Autoimmune Thyroid Disease in Children and Adolescents With Idiopathic Pulmonary Arterial Hypertension

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Background: Previous studies have reported a high prevalence of autoimmune thyroid disease (AITD) in adult patients with pulmonary arterial hypertension (PAH). The aim of this retrospective study was to determine the prevalence of AITD in children and adolescents with idiopathic PAH (IPAH).

Methods and Results: The study group included 16 patients who had been diagnosed as having idiopathic PAH when they were younger than 15 years old; all were younger than 20 years of age. Thyroid function and antithyroid antibody levels were examined regularly at 6–12-month intervals and when there were clinical signs of thyroid dysfunction. In total, 7 patients (44%) had AITD; 2 patients developed Graves’ disease, 2 developed silent thyroiditis, and 3 had antithyroid antibodies with euthyroidism. The duration after PAH onset and the prostacyclin (PGI2) treatment period were significantly longer in patients with AITD (7.6±2.1 and 7.4±2.3 years, respectively) than in patients without AITD (5.0±1.1 and 4.8±1.2 years, respectively; P<0.01 and P<0.05).

Conclusions: The prevalence of AITD is high in children and adolescents with IPAH, so evaluation of thyroid function is important to prevent deterioration of right heart failure. (Circ J 2010; 74: 371–374)

Key Words: Bone morphogenetic protein receptor II; Graves’ disease; Idiopathic pulmonary arterial hypertension; Silent thyroiditis

Pulmonary arterial hypertension (PAH) is a rare disorder of the small pulmonary arterioles and has a poor prognosis. Vascular obstruction progresses gradually and ultimately leads to severe right heart failure. PAH is classified into 5 groups according to the cause: sporadic idiopathic PAH (IPAH); familial IPAH; secondary PAH associated with other diseases or conditions; pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis; and persistent pulmonary hypertension of the newborn.1 Recently, mutations in the bone morphogenetic protein receptor II (BMPR2) gene2,3 and the activin receptor-like kinase 1 (ALK1) gene4 have been reported to cause sporadic and familial idiopathic PAH. BMPR2 and ALK1 are members of the tumor growth factor (TGF)-β receptor family. An imbalance in the activation of other TGF-β receptors, coupled with mutated BMPR2 or ALK1, is suspected to promote the development of PAH.5,6 Pulmonary vascular vasodilators, such as prostacyclins,7 endothelin-receptor-antagonists8 and phosphodiesterase-5-inhibitors,9 are used to treat PAH patients.

On the other hand, several reports have described an association between PAH and thyroid disease.10–17 Some of these reports did not test for the presence of antithyroid antibodies, and they did not sufficiently evaluate the causes of thyroid dysfunction. Four reports11,14,15,17 demonstrated a high prevalence of autoimmune thyroid disease (AITD) in adult PAH patients, and an immunogenetic overlap between PAH and AITD was suggested. However, there have been only a few reports dealing with the association between PAH and thyroid disease in children and adolescents with PAH,13 so the present study investigated the prevalence of AITD in children and adolescents with IPAH.

Methods

Subjects
Sixteen patients (6 females, 10 males), all under the age of 20 years and receiving continuous care at Toho University Omori Medical Center, were studied retrospectively. They had been diagnosed as having sporadic IPAH (14 patients) or familial IPAH (2 patients) at a mean age of 8.6 years (range, 2.9–12.8 years). PAH was diagnosed on right heart catheterization when the mean pulmonary arterial pressure was higher than 25 mmHg and pulmonary capillary wedge pressure was higher than 15 mmHg.
Pressure was lower than 15 mmHg at rest. Secondary PAH associated with congenital heart disease, collagen disease, portal hypertension, or lung diseases was excluded by clinical evaluation. Mutations of BMPR2 had been investigated in some patients and reported previously.18 Evaluation of Thyroid Function Serum free triiodothyronine (fT3), free thyroxine (fT4), thyroid-stimulating hormone (TSH), and antithyroid antibodies (thyroid peroxidase antibody; TPOAb; thyroglobulin antibody; TgAb; thyroid-stimulating hormone receptor antibody; TRAb) levels were regularly examined at intervals of 6–12 months and when there were clinical signs of thyroid dysfunction. Serum fT3, fT4, and TSH levels were measured by electrochemiluminescence immunoassay; the normal ranges were 2.26–4.15 pg/ml, 1.01–1.67 ng/ml, and 0.32–4.12 μIU/ml, respectively. TPOAb and TgAb levels were measured by immunoradiometric assay (normal range: ≤0.3 U/ml). TRAb was assayed on the basis of the levels of 125I-TSH binding to its receptor (normal range: <10%), and thyroid stimulating antibody (TSAb) was measured by immunoradiometric bioassay (normal range: <180%).

Diagnostic Criteria Graves’ disease was defined by the findings of primary hyperthyroidism (high fT3, high fT4, and low TSH levels), a diffuse goiter, the presence of anti-TSH receptor antibody (TRAb and/or TSAb), and increased blood flow in the thyroid gland on ultrasonography. Silent thyroiditis was defined by the findings of primary hyperthyroidism, a diffuse goiter without pain, and normal blood flow in the thyroid gland on ultrasonography, whether or not TRAb was present. Autoimmune thyroid dysfunction was defined as primary hyperthyroidism caused by an autoimmune mechanism, and AITD was defined as the presence of autoimmune thyroid dysfunction or euthyroidism with antithyroid antibodies.

Statistical Analysis The χ² test, Fisher’s exact test, and Student’s t-test were used for statistical comparisons. P<0.05 was considered significant.
Table 3. Comparison of Groups A and B

<table>
<thead>
<tr>
<th></th>
<th>(n) Group A</th>
<th>(n) Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>3/4</td>
<td>7/2</td>
<td>0.302</td>
</tr>
<tr>
<td>Sporadic/familial</td>
<td>7/0</td>
<td>2/7</td>
<td>0.009</td>
</tr>
<tr>
<td>Family history of AITD +/-</td>
<td>1/6</td>
<td>0/9</td>
<td>0.438</td>
</tr>
<tr>
<td>Mutations of BMPR2 gene +/-</td>
<td>1/4</td>
<td>3/2</td>
<td>0.286</td>
</tr>
<tr>
<td>CA at the diagnosis of PAH (years)</td>
<td>(7) 8.7±3.2</td>
<td>(9) 8.5±3.3</td>
<td>0.419</td>
</tr>
<tr>
<td>CA at the diagnosis of AITD or the most recent thyroid function evaluation (years)</td>
<td>(7) 16.4±2.0</td>
<td>(9) 13.3±3.4</td>
<td>0.027</td>
</tr>
<tr>
<td>Duration after PAH onset (years)</td>
<td>(7) 7.6±2.1</td>
<td>(9) 5.0±1.1</td>
<td>0.006</td>
</tr>
<tr>
<td>Treatment period (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGI2</td>
<td>(7) 7.4±2.3</td>
<td>(9) 4.8±1.2</td>
<td>0.011</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>(6) 3.4±0.3</td>
<td>(7) 3.3±1.3</td>
<td>0.896</td>
</tr>
<tr>
<td>Bosentan</td>
<td>(1) 0.1</td>
<td>(6) 2.5±0.6</td>
<td>–</td>
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</tbody>
</table>

Abbreviations see in Table 1.

Results

In total, 7 patients (43.7%) had AITD; 2 patients (12.5%) developed Graves’ disease, 2 patients (12.5%) developed silent thyroiditis, and 3 patients (18.7%) were positive for antithyroid antibodies with euthyroidism (Table 1). The clinical characteristics of the patients with autoimmune thyroid dysfunction are shown in Table 2. In 2 of the 4 patients with Graves’ disease or silent thyroiditis, thyroid function was evaluated because of worsening of the right heart failure. Plasma B-type natriuretic peptide (BNP) levels decreased after normalization of the thyroid functions in 3 of the 4 patients with Graves’ disease or silent thyroiditis. Patient 2 developed agranulocytosis (neutrophils 396/μl) at 2 months after the start of mechimazole, which was replaced with potassium iodide.

The patients were divided into 2 groups (Table 3): Group A, consisting of the 7 patients with AITD and Group B consisting of the 9 patients whose thyroid function was normal and in whom antithyroid antibodies were negative. The chronological age at the time of diagnosis of PAH was similar in both groups (8.7±3.2 vs 8.5±3.3 years, P=0.419). The interval between the diagnosis of PAH and the diagnosis of AITD in Group A was significantly longer than that between the diagnosis of PAH and the most recent thyroid function evaluation in Group B (7.6±2.1 vs 5.0±1.1 years, respectively; P=0.006). The period of prostacyclin treatment (PGI2: beraprost sodium or epoprostenol) was significantly longer in Group A (7.4±2.3 years) than in Group B (4.8±1.2 years; P=0.011). BMPR2 mutations were identified in 1 of 5 Group A patients and in 3 of 5 Group B patients (P=0.286).

Discussion

In the present study, 4 of 16 patients (25%) had autoimmune hyperthyroidism. Although there is no report describing the prevalence of hyperthyroidism in Japanese children, the prevalence in Japanese adults has been reported as approximately 0.2–0.5%. Therefore, the prevalence of autoimmune hyperthyroidism in the present group of children and adolescents with IPAH is significantly higher than the prevalence of hyperthyroidism in the general adult population (P<0.001). Because the prevalence of AITD increases with age, the prevalence of hyperthyroidism in Japanese children is suspected to be less than 0.2–0.5%. A prospective study is necessary to determine the precise incidence of AITD in children with IPAH, because the present results are from a retrospective study.

The duration both after the onset of PAH and of the PGI2 treatment period was significantly longer in patients with AITD than in patients without AITD in our study. Some studies have suggested the possibility that PGI2 is a trigger for the development of AITD, but others deny a relationship between PGI2 and AITD because the onset of AITD was earlier than the onset of PAH. Therefore, it is unclear whether PGI2 treatment is related to the development of AITD. On the other hand, it has been reported that PGI2 can stimulate adenyly cyclase activity in human thyroid tissue by the TSH-independent system, and the prevalence of non-autoimmune thyrotoxicosis in adult PAH patients being treated with PGI2 is high. It is also possible that PGI2 may induce non-autoimmune thyrotoxicosis.

One of the reasons for the high prevalence of AITD in PAH patients is suspected to be that PAH may itself be caused by an autoimmune mechanism. It has been reported that secondary PAH is associated not with only collagen diseases but also other autoimmune diseases, such as autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) and autoimmune hepatitis. This fact supports the possibility that an autoimmune mechanism may cause PAH. Nicoll et al suspected that in PAH patients, endothelial cell destruction by immune-mediated injury might result in the generation of apoptosis-resistant endothelial cells that have a malignant phenotype, proliferate rapidly, and ultimately lead to vascular occlusion.

Mutations in BMPR2 are reported to cause IPAH: they are in 26% of sporadic IPAH patients and in approximately 50% of familial IPAH patients. Ligands for BMPR2 are BMP2, 4, 6, and 7, and the BMPs were first discovered as cytokines that regulated growth and differentiation of cartilage and bone. BMPs also regulate the generation of mesenchymal and epithelial cells, have important roles in the repair and maintenance of bone and other tissues in adults, and control hormone production. Moreover, BMP2 and 4, BMPR2, 1a, and 1b are expressed in the thymus and are suspected to regulate T-cell differentiation and maturation. It is possible that mutations in BMPR2 may lead to AITD by causing abnormalities in T-cell differentiation and maturation. Roberts et al reported that 5 patients with BMPR2 mutation-positive IPAH (100%) had thyroid disease, but only 19 of 136 with BMPR2 mutation-negative IPAH (14%), had thyroid disease. However, in the present patients, the frequency of BMPR2 mutation-positive patients was lower in Group A (1 of 5) than in Group B (3 of 5).
In summary, the present study found a high prevalence of AITD in children and adolescents with IPAH. In hyperthyroidism, systemic vascular resistance and diastolic blood pressure decrease, but pulmonary pressure may increase. Therefore, PAH patients may suddenly experience rapid worsening of right heart failure when they develop hyperthyroidism. It may be important to regularly evaluate thyroid function in children and adolescents with IPAH to prevent aggravation of right heart failure. The mechanism of the relationship between PGI2 or BMPR2 mutations and the development of AITD remains to be evaluated.

References


