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Original Article

The prevalence of Lupus Anticoagulant in Iranian children and adolescents; Current status and comprehensive review of diagnostic approaches

Minoo Ahmadinejad[1*], Sahar Balagholi[1], Maryam Mashkooli[1]

[1]Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, Iran.

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***Corresponding authors:**
Minoo Ahmadinejad
Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, Iran
Email: minooam@gmail.com

Abstract

Background: Lupus anticoagulant (LAC) is an acquired IgG or IgM autoimmune antibody against platelet membrane phospholipids. LAC is an important cause of aPTT prolongation in children. We determined the prevalence of LA-positive results in ≤ 18 years patients referred to the Iranian Blood Transfusion Organization (IBTO) special reference coagulation laboratory.

Method: During a period of 27 months all patients ≤ 18 years old who were referred to IBTO and had results of aPTT and LAC were evaluated. LAC test panel included screening tests (aPTT-LA and DRVVT screen) and the mixing test and confirmatory tests (Hexagonal assay and/or DRVVT confirm) all performed by STAGO reagents and instruments. In cases with positive LAC, their follow-up refers to IBTO coagulation lab were evaluated after 12 weeks.

Results: Our data revealed a LAC prevalence of 2.4% in the referred patients ≤ 18 years who had aPTT test result and 31% in those whom the LAC test was performed for them. In more than half of the LA-positive patients, the main reason for referring was an incidental finding of aPTT prolongation noticed before surgery or during hospitalization. Interestingly only 21.6% of the patients with positive LAC results were requested by the physician.

Conclusions: LAC is not infrequent in children and adolescents however in most cases it is a transient problem without any significant clinical findings. Most of the cases (78.4%) were not suspected of LAC by their physicians so it may be frequently missed in children clinically.

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1. Introduction

Lupus anticoagulant (LAC) was reported in 1948 for the first time in some patients with SLE. These patients had prolonged aPTT that was not corrected after the mixing study (1). LAC is a member of the antiphospholipid antibodies in antiphospholipid syndrome (APS) that affect the coagulation cascade (2). APS is an autoimmune condition characterized by vascular thrombosis and/or recurrent miscarriages with permanently positive antiphospholipid antibodies (3). These antibodies include LAC, anticardiolipin antibody (ACA), and anti β2 glycoprotein I Antibody (B2GPI Ab) (4). In a case-control study, the prevalence of LACs, ACA, and anti-β2GPI antibodies in a population of 628 healthy women was detected to be 0.63%, 0.96%, and 0.95% respectively (5). Also, it is reported that the general prevalence of LAC is about %5 in healthy adults and it usually happens in females of reproductive age (6). The presence of aPL antibodies in apparently healthy children is higher in comparison with a normal adult population. Studies have shown it can be found in up to 25% of healthy pediatrics (7, 8). According to another study on 121 confirmed APS pediatrics, 33% of cases were found positive for all three types of aPL antibodies. Burk et al. reported a 0.7-2.4% LAC prevalence in children evaluated before surgery (9).

LAC is an acquired IgG or IgM autoimmune antibody against platelet membrane phospholipids (10). Since these antibodies prolong aPTT it is called lupus anticoagulant however it is a misnomer that not only usually causes thrombosis but also not all LAC-positive patients have lupus erythematosus necessarily (11). LACs are related to specific autoimmune conditions, connective tissue disorders, malignancies, special drugs, infections, and sometimes with no underlying diseases (12-15). The presence of LACs probably leads to arterial and/or venous thromboembolic events, sequential miscarriages, and rarely hemorrhagic symptoms or may be asymptomatic (16-18). Regarding limited data worldwide, the absence of any registered data on the rate of positive LAC tests among the pediatric group in Iran, and perceiving a high incidence of positive LAC tests in referral children to this laboratory we aimed to evaluate the rate of positive results of LAC in a group of patients who were ≤ 18 years old referred to the special coagulation lab of Iranian Blood transfusion Organization (IBTO). Also, we assessed the chief complaints of these patients and investigated the awareness of physicians about the possibility of LA as a cause of aPTT prolongation in children based on their laboratory requests.

2. Methods

During a period of 27 months in a retrospective study, all patients ≤ 18 years old who were referred to the special coagulation laboratory of the Iranian Blood Transfusion Organization (IBTO) and had results of aPTT and lupus anticoagulant (LAC) were evaluated. In all cases, if available, demographic data, chief complaints, and the results of procoagulant factor levels were recorded. Also, for all patients, primary coagulation tests PT and aPTT (Stago, France) were performed, and for abnormal results of aPTT, a mixing aPTT test was done. LAC screening panel tests including lupus sensitive aPTT (aPTT-LAC) and DRVVs screen (both from Stago company, France) were performed for all cases with the possibility of the presence of LAC according to the clinical and/or laboratory findings. In the event of abnormal aPTT-LA and/or DRVVs, mixing tests as well as confirmatory tests were carried out (Hexagonal phase phospholipids neutralization assay and DRVV confirm tests respectively). All tests were done by STA Compact fully automated coagulation analyzer (Stago, France). It is necessary to mention that the normal ranges of tests were determined in home by testing on at least 40 normal samples. In the cases with positive LAC results, their laboratory follow-up in the

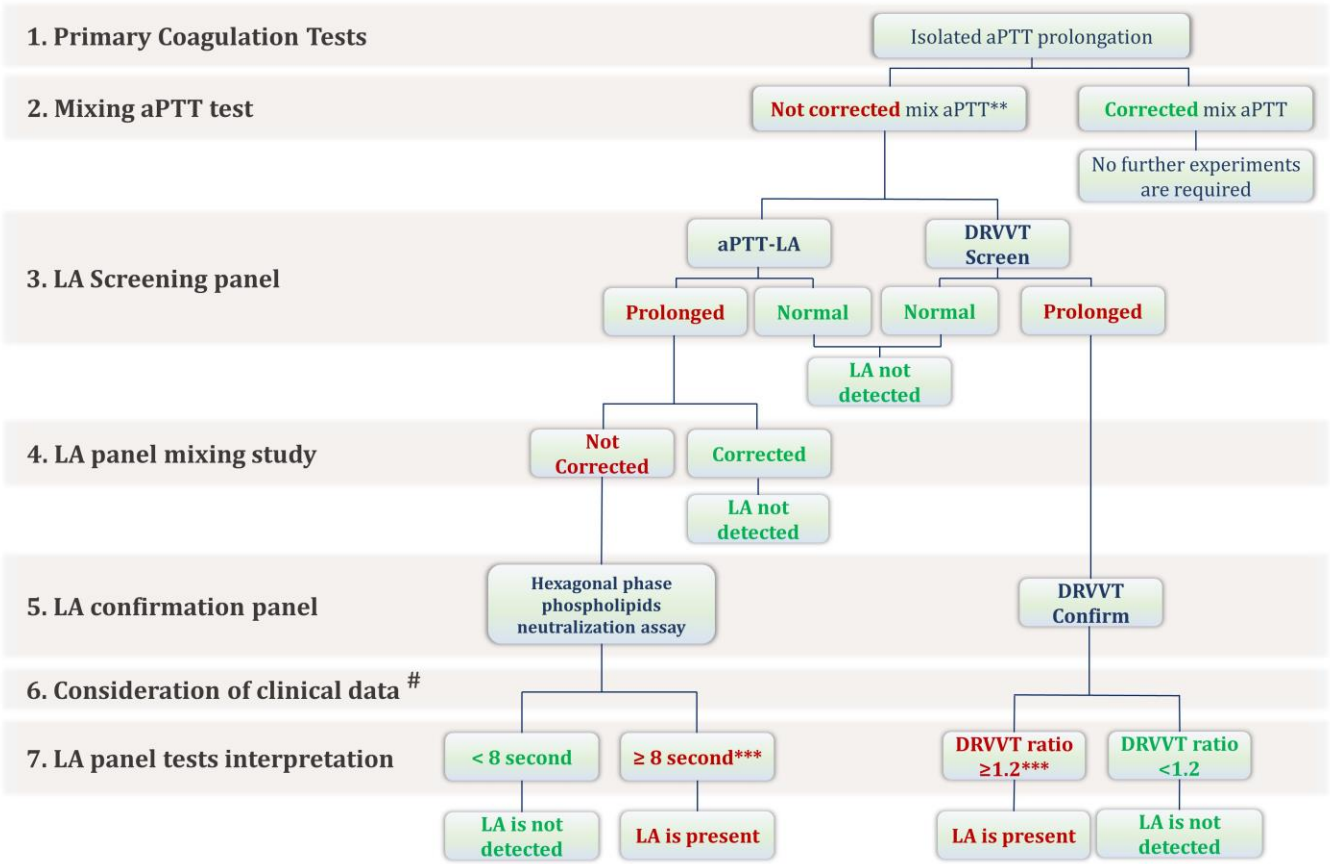

Figure 1. **Diagnostic flowchart of LAC in children and adolescent in IBTO special coagulation laboratory.**
* Prolongation defined in comparison with in-house-established reference interval (RI) for aPTT, DRVVT-screen, and PTT-LA on samples from healthy blood donors.
** Corrected: correction to within upper limit of parent test RI (±2SD).
*** The reagent specific cut off values should be considered.
# No treatment with anticoagulants especially DOACs in the recent week
#No history of hemophilia with inhibitor development
#No heparin contamination in the sample.

IBTO lab was evaluated after 12 weeks. In patients with positive LAC results and evidence of the low level of procoagulant factor levels, the clotting factors were re-assessed at multiple dilutions (so-called dilution study) for resolution of inhibitor interference and the highest apparent factor level was reported. SPSS version 20 was used for data collection and statistical analysis (**Figure 1**).

3. Results

During a period of 27 months, 2326 patients ≤18 y were referred to the special coagulation lab of IBTO (**Figure 2**). A number of 2099 of these patients had aPTT test result and in the 160 (7%) of these patients who were suspected for the presence of LAC, based on clinical data and prolonged aPTT & aPTT mixing test, the LAC screening panel was checked. Fifty-one (31%) of 160 patients were diagnosed positive for LAC according to the defined reference interval (**Table 1 and 2**).

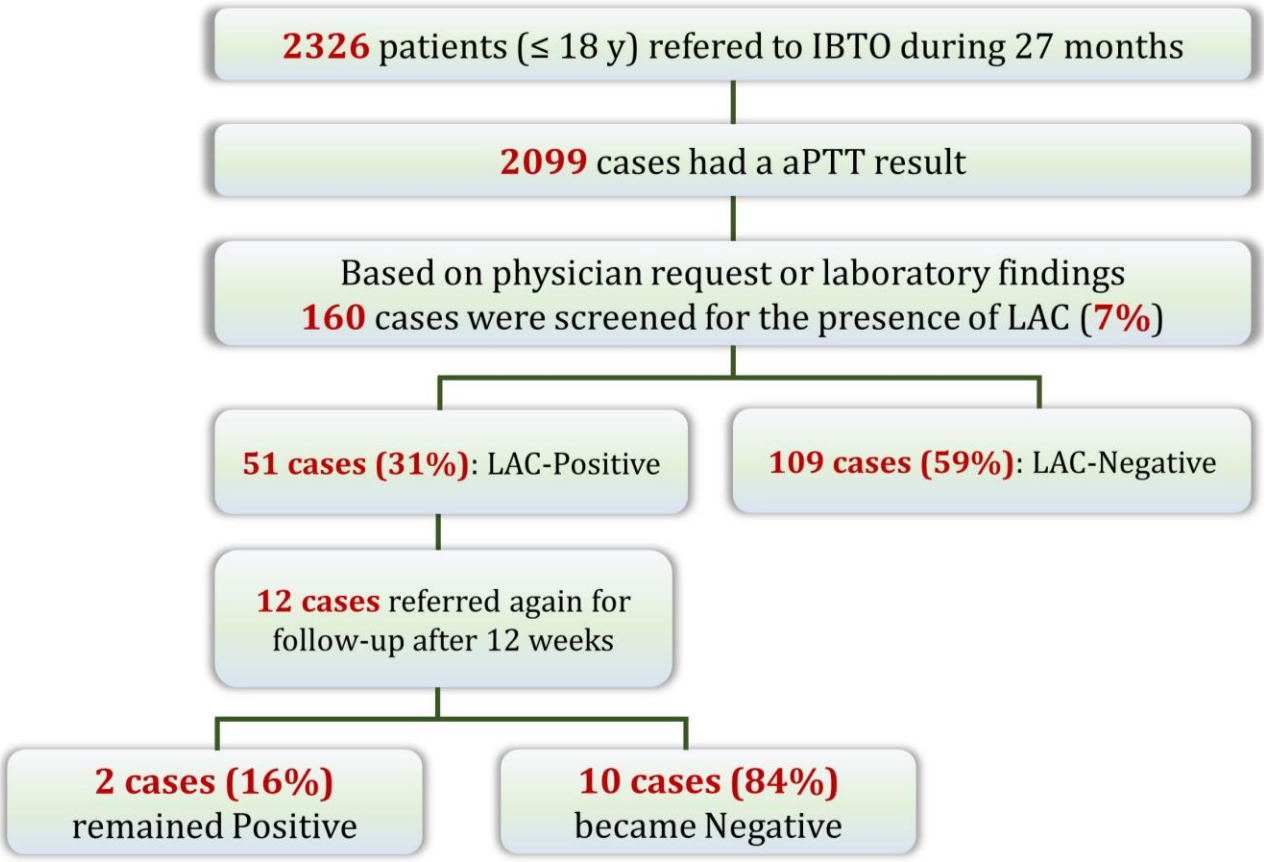

Figure 2. Summary of study populations results.

The median age was 3 years (age range 4 months to 18 years). The results showed that 40 cases (78.4%) of the LA-positive cases were referred to the special coagulation laboratory for a diagnostic approach of a prolonged aPTT which was incidentally noticed before surgery or during hospitalization. Interestingly in only 11 (21.6%) of the patients the LAC test were requested by the physician. In the follow-up of LAC positive cases, twelve cases were requested after 12 weeks for repeating LAC test in IBTO lab and 10(84%) of them became negative but 2 (16%) remained positive in their second evaluation.

4. Discussion

In the current study, the frequency of LAC in ≤18 y patients referred to the IBTO special coagulation laboratory was assessed during a 27 months period. The LAC incident was 2.4 % (51 cases) in 2099 patients with aPTT results. In agreement with this study Burk et al. reported a same rate of LAC positive result in 0.7-2.4% of children who were evaluated before a surgery and on repeat tests LAC became negative after weeks to months (9). In another study on the prevalence of LAC in children and adolescents among 112 patients with prolonged aPTT, 18 LAC-positive cases (16%) were found (19). In a similar study on 68 pediatric patients with prolonged aPTT, the prevalence of LAC was 71% (39 cases), and the median age was 8 years (20).

Table 1. Demographic information and chief complaint in 51 LAC-positive patients

Demographic Data		Chief Complaint			
Median Age (Range)	Sex F/M	Incidental findings before surgery or during hospitalization	Mucocutaneous bleeding	History of thromboembolic events	No clinical data
3 y (4 Months –18 y)	21/30	40(78.4%)	5(9.8%)	2(4%)	4(8%)

Table 2. Laboratory findings in 51 LAC-positive patients

`Test	Patients' results (Mean ± SD)	Normal range
aPTT (sec)	78 ± 22.5	29.5-41
Mixing aPTT (sec)	60.7 ± 12.2	29.5-41
PTT-LA (sec)	94.6 ± 30.8	33-47
Mixing PTT-LA (sec)	74 ± 23.7	33-47
dRVVT screen (sec)	66.6 ± 20.2	30-44
dRVVT confirm (sec)	39.8 ± 4.6	32-46
dRVVT Normalized ratio	1.65± 0.42	<1.20

4.1. LAC Diagnosis

Identification of LAC by laboratory testing is critical for investigating unexpectedly prolonged aPTT values and diagnosis APS. LACs are heterogenous class of immunoglobulins that specifically target the epitopes of the negatively charge phospholipid bindings protein which inhibit phospholipid-depended coagulation in vitro. LAC is a misnomer as it is neither only find in SLE, nor it mainly associated with hemorrhagic diathesis. LACs can develop in patients with APS, SLE, or other autoimmune disorder which are typically persistent in APS. It can be also detected transiently in patient with infections, malignancies or using some medications. (21,22) Persistent LAC is a most important acquired risk factor for new or recurrent thrombosis in patients with APS. (23)

In the current study for only 11 (21.6%) cases, LAC test was requested by the physician and the rest of them (40 cases (78.4%)) were diagnosed incidentally after a workup for a prolonged aPTT in the laboratory. LAC is a frequent cause of aPTT prolongation in children and is usually detected as an incidental laboratory finding during pre-operative screening tests (24). As LACs can be related to specific autoimmune conditions, connective tissue disorders, malignancies, special drugs, and infections, (12-15) physician should be aware about these underlying diseases. In this regard, studies showed that LAC was reported as Postinfectious LAC, Autoimmune disease-associated LAC, and Drug-Induced LAC. Postinfectious LAC in some children is created due to bleeding after hypoprothrombinemia.)25) In a study by Frauenknecht, APA positivity was detected in 122 children with prolonged aPTT in the presence of infection)26(. Studies also show that in these patients after recovery, their aPTT levels normalized and LAC became negative. (20) Autoimmune disease-associated LAC seen in adolescents also is associated with thromboembolic events and this is more persistent than pediatrics (25,27). In a series of pediatric patients with SLE, 19% to 62% prevalence for LAC was reported (28-33), Also, thrombosis occurred in 37–44% of patients with LAC or ACA positivity (28, 30,31). Some medications have been involved as possible causes of LACs. Drug-induced LACs are heterogeneous, depend on laboratory findings and related clinical complexity (34). Certain drugs, such as antibiotics, antipsychotics, antihypertensives, and immune modulators are

Table 3. **Seven LAC-positive case with single or more factor deficiencies in routine testing.**

#	Age	Sex	aPTT-LA	aPTT-LA mixing test	Hexagonal phase assay	dRVVT screen	dRVVT confirm	dRVVT NR*	Coagulation Factor assay	Bleeding symptoms
1	5 m	Male	176	68	Positive	43.7	NA	NA	F VIII<1IU/dL Without correction in the dilution study	Ecchymosis
2	4 y	Male	80	79.5	Positive	60	40	1.7	F II = 47 IU/dL Without correction in the dilution study	GI Bleeding
3	5 y	Male	82	94	Positive	75.6	43	1.4	F II= 36 IU/dL Without correction in the dilution study	Epistaxis
4	3 y	Female	160.5	113.5	Positive	90	36	2.2	F IX = 29 IU/dL F XI = 38 IU/dL F XII = 17 IU/dL All corrected after the dilution study	No bleeding symptoms
5	4 y	Male	109.5	105.5	Positive	79	45.3	1.8	F IX = 46 IU/dL Dilution study: NA**	No bleeding symptoms
6	12 y	Male	101	83.6	Positive	82.4	65.4	2.0	F XI = 38 IU/dL corrected after the dilution study	Ecchymosis
7	4 y	Male	99.7	91.8	Positive	110.3	44.4	2.3	F IX = 31 IU/dL F XI = 50 IU/dL Dilution study =NA	Epistaxis

*NR: Normalized Ratio
**NA: Not Assessed

related with LAC [1, 33]. Penicillin and its derivatives are found to be related to the formation of transient circulating inhibitors in children (35,37). However, it is unknown whether LAC in such cases is related to drugs or to the infectious process itself.

4.2. Clinical Manifestation in LAC

Data obtained from the current study revealed that 40cases (78.4%) of LAC-positive patients referred for prolonged aPTT and/or pre-operative checkups were clinically completely asymptomatic and the chief complaint of 5 cases (9.8%) was mucocutaneous bleeding. In LAC cases, bleeding probably occur due to capillaritis, microthrombosis, or thrombocytopenia (37). In a study by Becton and Stine 6 previously healthy children presented with clinical signs of bleeding and laboratory evidence of LACs and anticardiolipin which was a transient problem and both symptoms and laboratory antiphospholipid findings resolved after 3 to 6 months (38). Giordano et al. also revealed that 27% of patients with persistent LAC positivity had thrombocytopenia (39). In the other hand, "LAC-hypo-prothrombinemia syndrome" is a hemorrhagic phenomenon that has been described as increased clearance of prothrombin caused by non-neutralizing anti-prothrombin antibodies in LAC positive patients. It is reported in 10-20% of patients (17). Its symptoms have varied from mild bleeding such as bruising and hematoma to severe gum bleeding, epistaxis, and hemarthrosis. Severe bleeding crisis were especially likely to occur when

prothrombin activity was lower than 10% of normal (40-47) In a case report of transient LAC in a 3 years old girl who had been referred with spontaneous bruises, laboratory findings showed a low level of F II that returned to the normal range after three months along with the resolution of LACs (48). In another case study, two LAC-positive patients have been reported with hypoprothrombinemia and bleeding symptoms (49). In the current study, two children (No. 2 and 3 **Table 3**) with low levels of F II were detected. They were 4- and 5-years old boys and had been referred by GI bleeding and epistaxis respectively. The values of FII were 47% and 36% respectively and were not corrected with the dilution study. In this regard, it has been suggested that hypoprothrombinemia may occur in LAC-positive patients probably with pathogenesis of complexing of LAC with circulating prothrombin (50). The "hemorrhagic LA syndrome" should be considered in children with new-onset bleeding and prolonged activated partial thromboplastin time (38).

Unlike adults, thrombotic events were not the main presentation of disease in children (13,51) and this is observed in only two cases (4%) with thrombotic event (leg DVT). Studies demonstrated that creation of specific protein S autoantibodies, and transient protein S deficiency probably are responsible for hypercoagulability and thrombosis in such cases (52). Evidence also shows, high-titter of ACA IgG in children with thrombosis (26-28), is an established risk factor for thrombosis in adults (53). In a study by Galli et al. (23), it is confirmed that LACs are stronger risk factors for thrombosis than ACAs in the APS. This group previously showed that (54) 17 out 100 adult patients who had "transient" LAC positivity did not develop any thromboembolic events. Although, Giordano et al. (39) had reported a 9% rate of thromboembolic event in 44 pediatric cases with APA positivity. However, thromboembolic event was not observed in their "transient" LAC-positive patients. It seems that more incidence of thrombosis in LAC positive adult compare to pediatric patients is related to other risk factors such as smoking, hypercholesterolemia, atherosclerosis, in adults. However, a few cases of thrombosis in young children related to postinfectious presence of LAC without signs of autoimmune disease have been reported (52). Recently, aPL and thrombosis were reported after SARS-CoV-2 infection. aPL may also induce thrombotic events and thrombocytopenia following coronavirus disease 2019 (COVID-19) vaccination (55,56), but further prospective studies will be necessary to clarify these reports.

4.3. LAC and other factor deficiencies

Among 51 LA-positive patients in the current study, the level of procoagulants was assessed for 35 cases. Seven of 35 cases had single or more factor deficiencies. (**Table 3**) Among these seven cases, a 5-month boy (case No.1) was diagnosed as severe FVIII deficiency who presented with spontaneous cutaneous bleeding and simultaneously a non-specific anticoagulant. The FVIII level was reassessed by dilution study and FVIII inhibitor excluded by Bethesda assay. This case was a caution for clinicians about the coincident of LA with hemophilia. To our knowledge, there are some rare case reports about this co-association, however most of the studies focused on acquired type of hemophilia and differentiation of LACs. (57,58) However, a coincidence of LA with other coagulation deficiencies was reported. In this regard, a study by Seidizadeh et al. showed the coincidence of VWD and LA in two patients. (59) Another patient (case No. 6) was previously diagnosed as severe FXI deficiency referred to IBTO lab for definite diagnosis. He was a 12-year-old boy with the presentation of spontaneous cutaneous bleeding. Laboratory findings showed a prolonged aPTT that was not corrected after the mixing study. The lupus panel tests were performed and the result showed evidence of LAC. Given that LAC mostly

affected FXI level invitro with correction after dilution study, the level of FXI was corrected to minimum of 50 % and revealed that the diagnosis of severe F XI deficiency was a false laboratory diagnosis.

5. Conclusion

The presence of lupus anticoagulant in children is not rare. Most cases were diagnosed incidentally during follow-up of a prolonged aPTT which referred for evaluation of possible procoagulant deficiency. Based on current study a small percentage of physicians are aware of the presence of LAC in children in the differential diagnosis of prolonged aPTT. Since most of the cases in children are transient for LAC and may be accompanied by bleeding symptoms and/or underlying bleeding disorders, referring these cases to the specialized coagulation laboratories is necessary to discriminate the different causes of aPTT prolongation.

Conflict of interest

There is no conflict of interest.

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