterization of dermatomyositis with coexistence of Anti-Jo-1 and Anti-SRP antibodies. Intern Med 51:799–802
14. Schmidt WA, Wetzel W, Friedlander R, Lange R, Sorensen HF, Lichey HJ et al (2000) Clinical and serological aspects of patients with anti-Jo-1 antibodies: an evolving spectrum of disease manifestations. Clin Rheumatol 9:371–377

15. Janwityanuchit S, Verasertniyom O, Vanichapuntu M, Vatanasuk M (1993) Anti-Sm: its predictive value in systemic lupus erythematosus. Clin Rheumatol 12:350–353

16. Hochberg MC (1997) Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40:1725