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Review article

Value of Urinary Ceruloplasmin as a Marker in Juvenile SLE

[1]Elham M. Hossny, [1]Mohammad A. Sharaf, [2]Nancy Samir Wahba, [3]Abdulrahman A. Warsame

[1]Pediatric Allergy, Immunology and Rheumatology Unit, Children's Hospital, Ain Shams University; [2]Department of Clinical Pathology, Ain Shams University; [3]Public Health Hospital, Benadir, Somalia.

Abstract

There is substantial evidence that lupus nephritis (LN) is primarily related to type-III hypersensitivity reactions leading to immune complex deposition at the mesangial, subendothelial, and/or subepithelial space near the renal glomerular basement membrane. The search for a non-invasive urinary marker of lupus nephritis is an appealing point of research. There are few studies that have evaluated the role of urinary ceruloplasmin (CP) as a biomarker for LN. Being expressed at high levels by parietal epithelial cells of Bowman's capsule it could possibly detoxify molecules as they pass through the glomerular filter. CP is a highly effective antioxidant that can prevent oxidative damage to lipids, DNA, and proteins. However, it is unlikely that a single biomarker can replace clinical parameters to monitor disease progression and detect early renal flares.

Keywords: Juvenile SLE, urinary ceruloplasmin.

Renal affection in SLE

The incidence and prevalence of SLE and LN are influenced by age, gender, ethnicity, and geographic region. Childhood-onset systemic lupus erythematosus has an incidence of 0.3 to 0.9 per 100,000 children/year and a prevalence of 3.3-8.8 per 100,000 children. About 10-20% of cases of SLE are diagnosed during childhood with a median age of onset of 11-12 years, and these patients have increased disease severity and lower survival rates.[1] Between 40% and 70% of children with SLE develop LN, 10% to 30% higher than in adult-onset SLE.[2] Male gender is a risk factor for developing LN in addition to young adult age. The incidence of lupus nephritis in the US is greater than Europe. LN has a higher occurrence in Hispanics, blacks, and Asians and it occurs less in whites.[3]

The most serious complication associated with lupus nephritis (LN) is renal impairment. End stage renal disease has been reported to develop in 10-30% of patients with LN which needs either dialysis or a kidney transplant.[4]

Pathophysiology:

The pathogenesis of SLE involves a complex interaction between genetic susceptibility and environmental influence (viral infection, sun exposure, hormonal alterations, nutrition, physical and mental stress, and medication), which result primarily in loss of immune tolerance, production of antibodies against (chromatin, nucleosomes, DNA, RNA, ribonuclear proteins), deposition of immune complexes in target organs, and complement defects.[5]

While the pathogenesis of LN remains incompletely understood, there is substantial evidence that it is primarily related to type-III hypersensitivity reaction leading to immune complex deposition on the mesangial, subendothelial, and/or subepithelial space near the renal glomerular basement membrane. This leads to the commence of an inflammatory response. Abnormalities in innate and adaptive immunity contribute to the pathogenesis of LN. T cells have essential roles by helping B cells to produce autoantibodies against nuclear and cellular antigens including anti-DNA antibodies and related antinuclear antibodies. The B cells that produce these autoantibodies are consistently activated, partly due to various genetic polymorphisms. Anti-double-stranded DNA (anti-dsDNA) binds to DNA leading to accumulation of immune complexes in the glomeruli from the circulation or through in situ production. Such intraglomerular immune complexes can activate complement and engage leukocyte Fc receptors to initiate inflammation and injury.[6]

Abnormalities in B-cell tolerance also promotes activation of type I interferon (IFN-I) and various proinflammatory cytokines. TH1 cytokines are particularly over expressed in LN and promote inflammation through activation of the classical complement pathway and macrophages. Complement system protein C1q binds to the Fc region in immune complex deposits to enhance neutrophil activation for immune complex clearance which leads to the formation of chemo-attractant complement proteins (C3a and C5a). TH1

cells promote intrarenal inflammation through complement mediated kidney damage, especially through the alternative pathway. Moreover, activated neutrophils and macrophages cause renal injury through production of oxygen free radicals and various proteolytic enzymes.[5]

Signs and Symptoms of lupus nephritis:

The presence of proteinuria and cellular casts may be the early sign of the tubular or glomerular dysfunction of LN. Oedema, hypertension, and acute renal injury are common manifestations. However, many patients with LN may be asymptomatic.[7]

Hypertension in LN may be induced by several mechanisms. These include side effects of medications such as glucocorticoids and cyclosporine A that were found to be independent risk factors for the development of hypertension. Increase in vascular stiffness due to endothelial dysfunction and atherosclerosis are other factors. Metabolic changes in SLE with alterations in body composition may cause overexpression of leptin leading to the development of obesity-related hypertension.[8]

Severe LN is one of the most common secondary glomerular diseases that cause acute kidney injury (AKI). A study showed that 54% of diffuse proliferative lupus nephritis patients had AKI and AKI severity was positively correlated to progression of renal impairment.[9]

LN is characterized by the deposition of subendothelial and/or subepithelial immune complexes in the afflicted kidney, resulting in extensive injury and nephron loss during the acute phase and eventually chronic irreversible damage and renal function impairment if under-treated. End-stage renal disease (ESRD) is the most serious complication; however, this may take months or years to ensue.[10]

Diagnosis of lupus nephritis:

This is achieved by clinical evidence of nephritis (edema, hypertension +/- hematuria), in association with specific laboratory findings (proteinuria, leukocyturia +/- hematuria), and confirmed and classified histopathologically by renal biopsy.[11] The definition of lupus nephritis within the diagnostic criteria of SLE is displayed in Figure (1).

Lupus patients with an active urinary sediment or proteinuria should undergo a kidney biopsy unless biopsy is contraindicated. The International Society of Nephrology (ISN) and Renal Pathology Society (RPS) created a lupus nephritis classification system based on morphologic findings on kidney biopsy.[12,13]

- Class I – Minimal mesangial lupus nephritis
- Class II – Mesangial proliferative lupus nephritis
- Class III – Focal lupus nephritis (active and chronic; proliferative and sclerosing)
- Class IV – Diffuse lupus nephritis (active and chronic; proliferative and sclerosing; segmental and global)
- Class V – Membranous lupus nephritis
- Class VI – Advanced sclerosis lupus nephritis

Unlike other sample sources (serum or tissue) obtaining urine is not an invasive procedure and can be easily collected. Therefore, some urinary constituents such as cytokines, chemokines, complement proteins, adhesion molecules, and auto antibodies have been identified as potential biomarkers of LN activity.[14]

Ceruloplasmin as a marker of lupus nephritis

Non-invasive diagnostic measures of LN would be of value and the possible role of urinary transferrin and ceruloplasmin as biomarkers of LN activity have been suggested.[14,15]

Ceruloplasmin (CP) is a 122 kDa protein that carries the majority of circulating copper. It has the function of iron oxidase and is commonly associated with transferrin because CP oxidizes ferrous (which is toxic) to ferric that can later bind to transferrin. Molecules associated with iron metabolism (such as CP and ferritin) are over expressed in inflammatory situations because their production may be enhanced in the presence of proinflammatory cytokines such as IL-6 and IL-1. There are few studies that have evaluated the role of urinary CP as a biomarker for LN.[14] Being expressed at high levels by parietal epithelial cells of Bowman's capsule might suggest a role at this particular site. It possibly detoxifies molecules as they pass through the glomerular filter.[16] As a matter of fact, ceruloplasmin is a highly effective antioxidant that can prevent oxidative damage to lipids, DNA, and proteins.[17]

Ceruloplasmin also belongs to the group of acute-phase proteins that are elevated in blood and rapidly regulated, in an adaptive manner, in response inflammation, infection, and tissue injury. The plasma level of CP nearly doubles in response to inflammation. Expression of CP can be induced by interleukin-6, interferon-γ, and tumor necrosis factor α.[18,19]

Studies reported that CP levels are elevated in SLE patients with LN in comparison with those without renal involvement. Similarly, urinary CP levels were higher in patients with active LN and

are related to a higher activity index. Although urinary biomarkers are interesting tools in patients with LN because they are the direct products of kidney inflammation or injury, it should be noted that other serum and tissue biomarkers exist and have equal weight in the study of these patients; therefore, the development of an activity score will require the employment of both.[14,20] It is unlikely that a single biomarker stand-alone can replace conventional clinical parameters to monitor disease progression and predict renal flares. Instead, a constellation of biomarkers is required to develop a useful index for managing LN patients.

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

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If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Figure (1). Definition of SLE according to the ACR criteria (Martin et al, 2019)

Corresponding author
Abdulrahman Abdulkarim Warsame
E-mail: dr.abdiraxman@gmail.com

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