International Journal of Medical Toxicology & Legal Medicine **Volume 27, No. 5, 2024**
e-ISSN: 0974-4614
p-ISSN: 0972-0448
https://doi.org/10.47059/ijmtlm/V27I5/069

Relation between Change in Subclinical Cerebral and Disease Activity in Paediatric Lupus Nephritis.

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Received: 13.09.2024 Revised: 19.10.2024 Accepted: 26.11.2024

ABSTRACT

Background: Juvenile-onset systemic lupus erythematosus (JSLE) is a severe autoimmune disease with multi-organ system involvement, with one of its most important complications being lupus nephritis (LN). Complexity in disease pathophysiology, in addition to a lack of sensitive markers, creates difficulty in attaining timely diagnosis and effective therapy.

Objective: In this article, an attempt is made to review pathogenesis, clinical presentation, diagnostic criteria, and therapeutic approaches relevant to JSLE and LN, with specific regard for emerging trends in marker development and novel therapeutic approaches.

Methods: An in-depth review of current literature regarding JSLE and LN was performed, with a focus placed on disease prevalence, immune deregulation, and multi-visceral disease. In-depth analysis of current diagnostic tests, therapeutic interventions, and future markers has been performed.

Results: JSLE is characterized by significant morbidity, with a high prevalence in non-Caucasian populations, early disease onset, and high renal activity. Progress in immunohistochemical techniques has translated into a better prognosis for patients, but timely diagnosis continues to present a challenge. Emerging serum and urinary markers have high potential for use in non-invasive diagnostics. An inter-disciplinary approach in managing concomitant disease and long-term prognosis evaluation is critical.

Conclusion: Despite improvements in therapy and diagnostics, additional studies are critical to maximize therapeutic interventions, develop reliable markers, and prevent long-term complications. Patient-focussed and multi-disciplinary care is critical to maximize survival and enhance quality of life in afflicted subjects.

Keywords: Juvenile-onset systemic lupus erythematosus (JSLE), Subclinical Cerebral change, biomarkers, immunosuppressive therapy, multi-organ involvement, CD5.

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a challenging systemic autoimmune disease, its clinical expression is widely variable: indeed, all organs and systems may be potentially affected, including vital organs, such as brain, heart, blood and kidneys [1].

Juvenile-onset systemic lupus erythematosus (JSLE) accounts for up to 20% of all SLE patients. JSLE is usually a more serious disorder involving renal, neurological and hematological systems, resulting in lifelong damage compared to adult-onset lupus patients and has a widely diverse presentation and clinical outcomes [2].

- **Pathophysiology:**

Although the precise pathophysiology of JSLE is still unknown, a number of variables, including genetics, immune complex deposition, complement activation, hormonal factors, plasmacytoid dendritic cell release of interferon alpha, neutrophil defects in monocytes and immune cell dysregulation, are implicated to varying degrees. These findings suggest that future patient stratification based on immune phenotypes may be possible [3].

- **Epidemiology:**

Disease prevalence is greater in non-white children. Children of non-Caucasian descent also exhibit earlier onset ages and greater rates of renal involvement. End-stage renal disease and mortality are more common among African-American and Hispanic children with Juvenile SLE [4].

Children of African descent exhibited a greater incidence of early disease damage and a higher damage accumulation trajectory, according to a large Canadian cohort study of JSLE patients followed over time. The majority of these findings align with the demographic relationships found in SLE adults [5].

- **Diagnosis:**

The pathogenesis of SLE, a very complex disease, is yet unknown. The early identification and treatment of SLE are delayed due to the absence of pathognomonic molecular markers or nonspecific constitutional symptoms. This complex clinical feature and unknown pathophysiology make the diagnosis of SLE difficult [6].
In 2019, the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) developed new SLE classification criteria, including one obligatory entry criterion positive antinuclear antibody (ANA) followed by additional weighted criteria grouped into seven clinical (constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, and renal) and three immunologic (antiphospholipid antibodies, complement proteins, and SLE-specific antibodies) domains, weighted from 2 to 10 [7].
This review article aims to compare the results of treatment of degenerative lumbar disc disease with endoscopic TLIF versus MIS TLIF in the treatment of Degenerative Lumbar Disc Disease.

Table 1: Aringer et al. ARD 2019 [7].

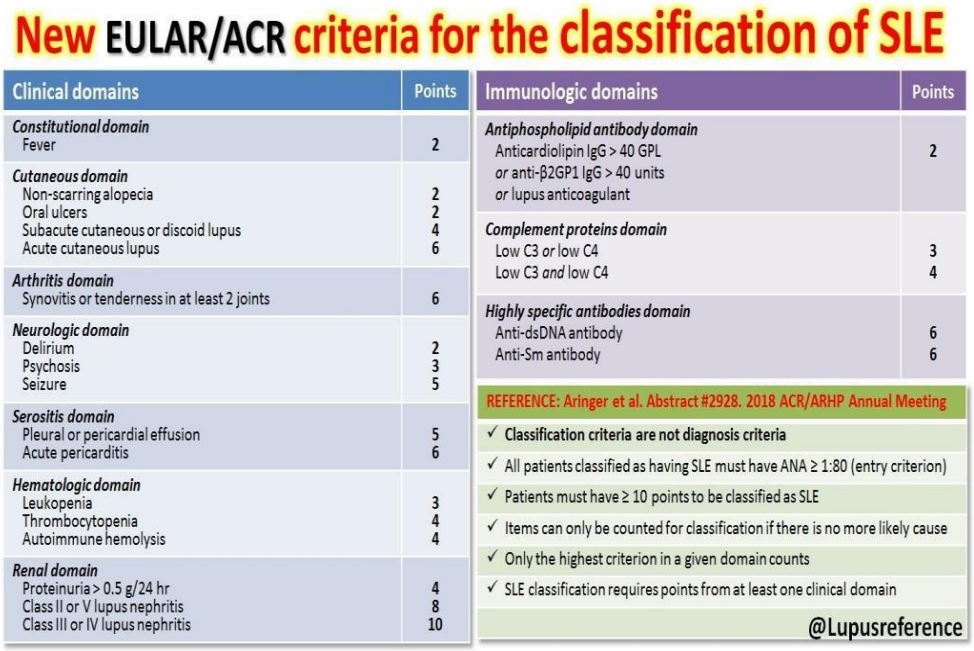

Table 2: Classification Criteria for Systemic Lupus Erythematosus[7].

Criterion	Definition
1. Malar rash	Flat or raised erythema over the malar eminences, spares the nasolabial folds
2. Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur
3.Photosensitivity	Skin rash following sunlight exposure, by history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless
5. Arthritis	Nonerosive arthritis involving two or more peripheral Joints,characterized by tenderness, swelling, or effusion
6. Serositis	Pleuritis—convincing history of pleuritic pain or rub on auscultation or evidence of pleural effusion or Pericarditis—documented by electrocardiogram, echocardiogram orrub
7. Renal disorder	Persistent proteinuria greater than 0.5 g/d or Cellular casts—may be red cell, hemoglobin, granular, tubular, ormixed
8.Neurological disorder	Seizures in the absence of offending drugs or metabolic derangements or Psychosis in the absence of offending drugs or metabolic derangements
9.Hematological disorder	Hemolytic anemia with reticulocytosis or Leukopenia less than 4000/mm^3 on two or more occasions, or Lymphopenia less than 1500/mm^3 on two or more occasions, or Thrombocytopenia less than 100,000/mm^3

10.Immunological disorder	Antibody to native DNA, orAntibody to Sm protein, orAntiphospholipid antibodies – either anticardiolipin antibodies, presence of the lupus anticoagulant, or false positive serological test for syphilis
11.Antinuclear antibody	Presence of antinuclear antibody by immunofluorescence or an equivalent assay

- **Manifestation:**

Patients with JSLE have increased risks of morbidity and mortality, which can result in significant disabilities [8]. Frequent clinical presentations include alopecia, photosensitivity, Raynaud's phenomenon, fever, arthritis, mouth ulcerations, and hair loss. The musculoskeletal system, the skin, the kidneys, the lungs, the heart, and many other organs can all be affected by SLE [9].

Since systemic lupus erythematosus patients are known to have a higher risk of developing certain comorbidities, such as cardiovascular disease (CVD), stroke, osteoporosis, and infection, preventative treatment should be started in patients with both Juvenile (JSLE) and adult-onset SLE, according to recent guidelines [10, 11].

Compared to matched young healthy individuals, JSLE patients have a higher incidence of comorbidity; nevertheless, because of their high level of heterogeneity, there are variations even within JSLE cohorts. Despite similar frequencies of severe cumulative symptoms, patients with early onset JSLE have increased mortality and neuropsychiatric/vascular/cutaneous damage and they should be continuously watched[12].

1. CUTANEOUS:

Cutaneous lupus comes in three primary forms: acute, subacute, and chronic. Multiple types may coexist in a single person. In general, the illness presents no threat to life and is not communicable. Nonetheless, the dermatologists at NYU Langone are aware that outwardly evident rashes and sores can impact your self-esteem and can assist you in long-term symptom management [13].

a) **Acute Cutaneous Lupus**
b) **Subacute Cutaneous**
c) **Chronic Cutaneous Lupus**

2) Haematology:

Anaemia is the most common hematologic abnormality in patients with systemic lupus erythematosus (SLE) and affects more than half of all patients. The only etiology listed in the categorization criteria is autoimmune hemolytic anemia (AIHA) [14].

Anemia, leukopenia, thrombocytopenia, lymphadenopathy, and/or splenomegaly are the main hematologic symptoms of SLE. These abnormalities could be the result of an SLE treatment, a coexisting condition, or an SLE manifestation [14].

Additionally, research demonstrates that children with SLE have a higher incidence of AIHA than do adults. It has been suggested that warm antibodies destroy red blood cells, causing AIHA [15].

AIHA mostly presents with biochemical features of hemolytic anemia and, in severe cases, hepatosplenomegaly, hemoglobinuria, and heart failure. It is diagnosed by a positive direct antiglobulin test (or Coombs test), anemia (low hematological parameters), elevated lactate dehydrogenase, indirect bilirubin, and reticulocyte count [15].

1) Pulmonary:

The majority of individuals diagnosed with SLE have involvement of lung, pleura, diaphragm, and/or pulmonary vasculature. Coughing, dyspnea, and/or pleurisy are frequently the initial signs of lung involvement or SLE itself [16].

2) Cardiovascular system(CVS):

One of the most common cause of mortality for SLE patients is cardiovascular illness. Coronary heart disease, myocarditis, valvulitis, and conduction anomalies are among the burden of cardiovascular disease. Moreover, electrocardiogram alterations without clinical heart illness have been reported, as well as left ventricular systolic and diastolic dysfunction, mitral and tricuspid valve insufficiencies [17].

3) Immunity:

SLE is characterized by a complex dysfunction of the innate and adaptive immunity. Genetic variant research, expression pattern analysis, and epigenetic studies have yielded important insights into the pathophysiology of SLE. The autoimmune disease's immunological pathogenesis has been associated with a distinct expression pattern of miRNAs, which have been connected to abnormalities in immune cell responses, cytokine and chemokine synthesis, cell activation, and apoptosis [18].

4) Neuropsychatry:

Neuropsychiatric systemic lupus erythematosus (NPSLE) is a potentially serious and life-threatening complication of SLE. Neuropsychiatric involvement in SLE can manifest in a variety of ways, both in terms of severity and presentation. Over half of SLE patients are affected by it. Direct effects on the neural tissue are possible, as the possibility of vascular involvement, which is mostly linked to anti-phospholipid antibodies [19].

5) Nephritis:

An inflammation of the kidneys brought on by systemic lupus erythematosus is known as lupus nephritis. It is a form of glomerulonephritis in which inflammation develops in the glomeruli. It might lead to blood in the urine, protein in the urine, high blood pressure, kidneys that don't work well or even kidney failure [20].

6) Macrophage Activation Syndrome (MAS):

MAS is a very severe, acute and potentially life-threatening condition, which is a complication of different rheumatic diseases, including pediatric Systemic Lupus Erythematosus. It is classified as a secondary form of hemophagocytic lymphohistiocytosis (HLH) [21].

- **Management:**

Rheumatologists as case managers, dermato-logists, nephrologists, hematologists, neuro-logists, radiologists, immunologists, gastroente-rologists, cardiologists, endocrinologists, and infectious disease experts are typically required due to the complexity of JSLE with multi-organ involvement [22].

The key for adequate comorbidity management is the appropriate patient stratification for tailored interventions. Lipid biomarkers, discovered recently, allowed categorization of JSLE patients according to their atherogenic lipid profile, and the immunological and metabolic signatures of these individuals can aid in the prediction of long-term results and CVR [23] .

- **Prognosis:**

Over the years the prognosis of SLE has improved probably due to early diagnosis and better use of immunosuppressive treatment, regular follow up and treatment of co-morbidities. The 10-year survival now approaches 90% and with new and targeted therapy it is hoped that the morbidity and organ damage can also be minimized [24].

- **Mortality:**

If the disease activity is not sufficiently managed by immunosuppressive medications, SLE is also linked to damage to several organs. Consequently, compared to the general population, SLE patients also have a higher death rate. Even though SLE therapy has advanced recently, there is still a significant relative risk of death from the condition.

Renal failure accounted for 65% of all mortality cases in JSLE patients. Heart failure (12.1%), cerebrovascular accidents (8.9%), pulmonary hemorrhage (8.3%), and cancer (8.3%) were the next most common reasons of death [25].

Adverse events of SLE

Lupus nephritis (LN) is the most common form of kidney involvement in SLE. The clinical presentations and pathological forms of LN in children might vary, posing challenges for both clinical diagnosis and therapy. These can include minor hematuria or proteinuria, nephrotic syndrome, and renal failure [26].

Furthermore, prolonged use of corticosteroids and immunosuppressive drugs can be harmful, leading to significant renal damage that can only be reversed with dialysis [26].

Cardiovascular events and infections are the leading causes of death for children with LN on maintenance dialysis. Hospitalization within the first year of starting dialysis and length of dialysis before a kidney transplant are risk factors for death from jSLE following renal failure [27].

Table 3: The evolution of LN classifications (adapted after [28]).

	WHO 1974	**WHO 1982**	**ISN/RPS 2003**	**ISN/RPS 2018**
Class I	**Normal glomeruli**	**Normal glomeruli** a. Nil (by LM/IF/EM) b. Normal by LM, but deposits by IF/EM	**Minimal mesangial LN** Normal by LM, mesangial deposits by IF/EM	**Minimal mesangial LN** Normal by LM, mesangial deposits by IF/EM
Class II	**Purely mesangial disease** a. Normocellular mesangium by LM but mesangial deposits by IF/EM b. Mesangial hypercellularity	**Pure mesangial alterations** a. Mild hypercellularity b. Moderate hypercellularity	**Mesangial proliferative LN** Mesangial hypercellularity with mesangial deposits by IF/EM	**Mesangial proliferative LN** Mesangial hypercellularity with mesangial deposits by IF/EM

	WHO 1974	WHO 1982	ISN/RPS 2003	ISN/RPS 2018
	with mesangial deposits			
Class III	**Focal proliferative GN (<50%)**	**Focal segmental GN** a. With ―active‖ necrotizing lesion b. With ―active‖ and sclerosing lesions c. With sclerosing lesions	**Focal LN (<50%)** Class III (A) Class III (A/C) Class III (C)	**Focal LN (<50%)** Modified NIH lupus nephritis activity and chronicity scoring system to be used instead of the A, C, and A/C parameters
Class IV	**Diffuse proliferative GN (≥50%)**	**Diffuse GN** a. Without segmental lesions b. With ―active‖ necrotizing lesion c. With ―active‖ and sclerosing lesions d. With sclerosing lesions	**Diffuse LN (≥50%)** Class IV-S (A) Class IV-G (A) Class IV-S (A/C) Class IV-G (A/C) Class IV-S (C) ClassIV-G (C)	**Diffuse LN (≥50%)** Elimination of S and G subdivisions Modified NIH lupus nephritis activity and chronicity scoring system to be used instead of the A, C, and A/C parameters
Class V	**Membranous GN**	**Diffuse membranous GN** a. Pure membranous GN b. Associated with lesions of class II c. Associated with lesions of class III d. Associated with lesions of class IV	**Membranous LN**	**Membranous LN**
Class VI	**Not defined**	**Advanced sclerosing GN**	**Advanced sclerosing LN**	**Advanced sclerosing LN**

Abbreviations: LN, lupus nephritis; LM, light microscopy; IF, immunofluorescence; EM, electron microscopy; GN, glomerulonephritis; NIH, National Institutes of Health; A, active; C, chronic; A/C, active/chronic; WHO, World Health Organization; and ISN/RPS, International Society of Nephrology/Renal Pathology Society.

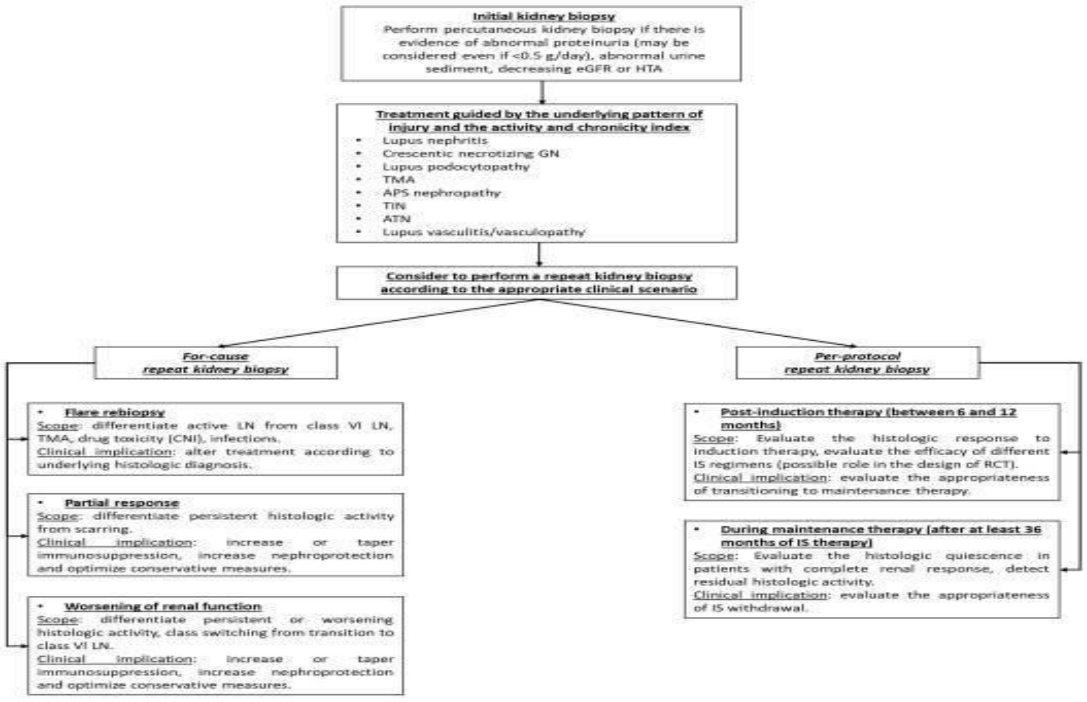

Fig. 1: The integration of percutaneous kidney biopsy in the management of patients with SLE and renal involvement (adapted after [29]).

BIOMARKERS

LN diagnosis is often made after the accrual of irreversible kidney damage because of the insensitivity of current clinical laboratory assessments (eg, glomerular filtration rate, microalbuminuria and proteinuria). Although kidney biopsy is the gold standard for clinical diagnosis, there are risks involved for patients undergoing this invasive procedure [30].

Furthermore, during a biopsy, a sample error could happen. Therefore, non-invasive diagnostic techniques are required to reliably and securely assess renal involvement at an earlier stage in SLE patients [30].

Proteins linked to inflammation, renal failure, and angiogenesis were shown to differ in both SLE and LN when compared to healthy individuals, according to proteomics screening.

In addition, a set of unique proteins was identified that were associated with LN but were distinct from both SLE and non-SLE kidney disease according to the National Institutes of Health Activity Index (NIH-AI) and the National Institutes of Health Chronicity Index (NH-CI) [31] such as:

1. **Anti-dsDNA antibody titers**
2. **Complement level**
3. **Biomarkers related to B cells & plasma cells**
4. **Cytokines**

- **Urinary markers:**

After briefly reviewing mechanisms involved in the pathogenesis of LN above, one may acknowledge that biomarkers in the serum may not represent the optimal pool of disease activity indicators. Urine is thought to better reflect the intra-renal milieu, therefore efforts to find biomarkers there have grown due to the differing amounts of cytokines in the kidney compared to peripheral blood[31].

- **Proteinuria**
- **Urinary neutrophil gelatinase associated lipoclain (NGAL)**
- **Urine sediment (leukocytes, red blood cells)**
- **Urinary CD25**
- **Monocyte chemoattractant protein (MCP)-1/CCL2**

CD25 Biomarke

CD25 is a membranous glycoprotein, which is responsible for forming the alpha chain of the interleukin-2 receptor. This receptor is essential for both cell proliferation and differentiation, and it is mostly expressed on activated T lymphocytes [32].

Previously, it was believed that CD25 was only expressed on natural killer cells until it was found to be expressed on activated T cells. Dissimilar to CD4 or CD8 antigens, which are exclusive to gamma/delta or alpha/beta T-cell receptors, respectively. Several CD34+ hematopoietic progenitors, eosinophils, basophils, and recent thymic emigrants (RTE) express CD25 when combined [32].

- **Mechanism of CD25 upregulation in T cells:**

When T cell receptors bind to mitogens or allo-antigens ,they are activated leading to an increase in intracellular calcium and phosphorylation of protein kinase C. Ultimately, the upregulation of CD25 that results from this cascade can be five to twenty times greater than the whole heterotrimeric IL2R complex [33].

Furthermore, exposure to IL2 induces CD25 expression, which sets up a positive feedback loop in which the IL2RA (CD25) gene locus is bound by a signal transducer and activator of transcription 5 (STAT5) [33].

- **Urinary CD25 Biomarker:**

Urine is an excellent noninvasive method for investigating the local immunopathogenesis of LN. Urine-derived molecules are typically regarded to reflect renal inflammation and irreversible kidney damage more accurately than serum-derived indicators, despite the fact that both have been evaluated for viable markers [34].

CONCLUSION

Juvenile-onset systemic lupus erythematosus (JSLE) is a complex autoimmune disease with widespread organ system involvement, with one of its most critical complications being lupus nephritis (LN). Despite improvements in therapeutic modalities with immunosuppression, early diagnosis of JSLE remains challenging in view of a lack of dependable biomarkers. Emerging studies in immune deregulation and new disease markers have proposed exciting avenues for early diagnosis and therapy. Adoption of a multidisciplinary care model, including collaboration between rheumatologists, nephrologists, and several other professionals, is critical for successful disease management. There is a critical need for additional studies focused on optimizing therapeutic options, minimizing complications, and enhancing long-term prognosis for patients afflicted with this disease.

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