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Recurrent Intraventricular Thrombosis in a Child with Dilated Cardiomyopathy and Antithrombin Deficiency

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Unfractionated heparin and long-term oral anticoagulation resulted in a disappearance of a left ventricular thrombus in a 2-year-old girl with dilated cardiomyopathy. One month later biventricular thrombosis developed in spite of oral anticoagulation. High-dose heparin and oral anticoagulation were applied with success. Nine months after discharge, the antithrombin activity was repeatedly subnormal (49%). The genetic analysis did not reveal any mutation responsible for antithrombin deficiency. There are no prospective controlled trials proving the benefits of anticoagulation in patients with DCM and sinus rhythm. Besides monitoring ventricular enlargement and dysfunction, the investigation of natural anticoagulant systems may identify a subgroup of patients at risk for developing ventricular thrombi and thromboembolism.

Keywords:
intracardiac thrombosis, dilated cardiomyopathy, antithrombin deficiency, child

Intracardiac thrombosis is a well-known complication of dilated cardiomyopathy (DCM). Systemic or pulmonary embolization contributes significantly to morbidity and mortality of DCM in childhood (1). Central nervous system (CNS) embolization is the most common manifestation of systemic embolization, and may lead to significant morbidity and mortality. CNS embolization is commonly seen without echocardiographic signs of intracardiac thrombosis (2). Anticoagulation may prevent thromboembolic events. However, except in patients with previous thromboembolic event, atrial fibrillation and newly formed left ventricular thrombus, currently available evidence is inconclusive whether or not the benefits of anticoagulation therapy outweigh its risks in other subgroups (3, 4).

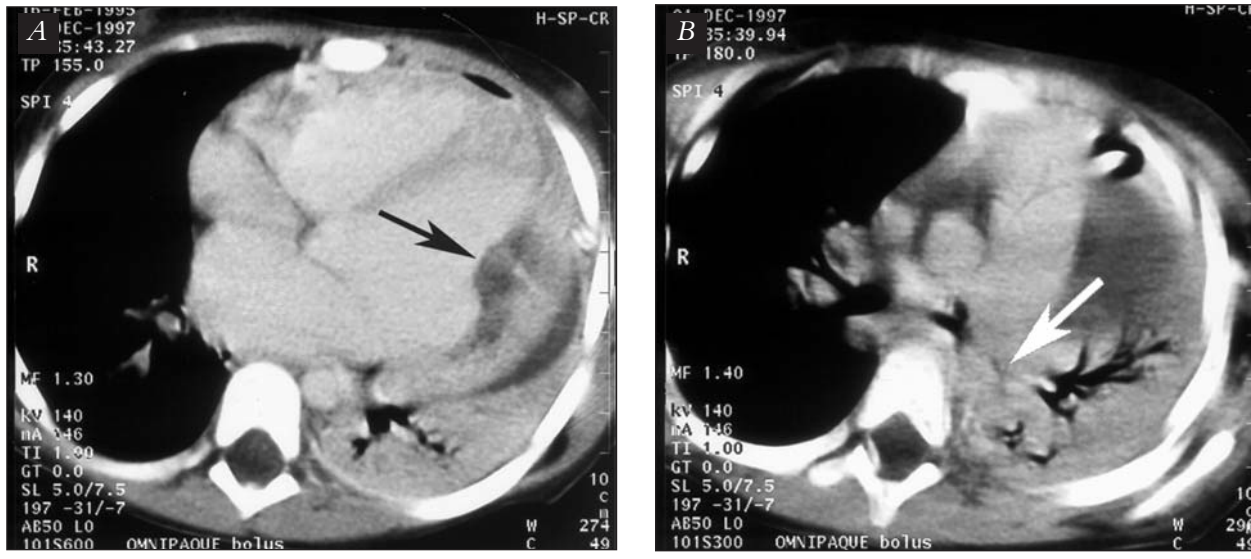

Figure 1. (A) Contrasted spiral CT scan of the heart: large flat thrombus (arrow) attached to the posterior wall of the left ventricle. (B) Left lung atelectasis owing to the compression of the left main bronchus (arrow)

DCM associated with acquired or congenital disorders of the natural anticoagulation systems including G1691A Factor V Leiden mutation, prothrombin G20210A mutation, protein C, protein S and antithrombin (AT) deficiency may represent another subgroup of patients who may benefit from oral anticoagulation therapy. Supporting this view we present the case of a 2-year-old girl with DCM and antithrombin deficiency that had recurrent intracardiac thrombosis.

Case Report

DCM was diagnosed in a two-year-old girl by non-invasive methods (ECG, echocardiography, laboratory tests). The fractional shortening of the left ventricle was 13% as checked by echocardiography. Introduction of furosemide, digoxin and enalapril resulted in an improvement in the circulatory condition of the patient. However, nine months later pallor and tachypnea developed. Chest x-rays showed extreme cardiomegaly, atelectasis of the left lung and pleural effusion requiring drainage. A thin-cut spiral computer tomograph (CT) scan revealed a large flat, non-pedunculated thrombus in the left ventricle (Fig. 1) and also showed a compression of the left main bronchus by the enlarged heart resulting in atelectasis. The fractional shortening of the left ventricle was 7% as checked by echocardiography.

Unfractionated Na-heparin infusion was started at a loading dose of 50 U/kgbw and maintained for four days at a dose of 45-50 U/kgbw/hr followed by a gradual switch to oral anticoagulation (acenocoumarol 1 mg daily). Heparin treatment resulted in only a moderate prolongation of activated partial thromboplastin time (aPTT) (patient: 46.3 s, control: 33.3 s). The intracardiac thrombus, monitored by transthoracic echocardiography shrank gradually (Fig. 2A) and disappeared completely after 20 days (Fig. 2B). No clinical symptoms, indicating an embolic event were detected. The patient was discharged and remained

Figure 2. (A) Four chamber view 2D echocardiogram: the left ventricular thrombus (arrow) diminished in size compared to the CT scan. (B) Four chamber view 2D echocardiogram: no thrombus can be detected

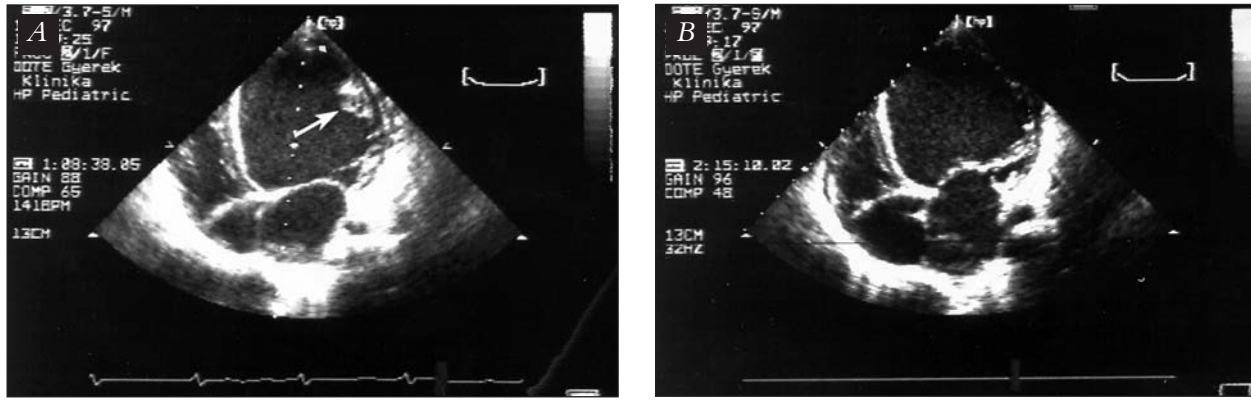

Table 1. Characterization of the hemostatic system of the patient 9 months after the second thrombotic event

Tests	Patient	Control/ Reference values
Prothrombin time (sec.)	25.6 s	9.2-11.5 s
INR	2,4	
Activated partial thromboplastin time (aPTT)	42.4 s	27.8-42.8 s
Thrombin time (TT)	17.1 s	15.4-23.4 s
Antithrombin-III activity	49%	80-120%
Protein C* activity	n.d.	70-130%
Protein S* activity	n.d.	65-140%
Plasminogen activity	89%	80-120%
Activated Protein C ratioe	2,25	>2,0
Factor V Leiden-mutation	wild type	wild type
Prothrombin 20210G A mutation	wild type	wild type
Fibrinogen	3,97 g/l	1,5-4,0 g/l

*Protein C and S levels were not determined (n.d.) because of acenocoumarol therapy.

on oral anticoagulation therapy (acenocoumarol 1 mg daily). INR values fluctuated between 1.77 and 4.65, possibly because of her unstable circulatory state. Thirty-six days after discharge, intracardiac thrombi were detected again in both ventricles by echocardiography. The left ventricular function, measured by echocardiography, was poor (fractional shortening 6%). We started unfractionated Na-heparin infusion again, but large doses (45-50 U/kgbw/hr) were required to maintain an acceptable anticoagulation effect (patient aPTT/reference aPTT ≥1.5). AT measurement by a chromogen test revealed reduced activity with 55% (reference value: 80-120%). Nineteen days later a transthoracic echocardiography indicated the disappearance of the thrombi. The patient was discharged again on oral anticoagulation (acenocoumarol 1 mg daily). The hemostasis was checked nine months later (Table 1). AT activity was repeatedly subnormal (49%). The patient did not have either a Factor V Leiden or a prothrombin G20210A mutation. Protein C and S activities were not determined because of vitamin K antagonist therapy (Table 1). At this time, the circulatory condition of the patient was relatively stable.

No thromboembolic event occurred in the parents and grandparents. The mother had no miscarriage. The child had one female sibling who was healthy. We were not able to determine AT levels in the parents and the sibling.

One year later the patient was hospitalized again suffering from severe congestive heart failure due to a progressive deterioration of left ventricular function. In spite of intensive treatment the child died at the age of five, two-and-a-half years after the diagnosis of DCM. Autopsy confirmed the presence of dilated cardiomyopathy associated with endocardiac fibroelastosis and the complications of severe congestive heart failure. However, the autopsy did not reveal any evidence of thromboembolic complications. We have sequenced AT gene, and found only three common polymorphisms. The first was a guanine-adenine (GTG→GTA) change at nucleotide 8130, the second was a guanine-adenine (CAG→CAA) change at nucleotide 8160 and the third was a thymine-cytosine (GTT→GTC) change at nucleotide 8199. No mutation, responsible for a genetic AT deficiency was found.

Discussion

The incidence of thromboembolism in children with DCM is 4%-16% (1, 3, 5–8). The most important predisposing factor is slow blood flow owing to impaired systolic function. According to Falk et al, a fractional shortening of less than 10% seems to be a risk factor (5). Our patient had a fractional shortening of 13% at the time of diagnosis. Günthard et al reported that a fractional shortening of less than 20% may already result in stasis and intracardiac thrombi in children (1). This study, involving a few number of children, suggested that long-term anticoagulation therapy may prevent the recurrence of thrombotic and embolic events (1). In our patient, oral anticoagulation did not prevent repeated thrombus formation.

The recurrence of intraventricular thrombi may be explained by a number of factors in the presented case.

- The dose of acenocoumarol did not result in a permanently effective anticoagulation as checked by the INR values.
- The ventricular function of the patient deteriorated progressively.
- The patient exhibited repeatedly diminished AT activity.

Congenital and acquired disorders of the natural anticoagulant systems increase the risk of clot formation (9, 10, 11). Intracardiac thrombosis in association with congenital or acquired protein C deficiency, Factor V Leiden, and prothrombin G20210A mutations have already been published (9, 10, 11).

Our patient required large doses of unfractionated heparin to achieve an aPTT within the therapeutic range. Besides AT deficiency several mechanisms for heparin resistance have been identified including increased heparin clearance, elevation in heparin-binding proteins and elevations in factor VIII levels and fibrinogen levels (12). There is evidence in adults with thrombosis and heparin resistance, that therapeutic levels of heparin as measured by the anti-factor Xa assay may be clinically efficacious even though the aPTT is subtherapeutic (13).

The potentiation of AT activity is the principle mechanism by which both heparin and low-molecular-weight heparin produce anticoagulation. The relative inefficiency of heparin treatment brought up the issue of AT deficiency in our case. That is why the initial AT level was drawn after heparin therapy was instituted. Although unfractionated heparin therapy can result in depression of the levels of AT, still we believe that our patient had low levels of AT, as the repeated AT determination when the patient was no longer on heparin was also depressed.

Congenital AT deficiency is an autosomal dominant disorder, associated with an increased risk of thrombosis, typically presenting in young adulthood. Severe congenital AT deficiency is an autosomal recessive condition associated with increased thrombogenesis, typically noted in infancy. Acquired deficiencies commonly are due to consumption. Other reported mechanisms of acquired AT deficiency include chronic liver disease, with resultant synthesis failure, and protein loss due to ascites or nephrotic syndrome. In our patient the genetic analysis did not reveal any mutation responsible for antithrombin deficiency. We consider the antithrombin deficiency acquired in the presented case.

The activation of the coagulation system has been demonstrated in adult patients with idiopathic cardiomyopathies (14). In patients with DCM, the thrombin-antithrombin complex levels showed a positive correlation with left ventricular end-diastolic volume and a negative correlation with fractional shortening of the left ventricle (14). Although, a similar mechanism may have played a role in diminished AT level, as observed in our patient, this would not account for such a decrease in AT level. *Erbay et al* (15) did not find antithrombin deficiency in patients with or without ventricular thrombus and dilated cardiomyopathy. Present literature data are inconsistent whether individuals with DCM and antithrombin deficiency at a higher risk than those with DCM alone. Our study implicates, that further investigations could establish whether acquired antithrombin deficiency is an independent risk factor in patients with DCM.

Our observations and other studies underline the need for characterizing the activation of platelets (16), the coagulation and fibrinolytic systems in children with DCM (10, 11, 14). A recent guideline on antithrombotic therapy in children (17) suggests vitamin K-antagonist therapy in children with DCM should begin no later than when the child is activated on a cardiac transplant waiting list. Probably, more detailed recommendation can be made if and how these patients should be anticoagulated to decrease the incidence of thromboembolic complications if hemostatic markers are taken into consideration.

Irodalom

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