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Lupus anticoagulant in pediatric populations: A comprehensive review of clinical Presentation, diagnostic approaches, and management strategies

Baraa A. Saeed[1*], Ahmed Abdulraheem Ibrahim Dahy[1] , Anwer J. Faisal[2], Bassam S. Mahmood[3]

[1]Ibn Sina University for Medical and Pharmaceutical Sciences, Baghdad, Iraq.
[2]Iraqi Center for Cancer and Medical Genetic Research, Mustansiriyah University, Baghdad, Iraq.
[3]Biotechnology Division, Applied Sciences Department, University of Technology, Baghdad, Iraq.

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Corresponding author:
Baraa A. Saeed, Ph.D.
E-mail: baraahmed1986@ibnsina.edu.iq
Mobile: (+)9647709393501

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ABSTRACT

Lupus anticoagulants (LAs) are a heterogeneous class of immunoglobulins that specifically target the epitopes of the negatively charged phospholipid binding protein of cell membrane, prothrombin, and beta2-glycoprotein I (beta2-GPI) which inhibit phospholipid-dependent coagulation. LAs, an acquired clotting factor inhibitor, poses unique diagnostic and clinical challenges in pediatric patients. This review highlights recent advancements in understanding pediatric LAs, focusing on their clinical significance, diagnostic methodologies, and therapeutic approaches. The association of LAs with autoimmune diseases, such as systemic lupus erythematosus and antiphospholipid syndrome, underlines their clinical relevance. Pediatric LAs may lead to thrombotic or hemorrhagic events, significantly impacting a child's quality of life. Diagnostic approaches include comprehensive clinical evaluations and laboratory testing, with assays like activated partial thromboplastin time (aPTT) and dilute Russell viper venom time (dRVVT) playing critical roles. Despite these tools, challenges remain due to the variability in test sensitivity and specificity, transient LAs positivity, and the potential for misdiagnosis. This work underscores the importance of multidisciplinary collaboration among pediatric hematologists, neonatologists, and intensivists to ensure accurate diagnosis and effective management. By addressing gaps in pediatric LAs research and highlighting emerging diagnostic and therapeutic strategies, this study aims to improve outcomes and quality of care for affected children.

Keywords: Antiphospholipid antibodies, Activated partial thromboplastin time**,** Lupus anticoagulant

Introduction

Lupus anticoagulant (LA) is an antiphospholipid antibody (aPL) with the strongest clinical correlation to thrombosis among the aPLs, placing adults at higher risk of venous and arterial thromboembolism. In recent years, the role of LAs in pediatric populations have been increasingly recognized, with an array of associated clinical manifestations and an emphasis on catering to the needs of pediatric practice rather than attempting to generalize data from adult studies. LAs in children can present with an expanded set of symptoms, including immune cytopenias, cutaneous manifestations, and other non-thrombotic findings (Torres-Jimenez et al., 2022). It occurs in pregnant women, irrespective of being a diagnosed antiphospholipid syndrome (APS) patient and subjects with non-thrombotic autoimmune diseases. Turbulent blood flow in the arteries or veins causes obstinate platelet adhesion and aggregation, which leads to the formation of a thrombus and a resultant block in blood flow (Yin et al., 2021). LAs were historically linked only to arterial or venous thrombosis, but LAs in children have a much broader clinical presentation, and a diagnosis must be made when children present with LA-related clinical

findings. Lately, more and more non-thrombotic features associated with LAs have also been identified. This review will focus on the autoimmune and non-thrombotic presentation of LAs in children and tackle the real-life challenges of dealing with patients positive for LAs and having no previous history of thrombosis.

LAs are antibodies against phospholipids. The immune system typically produces antibodies, which are defensive proteins that react to foreign substances. They aid in the foreign entity's removal from the body by attaching to an antigen, a molecule on its surface. LAs target healthy cells and cell proteins rather than the immune system (Yin et al., 2021). They specifically target the cell membrane's phospholipid component. All living cells, including blood cells and the lining of blood vessels, contain phospholipids. LAs can raise the risk of problems by interfering with the clotting process (Torres-Jimenez et al., 2022). Although the precise source of LAs is unknown, experts believe that autoimmune disorders, drugs, and infections can all contribute to the formation of these antibodies. People with systemic lupus erythematosus (SLE), and other autoimmune diseases frequently have LAs. But they can also happen to people who have human immunodeficiency virus (HIV), hepatitis, malaria, or who are on specific drugs like procainamide or chlorpromazine. A little proof according to a reliable source, the prevalence of LAs rises with age and is higher in women. LAs sufferers may not exhibit any symptoms. Blood clots can occasionally form as a result of specific stimuli (Favaloro, et al., 2022).

Background and significance

Recent advances in pediatric medicine have demonstrated evidence of considerable evolution in understanding and clinical practice of various diseases in children. This is particularly true when we refer to APS and lupus anticoagulant in children and adolescents. The term APS was introduced for the first time in 1983. Since that time, our understanding of antinuclear antibodies-related thrombophilic conditions has advanced significantly due to a better understanding of the variety of observed antibodies, clinical presentation, diagnostic approach, and specific therapeutic management (Knight et al., 2023). Although the literature on lupus anticoagulant in the pediatric population is still rare, many reports have demonstrated the clinical significance of introducing the concepts among pediatric hematologists. It is well reported that among children, similar to the adult population, an increase in some antibody titers, including lupus anticoagulant, has been reported. Furthermore, variable quantities of anti-phospholipid antibodies have been occasionally detected. Interestingly enough, childhood criteria are not limited by the presence of aPLs in the serum of the patient. Previous studies in adults have shown up to 38–68% cases of lupus anticoagulant misdiagnosis. This might lead to the administration of unnecessary anticoagulants in patients with disturbing side effects or, on the other hand, serial lupus anticoagulant positive results are not systematically addressed, leading to catastrophic thrombosis recurrence (Sun et al., 2023).

Even with a low demographic prevalence, lupus anticoagulant can seriously affect children, not only due to the risk of thrombosis but also because it is strongly associated with a specific class of disease, namely autoimmunity. The association between lupus anticoagulant and inflammatory or autoimmune diseases, such as SLE, juvenile idiopathic arthritis, APS, and Henoch-Schönlein purpura, has resulted in the annual medical visit rates, especially among pediatric patients, thus underlying the significance of detecting LAs (Liu et al., 2023). It is extremely uncommon for people on LAs to exhibit a prolonged prothrombin time and severe clinical bleeding because of a lowered prothrombin concentration. It is believed that the LAs in these people attach to prothrombin and take it out of the bloodstream. In these situations, LAs are nonneutralizing antibodies rather than prothrombin inhibitors. Due to the prothrombin deficit, these patients will have a longer prothrombin time than other lupus patients taking anticoagulants. These antiprothrombin antibodies cannot be found using a standard plasma mixing study because they are nonneutralizing. Antibodies to prothrombin should be taken into consideration in the

differential diagnosis when a patient with signs of LAs has an extended prothrombin time.

Purpose of the review

The purpose of this review is to provide a comprehensive review of pediatric LAs and expand on its clinical significance. Although several reviews have been published that provide clinical presentations, diagnostic methods, and management of LAs in adults, a lack of information regarding LAs in pediatric clinical practice has been noted. The understanding of pediatric LAs in both arterial and venous disease is scarce, thus making this article especially beneficial for healthcare professionals and investigators from practically every medical field. By sharing this valuable information, it is believed that an immediate positive impact will be realized for children who have laboratory evidence of prolonged global coagulation tests and are in need of lifelong anticoagulation. A treatment and/or prophylaxis approach should not only focus on antithrombotic and/or antihemostatic drugs but also on other treatments that might be required based on the clinical presentation of pediatric patients. Therefore, an association between a pediatric hematologist, neonatologists, pediatric first-aid doctors, emergency staff, and pediatric intensivists is highly recommended. (Yuan and Guan, 2022)

Understanding lupus anticoagulant

LAs is an acquired clotting factor inhibitor leading to increased persistence of activated partial thromboplastin time. Diagnosing LA is a long, imperfect chain of low positive yield testing. Physicians often use the association of prolonged aPTT, history of thrombosis, and positive screening tests to make a premature diagnosis of "probable LA." Though this approach often holds true, there are exceptions where it wouldn't. LA can exist for some yet not meet the clinical threshold for diagnosis; thus, the actual diagnosis is still best determined by a combination of clinical presentation and laboratory results. It is unique from other clotting inhibitor diseases due to the requirement of phospholipids in its detection. It is also unique among clotting inhibitors for its mechanism lying in the prolongation of the in vitro phospholipid-dependent kinase reaction and detection with the dilute Russell viper venom time (Tripodi et al., 2020).

LAs have been widely studied for adults, though much less studied in pediatrics. There indeed exists enough data in pediatrics to suggest some differences from adults. Frequently, due to adverse pregnancy outcomes or a positive calculation score, LA testing is done preemptively in asymptomatic pregnant women. Taking these individuals into account, most studies approximate the prevalence at 1-2% of the population. It is considered to be a marker for higher risk of thrombosis; however, an individual's chance of developing thrombosis lies in multiple factors including comorbid conditions, environment, and genetic predisposition (Madison et al., 2022). The pathophysiology of LA is not entirely understood. It involves groups of antibodies that target phospholipid-binding proteins and anionic phospholipids on the surface of platelets, endothelial cells, and micro particles. This causes decreased negative charge on cellular surfaces. By shortening the effects of the tissue factor degradation pathway, it can lead to an increased thrombotic tendency while in vivo. It can also result in increased bleeding complications due to clotting factor utilization. Different groups of biological explanations of LAs may help us target therapy used in those affected, give clinicians a better sense of what to expect in prognosis, and provide an overview of what we are really trying to achieve with treatment (Zhang et al., 2020).

3. Definition and mechanisms

LA is an antiphospholipid antibody that is used to identify patients with antiphospholipid antibody syndrome. These polyclonal antibodies attack complexes of negatively charged phospholipids and proteins. The complex formation at the affected surface then activates the cascade for coagulation and affects other parts of coagulation (Campos et al., 2024). Both hypercoagulopathy and increased procoagulation pathways increase the risk of formation and development of thrombus. Antiphospholipid antibodies (aPL) are divided into three groups: LA, anti-cardiolipin, and anti-β-2-glycoprotein antibodies. They are not the cause of thromboembolic events, but the presence of these

antibodies is a necessary factor in the development of thrombi. The most important thing for a healthcare provider to manage patients with LA is that the patient needs to be examined closely for acquired autoimmune risk factors. This can be done by following immunological and coagulation pathways that cause thrombotic events. The onset of disease occurs because of immunological and physiological interactions. The intricacy of these interactions is due to the large network of immuno-coagulation. The immunological cause for LA production is associated with tolerance and immune regulations. The coagulation pathway is associated with the tight connections between cellular membranes, phospholipids, coagulation protein complexes, and autoantibodies (Badal et al., 2021).

LA binds to phospho-lipids and does not enable attaching the prothrombinase complex to the cell. The prothrombinase complex (factor Xa and Va) assembles on negatively charged phospholipid membranes in the presence of calcium ions. The prothrombinase complex catalyzes the conversion of prothrombin to thrombin. The enzyme thrombin has procoagulant activity because it converts fibrinogen to fibrin; however, if it binds to thrombomodulin and the endothelial protein C receptor (EPCR), it reveals anticoagulant properties by activating protein C (APC). APC cleaves activated cofactors Va, VIIIa, and plasminogen activator inhibitor (PAI-1), causing a hypocoagulable and hyper-fibrinolytic state. Thus, LA is a class of APLAs, which causes a phospholipid-dependent prolongation of the clotting time but is associated with an increased risk of thrombosis and pregnancy complications. Beta 2-glycoprotein I (β2-GPI) consist in five domains (I–V), which can be present in two forms: open (J-shaped) and closed (circular). Domain V (DV) binds phospholipid, and its post-translational modifications cause a conformational change from the circular (closed) form to the open configuration. DV is responsible for binding to cell membranes. The open configuration causes the exposition of a previously hidden domain I (DI) epitope, which becomes a place of antibody binding. Anticardiolipin antibodies (anti-aCL) bind to cardiolipin on the mitochondrial surface and stimulate inflammation. Exacerbated inflammatory processes activate coagulation cascade and thrombosis (Reisinger et al., 2021).

Clinical presentation

LA is now a significant focus in medical literature due to the current devastating pandemic as well as complications from the vaccination. Systemic anticoagulation done before diagnosing these patients with LA could have prevented such outcomes in these afflicted patients. However, the medical field is still playing catch-up on trying to recognize these patients and getting them the proper medical attention that they require (Dabit, et al., 2021). In adults, aPL) are addressed in up to 20% of the patients who developed ischemic symptom episodes of arteries or veins. In children with SLE, the episodes of thrombosis show a significant link to aPL. However, negative test results for aPL are not excluded (Zhang et al., 2020).

Clinical suspicion and obtaining repeat testing may increase sensitivity-false negative testing can occur when testing is performed less than 12 weeks after LA confirmatory testing. Understanding the clinical presentation is critical as the approach to anticoagulation is different in these populations. In addition, understanding the differentials is critical as different treatments are employed in both disease states. The degree and phenotype of LA have not been shown to predict clinical outcomes, notably in terms of causation of thrombosis. Children can present differently from adults, and with emerging data, LA may be a factor involved. The typical LAs population may therefore present with thrombotic issues less typical than in the adult population. For a comprehensive overview, this section will be broken down into common presentations of children with LAs divided into thrombotic issues and bleeding complications (Zhang et al., 2020).

Thrombotic events

Venous thromboembolism is the most common thrombotic event seen in patients with LAs, with a notable increase in incidence in the first 3 to 12 weeks after diagnosis. Thrombosis of the deep vein thrombosis in the upper and lower extremities, as well as proximal lymph nodes, often shows recurrent symptoms in school-age children. Greater mortality and morbidity have

been reported in both cases. Arterial thrombosis, particularly cerebral ischemic attacks, has been recognized to cause significant mortality and morbidity among systemic inflammatory autoimmune disorders, and one third of these disorders are due to APS (Visaggi et al., 2021). Early and frequently diagnosed, arterial stroke has a bimodal recurrence pattern. Headache is typically most severe shortly after the diagnosis. However, an increasing prevalence has also been recorded months following the diagnosis of antiphospholipid antibodies. Incidences of thrombosis have been reported in the gastrointestinal and mesenteric veins, abdominal aorta, and sagittal brain vein. Clinical signs usually occur after diagnosis, but they are not always recorded. Early diagnosis and prevention, even before the induction of clinical symptoms, may benefit patients because of the potential morbidity involved. To avoid diagnostic delays and their discriminatory consequences, clinicians should not rely solely on laboratory findings for identifying thrombosis. A thrombosis range of 10% to 34% in children with elevated titers of LAs, aPL, and multiple aPL antibodies is defined in several small and large studies (Crescenzi-Lanna, 2020).

Bleeding complications

LAs represent paradoxical thrombosis predisposing pathophysiologic background. LAs can also result in spontaneous bleeding episodes. Hemorrhagic episodes of LAs may manifest in multiple ways. The frequency of major bleeding in patients with APS and coexistent LAs are estimated to be between 5.7% and 21% depending on the study. More frequently, the hemorrhagic symptoms are characterized by minor spontaneous mucocutaneous bleeding or hemorrhages from minor trauma (Long and Fink, 2021). The main driver for the risk of bleeding in LAs patients is the presence of a concomitant aPL. The underlying mechanisms of aPL-induced hypocoagulable status are uncertain but might include the direct interference of aPL with coagulation factors, the assembly of aPS/PT-biomembrane complexes in disease flare, and aPL-mediated platelet desensitization to mediators of platelet activation. Unfortunately, in clinical practice, it is still challenging to predict the risk of bleeding in detail in this complex situation. This uncertainty contributes to the already substantial challenges in the management of these patients. Bleeding complications in children represent a considerable impact on the patient's quality of life and may cause iron deficiency or anemia due to chronic bleeding and sometimes require transfusions or reduced anticoagulant management therapy. Nonetheless, detailed studies of bleeding manifestation in children are lacking. Data in pediatrics are limited. At the present time, a comprehensive analysis of reported children's cases with bleeding manifestations in association with LAs does not exist (Crescenzi-Lanna, 2020).

5. Diagnostic approaches

A comprehensive approach, comprising both clinical evaluation and laboratory tests, is essential to the diagnosis of lupus anticoagulant in pediatric patients. Because the clinical presentation of LA varies, the presence of unexplained or unusual thrombotic events or bleeding in conjunction with a suggestive family history should alert medical providers to consider LAs and tests for coagulation disorder. In pediatric settings, a review of the family and developmental history is strongly recommended in addition to a comprehensive list of potential comorbid conditions and a thorough physical exam to detect signs and symptoms of possible LAs-related vasculopathy (Tripodi, et al., 2020). This approach is summarized in a detailed medical visit flow sheet utilized in the evaluation and management of thrombosis. Laboratory tests to evaluate LAs should include activated partial thromboplastin time and measurement of endogenous heparin in an aPTT (Reisinger et al., 2021). These assays are particularly relevant to the study of a potential pediatric-specific diagnostic algorithm because of the high prevalence of a long aPTT in this population. All identified diagnostic difficulties remain and may be particularly challenging in patient groups with a shorter pre-illness state, a higher prevalence of infections, or in locations where infection-induced coagulopathy is extremely common. A range of tests and test algorithms with various sensitivities and specificities can be used to detect LAs in pediatric cases. The relative importance of each test depends on the specific diagnostic goals and is associated with a number

of options and potential hurdles. Familiarity with the utility of such tests in patients with SLE or with other potential confounding diseases is vital for pediatric patients and is currently undergoing evaluation in clinical trials (Visaggi et al., 2021).

Laboratory testing

Dilute Russell's viper venom time (dRVVT) and aPTT are widely used to screen for LAs. Confirmation and interpretation of these tests should be performed by skilled personnel working in specialized laboratories. For accurate and reliable results, pre-analytical procedures should ascertain indices of hemolysis, icterus, and lipemia and should prevent contamination of blood with suboptimal anticoagulant ratio. Post-analytical procedures should check for analytical interfering substances such as antiphospholipid antibody inhibitors or spurious LAs results due to hematocrit and clotting time inappropriately monitored by automated instruments (Sorrells et al.2021). There is no consensus regarding the recommended testing algorithm for pediatric patients who exhibit preliminary positivity for LA; most studies have merely relied on the presence of a LAs using one assay while others have utilized a panel. Nonetheless, it has been reported that approximately 25% of tested adult individuals who were identified as second stage LAs after confirmation of screening results were actually prospective LAs (Moore, et al., 2022). It has been suggested that the commercially available specific anticoagulant assays may not be indicative of the presence of LAs; the PT detects coagulation factor inhibitors, while the snake venom assays detect nonspecific antibodies directed against the reagent, calibrator, or component of the reagent. Therefore, follow-up testing after a positive screening test is required to observe temporal guidelines (Sorrells et al., 2021).

Screening tests

Finding LAs begins with screening tests. They are a first sign of LAs activities since they monitor the time it takes for blood to clot. Common diagnostic procedures consist of the following:

Activated partial thromboplastin time (aPTT) This is a typical coagulation test that lupus anticoagulant patients may need to extend. Calculates the clotting time of blood by analyzing the intrinsic and common coagulation pathways. The blood sample is prepared for clotting by adding reagents. A prolonged aPTT (showing a slower clotting time) is seen in people using lupus anticoagulant. The presence of heparin or deficiencies in clotting factors are two of the many factors that can affect the length of time it takes for the anticoagulant effects of lupus to wear off, but this is not unique to LAs (Devreese, et al, 2020).

Dilute Russell viper venom time

Direct reversal of venous thrombosis (dRVVT) assesses the shared clotting cascade pathway, making it a more sensitive and specific LAs test than aPTT. By passing the intrinsic mechanism, the venom of the Russell viper snake is utilized to directly activate Factor X. Therefore, dRVVT is better able to detect LA with high specificity and with reduced interference from intrinsic pathway defects. To further prove that the prolonged clotting time is caused by LA and no other causes, confirmatory testing with phospholipids is typically performed after this test if the clotting time is prolonged while using LAs (Hoxha, et al,2017).

Kaolin clotting time (KCT)

Another clotting test that is susceptible to interference by phospholipids is the KCT, which is less frequently used but still a strong indicator of lupus anticoagulant. In order to activate the intrinsic coagulation pathway, kaolin is given to the blood sample and the time it takes for the blood to clot is measured. The clotting time can be prolonged in tests involving lupus anticoagulant, much like in other cases. As an extra screening technique, KCT can be useful, albeit it is not as commonly available in labs and is typically less specific than dRVVT (Aryurachai, et al., 2014).

Confirmatory tests

In order to validate the results of screening tests that indicate the presence of lupus anticoagulant, more testing is conducted. To check if clotting times normalize, phospholipids are added to the blood sample. Phospholipids, when added, can counteract the effects of LAs (Pengo, et al., 2009).

Phospholipid neutralization test

It is supported that lupus anticoagulant is present if the addition of phospholipids rectifies the extended clotting time observed in first test.

Platelet Neutralization Procedure (PNP)

Using platelets to counteract LA's impact on clotting time is the same as the phospholipid neutralization test (Aryurachai, et al., 2014).

Mixing studies

LAs can be distinguished from clotting factor deficits, another cause of delayed clotting times, via mixing tests. The patient's plasma is mixed with normal plasma in a mixing trial. Instead of a clotting factor shortage, an inhibitor such as lupus anticoagulant would explain why the clotting time stays protracted in the mixture. Instead of lupus anticoagulant, a clotting factor shortage is typically the cause when the clotting time corrects. When the clotting test takes longer after adding pooled normal plasma (PNP), it means that an inhibitor is present. Patients who may be deficient in one or more coagulation factors can have them supplemented with PNP in their plasma. A factor deficiency may have been indicated by the clotting test's correction. Although the presence of LA is suggested by a prolonged clotting test, this could be because of other factors, such as a Factor inhibitor (anti-factor Ab) (Devreese, et al., 2015).

Repeat testing

Due to the potential for transient LAs (which can appear temporarily during infections or after certain medications), testing is typically repeated after 12 weeks (Exner et al., 2020). Persistent positivity over two tests is generally required for a diagnosis of APS when clinical criteria are also met (such as a history of thrombosis or pregnancy complications) (Cohen et al., 2019).

Result expression and cut-off values

The ratio between the PNP is used to measure how much the patient’s plasma differs from normal. A higher ratio may indicate an abnormality in the patient’s plasma. Additionally, mixing studies can be expressed as an Index of Circulating Anti-coagulants (ICA), also known as Rosner’s Index, which helps detect the presence of circulating inhibitors (such as LAs) that interfere with normal coagulation. To assess if a test result is abnormal, local cut-off values are determined by analyzing at least 120 normal samples (Tripodi et al., 2021). The 99th percentile of the resulting distribution is set as the cut-off point, meaning only values above this threshold are considered potentially abnormal. Outliers, or unusually high or low values, are removed to ensure accuracy and reliability of the cut-off. Instead of developing local cut-off values, laboratories may use cut-off values provided by the test manufacturer. However, it is essential to verify that these values are suitable for local conditions, as variations in sample populations and testing methods can influence accuracy (Tripodi et al., 2017).

Criteria for diagnosis

Diagnosing LA in pediatric populations is intricate since it requires the integration of clinical findings and the results of laboratory tests along with proper exclusion and differentiation of other disorders. Three primary medical society guidelines define the diagnostic criteria of APS, including specific criteria that focus on the recognized antibody, clinical criteria, and the required tests to diagnose APS (Reisinger et al., 2021). Both sets share the main clinical criteria but are mainly discussed in adult populations. Conversely, while one set of criteria has been revised, it solely focuses on the diagnosis of APS from pediatric populations. Since neither set provides a specified age for pediatric populations, they were utilized as criteria to diagnose LA in pediatric populations in some studies (Aubert et al., 2021).

The recognition of the variable clinical presentation compared to adults is substantial. In addition, a number of affirming laboratory tests are employed in both adults and pediatric populations. The difficulties with the diagnosis of LA arise due to the overlapping signs, symptoms, and laboratory findings of other conditions. These disorders, which mimic APS, include hematological, endocrine, cardio-vascular, infectious, malignant, and liver and kidney disorders. Hence, several researchers suggest that each patient requires a distinct approach. Therefore, a panel emphasized using clear and specific criteria for LA to avoid unnecessary misdiagnosis or underdiagnosis. As

such, clinical judgment is essential for the proper diagnosis and management of screening results, and pediatric patients must be correctly recognized by their medical condition. Development continues worldwide in targeting LA guidelines for use in adult and pediatric populations. In addition, the studies advocate for the development of pediatric LA guidelines for large-scale use for effective diagnosis (Visaggi et al., 2021).

Differential diagnosis

LA is often an unexpected finding in suspected patients. Confusion may emanate from the fact that some other conditions can produce symptoms mimicking LA, anticoagulant, and drug-induced coagulopathy. Alternative diagnoses are thrombotic disorders including arterial thrombosis, venous thrombosis, thrombosis in unusual localizations, recurrent fetal loss, intrauterine growth delay, vascular skin necrosis, and cerebrovascular accident, although it does not exhibit LA positivity in such cases. Other coagulation disorders, such as APS, SLE, other genetic or acquired coagulopathies, and any hemostatic disturbance, can cause thrombotic symptoms similar to LA positivity. APS is often linked to LA; however, LA could be present without APS. Since the LA test is complex and has several standardization problems, its false positive or negative results can be misleading, and thus result in missed or delayed diagnosis (Crescenzi-Lanna, 2020). Connecting the symptoms and determining their etiopathogenesis based merely on test results may also lead to therapeutic mistakes. Existing autoantibodies, as well as enhanced susceptibility for their occurrence related to overt or treated infections, could also favor LA positivity. Clinical history and examination are essential for obtaining a correct diagnosis; however, these may sometimes be time-consuming, and decisions have to be made quickly in urgent cases. Moreover, overlapping symptoms with chronic diseases, characteristic features of primary APS, SLE, other autoimmune diseases, inherited thrombophilias, viral, and protist systemic infections are frequent and may mislead clinicians. Autoimmune diseases such as SLE and APS are also known to coexist with other autoimmune disorders or to develop second-line autoimmune disorders such as autoimmune hemolytic anemia and autoimmune hemolytic thrombocytopenia purpura, which favor LA. It is not uncommon to encounter the absence of some or even one of the criteria of diagnostic tests when complicated with a secondary disease (Long and Fink, 2021).

Management strategies

The challenges in the management of patients with LA are minimizing the thrombus risk without causing undue bleeding and carefully monitoring for both. Management of pediatric patients with LAs require that interventional plans be tailored to the unique risks and symptoms of each patient. Additionally, these patients should be seen by specialists to help develop a more comprehensive care plan. If patients experience clotting events, then the professional's schedule may include specialists who specialize in treating children with clots or a pediatric specialist. General approaches to treatment for patients who have been diagnosed with LAs are to reduce the risk of clots and bleeding. The focus of treatment will rely upon the symptoms, age, and overall health of your child (Badal et al., 2021). Treatment options include pharmacological interventions to prevent blood clot formation or non-pharmacological interventions. Your healthcare professional will likely recommend the best treatment for your child, based on their signs and symptoms, age, and overall health. LAs are treated with anticoagulant medications to prevent blood clots from forming. These anticoagulants may be given by mouth or by injection. Regular monitoring is recommended to make sure the anticoagulant is working properly. Note that these drugs should never be used in a patient who is actively bleeding, who has a very low platelet count, or who has an existing blood clot without consulting a specialist. Anticoagulants are relatively safe medications; however, they increase the likelihood of bleeding because they interfere with the body’s process of making clots. To minimize bleeding risk, an individual anticoagulant dose is determined based upon the patient’s age, medical history, and other patient-specific factors (Visaggi et al., 2021).

Pharmacological interventions

Anticoagulant therapies

The most commonly used anticoagulant therapy is the vitamin K antagonist warfarin, which is effective in the secondary and lifelong prevention of venous and arterial thrombi. Warfarin is typically used in patients with LA-related spontaneous venous thromboses, APS-related venous thrombosis extending into the rare instances of arterial events, or patients with a single minimal or moderate risk APS event in whom indefinite anticoagulation is advised. Warfarin works by blocking the activity of vitamin K epoxide reductase, thereby inducing a deficiency in vitamin K-dependent coagulation factors including factors II, VII, IX, and X, as well as a natural anticoagulant protein C. Clinical practice guidelines suggest a target international normalized ratio (INR) of 2.0-3.0, with this range revealing satisfactory prevention of recurrent thromboembolic events and a reduction of associated risks. Due to warfarin's large pharmacokinetic and pharmacodynamic variability and narrow therapeutic index, a susceptible dosing approach utilizing a treatment guideline based on INR is applied. Tables of weekly doses for an INR range are used, with clotted specimens on recommended dosing days used to calculate accurate weekly averages and doses. (Aubert et al., 2021)

DOACs, also known as NOACs, are direct oral anticoagulants that can be used in the prevention of thromboembolic disease in patients with APS. These drugs work by directly inhibiting the essential blood clotting proteins, factor Xa or thrombin. Efficacy is dosing-induced and is mediated by rapid adsorption and significant accumulation in vascular tissue. Unlike VKAs, DOACs do not require routine monitoring, have limited known drug-drug or drug-disease interactions, and have a short half-life and reversible anticoagulant effect. However, creatinine clearance is relied upon for renal clearance, impeding the use of DOACs depending on a patient's age and renal function (Sorrells et al., 2021). Adverse effects of these drugs exist, and the cost of a DOAC can be a limitation. Dosing in special populations is also important. For example, in patients 2 to 17 years of age with venous thrombosis treated with rivaroxaban for thrombosis, safety and pharmacokinetic studies suggest rivaroxaban should be given using Body Weight Dose Conversion to attain an adult level of total drug exposure. The range is 20 mg/day–30 mg/day if body weight is lower than 50 kg and 30 mg/day–40 mg/day if body weight is 50 kg or higher. Although evidence of a large number of pediatric patients taking DOACs is still in development, studies investigating variations in efficacy, bleeding rates, and anticoagulant effects are underway. In addition, the optimal duration of DOACs in the treatment of LA-related venous thromboses is an area of active investigation in trials (Visaggi et al., 2021).

Non-pharmacological interventions

Two modalities of non-pharmacological interventions (NPI) available for managing patients with lower extremity venous thrombosis (LEVT) in the pediatric population have been classified: first, interventions aiming at the control of lifestyle and management of concomitant health problems; and second, interventions aiming to change patients' beliefs and practices towards self-care and pharmacological interventions. Most studies on LEVT management in children emphasize the need for patient education and comprehensive family support. Dietary advice in prophylactic treatment has been recommended in view of increased venous thrombosis in overweight patients, reduction of alcohol intake and smoking, influenza vaccination, and prompt treatment of respiratory tract infections. In view of the association of APS with other autoimmune diseases such as SLE, it has been proposed to reduce excessive exposure to the sun and infections (Crescenzi-Lanna, 2020). Therapists should direct changes in eating habits, starting from a balanced diet and plasma lipid profile, encourage regular exercise, weight loss in obese individuals, and medications if necessary. Repeated education of pediatric SLE patients about the underlying diseases, risk factors, and treatment, along with reassurance for those with mild counseling, may be beneficial (Lopez-Leon et al., 2022). This NPI may be beneficial in pediatric SLE patients' adherence to treatment in daily life since education about LEVT and other APS-related issues may affect patients' disease

outcomes favorably. Educational intervention may contribute to LEVT prevention rather than psychiatric patients, such as preventing mental implications on patient selection, and LEVT prevention may contribute to the low level of LEVT incidence apart from patient interference in adaptation to warfarin therapy.

Conclusion

In the current review, LA is a critical yet underexplored condition in pediatric medicine, posing unique diagnostic and therapeutic challenges. As a heterogeneous group of immunoglobulins targeting phospholipid-binding proteins, LA can disrupt coagulation pathways, leading to significant thrombotic or hemorrhagic complications. Its association with autoimmune diseases like systemic lupus erythematosus and APS underscores the importance of early detection and appropriate management. While diagnostic tools such as aPTT and dRVVT are indispensable, their limitations, including variability in sensitivity, specificity, and transient LA positivity, highlight the need for more robust and pediatric-specific diagnostic guidelines. Moreover, the absence of established treatment protocols tailored to children further complicates management.

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