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Case report

A pediatric case with prostaglandin I_2-associated thyrotoxicosis: Case report and the literature review

Sonoda et al. Prostaglandin I_2-associated thyrotoxicosis

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What is already known on this topic?

Continuous intravenous injection of epoprostenol (prostaglandin I2, PGI2) is an effective medication for patients with severe cardiac failure due to pulmonary artery hypertension. PGI2 may cause the life-threatening side effect of hyperthyroidism at an incident rate of 6.7%.

What this study adds?

We report the first pediatric case with portosystemic venous shunt syndrome, who developed thyrotoxicosis after 10 years of PGI2 treatment.

Earlier intervention may prevent patients with pulmonary artery hypertension from the onset of hyperthyroidism due to PGI2 treatment.

Abstract

Prostaglandin I_2 (PGI2) causes hyperthyroidism, a critical complication in patients with pulmonary arterial hypertension (PAH). However, it remains unknown whether PGI2 may have unfavorable effects on thyroid functions in children with congenital portosystemic venous shunt syndrome (CPSVS). We present a boy with CPSVS who developed PAH at 7 years of age. During the PGI2 therapy, he experienced thyrotoxicosis at 17 years of age. The literature review showed that the past 12 patients with PAH (median 11 years of age) developed hyperthyroidism during 1 to 11 years of PGI2 treatments. Only one patient survived the acute PAH crisis due to hyperthyroidism. These data provide evidence that prophylactic intervention against hyperthyroidism is indicated for children with CPSVS during the PGI2 treatments.

Keywords: Prostaglandin I_2; Pulmonary arterial hypertension; Congenital portosystemic venous shunt syndrome; and Hyperthyroidism

Introduction

Pulmonary arterial hypertension (PAH) is a rare vascular disorder that has annual incidence of 5 to 8 per million children under the age of 18 (1). Five-year survival for PAH has risen to 60% over the past decades with an advance in the pharmacological management (2). Continuous intravenous injection of epoprostenol (prostaglandin I_2, PGI2) has been applied for patients with PAH manifesting the

cardiac failure at NYHA class III and IV of severity (2). This medication has contributed to improving the prognosis of primary PAH. However, PGI2 may cause a side effect of hyperthyroidism at the incident rate of 6.7% (3). Thus, establishing the safest treatment strategies for PAH remains to be challenging.

Here we report a 17-year-old boy with congenital porto-systemic venous shunt syndrome (CPSVS), who developed severe hyperthyroidism during the PGI2 treatment. We also characterize the demographic features of the previous cases with PGI2-associated hyperthyroidism by collecting their profiles from the literature.

Case report

A 20-day-old male infant was referred to our hospital because of hypergalactosemia at the neonatal mass screening test. He was diagnosed with congenital portal vein hypoplasia and CPSVS. At 7 years of age, PAH was found in the regular checkup with echocardiography. Continuous intravenous PGI2 (47.2 ng/kg/min) was initiated at 9 years of age. The administration of bosentan hydrate (62.5 mg/day) was added at 10 years of age. The treatment strategy was based on his cardiac status at World Health Organization (WHO) functional class II. The right ventricular systolic pressure estimated from the moderate tricuspid regurgitation was 80 mmHg on echocardiography. He received the thyroid test once at 16 years of age. The test results showed low TSH (0.04 μU/ml, reference range [rr]: 0.27-4.20) and normal free T4 levels (1.42 ng/dl, rr: 1.00-1.80).

At 17 years of age, he was admitted to our hospital because of dyspnea, general fatigue and chest pain (WHO class IV). The body temperature was 37.5˚C and the heart rate was 120 bpm. On admission, his height was 162.4 cm (-1.1 SD), and the body weight was 44.1 kg (-1.8 SD, body mass index 16.4). Goiter was noted, and the liver was palpable at 4.0 cm below the costal margin. Intensified pulmonic sound with regurgitant systolic murmur was remarkable at the left sternal border. Cardiomegaly was noted on chest radiography. Echocardiography detected severe tricuspid regurgitation with elevated right ventricular systolic pressure (120 mmHg). The enlarged thyroid glands were detected on ultrasonography with increased blood flow, and the size was estimated as large as 3.1 g (right) and 16.7 g (left). Laboratory tests showed C-reactive protein of 1.8 mg/dl, brain-type natriuretic peptide at 601.1 pg/ml (cut-off ≤ 18.4), thyroid stimulating hormone (TSH) <0.01 μIU/ml, free T4 at 6.35 ng/dl (rr: 1.00-1.80), thyroid stimulating antibody (TSAb)

elevated to 2,691% (rr: < 180%), TSH receptor antibody (TRAb) to 10.7 U/L (rr: < 1.0 U/L), and thyroglobulin antibody to 1349.7 U/ml (rr: < 45 U/L).

Maximum doses of oral thiamazole, potassium iodide and intravenous hydrocortisone treatment failed to control the raging storm of hyperthyroidism. High-dose methylprednisolone therapy and destructive radioiodine ("RI" in **Table 1**) therapy were concurrently initiated on 88 days of admission. Hyperthyroidism gradually improved after the combined therapy. When PAH began to be controlled, the estimated right ventricular pressure declined to 70 mmHg. PGI2 was continued throughout the period of intensive care because PAH was severely worsened. The patient was discharged on 132 days after admission (**Figure 1**). PAH has been controlled with the euthyroid state thereafter. He has been free from antithyroid therapy for more than 4 years although TSAb, TRAb and anti-thyroglobulin antibody remains to be positive. None of his families were affected by autoimmune thyroiditis. He had no past history for other autoimmune disorders. He had never experienced hypoglycemia, hyperandrogenism or other metabolic attacks before and after this episode.

For the report of clinical information above, written informed consent was obtained from the patient and his parents.

Review of the literature

We performed the literature search for the patients under the age of 20 years, who presented with hyperthyroidism during the PGI2 treatments. We found that 12 such cases had been reported in years 2010 to 2017 (4,5). **Table 1** denotes the clinical profiles of these 12 cases and ours. The median age at diagnosis of PAH was 11 years ranging from 2 to 17 years, while the hyperthyroidism developed at median 15.8 years (from 6 to 19 years). Thus, duration to the development of PGI2-associated thyroiditis varied largely from 1 to 11 years after the diagnosis of PAH. Four patients (31%) died of complication, including cardiopulmonary dysfunctions. We found that 6 (Cases 8-13) among the 13 cases had severe cardiac dysfunction with WHO class IV. Although these 6 patients underwent thyroidectomy, propylthiouracil or RI therapies, only two (Case 12 and the present case) survived the critical period.

Discussion

We described a case with exacerbated PAH during the PGI2 treatment. The literature review for the past cases under 20 years of age indicated the high mortality rate (31%) for PAH patients when complicated with hyperthyroidism. Unfavorable prognosis of PAH was likely associated with the severity in cardiac function at the onset of hyperthyroidism.

PGI2 regulates both innate and adaptive immune responses. Recent studies showed evidence that it accelerates the differentiation of naïve T cells into Th17 cells and enhances Th17 cell functions (4,6-8). The Th17-IL17 axis may thus explain the mechanisms of PGI2-associated hyperthyroidism and thyroiditis. Considering that the past 12 presented with hyperthyroidism in years after the diagnosis of PAH, the pathogenic mechanisms were less likely to involve acute reactions to PGI2. We speculated that persistent exposure to PGI2 might deregulate the physiological immune system of PAH patients, thereby augmenting the activation process of hyperthyroidism. Although we have not analyzed the population of Th17 cells or IL17 in peripheral blood of our case, serial immunological studies may detect sensitively the prodromal signs of hyperthyroidism in PAH patients.

Experimental studies demonstrated that PGI2 regulates both innate and adaptive immune systems (9). PGI2 analogs were also shown to inhibit proinflammatory responses to lipopolysaccharides in monocyte and macrophage (10). Notably, inflammatory macrophages were expanded in the lungs of PAH model mice (11). Thus, delineating the downstream signals to PGI2 in the lung macrophage will be the key to understand its deleterious effects on thyroid functions. Among them, monocyte chemoattractant protein-1 (MCP-1/CCL2) is known as a downstream molecule to prostaglandins (12). Paradoxical effects of PGI2 on thyroid functions might therefore result from differential MCP-1 synthesis in each tissue with the long-term treatments.

We considered that the exacerbation of PAH resulted not only from the increased cardiac outputs with hyperthyroidism, but also from the direct effect of thyroid hormone on proliferative vascular endothelial cells (13). Together with our case report, the literature review also supports the necessity of prophylactic monitoring and management of thyroid function for PAH patients undergoing PGI2 treatment. Earlier intervention may prevent PAH patients from the progressive worsening of cardiac dysfunction. In this regard, prophylactic therapy might be recommended to start in our patient at age 16 years, when he showed a low TSH level on thyroid test. Future studies will clarify whether the alternative strategy might rescue their unfavorable outcomes.

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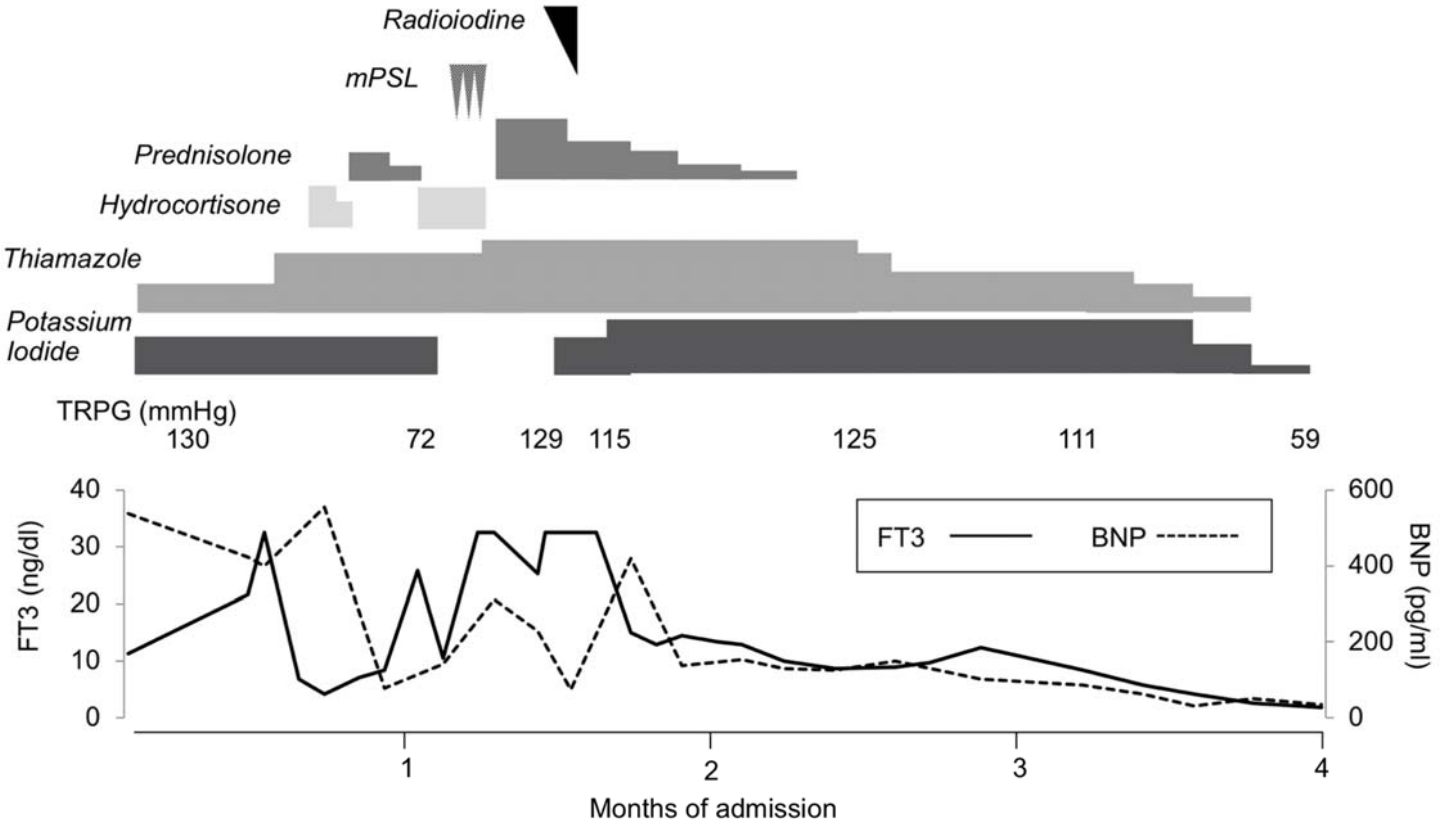

Sonoda_Figure 1

Figure 1. Treatment course of the present case after admission

Used medication (italic) and the duration of treatments (squares) are shown at the top. Radioiodine (410 MBq), methylprednisolone (mPSL, 1 g/day for 3 days), prednisolone (PSL, 10-45 mg/kg/day), oral administration of thiamazole (15-75 mg/day) and potassium iodide (200-300 mg/day) were used to control the thyrotoxicosis. Echocardiography-based measurements of tricuspid regurgitation peak gradient (TRPG) are shown in the middle. Line charts at the bottom indicate the declined levels of free-T3 (FT3, reference range: 2.2-4.4 pg/ml) and BNP (reference range: ≤ 18.4 pg/ml) over the 4 months of intensive care for the present case.

Table 1. Clinical characteristics of pediatric PAH patients complicated with hyperthyroidism during PGI_2 treatment

Patient number	Sex	Age at diagnosis of PAH (yr)	Age at diagnosis of hyperthyroidism (yr)	PAH severity (WHO functional class) at diagnosis of hyperthyroidism	Treatment of hyperthyroidism	Outcome	Reference
1	F	4	12	ND	MMI	Alive	[4]
2	F	4	15	ND	MMI	Alive	[4]
3	F	11	15	ND	MMI	Alive	[4]
4	M	11	19	ND	observation	Alive	[4]
5	F	2	6	II	MMI	Alive	[5]
6	F	4	9	II	MMI	Alive	[5]
7	F	6	11	II	MMI	Alive	[5]
8	F	11	15	IV	PTU, esmolol	Dead	[5]
9	F	11	15	IV	PTU, esmolol, CS	Dead	[5]

10	F	14	18	IV	esmolol	Dead	[5]
11	F	16	17	IV	PTU/MMI, SSKI, CS	Dead	[5]
12	F	17	19	IV	PTU/MMI, SSKI, CS, esmolol, thyroidectomy	Alive	[5]
13	M	7	17	IV	MMI, SSKI, CS, RI	Alive	The present case
Mean		9.2	14.7				
Median [range]		11 [2-17]	15.8 [6-19]				

PAH = pulmonary artery hypertension; ND = not described in the literatures; MMI = thiamazole or methimazole; CS = corticosteroids; PTU = propylthiouracil

RI = radioiodine; SSKI = saturated solution of potassium iodide.