Laboratory Testing for Diagnosis and Monitoring of Systemic Lupus Erythematosus

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Abstract

Aims: The purpose of this study was to assess laboratory test procedures recommended for diagnosis and monitoring of systemic lupus erythematosus (SLE). With a complex and hard-to-predict course, best laboratory practices need to be identified for lupus diagnosis and treatment.

Materials and methods: This study represents a qualitative meta-synthesis of 20 credible resources from peer-reviewed publications, particularly studies from journal articles evaluating laboratory tests for diagnosis and monitoring of lupus. The studies were reviewed and their results were analyzed and summarized based on major key findings. The reviewed studies were published between 2002 and 2018, with the majority being very recent.

Results and conclusions: The study concluded that laboratory testing for the diagnosis and monitoring of SLE should be conducted in consecutive stages to avoid subjecting the patients to unnecessary and costly tests. Since SLE is a multisystem disease that attacks many organs and body systems, monitoring should not be proceeded through one-stage testing. Additionally, SLE-specific autoantibodies lack adequate sensitivity. Moreover, unique biomarkers are currently not available, not just for diagnosing lupus but also for monitoring it; thus, defining and implementing standard approaches are imperative. Finally, mean platelet volumes of patients should be regularly checked because low mean platelet volume values indicates high SLE disease activity.

Keywords: Systemic lupus erythematosus; SLE; lupus; diagnosing; monitoring; laboratory test; guidelines.

Introduction

This study was conducted to address concerns regarding the lacking consensus about the most appropriate laboratory tests for the diagnosis and monitoring of lupus. Fernando and Isenberg[1] have described how, 100 years ago, syphilis was regarded as "the great masquerader" because of the high variability of its symptoms.

In that regard, lupus might be called the modern equivalent of syphilis.[1] Lupus is a chronic, multifaceted, inflammatory, autoimmune disease that predominantly affects young women. Diagnosis and monitoring of lupus are somewhat problematic because of its hard-to-predict pattern of relapse and remission, making the disease difficult to measure.[2] Al-Katheri et al.[3] have

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classified systemic lupus erythematosus (henceforth called SLE) as a "prototypic multisystem autoimmune disorder with a wide range of clinical presentations impacting almost all organs and tissues".

SLE is a chronic, recurrent disease that is usually identified through a combination of clinical and laboratory criteria.[3] The clinical criteria include effects on tissue and organ functions, whereas laboratory criteria are based on various lab tests that identify molecular and cellular markers of SLE.[3] Accurate and timely diagnosis of SLE has the potential to reduce mortality and morbidity in SLE patients.

The clinical criteria for the diagnosis of SLE are summarized by the "SOAP BRAIN MD" mnemonic to include arthritis, oral ulcers, blood disorders, serositis, photosensitivity, antinuclear bodies, renal involvement, malar rash, immunological phenomena, discoid rash, and neurologic disorders.[4] According to Liu et al.,[5] reliable SLE biomarkers for the diagnosis, monitoring, and prediction of response to therapy are lacking. A biomarker has been defined as "a measurement including, but not limited to, a genetic, biological, biochemical, molecular, or imaging event alteration that correlates with the pathogenesis and/or manifestations of a disease and can be evaluated qualitatively or quantitatively in laboratories".[5] Due to the recognition of the critical nature of the aberrant T-cell function in SLE, an array of gene expression comprising 30 genes, which are believed to contribute to SLE pathogenesis, has been identified. Gene expression is reportedly initiated by the access of transcription factors to specific DNA regions. Furthermore, when methylation levels of DNA decrease, gene expression may become aberrant. The cells will be identified as containing epigenetic alterations and representing possible epigenetic biomarkers;

CD4 T cells.[5]

A study conducted on 10 SLE patients, 6 rheumatoid arthritis patients, and 19 healthy individuals has shown that gene expression array robustly indicates disease-specific alterations of various gene expression levels.[5] Most importantly, a principal component analysis, which is an array of gene expression that includes 30 genes believed to be contributors to SLE pathogenesis, was used to evaluate the contribution of the gene array to the diagnosis of SLE. A clear distinction emerged between micro-RNA samples from individuals who had RNA cellular fragments that deter protein binding and ultimately block the ability to synthesize the protein and those who were healthy.[5] Notably, individual and principal components clearly matched with specific parameters of the disease, such as proteinuria and arthritis.[5]

Clinical immunology laboratories that play a critical role in the diagnosis and monitoring of SLE measure antinuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA), anti-histone antibody, anti-extractable clear antigens antibody (ENA), anti-ribosomal P protein, and anti-phospholipid antibody (aPLs) levels.[6] Specific roles of clinical immunology laboratory testing related to SLE include (1) confirmation or exclusion of the diagnosis, (2) monitoring of the fluctuating severity of the disease, and (3) identification of patient subgroups.[6] Because of their critical role in the monitoring of SLE, the immunologic assays that are used should have a high sensitivity and specificity, as well as a strong predictive clinical validity.[6]

One manifestation of SLE that is considered to be critical is kidney disease.[7] Laboratory markers that are currently used for lupus nephritis include proteinuria, urine creatinine-protein ratio, creatinine clearance, inadequate

levels of complements, and anti-dsDNA. However, these markers lack sensitivity similar to those laboratory markers that are used for the diagnosis and monitoring of SLE. Ideal biomarkers for lupus nephritis should correlate well with renal activity in relation to the urine sediments and proteinuria, and should be sensitive to change; thus, they should be suitable for serial monitoring of pathophysiological activity in the kidneys and for the use as an index of treatment response and clinical remission.[7] Moreover, laboratory testing for lupus nephritis should be simple and of low-cost. In a condition defined as "stand-alone" lupus nephritis, patients have typical renal biopsy features of lupus nephritis and exhibit positive results for ANA or anti-dsDNA antibody test, whereas other features of SLE are absent.[8] Thus, besides the difficulty in the monitoring of SLE, monitoring of similar conditions is equally problematic because there is no single test that can accurately help the diagnosis or monitoring of SLE. One of the tests used for monitoring SLE is erythrocyte sedimentation rate (ESR), a measure for quantifying red blood cells that precipitate in a tube after a defined time, which increases during inflammation. However, various factors may affect an SLE patient's ESR, including gender, age, blood hemoglobin concentration, and serum immunoglobulin levels.[9] ESR is not used for diagnosis but is useful for monitoring the disease activity and response to treatment.[9] ESR indicates the presence of infection or inflammation. Both C-reactive protein (C-RP) and C-reactive high-sensitivity assays measure an immune protein that is innate, and that assists in the opsonization of pathogens for phagocytosis and activates the complement system.[9] Because C-RP concentration fluctuates much more rapidly than ESR, C-RP is more likely to reflect a patient's current level of

inflammation more accurately.[9] However, C-RP measurement via enzyme-linked immunosorbent assays (ELISAs), which are commonly used to detect antibodies, lacks specificity.[9] Classically, ANAs hallmark the serologic diagnosis of SLE, but ANA is commonly detected in most autoimmune diseases. Methods used for detection utilize the immunofluorescence testing of the patient's serum, at various dilutions, using a cell substrate.[9] An additional, useful approach to monitor SLE is anti-dsDNA testing, in which antibodies that are highly specific markers for SLE are used. In the past, measurement of anti-dsDNA level was done via radioimmunoassay, particularly the Farr assay. However, currently, immunofluorescence assay (IFA) or ELISA tests are more commonly employed.[9] Immunofluorescence assays represent a two-tier assessment that has shown high levels of diagnostic specificity and sensitivity for SLE. However, these immunofluorescence assays are not specified for use in monitoring SLE. Although the complement C3 and C4 protein levels are generally measured in SLE patients, the serum levels are not sufficiently reflective of complement activation.[10]

Over the past 10 years, it has become clear that specific autoantibodies may be detected during preclinical stages of SLE.[11] Thus, there is an increased interest in specific monitoring of individuals who are in SLE remission.[11] Bead-based arrays are reported as a planar, two-dimensional array, which uses beads to carry the targets in chemiluminescence immunoassays (CLIAs), and addressable laser bead immunoassays (ALBIAs), subsequently resulting in an 86-specificity assay for selected autoantigens.[11] The ALBIAs were first used more than a decade ago as a rapid, cost-effective, quantitative, and reliable technology for the detection of autoantibodies directed against

multiple target autoantigens and are available on two primary technological platforms, i.e., BioFlash (CLIA) or CLIAs. The CLIAs are utilized to detect either autoantibodies or autoantigens.[11]

MATERIALS AND METHODS

This study entails the analysis of 20 peer-reviewed journal articles containing a description of lab tests for the diagnosis and monitoring of SLE. This study has been conducted using the qualitative methodology of a meta-synthesis of previously published research studies on lab tests used for the diagnosis and monitoring of SLE. Hoon[12] has described the meta-synthesis as "an exploratory, inductive research design to synthesize primary qualitative case studies for the purpose of making contributions beyond those achieved in the original studies". While some of the studies included in this study were qualitative, others were quantitative in nature. Recently conducted meta-syntheses have been described as empirical studies aimed at integrating research findings from qualitative studies. In particular, such integration should capture the primary reason for researchers to conduct their studies, i.e., the search for conclusions about knowledge in specific areas of practice.[13] A qualitative meta-synthesis is expected to produce an integration of findings that is more than the sum of parts, offering "novel interpretations of findings from individual studies".[13]

RESULTS

The monitoring guidelines developed by Tunnicliffe et al.[14] included laboratory tests for measuring serum creatinine, full blood count, urinalysis, complement C3 and C4 proteins, anti-phospholipid antibodies, anti-dsDNA, anti/RO-SSA, anti-C1g, C-RP level, serum albumin, urinary protein-creatinine ratio, and estimated

glomerular filtration rate (eGFR). Al-Katheri et al.[3] proposed that three specific stages of SLE monitoring should be distinguished. The first stage includes routine laboratory tests, e.g., those for blood counts, creatinine and urinalysis. If results for these tests are positive, stage 2 testing is initiated, which involves ANA testing. When ANA test results are positive, stage 3 is initiated, which includes testing for more specific antibodies [anti-SM, dsDNA, Ro/SSA, La/SSB, U1 ribonucleoprotein (RNP)].[3] Approximately 25% of patients with lupus have anti-U1 RNP antibodies. Anti-SM and anti-dsDNA are SLE specific, although there is a lack of sensitivity of anti-SM antibodies. Anti-dsDNA is present in 70% of patients with lupus, and 30% have anti-SM antibodies present. The anti-ribosomal P protein antibodies are highly SLE specific, but they have a low sensitivity for lupus.[3] This means that while positive test results can offer specific information, the lack of sensitivity may lead to poor identification of SLE when this test is used in isolation.[3]

Raissi et al.[15] stated that 89.4% of the patients showed no changes in the anti-ENA screening results. Approximately 3.3% of the patients were reported to change into positive from negative, with 7.3% changing to negative from positive on the follow-up test. Anti-ENA test results were found to infrequently change, particularly after one or more tests with negative results. The extremely high cost of testing coupled with lack of efficacy in the evidence that assists management indicates that routinely repeating testing of anti-ENA is not necessary.[15] Gladman et al.[16] reported that one of every four patients with lupus, over a period of 24 months, was found to have a single and silent variable that only routine lab testing could detect.[16] Kuhn et al.[17] suggested performing screening tests for creatinine level, erythrocyte sedimentation rate,

blood count and differential blood count, urinary status, urinary sediment, and ANAs and Hep-2 cell test with fluorescence pattern.[17] Lab test following a positive screening for ANA should be followed by additional differentiation to include anti-SM, -La/SSB, -Ro/SSA, -U1RNP antibodies, and -dsDNA antibodies; complement C3 and C4 proteins; anti-phospholipid antibodies; lupus anticoagulants; 24-hour urine if urine is protein-positive; glomerular filtration rate; lactate dehydrogenase; liver enzymes; creatine kinase if muscular symptoms are present; and comorbidities screening.[17] Thong and Olsen stated that monitoring of SLE can be performed via lab tests including hematology, urinalysis, biochemistry, ESR or C-RP acute phase reactants, complement C3 protein, and anti-dsDNA titers.[18] Furthermore, Binder, and Spencer[19] reported that antinuclear antibody testing has a specificity of 57% for SLE. Schäfer et al.[20] explained that while ESR is elevated during flare ups, it is also elevated in older patients and in those with infections. Moreover, the lack of specificity with other lab tests has been confirmed in another study by Felz and Wickham,[21] who indicated that ANA lacks specificity and that lab testing should include routine tests combined with immunologic assays and anti-SM, anti-dsDNA, and serum complement level measurements. Patients with stable disease were recommended to undergo lab testing for CBC along with differential CBC, urinalysis, and basic metabolic panel testing every 3 months, whereas patients with uncontrolled SLE should be tested weekly.[21] A latest finding by Khan et al.[22] clarified that low mean platelet volume (MPV) corresponds to high SLE disease activity. Sandhu and Quan[23] added that the activation of complement plays a primary role in SLE pathophysiology. They recommended the monitoring of serum complement C3 and C4 protein levels in an ongoing manner for monitoring SLE disease activity. However, a decrease in these levels did not consistently indicate SLE flare ups. Recommendations are made for the identification of new and novel methods for assessing SLE disease activity. It is specifically stated that the increased levels of serum for "cell-bound complement activation products may more accurately reflect disease activity than conventional serum C3 and C4 monitoring".[23] Cadet stressed the importance of urinalysis for the diagnosis and monitoring of proteinuria as a biomarker where vitamin C supplements can result in false negatives for SLE.[24] Anis[25] recommended that lab tests for monitoring SLE for the development of lupus nephritis should include complement C3 and C4 protein assays and ASOT antiDNAse B, rheumatoid factor, C-RP level, anti-phospholipid antibody, cryoglobulin, anti-PLA2R, serum immunoglobulin, immunofixation electrophoresis, HBsAg, and anti-HCV testing. Tozzoli et al.[26] stressed that ANA titer should not be used for the monitoring of SLE. Egner[27] found that anti-Ro testing is specific for cutaneous involvement because anti-Ro52 in isolation cannot be detected by Ro-60 assays only, and that complement C3 and C4 proteins and antiC1q ELISA testing are limited to clinical use. Similarly, Ospina et al. stated that measuring complement C3 and C4 proteins, anti-dsDNA antibodies, antiC1q antibodies, ESR, and urinary sediment activity are useful for the monitoring of SLE.[28]

Fernando and Isenberg,[1] additionally, observed that dropping levels of complement C3 and C4 proteins are indicative of SLE flare up. Furthermore, they recommended that when conducting a complete blood count, white blood cell differential should be included to assess

anemia, leukopenia, neutropenia, thrombocytopenia, and lymphopenia.[1] Additionally, paired ESR and C-RP and serum creatinine levels may be used to identify SLE flares owing to infection. Liver function testing for patients receiving antirheumatic drugs is also recommended, as well as red- and white-cell urine analysis, urinary protein, and cellular cast to identify clinically silent renal disease.[1] If abnormal results are obtained, these tests should be followed by renal ultrasound. Patients with renal disease should undergo annual assessment of their glomerular filtration rate using EDTA.[1] The unique findings of each study that are specific to lab testing have been highlighted and summarized into two tables. Table1 lists specific lab tests to be used for the diagnosis and monitoring of SLE. Table 2 lists specific lab tests to be used for the monitoring of SLE.

Table 1: Summary of key findings of studies reviewed for lab testing specific for SLE diagnosis and monitoring

Author	Key findings (lab testing for the diagnosis and monitoring of SLE)
Al-Katheri et al.	Established three stages of lab testing from routine to more specific tests[3]
Tunnicliffe et al.	Established guidelines using a panel of lab testing[14]
Keeling et al.	Noted: Considerable variation in practicing SLE management even while using "SOAP BRAIN MD" mnemonic lab testing criteria[4]
Kuhn et al.	Noted: Routine screening tests: if positive, then ANAs present and if positive, further diagnostics differentiation is recommended[17]
Khan et al.	Low MPV corresponds to high SLE disease activity[22]
Ramsey-Goldman et al.	EC4d and EC3d assessed were high in patients with SLE. EC3d and EC4d were significantly correlated with complement C3 and C4 proteins, respectively[10]
Cadet	Urinalysis for diagnosis and monitoring: Proteinuria is a urinary biomarker; Vitamin C supplements can result in false negative results. Second-level tests include ANAs, anti-dsDNA, complement C3 or C4 proteins, C-RP, and ESR tests. ANA has low specificity. Low complement C3 or C4 protein level indicates active SLE. ESR at high level indicates chronic inflammation[24]
Tozzoli et al.	ANA, ANA indirect immunofluorescence (IIF) to diagnose ARD, ANA titer (not for monitoring), ELISA-ANA screening for monitoring anti-dsDNA-SLE-positive individuals[26]
Egner	For cutaneous involvement, anti-Ro testing was recommended[27]
Ospina et al.	Complement C3 and C4 proteins, anti-dsDNA antibodies, anti-C1q antibodies, ESR, and urinary sediment[28]

Table 2: Summary of key findings of studies reviewed with respect to lab testing for the monitoring only of SLE

Author	Key findings (lab testing for the monitoring of SLE)
Fernando and Isenberg	FBC including WBC differential; paired ESR and C-RP; liver function testing; urine protein, cellular cast, red and white-cell analyses; and complement C3 and C4 protein falling. The preferred use of C3d or C4d complementary breakdown products was suggested[1]
Raissi et al.	Anti-ENA test results were found not to change frequently; anti-ENA on a routine basis is not necessary[15]
Gladman et al.	One of every four patients with lupus, over a period of 24 months, was found to have a single and silent variable that only routine lab testing could detect[16]
Thong and Olsen	Monitoring is via established routine lab testing. With positive screening for ANA, further differentiation is recommended[18]
Binder and Spencer	ANA titers are not effective in the monitoring of SLE. ESR, titers of anti-dsDNA with complement levels are recommended[19]
Schäfer et al.	ESR increases during flares and is also high in older and infected patients. C-RP levels cannot be used to discern between infections and flares[20]
Felz and Wickham	ANA test lacks specificity. Monitoring is based on the EULAR guidelines for lab testing including routine and immunologic assays, anti-SM assay, anti-dsDNA assay, and serum complement levels[21]
Sandhu and Quan	Stated that the increased levels of serum for cell-bound complement activation products may more accurately reflect disease activity than conventional serum complement C3 and C4 protein monitoring[23]
Anis	Monitoring SLE for development of lupus nephritis included assessing complement C3 and C4 proteins, ASOT antiDNAse B, RF,C-RP, anti-phospholipid antibodies, cryoglobulins, anti-PLA2R, serum immunoglobulins, immunofixation electrophoresis, and HBsAg, anti-HCV[25]
Olsen et al.	Lab testing includes indirect immunofluorescence (IIF) to detect ANAs as well as other autoantibodies, ELISAs, line immunoassays, ALBIAs, and planar array[11]

DISCUSSION

Several major conclusions may be drawn from the information reviewed in this study. First, the finding that lower MPV corresponds to a higher SLE disease activity has been confirmed by several other recent studies.[29] It is essential that laboratory testing for the diagnosis and monitoring of SLE is conducted in consecutive stages to ensure that the patient is not subjected to unnecessary and costly testing. More

importantly, anti-SM and anti-dsDNA testing, while being SLE specific, lack adequate sensitivity for anti-SM antibodies. In addition, anti-dsDNA is present in 70% of lupus patients, and anti-ribosomal P protein antibodies are highly SLE specific, but they show low sensitivity for lupus. Because SLE can and does attack many organs and body systems, monitoring cannot be merely one-pronged or proceeded through one-stage testing. Because unique biomarkers are lacking, not just for the diagnosis of lupus but also for its monitoring, it is important to define and implement standard approaches. Recent studies have led to several recommendations for genetic, biological, and biochemical testing as well as molecular imaging. Because of the aberrant T-cell function in SLE, an array of 30 genes has been identified and assumed to contribute to the pathogenesis of SLE.[5] It is imperative that the 2015 guidelines developed by Tunnicliffe et al.[14] for monitoring SLE will be widely implemented. The recommended panel of tests includes the measurements of serum creatinine, full blood count, urinalysis, complement C3 and C4 proteins, anti-phospholipid, anti-dsDNA, anti/RO-SSA, anti-C1g, C-RP, serum albumin, urinary protein-creatinine ratio, and eGFR. Furthermore, these tests should be conducted as part of a three-stage procedure described in the study by Al-Katheri et al.[3] Positive results during the first stage of routine laboratory testing for SLE, i.e., blood counts, creatinine, and urinalysis, should be followed by second-stage testing, or ANA testing, which, when positive, is followed by a third stage that includes testing for specific antibodies (anti-SM, dsDNA, Ro/SSA, La/SSB, U1 RNP). Further, it is recommended that MPVs of patients should be checked regularly, because low mean platelet volume values indicate high SLE disease activity.

Finally, a newer test worth to mention, which has been noted in many recent studies, has been a subject of recent conferences, and has been recommended to shed some light on by some rheumatologists, is the Anti-DFS70 antibodies (Dense Fine Speckled 70). It has been proposed that this test adds a value to the diagnosis confirmation of SLE, only if ANA is positive. Isolated anti-DFS70 reactivity without anti-ENA or anti- dsDAN has been proposed to be an exclusion marker for systemic autoimmune rheumatic diseases.[30] Mahler et al. concluded that while the clinical presentations of SLE are present, with positive ANA (ENA of HEp2 cells), it is recommended to test for anti-DFS70 using fluorescence. Further, the presence of anti-DFS70 combined with positive anti-ENA and/or positive anti-dsDNA and anti-nucleosome; suggests that lupus is highly probable. While, the presence of anti-DFS70 combined with negative anti-ENA and/or negative anti-dsDNA and anti-nucleosome; concludes that lupus is possible.[30]

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الفحوص المخبرية لتشخيص ومتابعة مرض الحمى الذؤابية

سارة ماهر أبو عبيد

فني أول مختبر رئيسي– تحاليل طبية: مختبر الحلول المتقدمة الطبي – ميدلاب.

مساعد أبحاث– تحاليل طبية: شركة الحلول المتقدمة للتكنولوجيا الصحية الأمريكية.

الملخص

المقدمة: الهدف من هذه الدراسة تقييم الفحوص المخبرية الموصى بها لتشخيص ومتابعة تطورات مرض الحمى الذؤابية؛لأن دورة هذا المرض معقدة ويصعب التنبؤ بها، وهناك حاجة لشرح وتحديد أفضل ممارسات اختيار الفحوص المخبرية لتساعد بالتشخيص والعلاج.

النتائج: تمثل هذه الدراسة تحليل تجميعي لتقييم 20 مصدراً موثوقاً من أبحاث ودراسات منشوره في المجلات والدوريات الطبية ولاسيما الدراسات منها المنشورة كمقالات محدده والمتعلقة بتقييم الفحوص المخبرية لتشخيص ومتابعة مرض الحمى الذؤابيه، وتم مراجعة الدراسات وتحليل نتائجها وتلخيصها على أساس النتائج الرئيسية الكبرى، والدراسات التي تم تقييمها في هذه الدراسة هي بين عامي 2009 و 2018، مع كون معظم الدراسات حديثة جداً.

الخلاصة: خلصت الدراسة إلى أن الفحوص المخبرية لتشخيص ومتابعة مرض الحمى الذؤابيه يجب أن تتم في مراحل متتالية لتجنب إخضاع المرضى لاختبارات غير ضرورية ومكلفة، وبما أن مرض الحمى الذؤابيه يهاجم العديد من أجهزة وأنظمة الجسم، فلا ينبغي المتابعة من خلال مرحلة واحدة من الفحوص المخبرية فقط، بالإضافة إلى ذلك، تفتقر الأجسام المضادة الذاتية الخاصة بمرض الحمى الذؤابيه إلى الحساسية الكافية. علاوة على ذلك، إن المؤشرات الحيوية الفريدة غير متوفره، ليس فقط لتشخيص هذا المرض ولكن أيضًا لرصده، ولذلك فإنه لا بد من تحديد النُهج المعيارية المثلى الخاصة بالتشخيص والمتابعه وتنفيذها. وأخيراً، يجب أن يتم التحقق من فحص متوسط قيم حجم الصفائح الدموية للمرضى بانتظام؛ لأن القيم المنخفضة تشير نشاط عالي للمرض.

الكلمات الدّالة:مرض الحمى الذؤابية، تشخيص، متابعة تطورات المرض، الفحوص المخبرية، النُهج المعيارية.