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Antithrombin activity in children with chylothorax

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Abstract

Objective: To determine whether increased antithrombin loss is present in children with chylothorax after cardiac surgery. **Methods:** Plasma and pleural effusion samples of children with chylous and non-chylous pleural effusion were assayed for antithrombin activity. **Results:** Ten children with chylothorax and five children with non-chylous pleural effusion were investigated. There was statistically significant increase in mean antithrombin activity in chylous samples (32.2 ± 11.4%) compared to non-chylous samples (14.4 ± 13.9%), and significant decrease in plasma of children with chylothorax (44.6 ± 15.4%) compared to children with non-chylous pleural effusion (69.9 ± 22.4%). Seven of 10 children with chylous and none of the children without chylous developed thrombosis ($p < 0.007$). **Conclusions:** Increased loss of antithrombin is present in children with chylothorax, potentially predisposing these children to an increased risk of thrombosis. Repeated antithrombin substitution should be considered in critically ill children with chylothorax.

Keywords: Chylothorax; Antithrombin; Thrombosis; Children; Neonate

1. Introduction

Antithrombin (AT) is the most important natural inhibitor of the coagulation cascade. By inhibiting the activity of most coagulation proteases including thrombin, factor (F) Xa, FIXa, FXIa, and FXIIa, AT prevents uncontrolled coagulation and thrombus formation [1]. Inherited or acquired deficiencies of AT lead to a significant increase in the risk of thrombosis. While inherited deficiency of AT is rare in the general population, acquired deficiency is frequently observed in patients with liver disease, nephrotic syndrome, and after major surgery, particularly cardiac surgery [2].

Chylothorax is a collection of a white milky drainage from the lymphatic system within the thoracic cavity. Chylothorax commonly develops secondary to thrombosis and/or high pressure in the superior vena cava, and an iatrogenic laceration of the thoracic duct during intrathoracic procedures [3,4]. Chylous is rich on fat and proteins of small molecular size, and contains all blood components except red cells and platelets [3]. This study aims to determine whether increased AT loss is present in children with chylothorax.

2. Materials and methods

2.1. Patient population

A cohort of consecutive children diagnosed with chylothorax after cardiac surgery at the University Children's Hospital of Zurich was included in this study. The initial suspicion of chylothorax due to the presence of a milky white pleural effusion was confirmed by laboratory examination of the pleural effusion in accordance to previously published diagnostic criteria, including (1) >1.1 mmol/L triglycerides (with oral fat intake) and (2) a total cell count >1000 cells/mL, with a lymphocyte fraction >80% [5]. Chylothorax was treated according to our hospital guidelines. Initial conservative management includes drainage of the pleural cavity and oral fat-free nutrition during 7 days, followed by 7 days of total parenteral nutrition with or without somatostatin infusion if chylous effusion persists. In children showing resolution of chylothorax, oral fat-free nutrition is continued for a total of 6 weeks. In children showing chyle leak for more than 4 weeks, a pleurodesis is performed. Age-matched children with non-chylous pleural effusion treated at the same institution served as controls. Clinical data collected of all children included underlying disease, type of surgery, and history of thrombosis. This study was approved by the Research Ethics Boards of the University Children's Hospital, Zurich, Switzerland.

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2.2. Laboratory methods

Chylous samples were collected on day 2–4 postoperatively when chylothorax diagnosis was confirmed. At the time of sample collection, all children with chylothorax were still on normal nutrition. Blood and pleural effusion samples were collected at the same time into 0.106 M buffered tri-sodium citrate. An assumption in both groups was that pleural effusion was not blood stained to prevent a contamination with AT. Measurements of AT activity in both plasma and pleural effusion were performed by a photometric assay (Coacute Antithrombin R, Chromogenix Instrumentation Laboratory SpA, Milan, Italy) following guidelines of the manufacturer. Briefly, samples were diluted with a buffer containing an excess of heparin. Aliquots of these sample dilutions were added to a cuvette containing a lyophilized mixture of FXa and a FXa-specific chromogenic substrate. After 5 min incubation, a stopper solution was added and absorbance of samples was read at 405 nm. Concentration of AT in percent of normal levels were derived from the appropriate standard curve given in the batch-specific insert.

2.3. Statistical analysis

Data of AT activity are expressed as means ± standard deviation (SD) as appropriate. Statistically significant differences between children with chylous and controls as regarding age, weight, amount of pleural effusion, and AT values in plasma and pleural effusion were tested by the Mann–Whitney test. Categorical variables were tested by Fisher's exact test. A p-value < 0.05 was considered significant. Analysis was performed by means of GraphPad InStat for Windows (GraphPad Software, San Diego, CA, USA; version 3.05).

3. Results

3.1. Patient population

A total of 10 children (mean age, 14 ± 23.5 months) with chylothorax and 5 children (mean age, 27 ± 15.7 months) with non-chylous pleural effusion were included in the study. Baseline characteristics of children with chylous and non-chylous pleural effusion are depicted in Table 1. Chylothorax had developed following cardiopulmonary bypass for congenital heart disease in all 10 patients. Non-chylous pleural effusion consisting of exudate had developed following cardiac surgery (Norwood I; repair of transposition of the great vessels) in two children, and as a complication of pneumonia in the other three children. Seven (70%) of the 10 children with chylothorax developed thrombosis during the course of the disease. Thrombosis was located in the aortic-pulmonary shunt (n = 1), the right iliac artery (n = 2), the left iliac artery (n = 1), the right subclavian vein (n = 2), and the cava superior vein (n = 1). In one child, thrombus extended in the superior vena cava, the jugular and subclavian vein, and in the cerebral sinus veins. None of the five patients with non-chylous pleural effusion developed thrombotic complications (p = 0.02).

Table 1
Baseline characteristics of children with chylous and non-chylous pleural effusion

Characteristics	Pleural effusion	
	Chylous (n = 10)	Non-chylous (n = 5)
Sex (n)		
Male	5	3
Female	5	2
Age (months)		
Mean	13.9	27.2*
Median	1.5	30*
Range	1–42	1–42
Weight (kg)		
Mean	5.3	11.6*
Median	3.9	11.4*
Range	2.1–12.1	3.2–22.0
Pleural effusion (mL/day)		
Mean	315.5	291*

* Not significant differences.

3.2. Antithrombin activity in pleural effusion and plasma

Mean AT activity was significantly increased in chylous samples (32.2 ± 11.4%) compared to non-chylous samples (14.4 ± 13.9%) (Fig. 1), and significantly decreased in plasma of children with chylothorax (44.6 ± 15.4%) compared to children with non-chylous pleural effusion (69.9 ± 22.4%) (Fig. 2). Mean antithrombin activity in children with chylothorax was also clearly decreased as compared to the published mean values of antithrombin in both healthy children aged 1–5 years and infants and young children on the second postoperative day following cardiac surgery (Fig. 2) [6–8].

In children with chylothorax, mean AT activity in chylous and plasma samples were not statistically different. By contrast, in children with non-chylous pleural effusion, mean AT activity in plasma samples was significantly increased as compared to the AT measured in non-chylous pleural effusion samples (p = 0.007).

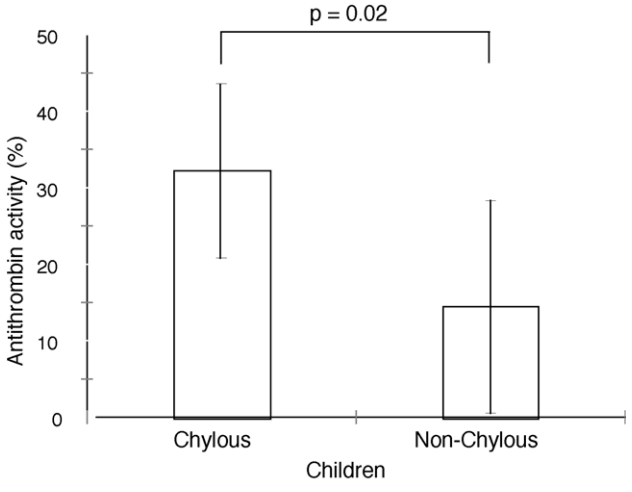

Fig. 1. Antithrombin activity in pleural effusion samples of children with chylothorax and children with non-chylous pleural effusion. Data are shown as mean (bar) ± standard deviation (vertical line).

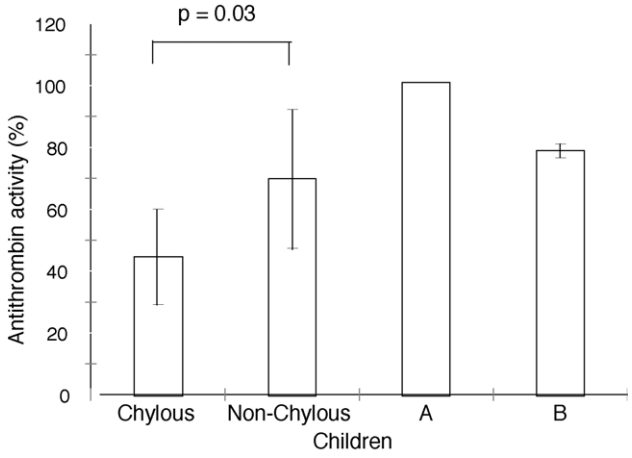

Fig. 2. Antithrombin activity in serum samples of children with chylothorax and children with non-chylous pleural effusion. Data are shown as mean (bar) ± standard deviation (vertical line). The bar A shows the mean normal value of antithrombin in healthy children aged 1—5 years [6,7]. The bar B shows the published mean value ± standard deviation (vertical line) of antithrombin in infants and young children on the second postoperative day following cardiac surgery [8].

4. Discussion

Chylothorax is a severe complication of cardiothoracic procedures causing the loss of large amounts of fluids and proteins, and consequently leading to an increased morbidity possibly compromising the postoperative course [2—4]. The aim of this study was to compare AT activity in children with chylothorax and non-chylous pleural effusion. Results of this study indicate that increased loss of AT is present in children with chylothorax, possibly increasing the thrombotic risk in these patients.

The chylous transported by the thoracic duct contains a combination of lymphatic and gut-derived substances including lymphocytes, immunoglobulins, electrolytes, enzymes, and fat. Iatrogenic lesions of the thoracic duct during cardiothoracic procedures cause the loss of large amount of chylous in the pleural cavity, and may lead to immunosuppression, electrolyte dysbalance, and malnutrition [3]. While the loss of large amount of coagulation proteins including fibrinogen and prothrombin with an increased risk of hemorrhagic complications has been described in patients with chylothorax, data on important inhibitors of coagulation possibly lost in chylous are not available. Despite the small number of patients, results of this study show that significantly increased loss of AT is present in children with chylothorax leading to a significantly decreased AT activity in plasma of these patients. These findings also suggest that decreased plasma AT activity may limit optimal anticoagulation and increase the risk of thrombosis in these children.

While advances in cardiac surgery techniques have significantly improved the survival rate of children with congenital heart disease, children undergoing cardiac surgery have become one of the major pediatric population developing thrombosis as secondary complication [9]. Several possible risk factors such as age, type of surgery, central venous lines, and low cardiac output have been reported in children with thrombosis following cardiac surgery [10]. As well, previous studies have demonstrated a global decrease of all components of the coagulation and fibrinolytic system in children undergoing cardiopulmonary bypass [8,11,12]. However, the role of coagulation disorders due to chylothorax in the development of thrombosis in these children has not been assessed so far. Our findings of increased AT loss in children with chylothorax together with the increased rate of thrombosis in these children suggest that chylothorax possibly represents a further risk factor for thrombosis in children undergoing cardiopulmonary bypass. Although in our seven patients developing thrombosis, a direct correlation between chylothorax and thrombotic event can be neither excluded nor confirmed, our data suggest that thrombosis should be considered not only a possible etiology but also a consequence of chylothorax. These findings also suggest that repeated antithrombin substitution should be considered in critically ill children with chylothorax.

Results of this study should be interpreted in the light of potential study limitations. Beside the small number of patients, the heterogeneous nature of children with non-chylous pleural effusion may have led to a misinterpretation of statistical differences in AT values between children with chylous and non-chylous pleural effusion. However, mean antithrombin activity in children with chylothorax was also clearly decreased as compared to the published mean values of antithrombin in both healthy children aged 1—5 years and infants and young children following cardiac surgery. Although of preliminary nature, results on antithrombin activity in our children with chylothorax describe a real problem causing significant management dilemmas in pediatric intensive care units, and provide the basis for further studies aiming to investigate the relation between chylothorax and thrombosis.

In summary, although both the small number of patients and the heterogeneous nature of the control group are clearly study limitations, results of this study show that an increased loss of AT is present in children with chylothorax, potentially predisposing these children to an increased risk of thrombosis. Repeated antithrombin substitution should be considered in these children to prevent thrombotic complications and optimize heparin therapy in those children requiring anticoagulation. Large studies are required to further investigate haemostasis in children with chylothorax, and the role of increased loss of all coagulation inhibitors in the development of thrombosis in these children.

References

[1] Travis J, Salvesen GS. Human plasma proteinase inhibitors. Annu Rev Biochem 1983;52:655—709.
[2] Bauer KA. Hypercoagulable states. In: Hoffman R, Benz EJ, Shattil SJ, Furie B, Cohen HJ, Silberstein LE, McGlave P, editors. Hematology. Basic principle and practice. New York, Edinburgh, London, Philadelphia: Churchill Livingstone; 2000.
[3] Merrigan BA, Winter DC, O'Sullivan GC. Chylothorax. Br J Surg 1997;84:15—20.
[4] Beghetti M, La Scala G, Belli D, Bugmann P, Kalangos A, le Coultre C. Etiology and management of pediatric chylothorax. J Pediatr 2000;136:653—8.

[5] Buttiker V, Fanconi S, Burger R. Chylothorax in children: guidelines for diagnosis and management. Chest 1999;116:682—7.
[6] Andrew M, Vegh P, Johnston M, Bowker J, Ofosu F, Mitchell L. Maturation of the hemostatic system during childhood. Blood 1992;80:1998—2005.
[7] Ehrenforth S, Junker R, Koch HG, Kreuz W, Münchow N, Scharrer I, Nowak-Göttl U. Multicentre evaluation of combined prothrombotic defects associated with thrombophilia in childhood. Eur J Pediatr 1999;158: S97—104.
[8] Gombotz H, Metzler H, Hiotakis K, Rehak P. Antithrombin III behavior in open heart operations in infancy and early childhood. Anasth Intensivther Notfallmed 1986;21:9—12.
[9] Monagle P. Thrombosis in pediatric cardiac patients. Semin Thromb Hemost 2003;29:547—55.
[10] Petäjä J, Lundström U, Sairanen H, Marttinen E, Griffin JH. Central venous thrombosis after cardiac operations in children. J Thorac Cardiovasc Surg 1996;112:883—9.
[11] Petäjä J, Peltola K, Sairanen H, Leijala M, Kekomäki R, Vahtera E, Siimes MA. Fibrinolysis, antithrombin III, and protein C in neonates during cardiac operations. J Thorac Cardiovasc Surg 1996;112:665—71.
[12] Chan AKC, Leaker M, Burrows F, Williams WG, Gruenwald CE, Whyte L, Dams M, Brooker L, Adams H, Mitchell L, Andrew M. Coagulation and fibrinolytic profile of paediatric patients undergoing cardiopulmonary bypass. Thromb Haemost 1997;77:270—7.