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Routine Lupus Anticoagulant Sensitive aPTT Testing Can Prevent Unnecessary LA Testing

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Abstract

Even though routine screening of the general hospital population is discouraged, medical laboratories may use a "lupus sensitive" activated partial thromboplastin time test (aPTT) with phospholipid concentrations that are susceptible to inhibition by lupus anticoagulant (LA), to screen for the presence of LA. If deemed necessary, follow-up testing according to ISTH guidelines may be performed. However, LA testing is a laborious and time-consuming effort that is often not readily available due to a lack of automation and/or temporary unavailability of experienced staff. In contrast, the aPTT is a fully automated test that is available 24/7 in almost all medical laboratories and is easily interpreted with the use of reference ranges. In addition to clinical signs, the result of an LA sensitive aPTT may thus be used to lower the suspicion of the presence of LA and reduce costly follow-up testing. In this study, we show that a normal LA sensitive aPTT result may be safely used to refrain from LA testing in the absence of strong clinical suspicion.

Keywords

lupus anticoagulant, aPTT, LA testing, cost effective

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Introduction

Lupus anticoagulant (LA) is a phospholipid-dependent coagulation inhibitor detected in clinical laboratories as a prolongation of clotting tests in which a limited phospholipid concentration is used. The LA phenomenon is caused by anti-phospholipid antibodies, that may be persistently present in the course of auto-immune disease or transiently after (viral) infections.[1] Persistent LA is associated with an increased risk of thrombosis.[2]

LA is readily detected with sensitive activated partial thromboplastin time tests (aPTT) reagents. During routine coagulation screening, hemostasis is assessed with a combination of prothrombin time (PT) and aPTT to screen for the presence of abnormalities in secondary hemostasis. The aPTT is primarily used to determine the (functional) presence of the clotting factors in the intrinsic coagulation pathway and requires sufficient amounts of phospholipids to initiate and sustain *in vitro* coagulation. The presence of LA hampers this process, which in turn may lead to a prolonged aPTT. Even though routine screening of the general hospital population is discouraged, medical laboratories may use a "lupus sensitive" aPTT with phospholipid concentrations that are susceptible to inhibition by LA, to screen for the presence of LA.[3]

The criteria for LA detection include a prolonged coagulation time in a phospholipid-dependent clotting assay, the

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inability of a mixing test to correct this prolongation, the correction of the coagulation time in the presence of high phospholipid concentrations, and the absence of inhibitors for specific coagulation factors. The International Society of Thrombosis and Haemostasis (ISTH) recommends the application of 2 tests based on different principles in LA detection.[4] Taken together, LA testing is a laborious and time-consuming effort that is often not readily available due to a lack of automation and/or temporary unavailability of experienced staff. In contrast, the aPTT is a fully automated test that is available 24/7 in almost all medical laboratories and is easily interpreted with the use of reference ranges. In addition to clinical signs, the result of an LA sensitive aPTT may thus be used to lower the suspicion of the presence of LA and reduce costly follow-up testing.

In practice, LA sensitive aPTTs are rarely used to rule out the presence of LA. In this study, we retrospectively determined the negative predictive value of a normal LA sensitive aPTT for the presence of a LA in the populations of a tertiary care hospital in the Netherlands.

Methods

A retrospective analysis of data from the Utrecht Patient Oriented Database in the UMC Utrecht (UMCU, university medical center, Utrecht, the Netherlands) between 2010 and 2021 was performed. Results from LA testing (according to ISTH guidelines[4]) were linked to the nearest previous routine LA sensitive aPTT result within a maximum time frame of 12 weeks. aPTT results were deemed "positive" if they exceeded their respective laboratories reference upper-limit (reference range 24-33 s). Subsequently, positive and negative predictive values were calculated (PPV, NPV, respectively). During the study period aPTTs were analyzed with STA APTT reagent on a Sta-Rack-evolution (Diagnostica Stago, Asnieres-sur-Seine, France) and Hemosil APTT-SP reagent on an ACL TOP 750 (Werfen, Barcelona, Spain).

PPV was calculated by dividing the number of true positives by the number of true positives plus the number of false positives. NPV value was calculated by dividing the number of true negatives by the number of true negatives plus the number of false negatives. For clarification, a "true positive" was defined as a prolonged LA sensitive aPTT AND a positive LA test. A "true negative" was defined as an LA sensitive aPTT within reference range AND a negative LA test. False positives and false negatives were defined relative to the aPTT.

A sensitivity analysis was performed to investigate whether clinical suspicion impacted PPV and NPV. To do so, results were grouped into patients with or without Diagnosis Treatment Combination related to thrombotic events. An overview of these DTCs can be found in Supplement 1.

Results

A total of 1721 complete datasets (LA result + aPTT prior to LA test) were extracted and after removal of duplicates, 1553 were analyzed (see Figure 1, not included in this analysis are 7086 LA results due to absence of an aPTT prior to LA testing). A total of 1190 aPTT results were prolonged (77%, mean 47 s, SD 16 s), while 363 were not (23%, mean 30 s, SD 3 s). Other patient demographics and test results are shown in Table 1. From the non-prolonged aPTTs, 346

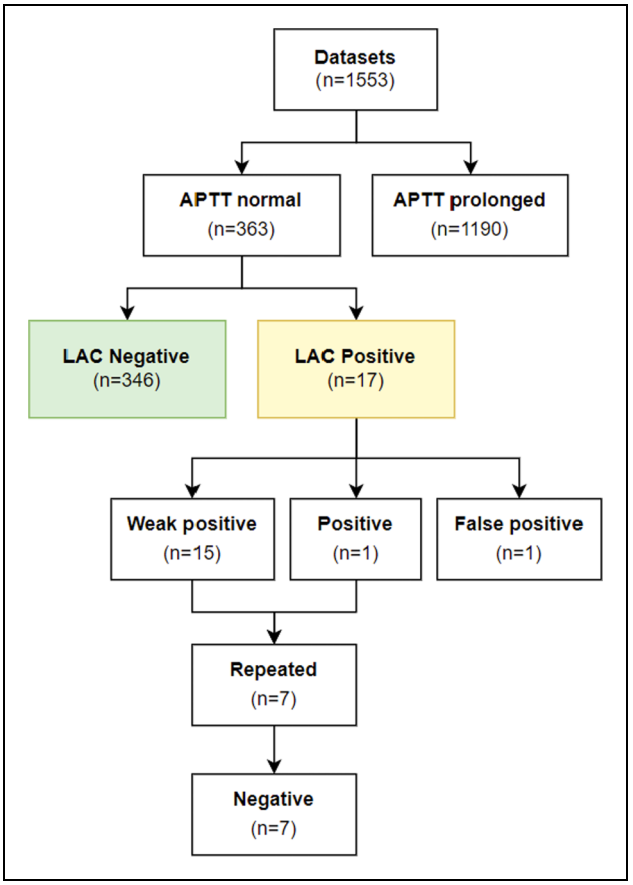

Figure 1. Datasets and results between 2010 and 2021.

Table 1. Patient Demographics and Test Results.

Group	Amount	aPTT (s)[a]	Male (%)	Age (years)	LA Associated Pathology (%)[b]
LA positive	266	55(19)	51	54(16)	32
LA negative	1287	41(14)	46	59(16)	32

Abbreviations: aPTT, activated partial thromboplastin time test; LA, lupus anticoagulant.
[a]Reference range for aPTT: 24–33 s.
[b]For LA associated pathology, please see Supplement 1.

Table 2. Details of Patients With Normal aPTT but Positive LA Test.

Patient	aPTT (s)[a]	LA	Repeat-LA	History/Remarks
1	28	Weak	Negative	Thrombosis
2	29	Weak	Negative	Pulmonary embolism
3	30	Weak	Negative	Pulmonary embolism
4	32	Weak	Negative	Pulmonary embolism
5	30	Weak	Negative	Ischemic stroke
6	30	Weak	Negative	Auto-immune disease
7	27	Weak	Negative	No relevant history
8	24	Weak	-	Pulmonary embolism
9	30	Weak	-	Ischemic stroke
10	32	Positive	-	Falsely elevated due to Rivaroxaban
11	32	Weak	-	No relevant history
12	33	Weak	-	No relevant history
13	31	Positive	-	No relevant history
14	33	Weak	-	No relevant history
15	27	Weak	-	No relevant history
16	26	Weak	-	No relevant history
17	24	Weak	-	No relevant history

Overview of patients with a normal aPTT and a positive LA test. Repeat-LA tests were performed 3 to 6 months after the initial LA test result.
Abbreviations: aPTT, activated partial thromboplastin time test; LA, lupus anticoagulant.
[a]Reference range for aPTT: 24-33 s.

subsequently tested negative for the presence of LA (95%). The remaining 17 non-prolonged aPTTs tested positive for LA, of whom 15 (88%) were deemed "weakly positive" and 2 "positive" (Figure 1). Of these "weak positives," 7 were repeated after 3 to 6 months and all 7 were subsequently negative for LA (see Table 2). The remaining 9 were not followed up. One LA result was falsely positive due to Rivaroxaban use. Patients with a non-prolonged aPTT and a positive LA test were categorized as "False Negatives" and evaluated for relevant diagnoses, of whom 8 had a history relevant for the suspicion of a LA; Pulmonary embolism (4), Ischemic Stroke (2), Thrombosis (1), or Auto-Immune disease (1).

Negative Predictive Value

Without regarding patient history and follow-up testing, a normal aPTT predicts a negative LA with a negative predictive value of 95%. When including repeat-testing and regarding the result of the follow-up LA test as final, the negative predictive value increases to 97%. The negative likelihood ratio was 0.2.

Discussion

In this retrospective data analysis of the Utrecht Patient Oriented Database, we investigated the negative predictive value of a normal aPTT to exclude a positive LA test. We found that a normal aPTT has an NPV of 95%, which increases to 97% when regarding repeated LA testing after 3 to 6 months according to ISTH guidelines. These results suggest that a normal aPTT can be utilized as a means to safely reduce amount of LA testing.

One of the biggest concerns when applying this strategy is that potentially clinically relevant LA are missed. In our analysis however, the few false negatives (eg, "missed Las"), occurred either in patients with a clinical history related to thrombosis or auto-immune disease and these patients would have been eligible for LA testing based on clinical suspicion. Regardless, the majority of false negatives were not followed up, which begs the question whether there was true clinical suspicion of LA in these cases. In the remaining cases, repeated testing according to ISTH guidelines resulted in a negative LA test, showing the transient and non-clinical relevancy of these "missed LAs."

In conclusion, a strategy of refraining from LA testing based on a normal lupus sensitive aPTT result would not have led to relevant missed cases.

Limitations

This is a single center study, and the results are limited to the aPTT reagents used. Laboratories that use LA sensitive reagent from other vendors may achieve different results. Therefore, the results may not be generalizable to other laboratories and reagents. Secondly, the majority of LA testing performed in the studied time period was not preceded by an aPTT, which may have introduced a selection bias.

Conclusion

A normal LA sensitive aPTT result may be safely used to refrain from LA testing in the absence of strong clinical suspicion.

Declaration of Conflicting Interests

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Ethics and Patient Consent

Ethical approval to report this case series was obtained from the Medical Research Ethics Committee (MREC) NedMec. Informed consent for patient information to be published in this article was not obtained because of the size and anonymized nature of the data.

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Supplemental Material

Supplemental material for this paper is available online.

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