Lupus nephritis in Sri Lankan patients

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Journal of the Ceylon College of Physicians, 1996, **29**/2, 71-74

(Key words: Lupus nephritis, renal biopsy, WHO classification, histology.)

Summary

The relationship between renal morphology and clinical disease was analysed in 200 patients with lupus nephritis. These patients fulfilled the 1982 revised classification criteria for SLE.

Out of 200 patients 173 were adults and 27 were children and the female to male ratio was 9:1. The renal tissue was assessed according to the World Health Organization classification on lupus nephritis. 66% of the patients showed proliferative type of glomerulonephritis (WHO class III and IV). Clinical renal disease was more in patients with proliferative glomerulonephritis than in any other type. Haematuria was more common in patients having WHO class III and IV lesions than in patients with other WHO classes. However some patients who presented with high serum creatinine and high blood urea, had non-proliferative lesions histologically (WHO class I and II). Without biopsy they might have been treated aggressively. Although the value of renal biopsy have been questioned, it is a very important investigation in the management of patients with lupus nephritis.

Introduction

Lupus erythematosus is a systemic autoimmune disease that affects both adults and children and has a wide variety of clinical manifestations. Based on clinical signs of renal disease the incidence of renal involvement in adult patients ranges from 50%-80%[1]. Clinicopathological correlations have demonstrated a significant relationship between the underlying histopathology of renal disease and the subsequent clinical course.[2,3]. Because of the broad spectrum of lesions that have seen in patients with lupus erythematosus, the World Health Organization (WHO) proposed a classification of lupus nephritis that included all morphological patterns[1]. The modified WHO classification as quoted by Gladman[2] comprises of 6 main classes (Table 1). The importance of this classification is that based on it, a renal biopsy can be used to determine the probable prognosis of an individual in terms of survival and renal function although it has been disputed in some studies. It also enables the clinician to select the appropriate medication for each case. A clinicopathological study of 32 patients with lupus nephritis had been done in Sri Lanka by Angunawela et al[4] in which 59% were proliferative glomerular leisions (class III and IV) in another study conducted by Angunawela et al[5]. out of 30 patients with lupus nephritis, 63% had proliferative lesions (WHO class III and IV) in which active lesions were very prominent. This study was performed to ascertain the correlation of clinical features of lupus nephritis with the histological lesions.

Table 1. WHO morphologic classification of lupus nephritis (modified)

I - Normal glomeruli

(a) Nil by all techniques
(b) Normal by light, but deposits on electron microscopy or immunofluorescence

II - Pure mesangial alterations

(a) Mesangial widening and/or mild hypercellularity
(b) Moderate hypercellularity

III - Focal segmental glomerulonephritis

(a) Active necrotizing lesions
(b) Active and sclerosing lesions
(c) Sclerosing lesions

IV - Diffuse glomerulonephritis

(a) Without segmental lesions
(b) With active necrotizing lesions
(c) With active and sclerosing lesions
(d) With sclerosing lesions

V - Diffuse membranous glomerulonephritis

(a) Pure membranous glomerulonephritis
(b) Associated with lesions of category I
(c) Associated with lesions of category II
(d) Associated with lesions of category III

VI - Advanced sclerosing glomerulonephritis

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Materials and methods

This study was conducted on 200 patients having lupus nephritis from January 1990 to January 1995. The diagnosis of SLE was confirmed by laboratory investigations. These patients fulfilled the 1982 revised classification criteria for SLE.[15] All renal function tests and bleeding time, clotting time and x-ray of genito-urinary tract were performed. All patients underwent one renal biopsy and also this was their first renal biopsy. The indications for renal biopsy was presence of proteinuria or haematuria (or both) or any evidence of abnormal renal function tests. 2 cores renal biopsies were obtained. One core was fixed in Duboscq Brazil Solution for light microscopic examination and other core was fixed in 10% formol saline for immunological studies.

Light microscopy

For light microscopic examination, the paraffin embedded were stained with Haematoxylin and Eosin, Periodic Acid Schiff and Silver Methanamine stains.

Immunohistochemistry

2-3 mili micron thick sections were made from formol saline fixed paraffin embedded tissue. Immunohistochemical were performed using Avidine Biotin Complex (ABC) method[8,9] All primary antisera were obtained commercially from Hoechst Behring Laboratories. Secondary antibody and ABC were obtained from Dakopats, Denmark. Trypsin was obtained commercially from Sigma chemicals. Reagent activity was confirmed with known positive and negative biopsies as controls.

All sections were deparaffinised in xylene and brought to alcohol Endogenous peroxidase activity was inhibited by reacting with hydrogen peroxide and methonol. The sections were then trypsinised for 15 minutes, washed with phosphate buffer and nonspecific protiens were blocked by adding 10% egg white solution, because normal swine serum was not available. The sections were then incubated at room temperature for 30 minutes with primary antisera; IgG, 1/800 dilution, IgA 1/600 dilution, IgM 1/500 dilution, C3 1/300 dilution and fibrinogen 1/600 dilution. After washing with buffer solution, biotinilated second antibody was added. ABC complex was added and after washing with the buffer solution the colour was developed with Diamino Benzidine (DAB). The stained sections were examined under the light microscope to identify the presence of immunecomplexes indicated by a brown stain.

Electron microscopic examination was not performed to comment on the presence or absence of electron dense immune complex deposits. According to the modified WHO morphological classification of lupus nephritis it has six main classes. Depending on the light microscopic, immunological and electron microscopic findings each class is subdivided into 2 to 4 sub types. However in this study electron microscopic examination was not performed and we have broadly divided into 6 main classes only.

Results

Out of 200 patients, 194 were Sinhalese, 3 were Tamils and 3 were Moors. 173 were adults and 27 were children. Among 173 adults there were 162 females and 11 males. Among children there were only 4 males and all the others were females. 80% of the adult patients were in the second and third decades. The renal lesions were classified according WHO classification of lupus nephritis (Table I).

2% had normal glomeruli both light microscopically and immunologically and they were classified as class I lesions. 16% of the patients had only mesangial proliferation under the light microscope and 3% of them had IgG, IgM and C3. One patient in this class had IgG, IgM, and C3. Patients in class III and class IV had immune complexes in large amounts. In this study majority of the patients were in class IV (48%). 18 patients (9%) were classified as having class V lesions. The characteristic "wire loop" capillaries were seen this class. Some of them had associated focal segmental lesions and some had diffuse proliferative lesions. Only one patient had pure membranous glomerulonephritis. 14 patients (7%) had extensive sclerosis of glomeruli with marked interstitial fibrosis and inflammation.

Table II shows the distribution of different lesions according to the WHO classification. The majority of the patients had diffuse proliferative lesions or class IV lesions.

The clinical presentation of patients in each WHO class is shown in Table 2. All the patients in WHO class VI had hypertension and none in class I. Out of 96 patients (48%) with class IV lesions 40% had hypertension and out of 36 patients (18%) with class III lesions 10% had hypertension. Haematuria was more common in patients with class III and class IV lesions. High blood urea and high serum creatinine was seen in 90% of patients with class

VI lesions or end stage renal disease. However 1 patient with class I lesion and 3 patients with class II lesions also had high blood urea and high serum creatinine.

Table 2. Clinical presentation of patients in each WHO class

WHO class	I	II	III	IV	V	VI
No of patients	4	32	36	96	18	14
Hypertension	-	2%	10%	40%	9%	7%
Haematuria	-	3%	60%	58%	5%	-
Albuminuria	100%	80%	100%	100%	90%	80%
High B. Urea	.5%	1.5%	18%	32%	2%	90%
High S. Creatinine	.5%	1.5%	10%	20%	-	90%

Discussion

SLE is the prototype of the multisystem disease of autoimmune origin, characterized by presence of many types of antibodies[1]. Acute or chronic in its onset, it is a chronic remitting and relapsing often febrile illness characterized principally by injury to the skin, joints, kidney and serosal membranes. Indeed the clinical presentation of SLE is so variable that the American rheumatism association has developed criteria for diagnosis of this disorder[14].

Like most other autoimmune diseases SLE is predominently a disease of women, common between the ages 20 and 64, and a female to male ratio of 9:1[1]. However in this study the female to male ratio was 12:1. Out of 173 adults 93 patients were between the ages of 20 and 30 years and 45 were between 12 to 20 years. In another smaller study conducted by Angunawela and Sheriff[5] the female to male ratio of patients with lupus nephritis was 7:1.

Although lupus erythematosus usually arise in the second and third decades it may become manifest at any age even in early childhood.

In this series there were 27 children and out of 27, 4 were males. As there were only 3 Tamils and 3 Moors in our study it was not possible to make any comparison of pathological lesions between the different races. Because of the broad spectrum of lesions that has been seen in patients with lupus nephritis, the WHO created a classification of lupus nephritis to combine all morphologic types of biopsy interpretation. 66% of the patients had proliferative lesions or WHO class III and class IV lesions. 27% of the patients had non-proliferative lesions or WHO class I, II and V lesions in the renal biopsies. Leaker etal[6] have reported that the survival was decreased among patients with WHO classes III, IV and VI compared to WHO classes I, II and V. Thus in this study the majority (73%) of the patients belonged to classes III, IV and VI which have a bad prognosis and a decreased survival rate[2,3,6].

Clinically patients with lupus nephritis presented with proteinuria, haematuria, nephrotic syndrome, nephritic syndrome, rapidly progressive renal failure or features of chronic renal failure. Haematuria was more common in patients with WHO class III and IV lesions than with any other type. However out of 4 patients who had fairly normal glomeruli or WHO class I lesion, 1 had microscopic haematuria. Though high blood urea and high serum creatinine was found in almost all the patients with end stage renal disease or WHO class VI lesions, one patient with class I lesion and three patients with class II lesions also had either high blood urea or high serum creatinine. Leaker etal[6] had studied the clinical course of 135 patients with lupus nephritis and shown that haematuria was more common in the severe group with proliferative lesions which also had a high disease activity. The lesions in class II or mesangial proliferative glomerulonephritis showed mesangial cell proliferation and expansion of the mesangial matrix. Leaker etal[6,13] in 1987 have shown that the survival was decreased among patients with class III, IV and VI compared to class I, II and V. In this series only 27% of the patients with lupus nephritis showed non-proliferativa lesions or class I, II and V which have a better prognosis than the proliferative lesions.

The role of renal biopsy in the management of SLE has been controversial. Initial studies carried out before the widespread use of WHO classification[11,12] and recent studies[4,5,6,7] have supported the concept that patients with diffuse proliferative lupus glomerulonephritis (WHO class 4) have a poor prognosis, both in terms of renal function and in terms of general survival. There have been several reports which denied the usefulness of renal biopsy information in predicting renal outcome[2]. These studies claimed that renal morphology did not add to clinical information obtained before biopsy. These studies did not include a systemic analysis of renal pathological abnormalities using the WHO classification. Indeed a further study[6,14] in which a systematic review of kidney biopsies according to WHO classification was performed, demonstrated that the information was important and helpful in predicting the effect of treatment of active lupus nephritis.

Since renal morphology may predict long term

prognosis and since no clinical feature uniformly predicted renal morphology, it is important for centres carrying out long term studies in SLE to continue to evaluate renal morphology.

Acknowledgements

I wish to thank all the consultants of the General Hospital Colombo, General Hospital Ragama, Sri Jayawardena Hospital and Lady Ridgeway Hospital for children, for providing me with renal biopsies to conduct this study.

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