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CASE REPORT

**Yasuhiko Itoh · Hisamitsu Hamada · Tohru Igarashi
Natsuko Kuwabara · Taiyo Imai · Osamu Fujino
Yoshitaka Fukunaga**

A case with chronic fatigue syndrome with positive antinuclear antibody followed by postpartum thyroiditis

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Abstract Autoimmune fatigue syndrome (AIFS) is defined by chronic nonspecific complaints, a positive antinuclear antibody (ANA) assay, and the absence of another explanation for the complaints. Some severe cases fulfill the criteria for chronic fatigue syndrome (CFS). CFS is a syndrome characterized by disabling severe fatigue and defined by the criteria proposed by the U.S. Centers for Disease Control and Prevention. In this report, a patient with chronic fatigue syndrome and positive ANA assay was described as having developed postpartum thyroiditis 5 years after the onset. Subchemical hypothyroidism is characterized by clinical hypothyroidism not meeting biochemical criteria but showing evidence of thyroid autoimmunity. The relation between AIFS and subchemical hypothyroidism is discussed.

Key words Antinuclear antibodies (ANAs) · Anti-thyroid anti-bodies · Autoimmune fatigue syndrome (AIFS) · Chronic fatigue syndrome (CFS) · Hypothyroidism

Introduction

Chronic fatigue syndrome (CFS) consists of a range of symptoms, including fatigue, headaches, sleep disturbances, difficulties with concentration, and muscle pain. The most frequently used definition is that based on the criteria proposed by the U.S. Centers for Disease Control and Prevention (CDC).[1] Children present with symptoms similar to those encountered in adults.[2] In school-age children, however, the syndrome may be associated with prolonged absence from school and restricted physical and social activity.[3] Although available evidence suggests that CFS is a heterogeneous disorder, in terms of both its clinical manifestation and proposed biological markers, some manifestations of CFS suggest that autoimmunity may be an important factor in its pathogenesis. The prevalence of antinuclear antibodies (ANAs) has been reported in as many as 60% of patients with CFS.[4,5]

On the other hand, there are children who do not fulfill any criteria of collagen vascular diseases and whose ANA assay is found to be positive. Previously, we studied the prevalence of ANAs in children with chronic nonspecific complaints and found that almost half of such children tested positive for ANA. Moreover, a novel autoantibody to the insoluble nuclear protein (anti-Sa) was detected by Western immunoblotting. in approximately 40% of the ANA-positive patients. These data suggest that an autoimmune mechanism may be implicated in the pathogenesis of this condition. Thus, we proposed a new disease entity called autoimmune fatigue syndrome (AIFS).[6] We had also observed that some AIFS patients later fulfilled the criteria for CFS proposed by the CDC, and most of them tested positive for anti-Sa. This suggests that anti-Sa may be considered a risk factor or a marker antibody for later development of CFS.[7]

A diagnosis of AIFS must be made carefully because of the risk for the future development of other autoimmune diseases. In fact, we have already reported that some AIFS patients whose sera were positive for anti-Ro/SS-A could be diagnosed with subclinical Sjögren's syndrome.[8] In this article, we mention another condition that must be carefully distinguished from AIFS. A patient with AIFS (who fulfilled the CFS criteria later) was described as having developed postpartum thyroiditis 5 years after the onset of AIFS. Autoimmune thyroiditis can result in hypothyroidism and, consequently, in severe fatigue. Recently, an additional condition termed "subchemical hypothyroidism" has interested many endocrinologists. This condition is defined by clinical symptoms indicating hypothyroidism, such as fatigue, myxedema, goiter, alopecia, and hypercholesterolemia, and laboratory findings showing euthyroidism with or without an elevated thyroid-stimulating hormone (TSH) level. Approximately half the patients with subchemical

Y. Itoh (✉) · H. Hamada · T. Igarashi · N. Kuwabara · T. Imai · O. Fujino · Y. Fukunaga
Department of Pediatrics, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan
Tel. +81-3-3822-2131; Fax +81-3-5685-1792
e-mail: yasuhiko@nms.ac.jp

hypothyroidism had a positive microsome test. To clarify the relation between AIFS and subchemical hypothyroidism, we investigated the patient's clinical course immunologically as well as endocrinologically.

Case report

A 12–year-old girl visited our outpatient clinic in September 1998 complaining of low-grade fever, fatigue, cervical lymphadenopathy, and nausea that had persisted for more than 3 months. She had neither goiter nor symptoms such as arthralgia or exanthema, indicating the presence of a collagen vascular disease. Laboratory examinations, including a complete blood count, blood biochemistries, and urinalysis, were all within normal limits. Immunological examinations revealed a positive ANA test (1:160, homogeneous and speckled), but no other autoantibodies related to collagen vascular diseases were found (e.g., anti-Ro/SS-A, anti-SS-B, anti-U1RNP, anti-Sm, anti-cardiolipin). Thyroid function tests such as free triiodothyronine (FT_3), free thyroxine (FT_4), and TSH were all normal (Table 1). Antithyroid autoantibodies could not be evaluated because of the euthyroidism. The patient tested positive for anti-Sa antibody by Western immunoblot based on the method previously described (Fig. 1).[6]

She became almost house-bound and had been unable to go to school since January 1999. She was diagnosed as having CFS because her complaints extended to low-grade fever, sore throat, headache, tender lymph nodes, muscular pain, nonrefreshing sleep, and impaired concentration. Moreover, her ANA titer went up to 1:1280 in July 1999, which prompted us to administer prednisolone (PSL) (5 mg/day doses PO) based on a previous trial reported by Cleare et al.[9] Her condition gradually improved, and she joined a local recovering class for school refusal pupils in April 2000. Although she stopped taking PSL in January 2001, she has appeared to be relatively active and positive ever since. ANA and anti-Sa titers were relatively low during this period.

She became pregnant in August 2002 and carried quite a stable pregnancy. She smoothly delivered a 2650-g girl on March 24, 2003 at the 38th gestational week. The baby was free of problems including cretinism as determined by Guthrie's mass-screening test. She breast-fed her baby for 2 months.

However, at the beginning of June 2003, she presented with low-grade fever, fatigue, and cervical lymphnode swelling; her thyroid gland also became swollen in July. She was diagnosed as having hypercholesterolemia (total cholesterol 235 mg/dl) and hypothyroidism (FT_3 1.5 pg/ml, FT_4

Table 1. Laboratory findings at onset of autoimmune fatigue syndrome and at onset of thyroiditis

Test	September 1998	July 2003
IgG (mg/dl)	1780	1685
IgA (mg/dl)	113	173
IgM (mg/dl)	206	159
IgE (mg/dl)	903	652
C3 (mg/dl)	110	87
C4 (mg/dl)	16	14
CH_{50} (U/ml)	34.1	33.3
RF	–	–
RAPA	–	–
ANA	1:160	1:640
Anti-ssDNA IgG (U/ml)	16	<5
Anti-dsDNA IgG (U/ml)	<5	<5
Anti-Ro/SS-A	–	–
Anti-La/SS-B	–	–
Anti-Sm	–	–
Anti-RNP	–	–
aCLβ2GP1 (U/ml)	<1.2	<1.2
Anti-Sa	++	++
FT_3 (pg/ml)	2.62	1.5
FT_4 (ng/ml)	1.16	0.4
TSH (μ IU/ml)	3.6	80
T-Chol (mg/dl)	155	235

Ig, immunoglobulin; C, complement; CH_{50}, 50% hemolyzing dose of complement; RF, rheumatoid factor; RAPA, rheumatoid arthritis particle agglutination; ANA, antinuclear antibody; aCLβ2GP1, anticardiolipin β2-glycoprotein 1; FT_3, free triiodothyronine; FT_4, free thyroxine; TSH, thyroid-stimulating hormone; T-Chol, total cholesterol

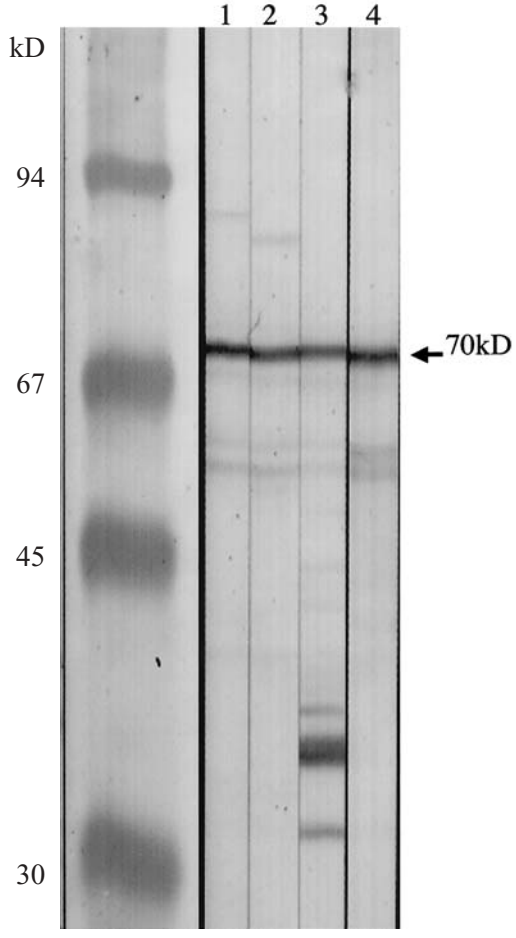

Fig. 1. Western blot analysis for anti-Sa based on the method previously described by Itoh et al.[6] HeLa cell extract was used as antigen source. The patient serum was reacted in lane *4*. *Lanes 1–3* are standard positive control sera for anti-Sa. Molecular weight markers are indicated on the left margin of the gel

Table 2. Thyroid-related test results

Test	9/24/1998	3/25/1999	7/22/1999	1/26/2001	7/18/2003
FT_3 (pg/ml)	2.62	ND	3	ND	1.5
FT_4 (ng/ml)	1.16	ND	1.09	ND	0.4
TSH (μ IU/ml)	3.6	ND	3.4	ND	80
Microsome test	1:6400	1:6400	1:6400	1:1600	1:25600
Thyroid test	<1:100	ND	<1:100	ND	<1:100
Anti-Tgl (U/ml)	2.5	2.2	4.3	<0.3	12
Anti-TPO (U/ml)	14.4	16.3	16.6	3.7	>60
Anti-TSHr (U/ml)	122	ND	133	ND	148

Tgl, thyroglobulin; TPO, thyroid peroxidase; TSHr, TSH receptor

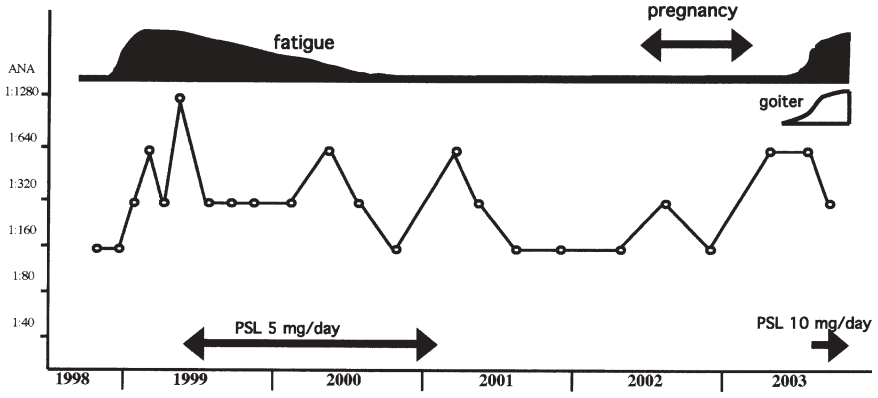

Fig. 2. Clinical course and antinuclear antibody (*ANA*) titers. *PSL*, prednisolone

0.4 ng/ml, TSH 80.0 μIU/ml) (Table 1). Ultrasonographic thyroidography revealed homogeneous hypertrophy. Anti-thyroid autoantibodies were positives, as the microsome test (1:25600), anti-thyroglobulin (Tgl) 12.0 U/ml, and anti-thyroperoxidase (TPO) >60 U/ml; but they were negative for the thyroid test and anti-TSH receptor (Table 2).

We examined her stock sera in thyroid-related tests and found that she had been continuously positive for anti-thyroid antibodies, although her thyroid hormone levels had been in the normal range until thyroid swelling occurred (Table 2). We started administering PSL 10 mg/day, and her thyroid hormone levels returned to normal. The goiter too disappeared within 2 months. However, she still complains of mild fatigue (December 2003). The overall clinical course is outlined in Fig. 2.

Discussion

Autoimmune fatigue syndrome is defined by chronic non-specific complaints, consistently positive ANA assays, and the absence of any other medical explanation for the complaints. In terms of the relation between AIFS and CFS, only about 10% of AIFS patients fulfill the criteria for CFS, although the most common complaint of AIFS patients is fatigue.

Approximately 40% of AIFS patients have autoantibodies against an insoluble nuclear protein termed anti-Sa, which has not been found in patients with other autoimmune diseases. We reported that approximately 80% of CFS patients who had initially been diagnosed with AIFS tested positive for anti-Sa. CFS patients might have heterogeneous pathophysiology, and in that case ANA-positive CFS patients could be categorized as the ones suffering from a severe form of AIFS.

The present patient had initially been diagnosed as having AIFS because positive ANA and anti-Sa were the only explanations for her symptoms, and she fulfilled CFS criteria about 6 months later. At this point, we do not believe that the diagnosis of AIFS needs to be eliminated, as she just developed a severe form of AIFS (=ANA-positive CFS). We do agree that after her goiter appeared she should have been diagnosed with postpartum thyroiditis, and that we should not be obstinate about the diagnosis of AIFS. However, the controversial matter is that she had anti-thyroid antibodies from the beginning, although her thyroid function was categorized as euthyroid.

The onset of hypothyroidism is often within 6 months of delivery. This type of occurrence is categorized as postpartum hypothyroidism or thyroiditis. Postpartum thyroiditis is a syndrome of transient or permanent thyroid dysfunction that occurs during the first year after delivery and is based on autoimmune inflammation of the thyroid. The prevalence ranges from 5% to 7%. Anti-thyroid antibodies (especially anti-TPO), complement, activated T cells, and apoptosis may be implicated in the outbreak of postpartum thyroiditis. Postpartum thyroiditis is conceptualized as an acute phase of autoimmune thyroid destruction in the context of an existing and ongoing process of thyroid autosen-

sitization. It occurs in 50% of anti-TPO antibody-positive women and is characterized by transient hyperthyroidism followed by transient hypothyroidism. Only approximately one-third of patients develop permanent hypothyroidism.[10] The relationship between Hashimoto's thyroiditis and this condition when positive for anti-thyroid antibodies remains controversial. However, recent information on the possible role of fetal microchimerism and the immunological consequences of intrathyroidal fetal cells may explain the pathophysiological difference of postpartum thyroiditis from Hashimoto's disease.[11] In addition, although further studies of women with persistent hypothyroidism after the postpartum year are needed, the enhanced activation of transforming growth factor-β1 (TGFβ1) may contribute to the resolution of thyroid inflammation postpartum.[12] An enhanced state of immune tolerance ensues from the pregnancy. A rebound reaction to this pregnancy-associated immune suppression after delivery explains the aggravation of autoimmune syndromes during the puerperal period.[13]

On one hand, our case is thought to be equivalent to postpartum thyroiditis, as the hypothyroid condition was smoothly alleviated by small doses of prednisolone. On the other hand, Wikland et al. proposed a novel disease entity termed subchemical hypothyroidism, which is characterized by clinical hypothyroidism not meeting conventional biochemical criteria but showing definite evidence of thyroid autoimmunity.[14] Fatigue, of course, is the most common symptom of hypothyroidism. Wikland et al. even insisted that 40% of patients with chronic fatigue had unequivocal evidence of autoimmune thyroiditis. The present case could be diagnosed as one of subchemical hypothyroidism if anti-thyroid autoantibodies had been examined at the first evaluation. However, her fatigue had been quite severe, and she never had other symptoms indicating hypothyroidism (e.g., goiter, alopecia, myxedema, hypercholesterolemia) until her delivery. It is difficult for us to understand how the existence of anti-thyroid antibodies could cause such serious fatigue without hypothyroid function in this patient. We still think that her fatigue had been at least partially caused by AIFS until her delivery.

We concluded, based on our assessment of her clinical course, that: (1) she had had AIFS, subchemical hypothyroidism, or both; (2) her condition worsened until it fulfilled the CFS criteria, maybe because she had anti-Sa; and (3) she developed postpartum thyroiditis because she had anti-thyroid antibodies.

What we should learn from this case is that anti-thyroid antibody tests should always be performed before diagnosing AIFS. Moreover, one should be well warned that there might be some patients with subchemical hypothyroidism who have been diagnosed as having AIFS or even CFS.

Myckatyn and Russell reported the outcome of individuals without connective tissue disease who tested positive for ANAs. They followed 53 such individuals for more than 8 years. Three of them developed connective tissue diseases (CREST syndrome, Sjögren's syndrome, scleroderma), and four developed hypothyroidism.[15] Similarly, Danieli et al. found that 6.6% of patients with undifferentiated connective tissue disease had autoimmune thyroid diseases.[16] Thus, autoimmune hypothyroidism, whether chemical or subchemical, could often be associated with an unexplained autoimmune condition. We are now conducting research on the prevalence of anti-thyroid autoantibodies in patients with AIFS, CFS, or both.

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