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Low Value of Activated Coagulation Factor VII in Young Primary Spontaneous Pneumothorax

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Abstract

Objectives: *We previously reported a young patient with a primary spontaneous pneumothorax who had a blood coagulation disorder that was not associated with a clinical bleeding tendency. Many of these patients showed an abnormal prothrombin time (PT). We decided to investigate the relationship between activated coagulation factor VII (FVIIa) and PT abnormalities.*

Methods: *The clinical records of patients treated for primary spontaneous pneumothorax at Sapporo City General Hospital Pneumothorax Center between July 2016 and August 2019 were reviewed retrospectively. Eighteen patients aged 25 years or younger with a spontaneous pneumothorax who had received PT and FVIIa tests during hospitalization were enrolled. The age range of the 17 male and 1 female patients was 13 to 23 years with a mean of 18.2 years.*

Results: *Eleven (61.1%) of the patients had a FVIIa level of <59%. These FVIIa abnormalities were not associated with the degree of the PT abnormality. However, none of the patients showed a bleeding tendency during drainage and surgical procedures.*

Conclusions: *Our results indicate that two-thirds of patients with a PT disorder have a low FVIIa level. However, it remains unknown whether these blood coagulation disorders are related to the onset of a primary spontaneous pneumothorax.*

Keywords: *prothrombin time test, activated coagulation factor VII, primary Spontaneous pneumothorax, young patients*

Abbreviation: *PT: prothrombin time, FVII: coagulation factor VII, FVIIa: activated coagulation factor VII*

1. Introduction

We have reported previously the case of a young patient with a primary spontaneous pneumothorax and a blood coagulation disorder who did not have a clinical bleeding tendency. Many of such patients have been reported to have an abnormal prothrombin time (PT) [1]. There are patients with abnormal PT values that persist even years after surgery [2]. PT is related to an extrinsic system solidification mechanism, with abnormalities possibility related to low levels of coagulation factor VII (FVII) [3]. Based on these findings we decided to investigate the levels of activated FVII (FVIIa) in a cohort of young patients with a primary spontaneous pneumothorax.

2. Patients and Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional review board of Sapporo City General Hospital (approval IRB No. R02-059-689). Considering the retrospective nature of this study, informed consent was obtained in the form of an opt-out clause on our website, and patients who rejected this option were excluded. Patients aged 25 years or younger with a spontaneous pneumothorax who had coagulation studies carried out before chest drainage during hospitalization at Sapporo City General Hospital Pneumothorax Center between July 2016 to August 2019 were selected for the study. Only patients with a PT disorder who had FVIIa measured were enrolled in the study, while patients who had

received an anticoagulant drug were excluded. The clinical records of the patients were reviewed retrospectively. Nineteen patients aged 25 years or younger with a spontaneous pneumothorax and measurements of PT and FVIIa during hospitalization were enrolled. The age range of the patients (17 males and 1 female) was 13 to 23 years old, with a mean age of 18.2 years.

The method for taking blood samples involved mixing 0.2ml of 3.2% sodium citrate and 1.8ml of patient blood in a glass test tube. The specimen was centrifuged at 1500 × g for 15 minutes, followed by separation of the plasma. The measurement of PT was as follows. A 0.1 mL aliquot of the patient's plasma was warmed at 37℃ for 3 minutes. These conditions increase the PT reagent (Coagpia-N; Sekisui Medical Co. Ltd, Tokyo) in the subject plasma and allow for measurement at 37℃ before plasma solidification. This formation of fibrin is measured using an auto analyzer and expressed as PT-international normalized ratio (PT-INR). A PT-INRvalue of 1.10 or less is considered normal. The measurement of FVIIa was as follows. After removal of all coagulation factors except FVII by dilution of the specimen with serum lacking FVII, a PT measurement was performed. The result was compared with a standard curve prepared using normal plasma.

3. Results

The data of patients with a PT disorder are shown in Table 1. Eight patients had a slight disorder with a PT-INR level of 1.11 to 1.15. Of the 18 patients, 10 (56%) had a PT-INR level of 1.16 or greater. As shown in Table 2, 11 (61.1%) of the patients had a FVIIa level of 59% or lower. The details of the combined PT and FVIIa measurements in the patients are shown in Table 3. The FVIIa abnormality existed in patients regardless of the degree of PT-INR abnormality. The clinical details of the patients are summarized in Table 4. No patient showed a bleeding tendency during drainage or surgical procedures.

4. Discussion

We reported previously a young patient with a primary spontaneous pneumothorax and a blood coagulation disorder who did not have a clinical bleeding tendency [1,2]. In almost all patients with a PT disorder it remains unknown whether a blood coagulation disorder is related to the onset of a primary spontaneous pneumothorax. While such patients exist clinically, they may not be identified because they do not have a bleeding tendency. PT is related to the extrinsic system solidification mechanism, with abnormalities indicating a possible factor VII deficiency. Therefore, in this study we investigated the possible involvement of FVIIa in the patients of a primary spontaneous pneumothorax.

A FVIIa disorder occurs in about two-thirds of patients with a PT disorder. Strangely, the severities of the PT and FVIIa abnormalities often do not necessarily accord. When the PT becomes abnormal, the single coagulation factor activity is generally 50% or lower. About one-third of patients with a FVIIa abnormalityhave a value of 50% or lower and it is thought that the majority of the remaining patients are influenced by a compound factor. FVII is a vitamin K-dependent coagulation factor and therefore liver disease and a lack of vitamin K may influence the PT value. On the other hand, other vitamin K-dependent coagulation factors exist such as FII, FIX, FX, protein C, and protein S. Therefore, decreases in PT and activated partial thromboplastin time (APTT) be associated with these factors [3]. Based on the results of our study we consider that a PT abnormality alone was not related to either condition.

The frequency of congenital VII deficiency disease has been reported to be 1 in 500,000 people. There is evidence that this disease is an auto some recessive heredity disorder and that it causes various kinds of bleeding tendency as a result of either a qualitative abnormal or quantitative lack of VII [4]. Generally, FVIIa detects a bleeding tendency in 2% or less of physically unimpaired people, although the presence of this symptom does not necessarily accord with test results [5]. After exclusion of a postnatal FVII inhibitor, lack of vitamin K, or the presence of liver disease, a definitive diagnosis can be made by measurement of FVIIa and immunological detection of the FVII antigen [4]. Because we were not able to measure the FVII antigen at our institute we could not make a definitive diagnosis. However, in cases with a relatively high FVIIa value we consider that congenital FVII deficiency disease is not present.

This study had several limitations. First, the study was carried out in only one institution and was a retrospective review, and it is possible that there may be local differences in

Japan. Second, we could not measure the FVII antigen and third we were unable to identify a postnatal FVII inhibitor. However, now it is thought that it is difficult to discover it for a small portion probably. Accordingly, in future studies it is necessary to identify the postnatal FVII inhibitor that reduces FVIIA and also to check whether or not this inhibitor is related to pneumothorax.

5. Conclusions

Our results indicate that two-thirds of patients with a PT disorder have a low FVIIa level. However, it remains unknown whether these blood coagulation disorders are related to the onset of a primary spontaneous pneumothorax.

6. Acknowledgments

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7. Ethics approval

This retrospective study was approved by the ethics committee of our institution (IRB No. R02-059-689). Considering the retrospective nature of this study, informed consent was obtained in the form of an opt-out clause on our website, and patients who rejected this option were excluded.

Table1. *Results of prothrombin time-international normalized ratio*

PT-INR	n=18
1.11-1.15	8
1.16-1.20	5
1.21-	5

Table2. *Results of activated coagulation factor VII values*

Activate FVII (%)	n=18
-39	1
40-49	2
50-59	8
60-62	2
63-	5

Table3. *The relationship between prothrombin time-international normalized ratio and activated coagulation factor VII values*

	Activate FVII				
PT-INR	-39	40-49	50-59	60-62	63-
1.11-1.15			5		3
1.16-1.20		1	1	2	1
1.21-	1	1	2		1

Table4. *Clinical characteristics of patients with prothrombin time-international normalized ratio and activated coagulation factor VII abnormalities*

Case	Age	Gender	PT-INR	Active FVII(%)	Operetion
1	19	Male	1.15*	59	+
2	15	Male	1.17*	60	+
3	18	Male	1.21*	69	+
4	13	Male	1.20	55	
5	21	Male	1.11	58	
6	18	Male	1.15	55	
7	21	Male	1.18	46	+
8	16	Male	1.20*	60	+
9	22	Male	1.27*	57	+
10	15	Male	1.33*	59	
11	19	Male	1.11*	68	
12	23	Male	1.11*	58	+
13	17	Male	1.33	47	+
14	22	Male	1.11*	66	+
15	16	Male	1.11*	77	+
16	17	Female	1.11*	54	+
17	18	Male	1.16*	64	+
18	18	Male	1.22*	39	+

*: *reexamination of PT-INR*

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