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Thrombocytosis in asplenia syndrome with congenital heart disease: A previously unrecognized risk factor for thromboembolism

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ABSTRACT

Background: Thrombocytosis and thromboembolic complications occur after splenectomy. However, there is no previous report investigating the presence of thrombocytosis and its association with thromboembolic events in patients having asplenia syndrome with congenital heart disease.
Methods: Enrolled were 161 consecutive patients with functionally single ventricle who underwent cardiac catheterization between 1997 and 2010. They were divided into two groups: patients having asplenia (Group A, n = 46) and patients having no asplenia (Group B, n = 115). Aspirin therapy was employed in all patients after surgical interventions except for pulmonary artery banding. We retrospectively reviewed the platelet counts at each seven stage of cardiac catheterization (for pre- and postoperative evaluation of the first palliation, Glenn operation, and Fontan operation, and for late evaluation after Fontan operation), incidence of thromboembolic events, and other possible risk factors for thromboembolism.
Results: The median platelet counts in Group A were consistently higher than those in Group B at any of the seven stages of cardiac catheterizations ($p<0.002$). The incidence of thromboembolic complications was also higher in Group A than that in Group B (28% vs. 10%, $p=0.030$). Univariate and multivariate logistic regression analyses showed that a platelet count of more than 550×10^9/L at the first cardiac catheterization was associated with thromboembolic complications (Odds ratio 3.17; $p=0.046$).
Conclusions: Persistent thrombocytosis is present in patients with asplenia syndrome. It may greatly contribute to the development of thromboembolism during the management of congenital heart disease than expected.

1. Introduction

Post-splenectomy thrombocytosis is reported to be a predisposing factor for thromboembolism. Thromboembolic complications following splenectomy occur in up to 10% of patients. These range from myocardial infarction, portal vein thrombosis, and pulmonary embolism to deep vein thrombosis [1–3]. Such thrombotic events could be observed not only immediately after surgery, but also several months or even years later in the patients in whom thrombocytosis persisted [4].

Congenital asplenia syndrome is a form of heterotaxy that is also known as right atrial isomerism. This syndrome is typically associated with severe heart defects and needs staged cardiac operations from infancy as a functionally single ventricle [5]. Thromboembolic events are often experienced before and after the completion of Fontan operation [6].

There are a few reported cases with secondary thrombocytosis caused by isolated spleen agenesis without cardiac defects, mimicking essential thrombocythemia [7,8]. Thromboembolism is one of the major complications during and after surgical intervention in patients with congenital heart disease. However, there is no previous report investigating the relationship between platelet count and thromboembolic events in patients with asplenia syndrome having congenital heart disease.

The objective of this study is to clarify the clinical significance of thrombocytosis and its impact on thromboembolic events in patients with congenital heart disease and asplenia.

2. Materials and methods

2.1. Patients

A total of 161 consecutive patients with functionally single ventricles who underwent cardiac catheterization at Kyushu University Hospital and Kyushu Koseinenkin

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Table 1
Patient characteristics.

	Group A (n = 46)	Group B (n = 115)
Anatomy of the congenital heart disease		
SRV	19	13
AVSD	14	6
DORV	7	23
SLV	2	15
CCTGA	2	13
TA	0	19
PAIVS	0	10
HLHS	0	8
MA	0	5
Others	0	3
Age	7 years (6 months–13 years)	7 years (4 months–13 years)
Sex	M/F = 22/24	M/F = 57/58
First palliation		
Blalock–Taussig shunt	38 (83%)	66 (57%)
Pulmonary artery banding	8 (17%)	41 (36%)
Norwood operation	0 (0%)	8 (7%)
Survival	33 (72%)	107 (93%)

SRV: single right ventricle, AVSD: atrioventricular septal defect, DORV: double outflow right ventricle, SLV: single left ventricle, CCTGA: congenitally corrected transposition of the great arteries, TA: tricuspid atresia, PAIVS: pulmonary atresia with intact ventricular septum, HLHS: hypoplastic left heart syndrome, MA: mitral atresia.

Hospital between 1997 and 2010 were enrolled in this study. No patients had any family history of thrombophilia. The patients were divided into two groups: patients having asplenia syndrome (Group A, n = 46) and those having no asplenia syndrome (Group B, n = 115). Patient characteristics of each group are shown in Table 1.

All patients underwent staged surgical procedures. Initial palliation included Blalock–Taussig (BT) shunt, pulmonary artery banding or Norwood operation as needed. The second stage operation was a bidirectional Glenn cavopulmonary connection performed on cardiopulmonary bypass. The third stage operation was Fontan operation using expanded polytetraflorethylene vascular graft as an extracardiac conduit. Fenestration was only performed for two patients with high pulmonary vascular resistance. All patients received cardiac catheterization for pre- and postoperative evaluation of each surgical procedure and for late evaluation after Fontan operation (Fig. 1).

Postoperative and interstage anticoagulation therapy was identically performed as follows: aspirin (3–5 mg/kg/day) after BT shunt, Norwood procedure, and Glenn operation; aspirin and warfarin (targeted prothrombin time-international normalized ratio [PT-INR] 1.5–2.0) for 1 year following Fontan operation; and only aspirin after 1 year following Fontan operation.

The diagnosis of asplenia syndrome was determined based on the presence of Howell–Jolly bodies in the peripheral blood smear and the absence of spleen assessed by computed tomography (n = 31) and/or ultrasonography (n = 46). The diagnosis of thromboembolic complications was determined using objective methods when they were suspected by clinical manifestation or when they were coincidentally found by the regular examinations. BT shunt malfunction was defined as shunt occlusion or stenosis which needs catheter intervention or surgery, assessed by computed tomography or cardiac catheterization. Cerebral infarction was diagnosed by computed tomography or magnetic resonance imaging. Diagnosis of venous thromboembolism was made by ultrasonography, computed tomography, or venography.

2.2. Methods

We retrospectively reviewed the medical records of all 161 patients to determine (i) the platelet counts at each seven stage of cardiac catheterization; (ii) the incidence of thromboembolic complications; and (iii) other clinical data that may be possible risk factors for thromboembolic complications in each group.

For the purpose of elucidating the association between platelet counts and thromboembolic events, we investigated the sequential changes of platelet counts, the timing of thromboembolic events, and the correlations among platelet counts at each stage of cardiac catheterizations.

We evaluated the effect of clinical parameters (platelet count, age, birth weight, hemoglobin concentration, activated partial thromboplastin time, ejection fraction of the systemic ventricle, atrioventricular valve regurgitation, presence or absence of BT shunt, size of the BT shunt, and presence or absence of pulmonary vein obstruction) as a risk factor of thromboembolic complications with univariate and multivariate logistic regression analyses.

2.3. Statistical analysis

Continuous variables were analyzed using the Mann–Whitney *U* test and categorical variables were analyzed using the chi-square test. The analysis of Pearson's correlation coefficient was used to evaluate correlations between platelet counts at each other stage of catheterization. Dichotomous variables were created out of continuous variables by using clinically important cutoff points. Univariate and multivariate logistic regression analyses were used to determine the relative contribution of various factors to the risk of thromboembolic events. *P* values of less than 0.05 were considered significant. All statistical operations were performed by using the JMP 8 statistical software package (SAS Institute. Inc. Cary. NC).

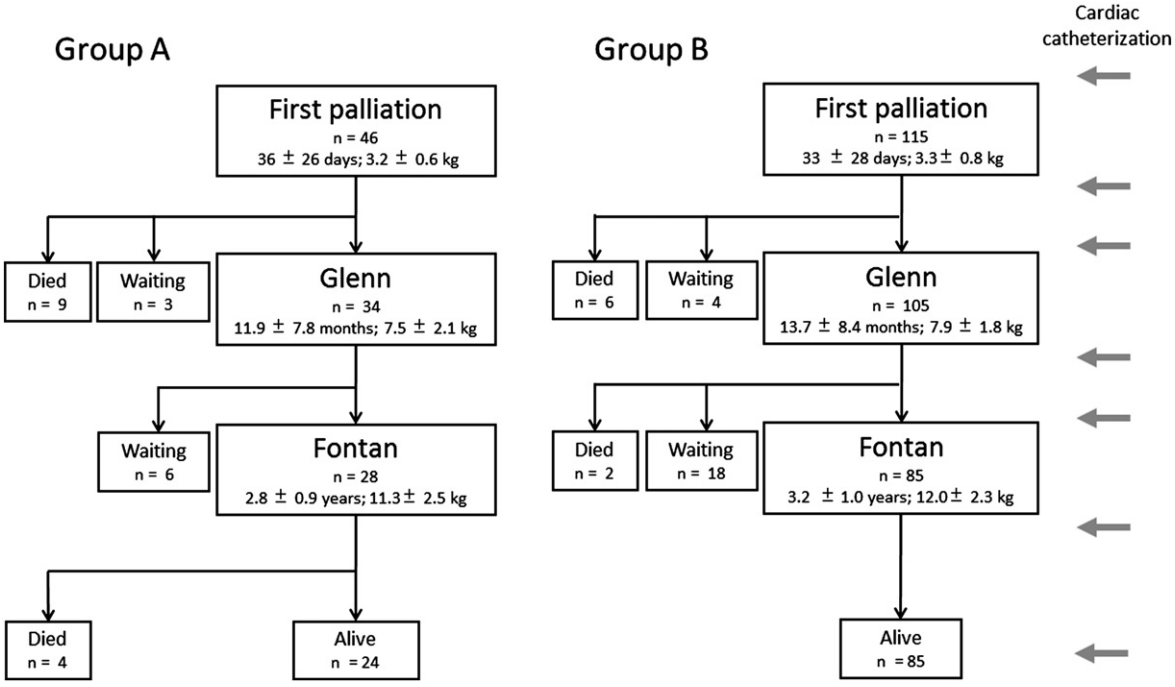

Fig. 1. Number of study patients, mean age and mean weight at each stage.