Pulmonary thromboembolism in childhood: A single-center experience from Turkey

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OBJECTIVE: This study was designed to evaluate the clinical characteristics, acquired and congenital risk factors, treatment strategies, and long-term outcome in pediatric pulmonary thromboembolism (PTE) cases followed in our center in Turkey.

SUBJECTS: Of the total 470 pediatric patients with thrombosis referred to our center, 16 (3.4%) had PTE. The mean age of the children with PTE was 10.3 ± 6.8 years (range: 1.5–20.0, median: 10.5), and 12 (75.0%) were boys.

RESULTS: The mean follow-up period was 28.9 ± 21.0 months (range: 3–66, median: 22). During the follow-up period, recurrence was observed in three children (18.8%). The mean time from the appearance of symptoms to accurate diagnosis was 6.4 ± 4.0 days (range: 2–10). Six patients (37.5%) were initially diagnosed as having pneumonia. After they were hospitalized and showed no clinical improvement with broad-spectrum antibiotic treatment, the accurate diagnosis of PTE was established. Of these 16 patients with PTE, 8 (50%) had associated thrombosis and 6 (37.5%) had congenital heart diseases. Infections including septic arthritis and osteomyelitis (n = 1), cytomegalovirus infection (n = 1), and infective endocarditis (n = 2) were detected in our patient group. In addition, two patients had a central venous line and one patient had obesity associated with malignancy. Other underlying diseases included thalassemia major, Behçet disease, antiphospholipid antibody syndrome, and autoimmune lymphoproliferative disorder in one patient each. Factor V G1691A heterozygous mutation was detected in two children, and methylene tetrahydrofolate reductase C677T homozygous mutation was detected in one child. A high level of factor VIII was the most common (8/16, 50%) laboratory risk factor in our patient group, and 12 children (75.0%) had a high D-dimer level. Among 16 children with PTE, one child had one, three children had two, five children had three, three children had four, and four children had five laboratory and/or clinical risk factors. Therefore, all children with PTE had at least one laboratory and/or clinical risk factor that facilitated development of thrombosis. In addition, according to the risk assessment for persistence or recurrence of venous thrombosis in children conducted by Manco-Johnson, 12 children (75%) with PTE in the present study had high-risk criteria.

CONCLUSION: When a child with thrombosis at any site of the body develops unexpected respiratory symptoms or pneumonia unresponsive to antibiotic treatment, imaging studies should be performed for diagnosis of PTE. Furthermore, thrombotic children with high-risk criteria should be followed closely for the development of PTE. (Heart Lung® 2009;38:56–65.)

Pulmonary thromboembolism (PTE) results from obstruction of the pulmonary artery by endogenous or exogenous embolus or local thrombus. It is an uncommon but life-threatening disorder in children. Because the clinical findings are nonspecific, suspicion is required for early and accurate diagnosis of pediatric PTE. In childhood, PTE is often overlooked because the clinical presentation may be altered or masked by other concomitant diseases. The incidence of PTE is much less in children than in adults. In recent years, mostly case reports and case series have been reported in the literature.[1-7] However, large studies in children with PTE have been conducted on autopsy examination. An incidence of PTE ranging from .73% to 4.3% has been reported in pediatric autopsy studies.[8,9] With improvement in imaging techniques and increased disease recognition, the incidence of pediatric PTE

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has gradually increased. In Canadian and Dutch pediatric registries, incidence rates of PTE were found to be .86 per 10,000 pediatric hospital admissions and .14 per 100,000 children (range: 0–18 years) annually.[2,10]

Nevertheless, there are a limited number of publications about pediatric PTE, and some of them are review articles that explain the incidence of PTE.[1-7] However, clinical characteristics, risk factors, treatment, and outcome in pediatric PTE are not sufficiently understood. Therefore, we aimed to evaluate clinical characteristics, acquired and congenital risk factors, treatment strategies, and long-term outcome in pediatric PTE cases followed in our center.

MATERIALS AND METHODS

Between January of 1998 and August of 2006, 470 pediatric patients were admitted to Hacettepe University Faculty of Medicine, Pediatric Hematology Unit, for evaluation of thrombosis. Of these 470 children with thrombosis, those with respiratory symptoms and young children with pneumonia who do not improve with antibiotic treatment were evaluated with imaging studies for PTE; as a result of this evaluation, 16 children (3.4%) were diagnosed with PTE.

These 16 patients' outpatient and inpatient charts were reviewed for additional thrombosis, underlying diseases, prothrombotic risk factors, type and duration of anticoagulation therapy, resolution of thrombosis, and outcome. The diagnosis of PTE was made using ventilation-perfusion scintigraphy, helical computed tomography, magnetic resonance imaging, and pulmonary angiography. In addition, the diagnosis of associated thrombosis was made using Doppler ultrasonography, computed tomography, and magnetic resonance imaging techniques.

Thrombotic workup, including protein C, protein S, antithrombin III, lipid profiles (triglycerides, cholesterol, very low-density lipoprotein, low-density lipoprotein, high-density lipoprotein), lipoprotein A level, homocysteine level, anticardiolipin and antiphospholipid antibodies (APAs), factor II, V, VII, VIII, IX, and XI levels, factor V G1691A (FV Leiden), prothrombin G20210A, and methylene tetrahydrofolate reductase (MTHFR) mutations, was performed in all patients with PTE. Fibrinogen (normal values, 144-430 mg/dL), factor II (normal values, 70%-120%), factor V (normal values, 70%-120%), factor VII (normal values, 70%-130%), factor VIII (normal values, 53%-170%), factor IX (normal values, 60%-170%), and factor XI (normal values, 70%-150%) were studied by measurement of the clotting time (Diagnostica Stago, Asnieres, France). Plasma protein C activity (normal values, 70%-130%) and antithrombin III activity (normal values, 80%-120%) were measured with the use of calorimetric substrates (STA Stachrom, Diagnostica Stago). Free protein S antigen was measured using commercially available immunoturbidimetric assay kits (normal values, 70%-130%) (STA Liatest, Diagnostica Stago). APAs (normal values, 0-10 RU/mL) were determined with enzyme-linked immunosorbent assay techniques (Euroimmun, Lübeck, Germany). Homocysteine (normal values, 5-15 μmol/L) and lipoprotein a (normal values, 0-30 mg/dL) were tested using the Immage immunochemistry system by the nephelometry method (Beckman, Fullerton, Calif).

High molecular weight DNA was extracted from peripheral blood by standard procedures. FV G1691A, prothrombin G20210A, and MTHFR C677T mutations were detected using the methods described earlier.[11-13] SPSS for Windows version 10.0 (SPSS Inc, Chicago, Ill) was used for evaluation of the data. Type of thrombosis, underlying diseases, prothrombotic risk factors, type and duration of anticoagulation therapy, and outcome in children with PTE are shown in Table I.

RESULTS

The mean age of the 16 children with PTE (12 boys, 75%) was 10.28 ± 6.83 years (range: 1.5–20.0, median: 10.5 years). Although three patients (case numbers 2, 5, and 12) were aged more than 18 years (20, 20, and 19 years), they continued to be followed at the children's hospital by their primary physicians because of their chronic and congenital diseases. The mean follow-up period was 28.88 ± 21.00 months (range: 3–66 months, median: 22 months). During the follow-up period, recurrence was observed in 3 (18.8%) of the 16 children. All of the clinical and laboratory data of the patients with PTE are presented in Table I. Data of completely or partially recovered patients are presented in Table II.

Clinical features

All patients had respiratory symptoms, including tachypnea, cough, and respiratory distress, at the time of diagnosis. The mean time from the appearance of the symptoms to accurate diagnosis was 6.4 ± 4.0 days (range: 2–10 days). Six patients (37.5%) were initially diagnosed as having pneumonia. After they were hospitalized and no clinical improvement was observed after broad-spectrum antibiotic treat-

Table I
Site of thrombosis and risk factors in patients with pulmonary thromboembolism

Case No.	Age (y)/ gender	Type of thrombosis	Underlying diseases	Prothrombotic risk factors	Type and duration of anticoagulation therapy	Outcome
1	13/M	PTE and DVT at right femoral vein	Operated craniopharyngioma and obesity	Hyperlipidemia, lupus anticoagulant positivity, and MTHFR homozygous mutation	Unfractionated heparin for 10 d and LMWH for 6 mo	Alive with partial recovery
2	20/F	PTE	Operated congenital heart disease (truncus arteriosus) and infective endocarditis (blood culture: *Acinetobacter baumannii*)	—	TPA (once), unfractionated heparin for 10 d, and oral anticoagulant for 6 mo	Exitus with complicated congenital heart disease and infective endocarditis; complete recovery
3	2.5/M	PTE and DVT at right femoral vein	Pneumonia	Hyperlipidemia and elevated level of factor XI	Unfractionated heparin for 14 d and LMWH for 6 mo	Alive with complete recovery
4	4.5/M	PTE and DVT at right vena cava superior	Vitamin D-resistant rickets, pneumonia, and presence of catheter	Elevated levels of lipoprotein a, fibrinogen, factor VIII and XI	Thrombectomy for DVT; Unfractionated heparin for 10 d and LMWH for 6 mo for PTE	Alive with complete recovery
5	20/M	PTE and DVT at right axillary, vena cava inferior, and subclavian veins	Thalassemia major, splenectomy, and heart failure	Protein C deficiency, elevated levels of fibrinogen and factor VIII	TPA (twice), unfractionated heparin for 12 d, and long-term LMWH therapy	Recurrence of DVT, alive with complete recovery
6	2/M	PTE	Pneumonia, CMV infection	Protein C deficiency, elevated level of factor VIII	TPA (once), LMWH for 10 d, and oral anticoagulant for 6 mo	Alive with complete recovery

Table I
Continued

Case No.	Age (y)/ gender	Type of thrombosis	Underlying diseases	Prothrombotic risk factors	Type and duration of anticoagulation therapy	Outcome
7	1.5/M	PTE, cerebral infarct, renal vein thrombosis, and DVT at right subclavian and internal jugular veins	Down syndrome, congenital heart disease (atrioventricular septal defect), pneumonia, pulmonary binding operation, and presence of catheter	Protein C deficiency	TPA (twice), and long term LMWH treatment for recurrent thrombosis	Exitus with recurrent thrombosis; partial recovery
8	15/M	PTE and thrombosis in the right ventricle	Congenital heart disease (corrected transposition of great arteries, ventricular septal defect, pulmonary stenosis), Blalock-Taussig shunt operation	Protein S deficiency	Unfractionated heparin for 10 d and LMWH for 6 mo for PTE	Alive with complete recovery
9	17/M	PTE	Behçet disease (lung involvement), aneurysm in pulmonary artery	Elevated level of homocysteine	LMWH for 6 mo, high-dose methylprednisolone (500 mg), and cyclophosphamide	Alive with partial recovery and pulmonary hypertension
10	9/F	PTE	Infective endocarditis, operated congenital heart disease (atrial septal defect, mitral and tricuspid insufficiency), and pneumonia	—	LMWH for 6 mo	Alive with complete recovery
11	12/M	PTE and DVT at right femoral vein and vena cava inferior	Septic arthritis and osteomyelitis at right femur, pneumonia	FV G1691A heterozygous mutation, hereditary protein C deficiency, hyperlipidemia, and elevated level of factor VIII	TPA (twice), unfractionated heparin for 10 d, LMWH for 6 mo, and long-term oral anticoagulant treatment	Recurrence of DVT, alive with complete recovery

Table I
Continued

Case No.	Age (y)/ gender	Type of thrombosis	Underlying diseases	Prothrombotic risk factors	Type and duration of anticoagulation therapy	Outcome
12	19/F	PTE	Congenital heart disease (truncus arteriosus, ventricular septal defect, pulmonary atresia) and Fontan operation	Elevated level of factor VIII	Unfractionated heparin for 10 d, LMWH for 10 d, and oral anticoagulant treatment for 6 mo	Alive with partial recovery and pulmonary hypertension
13	1.5/M	PTE	Infective endocarditis (blood culture: *Candida albicans*), aganglionic megacolon	Elevated level of factor VIII	LMWH for 6 mo	Alive with sequela and partial recovery
14	14/M	PTE	Autoimmune lymphoproliferative disorder	Elevated level of factor VIII and factor XI	Unfractionated heparin for 10 d and LMWH for 6 mo	Alive with complete recovery
15	7/F	PTE and DVT at left internal carotid artery and cerebral infarct	Antiphospholipid antibody syndrome	FV G1691A heterozygous mutation, elevated levels of factor II and VIII, antiphospholipid IgM (+) and anticardiolipin IgM (+)	Unfractionated heparin for 10 d and acetyl-salicylic acid and LMWH for 6 mo	Alive with sequela (hemiplegia) and partial recovery
16	6.5/M	PTE	Congenital heart disease (atrial septal defect, pulmonary stenosis, pulmonary valvular insufficiency)	Hereditary protein C deficiency	Unfractionated heparin for 10 d and LMWH for 6 mo	Alive with partial recovery and pulmonary hypertension

PTE, Pulmonary thromboembolism; *DVT,* deep vein thrombosis; *LMWH,* low-molecular-weight heparin; *TPA,* tissue plasminogen activator; *CMV,* cytomegalovirus; *Ig,* immunoglobulin; *FV,* factor V; *MTHFR,* methylene tetrahydrofolate reductase.

Table II
Data of patients with complete and partial recovery

	Complete recovery	Partial recovery
No. of patients*	8	6
No. of risk factors in each patient	3.6	3.1
Mean age (mean ± SD; range)	9.9 ± 6.5 y (2-20)	10.7 ± 6.8 y (1.5-19)
Underlying disorder	Pneumonia (2)	Craniopharyngioma and obesity (1)
	Pneumonia and catheter (1)	Congenital heart disease, pneumonia, and catheter (1)
	Thalassemia, splenectomy, and heart failure (1)	Behçet disease, aneurysm in pulmonary artery (1)
	Congenital heart disease and Blalock-Taussig shunt (1)	Congenital heart disease and Fontan operation (1)
	Pneumonia, congenital heart disease, and infective endocarditis (1)	Antiphospholipid antibody syndrome (1)
	Septic arthritis and osteomyelitis (1)	Infective endocarditis (1)
	Autoimmune lymphoproliferative disorder (1)	
Prothrombotic risk factors	Hyperlipidemia (2)	Hyperlipidemia (1)
	Protein C deficiency (3)	Factor II ↑ (1)
	Protein S deficiency (1)	Factor VIII ↑ (3)
	Lipoprotein a ↑ (1)	Lupus anticoagulant positivity (1)
	Homocysteine ↑ (1)	Antiphospholipid IgM (+) and anticardiolipin IgM (+) (1)
	Fibrinogen ↑ (2)	FV G1691A heterozygous mutation (1)
	Factor VIII ↑ (5)	MTHFR homozygous mutation (1)
	Factor IX ↑ (1)	
	Factor XI ↑ (2)	
	FV G1691A heterozygous mutation (1)	

SD, Standard deviation; *Ig,* immunoglobulin; FV, factor V; *MTHFR,* methylene tetrahydrofolate reductase.
*Expired patients were not evaluated in this table.

ment, the accurate diagnosis of PTE was established.

Imaging studies

Of these 16 patients with PTE, all had chest radiography studies, whereas hard copies of chest radiography were available for 10 of 16 children, which revealed nonspecific abnormalities including infiltration, consolidation, and opacities. In the diagnosis of PTE, both ventilation-perfusion scintigraphy and helical computed tomography were used in eight patients, only ventilation-perfusion scintigraphy was used in four patients, only helical computed tomography was used in three patients, and pulmonary angiography was used in one patient. Therefore, ventilation-perfusion scintigraphy was the most common diagnostic imaging technique used in this group of patients (75%). In addition, two imaging techniques were preferred in half of the patients for the accurate diagnosis of PTE.

Associated thrombosis

Of these 16 patients with PTE, 8 (50%) had associated thrombosis. Two patients had deep vein thrombosis (DVT) at lower extremity veins, two patients had DVT at upper-extremity veins, one patient had DVT at both upper and lower-extremity veins, two patients had cerebral infarct associated with DVT, and one patient had intracardiac thrombosis (Table I).

Underlying diseases

Six patients (37.5%) had congenital heart diseases; one underwent the Fontan operation, one underwent the Blalock-Taussig shunt operation, and four underwent other operations, including pulmonary binding operation, correction of truncus arteriosus, and atrial septal defect. Six patients (37.5%) had probable pneumonia. Infection other than pneumonia was also detected in our patient group: septic arthritis associated with osteomyelitis in one patient, cytomegalovirus infection in one patient, and infective endocarditis in two patients. *Acinetobacter baumannii* and *Candida albicans* were detected in the blood culture of two patients with infective endocarditis. In addition, two patients had a central venous line (CVL) and one patient had obesity associated with malignancy. Other underlying diseases included thalassemia major, Behçet disease, APA syndrome, and autoimmune lymphoproliferative disorder in one patient each. Thus, all of our patients had clinical risk factors for thrombosis (Tables I and II).

Laboratory risk factors

FV G1691A heterozygous mutation was detected in two children, and MTHFR C677T homozygous mutation was detected in one child. Hyperlipidemia was detected in three children (18.75%), APA positivity in one child (6.25%), and lupus anticoagulant positivity in one child (6.25%) at the time of diagnosis. In addition, five children (31.25%) had protein C deficiency, and one child (6.25%) had protein S deficiency; elevated levels of factor XI, fibrinogen, factor II, homocysteine, and lipoprotein A were detected in three children (18.75%), two children (12.5%), one child (6.25%), one child (6.25%), and one child (6.25%), respectively. A high level of factor VIII was the most common (8/16, 50%) laboratory risk factor in our patient group. Furthermore, 12 (75.0%) of 16 children with PTE had a high D-dimer level (normal range in our center: .0–.5 U/dL) at the time of diagnosis. The mean D-dimer level was 4.7 ± 6.6 U/dL: (range: .61–18.98, median: 2.07 U/dL).

Thus, among 16 children with PTE, one child had one, three children had two, five children had three, three children had four, and four children had five laboratory and/or clinical risk factors. Therefore, all children with PTE had at least one laboratory and/or clinical risk factor that facilitates development of thrombosis.

According to the risk assessment for persistence or recurrence of venous thrombosis in children conducted by Manco-Johnson,[14] 12 of 16 children with PTE in the present study had high-risk criteria.

Treatment modalities and outcome

After the diagnosis of PTE, oxygen saturation should be monitored closely. Because children with PTE may need mechanical ventilation, unfractionated heparin was used to achieve a therapeutic partial thromboplastin time of 60 to 85 seconds as initial anticoagulation therapy in 8 (50%) of 16 children. Thrombolytic therapy (tissue plasminogen activator [TPA] .5 mg/kg/h for 6 hours) was used in five children (31.25%). In three of them, TPA treatment was applied twice, whereas it was applied only once in the other two children. Low-molecular-weight heparin (LMWH) was used in three children (18.75%) as initial treatment.

In the follow-up treatment, LMWH was used in most of the children (12/16, 75%) with the exception of four adolescent patients who received oral anticoagulant treatment. The duration of the anticoagulant treatment was generally 6 months, except for three patients who were recommended to have long-term anticoagulant treatment in view of their

recurrent thrombosis despite receiving anticoagulation therapy. Two of the patients with recurrent thrombosis had only DVT and not PTE recurrence, and they are doing well with oral anticoagulation therapy. However, the other patient had recurrent and multiple thrombosis, including PTE, cerebral infarct, renal vein thrombosis, and DVT at the right subclavian and internal jugular veins, and he did not recover completely with anticoagulant therapy; he died of multiple progressive thrombosis. Anticoagulant therapy was well tolerated; major bleeding related to anticoagulant therapy was not observed in our patients. During the follow-up, seven children had partial dissolution and nine children had complete dissolution of thrombosis. Two patients died: one as the result of infection (infective endocarditis) and one as the result of recurrent, multiple, and progressive thrombosis as described earlier. On the follow-up imaging studies, three of seven children who had partial dissolution of PTE had pulmonary hypertension as a sequela (Table I).

DISCUSSION

The incidences of PTE have varied between 1.7% and 40% in selected pediatric patient populations with the diagnosis of nephrotic syndrome, burns, trauma, leukemia, bone marrow transplantation for leukemia, and heart transplantation for dilated cardiomyopathy and congenital heart disease.[15-20] On the other hand, PTE has been diagnosed in 10% to 20% of children with venous thrombosis in pediatric studies.[10,21,22] The present study was not performed in any selected pediatric population; instead, clinical characteristics, acquired and congenital risk factors, treatment strategies, and long-term outcome in pediatric PTE cases followed in our center were evaluated in this study. Of the total 470 pediatric patients with thrombosis referred to our center, 16 (3.4%) had PTE and 2 (.4%) with PTE were lost to follow-up.

PTE commonly occurs in association with DVT. Many PTE cases may be clinically silent or masked by associated symptoms related to underlying diseases.[1,23] Therefore, all children with documented DVT, moreover any type of thrombosis at any organ, should also be evaluated for PTE. van Ommen et al[10] reported 10 patients with PTE, and in their series, five cases (50%) were associated with DVT. In our series, 8 (50%) of 16 cases with PTE also had associated thrombosis. These two studies suggest that half of the patients with any type of thrombosis may be associated with PTE.

In children, idiopathic thrombosis occurs rarely, and most of the thrombotic episodes occur in association with underlying malignancy, congenital heart diseases, the presence of CVL and catheters, collagen tissue disorders, renal diseases, burn, dehydration, immobility, obesity, shock, sepsis, surgery, trauma, and vascular malformation.[1,2,10] In the present study, all children with PTE had at least one laboratory or clinical risk factor that facilitates development of thrombosis. Furthermore, 15 children (93.8%) had more than one prothrombotic risk factor in this study. Spontaneous PTE is rare, whereas laboratory and/or clinical risk factors for thrombosis increases the risk of PTE development in children.

In our patient group, 6 (37.5%) were initially diagnosed as having pneumonia for which they received broad-spectrum antibiotic treatment, but clinical improvement was not observed in these patients. Imaging studies performed later led to the accurate diagnosis of PTE. In case numbers 3, 4, 7, and 11 with PTE and pneumonia, associated thrombosis that may facilitate the development of PTE was also detected. In these cases, associated thrombosis and PTE may produce an image suggestive of pneumonia on chest radiograph. In case number 6, pneumonia may have resulted from cytomegalovirus infection, and in case number 10, atrial septal defect may have caused the development of pneumonia; pneumonia is a common infection in left-to-right shunted congenital heart diseases. The mean age of all patients with PTE was 10.28 $\pm$ 6.83 years (median: 10.5), whereas the mean age of the patients initially diagnosed with pneumonia was 5.25 $\pm$ 4.29 years (median: 3.5), which was younger than that of all patients. The younger patients with PTE may not clearly state the chest pain, which may contribute to the initial misdiagnosis or delay in the accurate diagnosis of PTE. Therefore, especially in young children with pneumonia, PTE should be suspected and imaging studies should be performed when the respiratory symptoms of young children with pneumonia do not improve with antibiotic treatment.

In our series, 6 (37.5%) of 16 patients had congenital heart diseases; five patients (31.25%) underwent cardiac surgery, and one patient underwent the Fontan procedure. Children with congenital heart disease can develop thromboembolic complications as a result of altered hemodynamics, prosthetic materials, damaged blood vessels, use of CVLs, and catheterization. PTE is common after right-sided heart bypass surgery, especially the Fontan procedure.[1,9] Long-term clinical follow-up of patients with congenital heart disease should be per-

formed with respect to the development of PTE and other thromboembolic complications, especially after cardiac surgery.

Although pediatric malignancy can also lead to the development of PTE, only one child had malignancy in our series. Frequent use of CVLs, coagulation abnormalities resulting from disease or cancer treatment, endothelial damage caused by chemotherapy, use of total parenteral nutrition, and underlying thrombophilia are factors that facilitate thromboembolic complications in malignancy. PTE can be seen in solid tumors and leukemias.[1,23] It should be kept in mind that acute respiratory distress may be caused by infection, drug reaction, and PTE in a child with malignancy.

In our series, one patient (case 5) with beta thalassemia major who underwent splenectomy first had DVT at the right vena cava inferior, axillary, and subclavian veins, and he received unfractionated heparin treatment. He had cardiotoxicity and hepatotoxicity caused by the high levels of ferritin. Laboratory studies of the patient revealed that he had acquired protein C deficiency and high levels of fibrinogen and factor VIII levels. Therefore, he had high-risk criteria for recurrence and persistence of venous thrombosis.[14] In addition, ongoing hemolysis, recurrent infections, and postsplenectomy thrombocytosis in thalassemia major facilitate development of PTE.[24] After 3 months, he had a second attack of DVT at the same veins and developed PTE, despite receiving LMWH treatment. Supportive therapy for cardiac insufficiency and aggressive anticoagulation therapy (TPA twice, unfractionated heparin for 12 days, and long-term LMWH therapy) were applied, and complete recovery was achieved in this patient.

The patients were also evaluated according to the number of risk factors in each patient: The mean number of risk factors was 3.6 for completely recovered patients and 3.1 for partially recovered patients. Although the number of patients with PTE was limited in the present study, this finding suggests that the type of risk factor in each patient, rather than the number, is an important factor for recovery (Table II). We observed that infection is a more common risk factor in completely recovered patients, whereas noncorrectable underlying disconditions, such as Behçet disease, aneurysm of the pulmonary artery, APA syndrome, Fontan operation, and craniopharyngioma, are among the risk factors in partially recovered patients. In completely recovered patients, three had received TPA and one had undergone thrombectomy for the treatment of PTE, and this may also affect the recovery of the patients (Table II). Because the numbers of completely and partially recovered patients were limited, no statistical comparison was performed. We suggest that further studies are necessary to confirm our observation obtained from this study.

The D-dimer test is commonly used in the initial clinical evaluation of PTE in adult patients because it has been reported that an elevated D-dimer test result is sensitive in 97.0% of cases and has a negative predictive value of 99.6% in adult cases.[3] However, the role of D-dimer in the diagnosis of pediatric PTE has not been studied in large series. Rajpurkar et al[3] reported that 4 (40%) of 10 children with PTE had a normal D-dimer level in their series; 12 (75%) of 16 children with documented PTE had a high D-dimer level at the time of diagnosis in our patient group. Still, we suggest that D-dimer can be used as a predictive marker for the diagnosis of pediatric PTE.

As is known, hereditary and acquired risk factors are important in the pathogenesis of PTE, as in the development of other thrombosis. Two children with PTE had FV G1691A heterozygous mutation, and one child had MTHFR C677T homozygous mutation in this group of patients. Elevated FVIII level is recognized as one of the high-risk criteria for the persistence or recurrence of venous thrombosis; 8 (50%) of 16 patients had high FVIII levels in this study.[14] Another important point in the present study is that 12 patients (75%) with PTE had three or more risk factors for thrombosis. The patients with three or more risk factors can develop thrombosis easier than those with one to two risk factors.[14] This study indicates that patients with high-risk criteria can develop PTE easier than those with standard or low-risk criteria. We suggest that thrombotic children with high-risk criteria should be closely followed for development of PTE.

In the diagnosis of PTE, ventilation-perfusion scintigraphy has been the usual initial diagnostic test in both children and adults for more than three decades. The application of the test is easy even in small children. In addition to ventilation-perfusion scintigraphy, helical computed tomography is becoming the preferred diagnostic imaging technique for pediatric PTE in many centers. It can visualize the emboli and be performed quickly even in critically ill children.[3,25,26] In our center, both imaging techniques have been used in the diagnosis of PTE.

CONCLUSIONS

When a child with thrombosis at any site of the body develops unexpected respiratory symptoms or

pneumonia resistant to antibiotic treatment, imaging studies should be performed for diagnosis of PTE. Prompt diagnosis, early administration of anticoagulation therapy, and supportive therapy may rescue the life of children with PTE, and complete recovery can be achieved in these children. Furthermore, patients with high-risk criteria, including three or more risk factors, should be followed closely for the development of PTE and treated with effective anticoagulant therapy for complete recovery.

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