Juvenile idiopathic arthritis associated with autoimmune thyroid disorders and autoimmune cholangitis

SIR, We describe a 17-yr-old female with juvenile idiopathic arthritis (JIA) accompanied by autoimmune thyroid disorders and autoimmune cholangitis (AIC). She was the first child of unrelated parents, with a family history of dermatomyositis in her father, who died of arrhythmia at age 41 yr, Graves disease in her paternal cousin and rheumatoid arthritis (RA) in her maternal grandmother. At age 6 yr she had joint pain, swelling of her knees and ankles, uveitis and iridocyclitis, and was diagnosed as having JIA, oligoarthritis with the presence of antinuclear antibodies (ANA) but not rheumatoid factor. The joint pain was relieved by occasional use of aspirin. No other drugs were used. She developed diffuse goitre and hypothyroidism [free thyroxine 0.7 ng/dl, thyroid-stimulating hormone (TSH) 92.1 μU/ml] with increased anti-thyroglobulin antibody (1 : 10^5) and anti-thyroid microsomal antibody (1 : 640^2), and was diagnosed as having Hashimoto thyroiditis at age 7 yr. TSH-binding-inhibiting immunoglobulin (TBII) was negative. Thyroid function was controlled by laevothyroxine replacement. Arthritis extended to the proximal interphalangeal (PIP) joints of the fingers, but the pain became less severe. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels had been elevated since the age of 9 yr. At age 17 yr she was admitted to our hospital complaining of a weight loss of 15 kg during the past 3 months. Her height was 154.0 cm and her weight 33.0 kg. Mild goitre was noted, without exophthalmos. Slight swelling of the PIP joints of the fingers was found without tenderness, redness or restricted range of movement. Laboratory tests showed a white blood cell count of 3810/μl, a haemoglobin level of 15.1 g/dl and a platelet count of 131 000/μl. AST, ALT, total bilirubin and bile acid levels were elevated (129 IU/l, 152 IU/l, 1.4 mg/dl and 20.9 μmol/l respectively). Serum alkaline phosphatase, blood urea nitrogen, creatinine and electrolytes showed no abnormalities. Serological studies for hepatitis viruses were all negative. Flow cytometric analysis of peripheral lymphocytes revealed 25.7% CD19^+ cells and 72.1% CD3^+ cells. Human leucocyte antigen-DR^+CD3^+ cells were increased (15.3%). Concentrations of immunoglobulins G, A and M were 2100, 238 and 324 mg/dl respectively. She was positive for ANA (1 : 80) and negative for the lupus erythematosus test, rheumatoid factor, anti-double-stranded DNA antibody, anti-Sm antibody, anti-ribonucleoprotein antibody, anti-smooth muscle antibody, anti-mitochondrial antibody and antibodies to glutamic acid dehydrogenase, and adrenal and pituitary gland. Anti-thyroglobulin and anti-thyroid microsomal antibodies were positive (1 : 10^5 and 1 : 320^2 respectively). TBII, TSH receptor-stimulating antibody and TSH receptor-blocking antibody were positive, at 45.1% (normally 15–15%), 223% (normally <180%) and 77.7% (normally 0–30%) respectively.
Serum levels of both free thyroxine and free triiodothyronine were elevated (3.5 ng/dl and 7.7 pg/ml respectively); TSH was undetectable (< 0.03 μU/ml). Radioiodine uptake by the thyroid, which had been 20.4% at 5 h and 29.3% at 24 h at the initial diagnosis of Hashimoto thyroiditis, was increased to 48.8% at 5 h and 60.4% at 24 h. The pathological findings of liver biopsy were compatible with chronic non-suppurative cholangitis. She was diagnosed as having Graves disease with AIC and placed on methimazole, which replaced her previous treatment. Thereafter, she gained weight favourably and her thyroid function improved.

In oligoarticular JIA there is an increased number of activated T cells [1] and elevated levels of cytokines such as tumour necrosis factor α, interleukin-1β and soluble interleukin-2 receptor in synovial fluids [2]. Similar pathophysiological findings have been found in the target organs in Hashimoto thyroiditis [3] and primary biliary cirrhosis (PBC) [4]. In contrast to polyarticular JIA, oligoarticular JIA has not been reported to be associated with Hashimoto thyroiditis. Hashimoto thyroiditis and Graves disease sometimes coexist within the same family or individual, but it is rare that Graves disease develops after hypothyroidism. In the present case, TBII had been negative during the hypothyroid state, but it became positive when hyperthyroidism developed. Thus, it is likely that an epitope spreading to other thyroid antigens induced the production of anti-TSH receptor autoantibody, mimicking the effects of TSH, which may have contributed, at least in part, to a phenotypic change from Hashimoto thyroiditis to Graves disease [5]. PBC or its variant, AIC, is known to be frequently associated with other autoimmune diseases, but not JIA. Apoptosis due to interaction between CD95 (Fas) on the target cells and Fas ligand on activated T cells is considered to be one of the major mechanisms leading to progressive destruction of target organs in AIC [6] and Hashimoto thyroiditis [7].

Multiple autoimmune diseases develop in an individual or a family in the presence of certain genes, such as the autoimmune regulator gene involved in autoimmune polyendocrinopathy syndrome type 1 [8]. On the other hand, it has recently been suggested that clinically distinct autoimmune diseases may be controlled by a common set of susceptibility genes [9]. The family history of the present patient and her young ages at onset of Hashimoto thyroiditis and AIC also suggest strong genetic susceptibility to autoimmune disease. Detection of a unique genetic background with DNA chips can easily identify polymorphisms or mutations in multiple candidate genes for autoimmunity, including genes for human leucocyte antigens, cytokines and other immunoregulatory molecules. This should help in the understanding of any shared pathophysiology involved and may, in future, assist in the design of personalized treatments matched to genetic profiles [10].

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Accepted 27 December 2000

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