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Review

Role of Autoantibodies in the Diagnosis of Juvenile-Onset Systemic Lupus Erythematosus (jSLE): An Updated Review

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ABSTRACT

Childhood-onset systemic lupus erythematosus (cSLE) is a multisystem autoimmune disease that begins before the age of 18 and is typically more severe than the adult-onset form. Autoantibodies play a central diagnostic role, supporting not only disease confirmation but also risk stratification and activity monitoring. Clinically relevant autoantibodies include antinuclear antibodies (ANA), double-stranded DNA antibodies (anti-dsDNA), anti-Sm, anti-SSA/Ro, anti-SSB/La and antiphospholipid antibodies (aPL). ANA show high sensitivity (> 95 %) but low specificity, making them a useful initial screening test. Anti-dsDNA antibodies have prognostic value in lupus nephritis, correlating with renal activity and fluctuating with disease course. Anti-Sm antibodies are highly specific (> 95 %) yet present in fewer than 30 % of patients, serving as confirmatory markers. Anti-SSA/Ro and anti-SSB/La antibodies are linked to cutaneous manifestations and Sjögren syndrome, whereas aPL predispose patients even in pediatric populations to thrombotic events and obstetric complications. Diagnosis relies on clinical and laboratory criteria (e.g., EULAR/ACR), which incorporate autoantibody results into the diagnostic score. Advances in detection methods, such as high-affinity ELISA and cell-substrate immunofluorescence, have improved accuracy and reduced false positives. Autoantibody profiles can also guide targeted biologic therapy, such as belimumab in patients with high anti-dsDNA titres. Challenges remain in laboratory standardization and interpretation of results in preclinical disease phases. An in-depth understanding of autoantibodies in cSLE is therefore essential for early diagnosis organ-damage prevention and personalized treatment strategies.

Keywords: Childhood-onset systemic lupus erythematosus; Autoantibodies; Anti-dsDNA; Antiphospholipid antibodies; Laboratory diagnosis

Introduction

Childhood-onset systemic lupus erythematosus (cSLE) is a systemic autoimmune disease that manifests before 18 years of age and follows a more aggressive clinical course with more severe organ involvement than adult-onset lupus[1]. Estimated annual incidence ranges from 0.3 to 0.9 cases per 100 000 child-years, with a female-to-male ratio of approximately 4: 1, particularly after puberty. Initial manifestations are often non-specific such as fatigue, fever of unknown origin and arthralgia which can delay clinical recognition and treatment initiation. In this setting, autoantibodies are crucial not only for confirming diagnosis but also for stratifying risk and monitoring disease activity. The 2019 EULAR/ACR criteria assign specific points to each autoantibody, awarding up to 10 points for anti-dsDNA or anti-Sm positivity, underscoring their central role in early cSLE identification[2].

Antinuclear antibodies (ANA) are used as an initial screening test, with sensitivity above 95 % in cSLE, but they have low specificity, as they can appear in other autoimmune diseases and in up to 20–30 % of healthy children especially during viral infections or after exposure to immunomodulatory drugs. Positive ANA results therefore require more specific follow-up tests to avoid false positives[3-5].

Double-stranded DNA antibodies (anti-dsDNA) have specificity greater than 90 % for SLE and are strongly associated with lupus nephritis activity. Rising anti-dsDNA titres often precede renal flares, serving as predictive biomarkers that guide adjustments to immunosuppressive regimens. Anti-Smith antibodies (anti-Sm) Although detected in only 10–30 % of cases, anti-Sm antibodies are > 95 % specific and are considered confirmatory markers when ANA are positive and anti-dsDNA negative[2]. Combined anti-Sm and anti-dsDNA positivity raises diagnostic probability to nearly 100 %, occasionally obviating the need for renal biopsy.

Anti-SSA/Ro and anti-SSB/La antibodies These antibodies are associated with cutaneous manifestations and neonatal heart block in offspring of positive mothers. Although less central to initial paediatric diagnosis, they help phenotype characterisation and obstetric risk stratification in adolescents. Antiphospholipid antibodies (aPL)[6]. Present in up to 30 % of patients, aPL correlate with thrombotic events (stroke, deep-vein thrombosis) and obstetric complications. Persistent aPL in prepubertal children prompt debate on prophylactic low-molecular-weight heparin, particularly during surgery or puberty when thrombosis risk increases.

Technological advances such as chemiluminescence assays and multiplex bead arrays have enhanced both sensitivity and specificity, reducing false positives and enabling simultaneous detection of multiple autoantibodies[7]. Nonetheless, lack of reagent and protocol standardization across laboratories remains a barrier to widespread adoption. Integrating serological, clinical and genomic data is paving the way for precision medicine approaches. HLA polymorphisms and variants in the BLyS pathway appear to influence both autoantibody production and response to biologic therapies such as rituximab and belimumab[8]. Adult studies show significant autoantibody reductions after such therapies, but controlled pediatric data are limited, restricting routine recommendations.

Objectives

This review critically examines the role of autoantibodies in the diagnosis of cSLE, focusing on detection methods, correlations with clinical phenotype, therapeutic implications and future translational research prospects.

Materials and Methods

A literature review was conducted using the PubMed, SciELO, Google Scholar and ScienceDirect databases.

Discussion

Serology in cSLE poses analytical and clinical challenges that directly affect comprehensive patient management. A major obstacle is the high sensitivity but low specificity of ANA testing[9,10]. Studies indicate that up to 30 % of children with viral infections may show positive indirect immunofluorescence results, leading to unnecessary investigations and family anxiety. Current protocols recommend that positive ANA results be followed by specific anti-dsDNA and anti-Sm assays to confirm diagnosis and rule out other autoimmune diseases[2].

Monitoring anti-dsDNA titres is widely accepted as a marker of lupus nephritis activity. In a longitudinal cohort, Petri et al, showed that persistent anti-dsDNA elevations during remission quadrupled renal-flare risk, allowing clinicians to intensify treatment before irreversible damage occurs[11]. However, ELISA-to-ELISA variability can compromise comparability; chemiluminescence assays, with inter-laboratory coefficients of variation below 5 %, are therefore recommended. In contrast, anti-Sm antibodies, though less common, offer high diagnostic specificity and eliminate the need for further confirmation when positive. Concurrent anti-Sm and anti-dsDNA positivity virtually confirms cSLE, reducing reliance on invasive diagnostics.

Anti-SSA/Ro and anti-SSB/La antibodies, while secondary for diagnosis, are essential for identifying cutaneous phenotypes and obstetric risk. Fanouriakis, et al, advocate routine anti-SSA/Ro testing in adolescents with subacute skin lesions and photosensitivity because these antibodies may also indicate cardiac or neurological involvement[12], informing interdisciplinary care. The presence of aPL necessitates vigilant surveillance and, in some cases, thrombosis prophylaxis. Giannakopoulos & Krilis found that persistent IgG anti-β2-glycoprotein I titres above 40 GPL increased thrombotic risk six-fold, even in regions where pediatric stroke is rare. Decisions about prophylactic anticoagulation must balance bleeding risk against thrombotic recurrence, recommending regular platelet and hemostasis monitoring.

Emerging multiplex platforms can transform serology by detecting both classic and novel antibodies (anti-C1q, anti-NR2, anti-RNP) with > 98 % sensitivity and > 95 % specificity. These platforms shorten diagnosis time and reduce blood-sample volume key advantages for pediatric care yet high costs and the need for multi-ethnic validation limit widespread use. The International Consensus on ANA Patterns (ICAP) is addressing inter-laboratory variability by standardizing fluorescence interpretation[13].

Precision-medicine prospects rely on correlating serological profiles with genotyping. Wang et al. (2018) showed that specific HLA-DRB1 haplotypes and B-cell regulatory gene variants (e.g., BANK1) are linked to higher anti-dsDNA titers and faster

belimumab response. Adult trials report ~60 % anti-dsDNA reductions after six months of biologic therapy, but pediatric evidence remains scarce[14]. Multicenter randomized studies are needed to establish safe, effective protocols for children. Another under-explored area is identifying biomarkers that predict transition from preclinical to active disease. In adults, anti-C1q antibodies precede nephropathy by up to 12 months, but robust pediatric data are lacking. Prospective pediatric studies could define therapeutic windows for early interventions, potentially altering disease trajectory[15].

Conclusion

Childhood-onset systemic lupus erythematosus (cSLE) poses diagnostic and therapeutic challenges that demand an integrated analysis of clinical, serological and genomic findings to achieve truly personalized care. Autoantibodies fulfil complementary roles along this continuum. Screening begins with highly sensitive ANA testing, which though > 95 % sensitive must be confirmed with more specific markers to avoid false positives.

Diagnostic confirmation and prognostic assessment rely chiefly on anti-dsDNA and anti-Sm antibodies, which offer high specificity (> 90 % and > 95 %, respectively) and correlate strongly with lupus nephritis activity, enabling early therapeutic adjustments to prevent irreversible renal damage[2]. Anti-SSA/Ro and anti-SSB/La antibodies provide valuable information on cutaneous phenotypes and cardiac risk, guiding multidisciplinary management and obstetric monitoring for future pregnancies. The detection of antiphospholipid antibodies observed in up to 30 % of pediatric patients signals heightened thrombotic potential and justifies continuous surveillance and, when risk rises (e.g., surgery or puberty), consideration of anticoagulant prophylaxis, carefully balancing haemorrhagic risk.

Advances in detection technology particularly chemiluminescence assays and multiplex bead arrays have improved diagnostic accuracy by reducing inter-laboratory variability and enabling simultaneous detection of multiple markers with > 95 % sensitivity and specificity. Widespread adoption, however, is limited by cost and global standardization gaps needs addressed by initiatives such as ICAP and the 2019 EULAR/ACR guidelines[2]. Precision-medicine research, linking serological and genotypic profiles to targeted biologic therapy (e.g., rituximab, belimumab), shows promise: adult trials report up to 60 % reductions in anti-dsDNA titres after six months. Yet pediatric data remain preliminary, underscoring the urgent need for multicenter randomized trials to validate efficacy and safety in children and adolescents.

Finally, emerging autoantibodies such as anti-C1q, anti-NR2 and anti-RNP may serve as predictive markers in the preclinical phase of cSLE, redefining therapeutic windows and potentially altering the disease's natural history. Including ethnically diverse cohorts and standardizing methodologies in prospective studies are crucial to reducing diagnostic and treatment disparities, ensuring that all pediatric cSLE patients receive high-quality care that minimises morbidity and markedly improves long-term quality of life.

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