Ochsner Journal 16:172–175, 2016

Prevalence and Resolution of Lupus Anticoagulant in Children

Chandra Kallanagowdar, MD,[1] Aman Chauhan, MBBS,[2] Mora V. Puertolas,[3] Rajasekharan Warrier, MD, FAAP, FIAP[3,4]

[1]Department of Hematology/Oncology, Louisiana State University Health Sciences Center/Children's Hospital, New Orleans, LA [2]Department of Pediatrics, Louisiana State University Health Services Center/Children's Hospital, New Orleans, LA [3]The University of Queensland School of Medicine, Ochsner Clinical School, New Orleans, LA [4]Department of Pediatric Hematology/Oncology, Ochsner Clinic Foundation, New Orleans, LA

Background: Lupus anticoagulant (LA) is an autoantibody that inhibits phospholipid-dependent reactions. Studies on the incidence and prevalence of LA in the pediatric population are lacking. The objective of our study was to determine the incidence and potential risk of complications of LA in children presenting with abnormal partial thromboplastin time (PTT). Our secondary objective was to identify signs, symptoms, and medical history associated with the presence of LA as documented in the literature. We focused on the correlation between signs of LA in the form of laboratory values consistent with bleeding abnormalities and the presence of clinical symptoms of bleeding.

Methods: We conducted a record-based retrospective analysis of 112 children and adolescents referred to the Department of Hematology/Oncology at Children's Hospital of New Orleans for abnormal coagulation profiles and/or history of mucocutaneous bleeding. Participants were followed up until PTT values normalized.

Results: In our study population with suspected bleeding disorder, the preliminary incidence of LA was 21%. We found that resolution of LA correlated with correction of PTT in 90% of patients.

Conclusion: To minimize extensive and expensive blood workup, we recommend that screening for LA be included in the evaluation of children with prolonged PTT, even if they have a negative history of bleeding problems.

Keywords: *Antibodies–anticardiolipin, lupus coagulation inhibitor, lupus erythematosus–systemic, pediatrics*

Address all correspondence to Rajasekharan Warrier, MD, FAAP, FIAP, Department of Pediatric Hematology/Oncology, Ochsner Clinic Foundation, 1315 Jefferson Hwy., New Orleans, LA 70121. Tel: (504) 842-5230. Email: rwarrier@ochsner.org

INTRODUCTION

Lupus anticoagulant (LA) is a misnomer because it is an acquired immunoglobulin G or immunoglobulin M antibody that inhibits phospholipid-dependent reactions. LA is usually associated with certain autoimmune conditions, drugs, infections, pregnancy loss, bleeding disorders, and malignancies.[1] The prevalence of LA is believed to be approximately 5% in adults, with a predominance among females of reproductive age.[2]

The aim of our study was to determine the incidence and potential risk of complications of LA in children presenting with abnormal partial thromboplastin time (PTT). Our secondary objective was to identify signs, symptoms, and medical history associated with the presence of LA as documented in the literature.

METHODS

We conducted a retrospective longitudinal analysis of the medical records of 112 patients who were referred to the Department of Hematology/Oncology for abnormal coagulation profiles and/or a history of mucocutaneous bleeding. The abnormal coagulation profiles were incidental findings during preoperative evaluation. Patients were included in the trial if they had an abnormally elevated PTT in the absence of a known bleeding disorder or systemic illness associated with a bleeding disorder, such as systemic lupus erythematosus (SLE). The study was conducted using the records of patients treated at Children's Hospital of New Orleans during a period of 3 years. Age, sex, clinical features, family history of symptomatic bleeding, and coagulation profiles (mixing study defined as normal if PTT does not normalize with the addition of normal pooled plasma, prothrombin time with the reference range defined as 11-13.5 seconds, PTT with the reference range defined as 25-35 seconds, dilute Russell viper venom time [dRVVT] with the reference range defined as 29-42 seconds, and factor levels when indicated by history) of the patients were analyzed. Every patient was followed up for PTT and LA every 12 weeks until all laboratory values returned to reference range. Appropriate ethical committee clearance

was obtained from the institutional review board at Children's Hospital prior to commencing the study.

RESULTS

Of the 112 children and adolescents who were referred for abnormal hematologic parameters following preoperative evaluation for a variety of minor surgical procedures, 84 (75%) were found to have prolonged PTT when a coagulation profile was repeated in our Department of Hematology/Oncology. These 84 patients underwent mixing studies, platelet neutralization procedure, dRVVT, factor levels, and evaluation for antiphospholipid antibody. Twenty-one percent (n=18) of the prolonged PTT population were LA positive. The Figure depicts the initial and follow-up PTT values in the 18 LA-positive patients. Sixty-seven percent (n=12) of these LA-positive patients were female, and the mean age was 6.05 years.

Eighty-nine percent (n=16) of LA-positive patients were clinically asymptomatic. The two who were symptomatic had epistaxis; one required cauterization, and the other had concomitant thrombocytopenia. Only 2 of the 18 LA-positive patients had a family history of bleeding disorders; none of these family members was symptomatic for these disorders at the time the study was conducted. None of the LA-positive patients had concomitant factor VIII or factor IX deficiency. No thrombotic or major hemorrhagic events were documented in the LA-positive study population.

Ten of 18 LA-positive patients later became negative for LA. PTT normalized in 9 of these 10 patients. The mean time for normalization of PTT was 3.3 months (range, 3 weeks to 9 months). Eight patients of the 18 initially LA-positive patients remained positive for LA throughout the follow-up period. We observed normalization of PTT values in 5 of these 8 patients. Two of the 8 LA-positive patients had persistently elevated PTT. One of the 18 initially LA-positive patients was lost to follow-up.

DISCUSSION

The search for LA began in 1948 when Conley and Hartmann[3] discovered that some of their patients with SLE had prolonged activated PTT that did not correct after mixing normal plasma with the patient's blood. The unknown compound was named LA, and it was hypothesized to act against negatively charged phospholipids present on the surface of activated platelets. These phospholipids are an integral part of the vitamin K–dependent clotting factor homeostatic cascade. LA belongs to the group of antiphospholipid antibodies that also includes the anticardiolipin antibody and the anti-beta-2 glycoprotein I antibody.

For many years, LA was considered insignificant because patients who tested positive for LA were clinically asymptomatic despite their prolonged activated PTT. Attitudes among clinicians regarding the ramifications of having a positive LA have changed since 1963 when Bowie et al[4] reported thrombotic events in LA-positive patients with prolonged activated PTT. Today, the presence of LA is no longer taken to imply that the patient will have a lifelong history of thrombotic events. In fact, the effect of LA may only manifest as a transient elevation in PTT without clinical symptoms as demonstrated in our study. We found LA

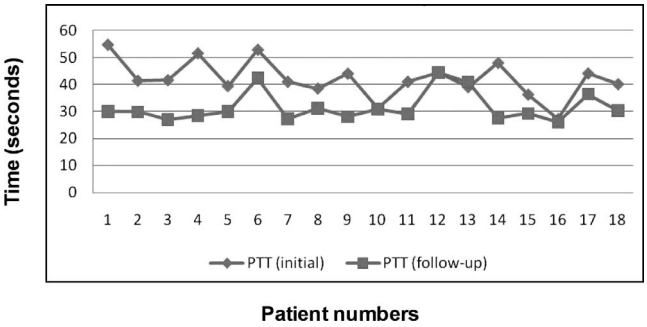

Figure. Value of partial thromboplastin time (PTT) at initial presentation and follow-up in 18 patients positive for lupus anticoagulant.

positivity to be a transient finding in most of our study population. Diagnosis of LA is based on the recommendations of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis.[5]

No specific tests are available to conclusively diagnose LA, so the diagnosis is made indirectly. Phospholipid-dependent tests such as activated PTT and dRVVT are used as screening tests. The patient's plasma is mixed with normal plasma (mixing study), and normalization of clotting time indicates that confirmatory testing should be done. Today, phospholipids are added to the patient's plasma, and if this addition brings the patient's clotting time into the reference range, the patient is said to be positive for LA.

Once a patient's blood is established as positive for LA, repeat confirmatory tests that may include correction/neutralization are done after a 12-week gap. Confounding factors in the detection of LA are prior treatment with heparin and freezing of the sample, factors that can have more of an effect on the results when LA levels are low and lead to an increase in the number of false-negatives. Delaying testing for LA is advisable during or immediately after a thrombotic event or if the patient is taking anticoagulants.[5-9]

Patients who are positive for LA are generally asymptomatic but can present with a thromboembolic event.[10] Bleeding is uncommon in LA-positive patients and is usually associated with an accompanying factor or platelet deficiency.[11,12]

LA is an acquired immunoglobulin G or immunoglobin M antibody that inhibits in vitro phospholipid-dependent reactions. LA assays do not measure antibody titers but are nonetheless functional tests. Although 1 positive test is sufficient for LA positivity, 2 or more tests with different assays are recommended because no single test is 100% sensitive for LA.[13]

Continued long-term follow-up and further evaluation are needed for patients who have persistently prolonged PTT. It may also be advisable to postpone any planned elective surgery until the LA has disappeared. In a child with elevated PTT because of LA, emergency surgery can be carried out with appropriate precautions such as the availability of plasma factors. Careful hematologic follow-up to avoid thrombotic complications is indicated if surgery is unavoidable. In future work, we hope to address the long-

term effects of LA in children and adolescents with both resolved and unresolved prolongation of PTT as they transition into adulthood.

This condition has principally been studied in the adult population in whom the prevalence is approximately 5%; scarce literature is available regarding LA in the pediatric age group.[14] Most physicians agree that LA is a benign condition often with a transient course lacking significant clinical issues.[15,16] Rare reports exist of thrombosis and bleeding episodes associated with LA. Patients with such complications are usually not just positive for LA but also have coexisting conditions such as factor deficiency, SLE, and antiphospholipid antibody syndrome.[17] Studies report an association between LA and autoimmune conditions such as SLE, rheumatoid arthritis, malignancies, urticaria, vasculitis, and lymphoproliferative disorders.[18] Patients with antiphospholipid syndrome associated with autoimmune disease are more likely to be older and have a higher frequency of venous thrombotic events with hematologic and skin manifestations compared to patients with primary antiphospholipid syndrome who are more likely to be younger and have arterial thrombotic events.[19] These differences suggest that the manifestations of LA can be distinguished based on its association with autoimmune disease or infection. Drugs such as chlorpromazine; antibiotics such as amoxicillin; hydralazine; and some viral, bacterial, and protozoal infections are also associated with LA.[20,21]

One limitation of our study is that it is retrospective. Another limitation is that participants were only followed until their PTT values normalized. Future work could focus on the longitudinal effects of LA positivity with or without the resolution of prolonged PTT, especially in asymptomatic participants. Long-term effects of LA positivity may be expected, particularly in females, as anticardiolipin antibodies are associated with an increased risk of miscarriage.[22] This risk is relevant in our study population, considering that LA was more common in females than males. An additional limitation is the lack of a control group. Future studies could include a group of participants with prolonged PTT who are not positive for LA to elucidate how prolonged PTT in the context of LA positivity differs from prolonged PTT because of other hematologic anomalies.

CONCLUSION

Based on our study results, we conclude that LA is common in children and adolescents with abnormal hematologic parameters and is associated with asymptomatic presentation notable for prolonged PTT that may come to medical attention in the context of preoperative evaluation or other unrelated workup. In our study population with suspected bleeding disorders, the preliminary incidence of LA positivity was 21%. We found that the resolution of LA correlated with correction of PTT in 90% of our patients. To minimize extensive and expensive blood workup, we recommend that screening for LA be included in the evaluation of children with prolonged PTT, even if they have a negative history of bleeding problems.

ACKNOWLEDGMENTS

The authors have no financial or proprietary interest in the subject matter of this article.

REFERENCES

1. Ciaudo M, Horellou MH, Audouin J, De Carbonnieres C, Conard J, Samama M. Lupus anticoagulant associated with primary malignant lymphoplasmacytic lymphoma of the spleen: a report of four patients. *Am J Hematol*. 1991 Dec;38(4):271-276.
2. Shi W, Krilis SA, Chong BH, Gordon S, Chesterman CN. Prevalence of lupus anticoagulant and anticardiolipin antibodies in a healthy population. *Aust N Z J Med*. 1990 Jun; 20(3):231-236.
3. Conley CL, Hartmann RC. A hemorrhagic disorder caused by circulating anticoagulant in patients with disseminated lupus erythematosus. *J Clin Invest*. 1952;31:621-622.
4. Bowie EJ, Thompson JH Jr, Pascuzzi CA, Owen CA Jr. Thrombosis in systemic lupus erythematosus despite circulating anticoagulants. *J Lab Clin Med*. 1963 Sep;62:416-430.
5. Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. On behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. *Thromb Haemost*. 1995 Oct;74(4):1185-1190.
6. Greaves M, Cohen H, MacHin SJ, Mackie I. Guidelines on the investigation and management of the antiphospholipid syndrome. *Br J Haematol*. 2000 Jun;109(4):704-715.
7. Exner T, Triplett DA, Taberner D, Machin SJ. Guidelines for testing and revised criteria for lupus anticoagulants. SSC Subcommittee for the Standardization of Lupus Anticoagulants. *Thromb Haemost*. 1991 Mar 4;65(3):320-322.
8. Guidelines on testing for the lupus anticoagulant. Lupus Anticoagulant Working Party on behalf of the BCSH Haemostasis and Thrombosis Task Force. *J Clin Pathol*. 1991 Nov;44(11):885-889.
9. Tripodi A. Testing for lupus anticoagulants: all that a clinician should know. *Lupus*. 2009 Apr;18(4):291-298.
10. Cuadrado MJ, Hughes GR. Hughes (antiphospholipid) syndrome. Clinical features. *Rheum Dis Clin North Am*. 2001 Aug;27(3):507-524, v.
11. Vivaldi P, Rossetti G, Galli M, Finazzi G. Severe bleeding due to acquired hypoprothrombinemia-lupus anticoagulant syndrome. Case report and review of literature. *Haematologica*. 1997 May-Jun;82(3):345-347.
12. Bernini JC, Buchanan GR, Ashcraft J. Hypoprothrombinemia and severe hemorrhage associated with a lupus anticoagulant. *J Pediatr*. 1993 Dec;123(6):937-939.
13. Mikayis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006 Feb;4(2):295-306.
14. Singh AK, Rao KP, Kizer J, Lazarchick J. Lupus anticoagulants in children. *Ann Clin Lab Sci*. 1988 Sept-Oct;18(5):384-387.
15. Male C, Lechner K, Eichinger S, et al. Clinical significance of lupus anticoagulants in children. *J Pediatr*. 1999 Feb;134(2): 199-205.
16. Casais P, Meschengieser SS, Gennari LC, et al. Morbidity of lupus anticoagulants in children: a single institution experience. *Thromb Res*. 2004;114(4):245-249.
17. Manco-Johnson MJ, Nuss R. Lupus anticoagulant in children with thrombosis. *Am J Hematol*. 1995 Apr;48(4):240-243.
18. Giordano P, Tesse R, Lassandro G, et al. Clinical and laboratory characteristics of children positive for antiphospholipid antibodies. *Blood Transfus*. 2012 Jul;10(3):296-301.
19. Avcin T, Cimaz R, Silverman ED, et al. Pediatric antiphopholipid syndrome: clinical and immunologic features of 121 patients in an international registry. *Pediatrics*. 2008 Nov;122(5): e1100-e1107.
20. Follea G, Coiffier B, Viale JP, Dechavanne M. Antiprothrombinase and factor II deficiency in a non SLE patient. *Thromb Haemost*. 1981 Oct;46(3):670.

21. Bajaj SP, Rapaport SI, Fierer DS, Herbst KD, Schwartz DB. A mechanism for the hypoprothrombinemia of the acquired hypothrombinemia-lupus anticoagulant syndrome. *Blood*. 1983 Apr;61(4):684-692.

22. Jameil NA, Tyagi P, Shenefy AA. Incidence of anticardiolipin antibodies and lupus anticoagulant factor among women experiencing unexplained recurrent abortion and intrauterine fetal death. *Int J Clin Exp Pathol*. 2015 Mar 1;8(3):3204-3209.

This article meets the Accreditation Council for Graduate Medical Education and the American Board of Medical Specialties Maintenance of Certification competencies for Patient Care, Medical Knowledge, and Practice-Based Learning and Improvement.