

Pericardial effusion due to hypothyroidism in Down syndrome: report of four cases

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Abstract

Pericardial effusion may be the first sign of congenital or acquired hypothyroidism and will completely resolve after thyroxin therapy. Hypothyroidism is more common in Down syndrome population than normal population. In this report we present four infants with Down syndrome who have pericardial effusion due to congenital hypothyroidism. All of these children with Down syndrome were admitted to our clinic with pericardial effusion. Pericardial effusion was completely resolved with thyroxin therapy without pericardiosentesis. Any child with Down syndrome who present with dyspnea and cardiomegaly should be suspected of having pericardial effusion due to hypothyroidism and echocardiography examination should be performed immediately. Pericardial effusion due to hypothyroidism will completely resolve with L-thyroxin therapy without pericardiosentesis. In conclusion, since a delayed diagnosis of hypothyroidism is likely and may favor the development of massive pericardial effusion and because of the difficult diagnosis of the hypothyroidism in Down syndrome, periodic follow-up of thyroid function tests are important.

INTRODUCTION

Thyroid disorders are common in Down syndrome [1]. The incidence of the congenital hypothyroidism in Down syndrome is also higher than in normal population [2,3]. Subclinical or overt hypothyroidism, hyperthyroidism was also reported in Down syndrome and overt hypothyroidism was related with thyroid autoimmunity [1]. About 40% of cases with Down syndrome have congenital heart

disease, especially atrioventricular septal defect (40%) [4]. Pericardial effusion is commonly related with congestive heart failure, but may be the first sign of congenital or acquired hypothyroidism and will completely resolve after thyroxin therapy [1,5]. In this report we present four infants with Down syndrome who have pericardial effusion due to congenital hypothyroidism.

CASE REPORTS

Case 1

A seven-month-old boy presented with persistent respiratory distress and non-productive cough with duration of two months. He was the sixth child of the non-consanguineous healthy 38-year-old mother and 38-year-old father. On physical examination, he was hypotonic, had Down syndrome phenotype. His weight was 5100 g and height 66 cm, both were below the 5th percentile, head circumference 38.5 cm (below the 5th percentile). He had tachycardia with a pulse rate of 168/minute and tachypnea with a respiratory rate of 64/minute. Also he had pallor, mongoloid palpebral fissures, epicanthic folds, hypotelorism and simian crease in the right hand. The liver was palpable 4 cm below the right costal margin. Heart sounds were muffled and a grade 3/6 systolic murmur was heard on the mezocardiac area. There were bilateral basilar rales on the chest examination. Laboratory evaluation revealed a hemoglobin level of 9.4 g/dl, leukocyte count of 11.400/mm³, consisting of 60% segmented neutrophils, 40% lymphocytes, platelet count of 267 000/mm³. Serum C-reactive protein concentration was 0.1 mg/dl, threeiodothyronin (T3) level 1.62 ng/ml (1.07–3.18 ng/ml), tetraiodothyronin (T4) level 4.1 µg/dl (6.1–14.9 µg/dl), thyroid-stimulating hormone (TSH) 21 µIU/ml (0.9–7.7 µIU/ml), free T3 (fT3) 0.92 pg/ml (3.5–6.5 pg/ml), reverse T3 (rT3) 26 ng/dl (10–50 ng/dl), free T4 (fT4) 0.76 ng/dl (0.9–2.6 ng/dl). Anti TPO Ab level was <1.0 IU/ml (1–6 IU/ml) and anti-thyroglobulin Ab level was <5.0 IU/ml (5.0–100.0 IU/ml). Ultrasonographic examination of the thyroid gland was normal and ^{99m}Tc-pertechnetate scan revealed diminished radionuclide uptake. Chest X-ray showed cardiomegaly with a cardiothoracic ratio of 0.65. Echocardiographic examination showed an atrial septal defect of the secundum type with a dimension of 9 mm at the region of fossa ovale, left to right shunt at the atrial level, right atrial dilation and massive pericardial effusion measuring 9 mm on posterior wall of left ventricle by M-Mode echocardiography, ejection fraction was 80%. Five milliliters of pericardial fluid, which was yellow colored, containing 200 white blood cells per mm³ was aspirated, gram and Ziehl-Nielsen stains of the fluid did not reveal any organism. Bacterial culture was negative. Viral serology was not available. Pericardial fluid glucose level was 78 mg/dl, protein content 4.9 g/dl (simultaneous serum protein level was 5.9 g/dl), albumin 3.2 g/dl, LDH 546 IU/L (simultaneous serum LDH level was 666 IU/L). Chromosomal analysis showed trisomy 21 pattern. Digoxine, captopril and furosemide were given for the treatment of congestive heart failure. After this therapy, tachycardia was resolved, but pericardial effusion was still persisted. Thinking that the reason of pericardial effusion in the patient was hypothyroidism, L-thyroxin therapy (5 µg/kg) was started and slightly increased. After one week of L-thyroxin therapy, pericardial effusion resolved to 6 mm and to 2 mm at the second month of the therapy and completely resolved at the third months.

Case 2

A two-year-old boy with Down syndrome presented with the complaints of cough and fever for four day duration. Echocardiographic examination showed ventricular septal defect and pulmonary hypertension when he was 6 month old. He was the first child of the non-relative healthy 30-year-old mother and 34-year-old father. His weight was 11 500 g and height 82 cm (both under the 5th percentile) and head circumference was 49 cm (between the 5th and 10th percentile). He had mongoloid face appearance consisting of mongoloid palpebral fissures, epicanthic folds, hypotelorism, pectus excavatum, and simian line in both hands. Cardiac auscultation revealed muffled heart sounds and a grade 3/6 pansystolic murmur at the mezocardiac area without thrill. Also he had syndactyly between the second and third fingers of the left foot and bilateral hip dislocation. Laboratory evaluation revealed that serum T3 level was 0.58 ng/ml (1.07–3.18 ng/ml), T4 level 5.85 µg/dl (6.8–13.5 µg/dl), TSH level 17.90 µIU/ml (0.6–5.5 µIU/ml), fT3 level 3.07 pg/ml (3.5–6.5 pg/ml), rT3 34 ng/dl (10–50 ng/dl), fT4 level 0.93 ng/dl (0.8–2.2 ng/dl). Antithyroglobuline Ab and anti TPO Ab was negative. Ultrasonographic and schintigraphic examinations of the thyroid gland were normal. Chromosomal analysis showed trisomy 21 pattern. Chest X-ray showed severe cardiomegaly. Echocardiographic examination showed perimembraneous ventricular septal defect with a dimension of 4 mm, left to right shunt and pericardial effusion measuring 6 mm. Digoxine, captopril and furosemide were given. At the end of the first week, clinical symptoms were resolved but pericardial effusion was not improved. L-thyroxin therapy was started at the dose of 8 µg/kg. On 13th day of L-thyroxin therapy, echocardiographic evaluation revealed that pericardial effusion regressed to 4 mm thickness. After second month of L-thyroxin therapy, pericardial effusion was completely resolved.

Case 3

A thirty-month-old girl with Down syndrome presented with the complaints of dyspnea and abdominal distention during one week. She was the first child of the non-relative healthy 40-year-old mother and 43-year-old father. His weight was 10 700 g, height 79 cm, and head circumference was 44 cm and all of them were below the 5th percentile. He had mongoloid face appearance consisting of hypotelorism, mongoloid palpebral fissures, epicanthal folds, pectus excavatum, and unilateral simian line at the left hand. Cardiac auscultation revealed muffled heart sounds and a grade 2/6 midsystolic murmur at the mezocardiac area. Laboratory evaluation revealed that serum T3 level was 0.4 ng/ml (1.07–3.18 ng/ml), T4 level 6.78 µg/dl (6.8–13.5 µg/dl), TSH level 16.8 µIU/ml (0.6–5.5 µIU/ml), fT3 level 1.4 pg/ml (3.5–6.5 pg/ml), rT3 32 ng/dl (10–50 ng/dl), fT4 level 1.1 ng/dl (0.8–2.2 ng/dl). Antithyroglobuline Ab and anti TPO Ab was negative.

Ultrasonographic and scintigraphic examinations of the thyroid gland were normal. Chromosomal analysis showed trisomy 21 pattern. Chest X-ray showed severe cardiomegaly. Echocardiographic examinations showed pericardial effusion measuring 9 mm on the posterior wall of left ventricle. Digoxine, captopril and furosemide were given. At the end of the first week of the therapy, clinical symptoms were resolved but pericardial effusion was not improved. On the second month of the L-thyroxin therapy (8 µg/kg), echocardiographic evaluation revealed that pericardial effusion has resolved.

Case 4

A five-month-old boy with Down syndrome presented with the complaints of dyspnea and fever during the last 5 days. He was the fourth child of the first degree relative healthy 29-year-old mother and 35-year-old father. He had mongoloid face appearance consisting of hypotelorism, mongoloid palpebral fissures, epicanthal folds, pectus excavatum, and unilateral simian line at the right hand. Cardiac auscultation revealed muffled heart sounds and a grade 2/6 midsystolic murmur at the mezocardiac area. He had also wheezing and rales on chest examination. Laboratory evaluation revealed that serum T3 level was 1.36 ng/ml (1.07–3.18 ng/ml), T4 level 8.18 µg/dl (6.1–14.9 µg/dl), TSH level 18.06 µIU/ml (0.9–7.7 µIU/ml), fT3 level 1.2 pg/ml (3.5–6.5 pg/ml), fT4 level 1.6 ng/dl (0.9–2.6 ng/dl). Antithyroglobuline Ab and anti TPO Ab was negative. Ultrasonographic and scintigraphic examinations of the thyroid gland were normal. Chromosomal analysis showed trisomy 21 pattern. Chest X-ray showed hyperaeration, and cardiothoracic index was 0.5. Echocardiographic examination showed pericardial effusion measuring 4 mm and patent foramen ovale. His respiratory symptoms were completely resolved with oxygen and salbutamol therapy. On the second month of L-thyroxin therapy (8 µg/kg), echocardiographic evaluation revealed that pericardial effusion has resolved. Demographic, clinical and laboratory findings of four consecutive cases were summarized in Table 1.

DISCUSSION

Pericardial effusion due to congenital or acquired hypothyroidism in Down syndrome was previously reported in childhood [2,3,5,7]. Pericardial effusion may be commonly seen in adult patients with myxedema [6]. Pericardial effusion is more frequent in more severe hormone defect such as agenesis and dyshormonogenesis [5]. Hypothyroidism is more common in Down syndrome population than normal population. The significantly lower T4 levels and elevated mean TSH levels in Down syndrome newborns are indicative of mild hypothyroidism [5]. Because of the similarity of the symptoms of Down syndrome and congenital hypothyroidism, early diagnosis and treatment of hypothyroidism are difficult. The delay of the diagnosis may favor the development of massive pericardial effusion [8]. Cardiac dysfunction due to congenital hypothyroidism is well-described and systolic and diastolic functions of the left ventricle are improved during thyroxin therapy [9]. Congenital hypothyroidism causes a myocardial relaxation abnormality and an increase in left ventricular mass [9]. Pericardial effusions that resolved after L-thyroxin therapy also suggested that they were caused by hypothyroidism like in our patients [2,3,5,7–11]. Our four cases had no etiological factors for congestive heart failure and we concluded that clinical findings of congestive heart failure are associated with pericardial effusion. Our first case presented with pericardial effusion, and his symptoms were resolved with the treatment of congestive heart failure, but pericardial effusion still persisted. Pericardial effusion was resolved with L-thyroxin therapy. Balducci et al. [12] reported that four of eleven congenital hypothyroid infants had pericardial effusion, and effusion was resolved after the L-thyroxine therapy. Pericardiocentesis may be performed in patients with large effusions and will demonstrate elevated pericardial fluid cholesterol levels [6]. We performed pericardiocentesis only in the first case. L-thyroxine therapy was started without pericardiocentesis for other three cases.

Table 1. Demographic, clinical and laboratory findings of cases.

| | Age (month)/Sex | Echocardiographic feature | Pericardial Effusion | T3 ng/ml | T4 µg/dl | TSH µIU/ml | FT3 pg/ml | rT3 ng/dl | Ft4 ng/dl | Anti-TPO Anti-thyroglobulin Ab | Thyroid ultrasonography Scintigraphy |
|---------------|-----------------|---------------------------|----------------------|----------|----------|------------|-----------|-----------|-----------|--------------------------------|--|
| CASE 1 | 7/Boy | Secundum ASD | 9 mm | 1.62 | 4.1 | 21 | 1.92 | 26 | 0.76 | Negative | diminished radionuclide uptake USG normal |
| CASE 2 | 24/Boy | VSD | 6 mm | 0.58 | 5.85 | 17.90 | 3.07 | 34 | 0.93 | Negative | Normal |
| CASE 3 | 30/Boy | Normal | 9 mm | 0.4 | 6.78 | 16.8 | 1.4 | 32 | 1.1 | Negative | Normal |
| CASE 4 | 5/Boy | Patent foramen ovale | 4 mm | 1.36 | 8.18 | 18.06 | 1.2 | 28 | 1.6 | Negative | Normal |

Since the autoimmune thyroid dysfunction is frequently reported among the patients with Down syndrome [1], antithyroglobulin and anti TPO antibodies were studied in our cases, and both of them were negative in all of our patients. Karlsson et al. [13] reported that the autoimmune thyroid disease was seen among the patients with Down syndrome especially after the age of eight. Cutler et al. [14] reported that thyroid antibodies were negative in two patients with Down syndrome who also concomitantly had congenital hypothyroidism. The etiology of hypothyroidism is unclear in four children we studied neither of them had thyroid antibodies nor had evidence of agenesis or ectopic thyroid tissue.

Pathogenesis of the pericardial effusion due to hypothyroidism is not well-understood. Kessel et al. [15] suggested that, non-immune hydrops fetalis due to congenital hypothyroidism may be caused by lymphatic congestion attributable to an impairment of lymphatic flow and delayed return of lymph to the vascular compartment due to reduced adrenergic stimulation of the lymphatic system. Also solitary pericardial effusion may be explained with the same mechanism. In severe hypothyroidism, ascites and pericardial effusion may be seen due to increased capillary permeability to protein coupled with fluid retention and abnormal lymphatic dynamics [7]. The extend of pericardial effusion due to hypothyroidism is mainly related to thyrotrophin level [11]. Our four cases have pericardial effusion while they have no severe hypothyroidism. But Kabadi and Kumar [16] reported an association between pericardial effusion and early mild stage hypothyroidism while pericardial effusion may be a frequent manifestation in myxedema at advanced severe stages.

A variety of nonthyroidal illness (NTI) has been stated to produce alterations in thyroid function. The most common thyroid hormone abnormality in NTI is a depression in serum total T3 and fT3 concentrations producing low T3 state in this condition, the serum fT4 and TSH concentrations are normal. A subgroup of patients with low T3 state may also have low T4 concentrations producing the low T3-lowT4 state. The serum TSH is low this situation. The most prominent alterations are low serum T3 and elevated rT3 leading to the general term low T3 syndrome [17]. On the contrary, in our patients we stated low T4 high TSH, normal rT3 concentrations as in the situation of hypothyroidism. Hence we evaluated this situation as linked to Down syndrome associated with hypothyroidism.

Thus, early evaluation of thyroid dysfunction and beginning of the treatment will prevent further mental deterioration and will promote than patients overall development and educational success as well as his or her quality of life. In conclusion, because of the difficult diagnosis of the hypothyroidism in Down syndrome, periodic follow-up of thyroid function tests are important in Down syndrome. Since a delayed diagnosis of hypothyroidism is likely and may favor the development of massive pericardial effusion, any child with Down

syndrome who present with dyspnea and cardiomegaly should be suspected of having pericardial effusion due to hypothyroidism and echocardiography examination should be performed immediately. Finally, pericardial effusion due to hypothyroidism will completely resolve with L-thyroxin therapy without pericardiocentesis.

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