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Dilated cardiomyopathy and thrombo-embolism

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Abstract The purpose of this study was to investigate the incidence, outcome and prevention of thrombo-embolism in children with dilated cardiomyopathy. From 130 patients with dilated cardiomyopathy, 17 (14%) showed evidence of thrombo-embolism. Seven had initial cardiac thrombus, 7 exhibited initial embolus and in 3 thrombo-embolism was only diagnosed at autopsy. All 17 patients showed seriously impaired systolic function of the left ventricle with fractional shortening (FS) of 10 ± 3%, range 5%–17%, as compared to those without thrombo-embolism with FS of 17% ± 6%, range 5%–26% ($P < 0.0001$). Seven patients were treated with oral anticoagulants once thrombo-embolism had been diagnosed; one of them experienced a further embolic event as opposed to three out of four patients not treated with anticoagulants.

Conclusion All children with dilated cardiomyopathy and fractional shortening below 20% should be treated with prophylactic anticoagulative agents

Key words Dilated cardiomyopathy · Thrombo-embolism · Prevention

Abbreviations *DCM* dilated cardiomyopathy · *FS* fractional shortening

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Introduction

Thrombo-embolism is a frequent complication of dilated cardiomyopathy (DCM) in adults [12, 13, 25, 27], and there is general agreement on the appropriate management. Although DCM is also a well-known myocardial disorder in childhood [6, 11, 14, 20, 28] there is little information on thrombo-embolism [4, 18, 19, 23, 24] and the purpose of this study was to ascertain incidence and outcome and to evaluate possible therapeutic prevention of thrombo-embolism in children with DCM.

Subjects and methods

From five Swiss divisions of paediatric cardiology, 130 children up to 16 years of age who presented with DCM between 1982 and 1994 were collected. DCM was defined on the basis of echocardiographic data, with end-diastolic and end-systolic left ventricular dimensions above the 95th percentile for body height [9] and with fractional shortening (FS) below 28% [16], regardless of the underlying myocardial disorder. The patients, whose medical records showed evidence of systemic thrombotic and/or embolic complications formed the study group. Thrombo-embolism was defined as follows: (1) the presence of an intracavitary thrombus on 2D-echocardiography or at autopsy; (2) central nervous symptoms, lesions on cranial CT or peripheral ischaemia indicative of embolization. In these patients 2D-echocardiographic findings and the nature of medical management and outcome were studied.

Statistical analysis

Echocardiographic values of FS were expressed as mean ± 1 SD and range. Comparative statistics were performed by non parametric unpaired *t*-test (Mann-Whitney U test) significance level was $P < 0.05$ [27].

Results

From the 130 children with DCM, 17 had systemic thrombo-embolic complications, an incidence of 14% for the whole group. Two patients suffered from adriamycin

toxicity, two patients from M. Duchenne and two patients had cardiomyopathy after surgical correction of anomalous origin of the left coronary artery. In the remaining 11 patients DCM was idiopathic or due to acute myocarditis.

In the group with thrombo-embolic complications as a whole, echocardiographic diastolic diameter of the left ventricle ranged from 115% to 170% (mean 134%), and systolic diameter from 148% to 250% (mean 186%) of the 95th percentile values of healthy children aged 0–16 years. The myocardial function, as assessed by FS was severely impaired and below 10% in 9, between 11% and 15% in 7 patients and 17% in 1 patient. All 17 patients were in sinus rhythm. Table 1 shows the FS on echocardiography in the patient group with DCM and thrombo-embolic event compared to the group who did not experience thrombo-embolism. FS was significantly lower in the group with a thrombo-embolism than in the group without ($P < 0.0001$).

Table 2 summarizes age at diagnosis of DCM, features on initial presentation of thrombo-embolism, medical management and follow up. In seven patients the initial presentation of thrombo-embolism was an intracardiac thrombus on 2D-echocardiography without signs of embolism. The time interval from diagnosis of DCM to detection of intracardiac thrombus varied from 1 day to 8 months (mean 3 months). In a further seven patients the initial event was a systemic embolus without evidence of intracardiac thrombosis on 2D-echocardiography. In these subjects the time interval from diagnosis of DCM to the occurrence of an embolic event varied from 1 day to 9 months (mean 3 months). In three patients thrombosis and embolism were only diagnosed at autopsy.None of the patients was treated with oral anticoagulants or salicylic acid prior to the first thrombo-embolic event. Embolization to the CNS was predominant since in the whole group of 17 children 10 of 12 embolic events lead to CNS infarction with lethal outcome in two of them.

Seven patients were treated with oral anticoagulants following the diagnosis of intracardiac thrombus or systemic embolus. Only one of them had a second systemic embolic event and none of them was reported to suffer from haemorrhagic complications. Four patients were not treated with anticoagulants and three of them experienced a systemic embolus during a follow up time from 6 months to 10 years. One patient was treated with salicylic acid and did not experience further embolism. Two patients died a few days after the thrombo-embolic event and were not considered for follow up.

Table 1 Fractional shortening (%) on echocardiography

	Patients with thrombo-embolism	Patients without thrombo-embolism	
n	17	113	
mean ± 1SD	10 ± 3	17 ± 6	
range	5–17	5–26	$P < 0.0001$

Discussion

The incidence of thrombo-embolism in children with DCM of 14% in our study was comparable to the frequencies of 4%–16% reported in the literature [2, 20, 21, 30]. Although this incidence is lower than that of 13%–

Table 2 Age at diagnosis of DCM, features on initial presentation and follow up after diagnosis of thrombo-embolism (*FS* fractional shortening)

Patient	Age at diagnosis DCM	Time interval to thrombo-embolism	FS (%)	Left ventricular thrombus	Embolism (CNS)	Oral anticoagulants	Follow up time	Further embolism (CNS)
1	8 months	2 days	12	+	–	–	9 years	+
2	16 months	8 months	8	+	–	–	10 years	+
3	5 years	2 days	9	+	–	–	6 months	+
4	6 months	1 day	11	+	–	+	9 years	–
5	13 months	5 months	10	+	–	+	6 months	–
6	10 years	5 months	13	+	–	+	7 months	–
7	16 years	5 months	17	+	–	+	1 year	–
8	20 months	1 day	13	–	+	–	6 years	–
9[d]	18 months	9 months	13	–	[b]	–		
10[d]	3 years	2 days	10	–	+	–		
11	14 months	1 day	8	–	+	+	7 months	–
12	27 months	1 month	8	–	+	+	7 years	–
13	13 years	8 months	12	–	+	+	2 years	[b]
14	6 months	3 months	5	–	+	[a]	7 years	–
15	9 years	1 month	13	[c]	–			
16	9.5 years	5 months	6	[c]	–			
17	15 years	2 months	7	[c]	[c]			

[a] Salicylic acid
[b] Embolus to the leg
[c] autoptic finding
[d] Patient 9 and 10 died a few days after the initial presentation of thrombo-embolism

38% reported in adults [12, 13, 26], the reports of paediatric autopsy studies indicate a higher frequency of 43%–57% [2, 7]. This illustrates that thrombo-embolism is often missed during life, adds significantly to the mortality and is as frequent as in adults. Therefore it seems surprising that there are only rare comments on the outcome and the therapeutic management of this complication in childhood.

In all patients a dilated left ventricle with markedly impaired systolic function was the main cause for intracavitary thrombosis. Slow flow predisposes to thrombus formation [1, 3, 10] and FS of less than 15% seems to be a high risk factor in the paediatric age group as well as in adults [10, 18, 19, 24]. One patient in our series and one patient reported in the literature had a higher FS of 17% and 19% respectively [19], which suggests that FS of less than 20% may already cause blood stasis and intracardiac thrombi.

Adults with DCM are considered to be at high risk for thrombo-embolism and there is general agreement that they should be treated with prophylactic oral anticoagulants [1, 22, 28]. Even though the number of patients in our study is small, we were able to show that oral anticoagulant treatment prevented thrombo-embolism in 6/7 children whereas 3/4 patients without such treatment experienced embolization. Notably none of the children treated with coumarin suffered from obvious haemorrhagic complications. In this study the number of cases treated with salicylic acid was too low to evaluate the benefit of such treatment. However it is known that inhibitors of platelet aggregation do not reduce the incidence of thrombus formation and do not lead to thrombus resolution as is the case for anticoagulants [19]. Other interventions, for example lysis of left ventricular thrombi has been reported in adults but is of limited efficacy [17]. Also thrombolysis was successfully attempted in a 2-year-old boy with DCM, but the safety of such a therapy in children remains questionable [18].

The presently accepted approach to children with DCM is to administer oral anticoagulants following an embolic episode or once when a thrombus has been detected, but there is some doubt whether medical prevention should be based on the diagnosis of intracardiac thrombus [15, 28]. In this study a poor relation between the presence of intracardiac thrombus and embolization was found. Only 7 of our patients had thrombus on echocardiography, while 7 had already experienced embolization without echocardiographic signs of thrombosis. Studies from adults show no statistical difference in the occurrence of embolism whether an intracardiac thrombus was found or not [8, 13]. One of the main reasons for such a discrepancy is the difficulty in diagnosing intracardiac thrombosis. 2 D-echocardiography offers a reliable non-invasive method with a sensitivity of 92% and a specifcity of 88% [5, 31]. Trans-oesophageal echocardiography appears to be even superior than the trans-thoracic approach for detection of intracardiac thrombi. However the main limitations of this technique are the difficulty in examining the apex of the heart, where the thrombus is frequently located and where multiple artifacts add to misinterpretation and false-positive and false-negative results. Furthermore, since in this patient group there was an equal likelihood for cardiac thrombosis or embolism to occur within a mean of 3 months after diagnosis of DCM, anticoagulant treatment should not be dependent on the detection of intracardiac thrombi.

Our study shows that systemic embolization adds significantly to the morbidity and mortality of DCM in childhood. In most cases emboli affect the CNS and lead to persistent palsy or death. Moreover, autopsy findings reveal that intracardiac thrombosis occurs as frequently in children as in adults, that a right-sided thrombus is as common as a left-sided one and that pulmonary emboli are probably a frequent non-diagnosed complication [25]. Therefore it is essential to take measures to prevent thrombo-embolism. In conclusion, we recommend oral prophylactic anti-coagulant treatment in all children with DCM and FS below 20%, regardless of the absence of intracardiac thrombosis or embolic event. Anticoagulant therapy should be maintained until systolic function has markedly improved.

Further prospective studies are advisable to fully confirm the benefits of oral anticoagulant therapy and to conclusively evaluate a possible role for salicylic acid treatment in such patients.

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