

ORIGINAL ARTICLE: CASE SERIES

Graves' disease and juvenile idiopathic arthritis

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Abstract

We report 2 cases of juvenile idiopathic arthritis (JIA) and associated Graves' disease. This is the first reported association between these 2 autoimmune disorders. The possible connection and genetic links between JIA and autoimmune hyperthyroidism are explored.

Introduction

Population-based studies demonstrate an increased prevalence of hypothyroidism in adults with systemic lupus erythematosus and rheumatoid arthritis. [1-2] Similarly, there appears to be an association of autoimmune hypothyroidism (Hashimoto's thyroiditis) and juvenile idiopathic arthritis (JIA). [3] By contrast, there have been no reports of autoimmune hyperthyroidism (Graves' disease) in association with JIA. We describe 2 children with both JIA and Graves' disease. A possible link between the 2 autoimmune disorders is discussed.

Case Reports

Case 1:

A 17-year-old Caucasian female developed Graves' disease at age 2 years and 10 months of age. The initial clinical presentation of hyperthyroidism included a prominent thyroid gland and exophthalmos. Laboratory studies supported a diagnosis of Graves' disease, including a suppressed thyroid stimulating hormone (TSH) level and elevated thyroid hormone concentrations. Anti-thyroid antibody studies were not measured at onset, but were later noted to be present. She developed an allergic reaction to propylthiouracil (PTU) and was subsequently treated with methimazole. At 10 years of age, she went into remission

and methimazole was discontinued. Her growth and development have been normal for age. She remains in remission clinically and by lab studies with normal yearly thyroid function levels; however, thyroid antibodies persist.

At 13 years of age, she developed diffuse arthralgias and finger swelling and was found to have arthritis in multiple joints, including bilateral TMJ, right shoulder, bilateral wrist, bilateral MCP, PIP, and DIP of the hands, knees, right ankle, several MTP joints, and her left elbow. Laboratory examination revealed a positive rheumatoid factor of 91 IU/ml (0-39 IU/ml) and a negative anti-nuclear antibody (ANA, <1:40), Westergren erythrocyte sedimentation rate of 40 mm/hr (<= 20 mm/hr) and a C-reactive protein of 3.24 mg/dl (<0.80). She was diagnosed with rheumatoid factor (RF) positive JIA [4], and was started on naproxen, weekly methotrexate subcutaneous injections, briefly low-dose oral prednisone, hydroxychloroquine, and the tumor necrosis factor inhibitor, etanercept. Her arthritis resolved over 15 months and she remained in remission for a period of 15 months. At that time, she presented with an active left elbow that responded well to an increase of etanercept from 20 mg twice weekly to 25 mg twice weekly. She has remained in remission for 17 months on this dosing regimen.

Case 2:

A 9-year-old Caucasian female developed juvenile idiopathic arthritis at 20 months of age involving both knees and right ankle. Her ANA was positive and RF titers were negative. She was initially treated with naproxen, but later required weekly oral methotrexate. She had intra-articular corticosteroid injections of both knees and the right ankle, on multiple occasions, with rapid resolution of joint effusions. At age 7 years, she demonstrated poor weight gain and tachycardia, and was evaluated for failure to thrive. At that time, her laboratory tests revealed the following: total T3, 396 ng/dl (127-221); free T4, 3.7 ng/dl (0.9-1.6); total T4, 18.6 µg/dl (4.5-12.5); TSH <0.01 mIU/ml (0.70-6.40); thyroglobulin antibodies, 3 IU/ml (<2); thyroid peroxidase antibodies, >70 IU/ml (<2). She was diagnosed with Graves' disease and was started on methimazole and propranolol. Her weight gain improved, but she developed a psoriaform rash over her left elbow, consistent with psoriatic arthritis. To date, her arthritis has been in remission, off medication, for 17 months and her hyperthyroidism has been controlled on methimazole.

Discussion

We report 2 cases of Graves' disease associated with JIA. Graves' disease preceded the diagnosis of RF positive polyarticular JIA by 10 years in one case and appeared 5 years after the onset of psoriatic JIA in the other.

Graves' disease is an autoimmune form of hyperthyroidism resulting from the abnormal production of thyroid-stimulating antibodies. Graves' disease is the most common form of hyperthyroidism with an incidence reported to be 36.8 females and 8.3 males per 100,000 [5-6]. Only 1 to 5% of these cases occur in children less than 15 years of age, but Graves' disease accounts for 10-15%

of all childhood thyroid disorders. [7] The female to male ratio of children with Graves' disease has been estimated as 4-10 girls: 1 boy, which is similar to adults [8]. There are three major manifestations: hyperthyroidism with a diffuse goiter [9], ophthalmopathy, and dermopathy. [7] By comparison, arthritis is rare in Graves' disease and the incidence of Graves' disease was found to be similar in relatives of patients with JIA compared to controls, although the odds ratio of 2.8 compared to controls suggest there may be an association, possibly with a subtype of JIA. [10] Similarly, Graves' disease has only rarely been associated in adults with rheumatoid arthritis. [11] Thus, the association with Graves' disease and chronic arthritis may be a coincidence. In contrast, there seems to be an association of Graves' disease and Sjögren syndrome in both adults [12] and children. [13] Moreover, there is clearly a link between Graves' disease and the presence of ANA development in adults [9] and children. [14]

Graves' disease is clearly autoimmune in nature. T lymphocytes are believed to be sensitized to antigens in the thyroid gland. The antigens then stimulate B lymphocytes to synthesize antibodies directed against the thyrotropin receptor. [15] The presence of these autoantibodies positively correlates with active disease. [15] A variety of genetic susceptibility loci have been implicated in the etiology of Graves' disease. These include the major histocompatibility complex [16] and the T cell inhibitory receptor, CTLA-4. [17] Recently, a

polymorphism in a gene encoding an intracellular tyrosine phosphatase was identified as conferring risk for development of adult rheumatoid arthritis, Hashimoto thyroiditis, and other autoimmune disorders, including type 1 diabetes and systemic lupus erythematosus. [18] Interestingly, there was no association noted for Graves' disease or JIA with this allele. [18] By comparison, there is a clear association between JIA and Hashimoto's thyroiditis [3,14], but whether a similar genetic link exists between JIA and Graves' disease remains unclear. In addition to the 2 cases of JIA and Graves' disease reported herein, further reports may help to establish an autoimmune association.

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