# Activated partial thromboplastin time (APTT) of persons with haemophilia A can serve as a surrogate marker of their factor VIII activity.

Category:
Hemostasis test and assay

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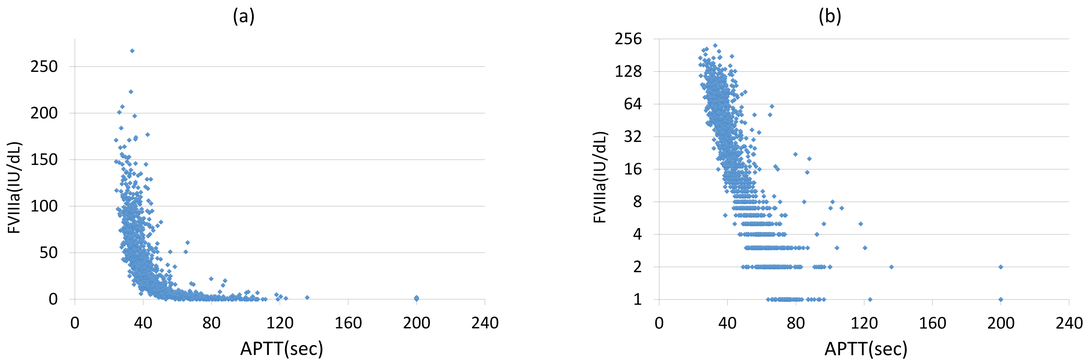
【Introduction & Objectives】To determine factor VIII activity (FVIIIa) of the patients with haemophilia A (PWHA), one stage coagulation assay or chromogenic assay is common. However, as the chromogenic assay for FVIIIa has not been licensed in Japan, one stage coagulation assay is exclusively used. In most of the hospitals in Japan, FVIIIa cannot be measured inside respective laboratories and is often performed via outsourcing. Consequently, as it takes several days to obtain the result. The clinicians occupied in such hospitals have no way of knowing the patients' FVIIIas in case of operations or intracranial bleedings in real time. In reality, we cannot be helped guessing the patients' FVIIIas from their APTT values, which can be measured inside almost all hospitals. Although we always confirm the results of FVIIIas obtained several days later, our expectations sometimes may be wrong. There has been few reports mentioned about the relationship APTT with FVIIIas or whether the APTT can substitute for FVIIIas or not. However, as one stage coagulation assay is APTT-based, the APTT may correspond to the FVIIIa unless it is quite low or high. Therefore, the objective of this study is to consider whether APTT serves as FVIIIa or not.




【Fig.1】FVIIIa and the corresponding APTT(All samples). (a) In samples within 4 IU/dL of FVIIIa, the APTT corresponded with them varied greatly. However, It could be abated if the graph showed as semilogarithm. (b).

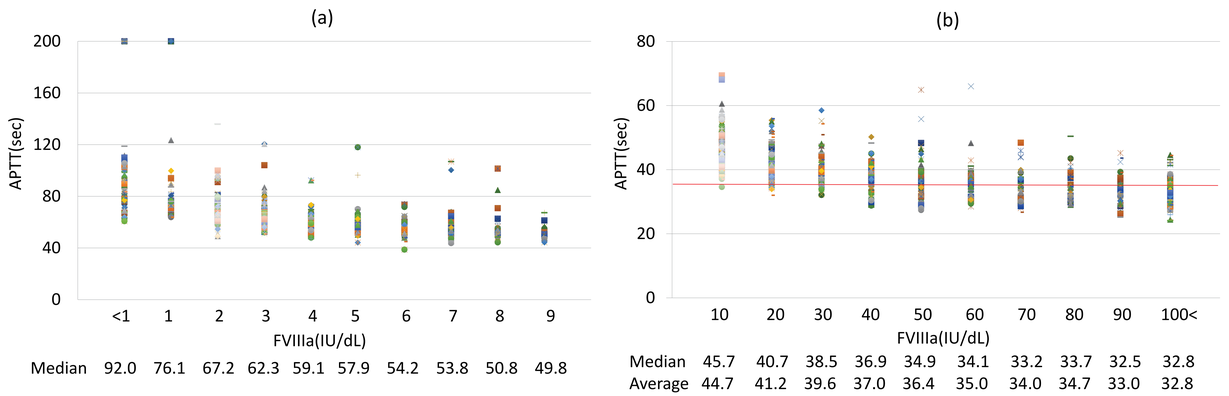
| FVIII(IU/dL) | <1 - 4 | | 5 - 39 | | 40 - 59 | 60 - 79 | 80 - 99 | 100< |
|---|---|---|---|---|---|---|---|---|
| | <1 - 1 | 2 - 4 | 5-19 | 20 - 39 | | | | |
| APTT(sec), Range (min-max) | 53.2 - >240 | 47.1 - 136 | 34.6 - 118 | 32.1 - 87.9 | 27.4 - 64.9 | 26.7 - 66.0 | 26.2 - 50.4 | 24.2 - 44.6 |
| rs* | -0.2275 | -0.3902 | -0.6661 | -0.3062 | -0.1587 | -0.0879 | -0.1687 | -0.3092 |
| | -0.6455 (<1 - 4) | | -0.7746 (5 - 39) | | -0.2924 (40<) | | -0.1906 (60<) | |

【Table.1】 Correlations between APTT and FVIIIas divided into several groups. *Spearman's rank correlation coefficient. The numbers showed in red meant that there was not a correlation between them.

【Results】There was a negative correlation between APTT and FVIIIa (Spearman's rank correlation coefficient, rs=-0.9153) in all samples (Fig.1). The strongest correlation coefficient was calculated in samples from 5 to 40 IU/dL of FVIIIa concentration (Table.1). There was a very weak correlation in samples over 60 IU/dL. In samples from 0 to 1% of FVIIIa, the APTT corresponded with them varied from 53.2 to over 240 seconds. Although the APTT became to shorten with statistical difference every IU/dL from 0 to 3(p<0.01, all of them), the difference was not significant every IU/dL from 4 to 9 (4 vs 5; p=0.093, 5 vs 6; p=0.0114, 6 vs 7; p=0.4265, 7 vs 8; p-0.1532, 8 vs 9; p=0.1751)(Fig.2(a)). The reduction of APTT gradually became unclear with an increase of FVIIIa. The significant difference of APTT could show only every 10 IU/dL in more than 10 IU/dL (p<0.01, all of them), and APTTs did not statistically become different over 60 IU/dL (Fig.2(b)). Both of average and median APTTs were below the upper limit of the reference range (RV) in samples over 50 IU/dL. We simultaneously measured APTT and FVIIIa in 11 PWHAs both when bleeding and non-bleeding. Compared with the time of non-bleedings in 8 of 11 PWHAs, the absolute values of the correlation coefficients between APTT and FVIIIa became lower at the time of bleedings (Table. 2).

【Conclusion】APTT cannot substitute for FVIIIa to classify the disease severity. However, it can be a surrogate when we have to monitor the patient's hemostatic status and should consider infusion of additional coagulation concentrates, considering that the APTT within the RV indicates over 50 - 60 IU/dL of FVIIIa.

【Materials & Methods】Subjects were 1,621 plasma samples from 44 PWHAs who have visited our hospital from 2000 to 2014. All of them were adult men (their ages ranged from 24 to 76 years old), had not had inhibitors, and were measured their APTTs and FVIIIas at the same time. The FVIIIa was measured one stage APTT-based clotting assay in our hospital. The measurement reagents made by Sysmex® were consequently used. Ellagic acid and cephalin derived from rabbit brain were used as an activator and a phospholipid for accelerating coagulation response, respectively. The relation between APTT and FVIIIa was examined by statistical analysis. P<0.01 indicated statistical/significant difference. Furthermore, we compared with the APTTs in PWHAs measured both when they had some little bleedings and not (e.g. surgery).




【Fig.2】APTTs equivalent to FVIIIas divided into every IU/dL from <1 to 9 (a) and every 10 IU/dL from 10 to 100< IU/dL(a). The numbers below the graph indicated the median APTT(sec) (a) and the median and average (b) equivalent to the respective concentrations. The averages in (a) were omitted because of many outliers within 4 IU/dL of FVIIIas. The numbers of X axis means the values omitted the second figures of significant digits(e.g. 10 includes from 10 to 19 IU/dL). The horizontal red line in (b) indicates upper limit of reference values (RV) in our hospital (37.0 seconds).

| | Subject 1 | Subject 2 | Subject 3 | Subject 4 | Subject 5 | Subject 6 | Subject 7 | Subject 8 | Subject 9 | Subject 10 | Subject 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs-nb | -0.938 | -0.877 | -0.934 | -0.950 | -0.945 | -0.871 | -0.818 | -0.909 | -0.945 | -0.647 | -0.916 |
| rs-b | -0.734 | -0.796 | -0.321 | -0.999 | -0.808 | -0.848 | -0.999 | -0.749 | -0.707 | -0.809 | -0.861 |
| Remarks | Surgery; Peritoneo-tomy, TKA) | Surgery; Hepatec-tomy, ICH | Surgery; TKA | Surgery; Heniotomy | Surgery; 2 TKA | Surgery; CV surgery, Endovascu-lar stent graphting | ICH | Surgery; 2 Debride-ment of abcess | Surgery; Debride-ment of abcess, THA, Hepatec-tomy, ICH | Surgery; THA, TKA, Hepatec-tomy | Surgery; TKA, Fracture reduction |

【Table.2】Spearman's rank correlation coefficients between APTT and FVIIIa in 11 PHAs measured when bleeding(rs-b) and non-bleeding(rs-nb).

【Discussion】In general, APTT can substitute for FVIIIa because our date indicated a strong correlation between them. However, the relationship became greatly weaker when the FVIIIa concentrations were below 4 or above 60 IU/dL. Because there were many outliers of APTT within 4 IU/dL of FVIIIa, and the APTT even when FVIIIa were excessive could not shorten according to the FVIIIa concentrations and reach the lower limit of the RV of APTT. Whereas, APTT cannot substitute for FVIIIa to classify the disease severity because it is decided in lower levels of FVIIIa. On the other hand, we can guess that the APTT within the RV is above 50 IU/dL of FVIIIa at least. The hemostasis of PWHAs is almost normalized if their FVIIIas are above 50 IU/dL although guidelines recommend that FVIIIas are desired above 80 IU/dL during the surgery. When some little bleeding occurs such as pre- or post surgery, APTTs are sometimes not normalized by decrease of some other coagulation factors or some kinds of influence accompanied with the surgeries and/or hemorrhage. Thus, we can estimate that FVIIIas are above 50 IU/dL at least, possibly reach above 80 IU/dL, when APTTs are within the RV during the surgery.

【References】

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