Lupus nephritis among children in Indonesia

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Abstrak

Antara tahun 1985-1995 (10 tahun) telah dilakukan penelitian terhadap 30 anak dengan nefritis lupus yang dikumpulkan dari 7 pusat Nefrologi Anak di Indonesia. Umur rata-rata penderita ialah 11,7 tahun (berkisar antara 8 sampai 18 tahun) dengan perbandingan anak perempuan terhadap laki-laki 5 berbanding 1. Gejala klinis yang terbanyak ditemukan adalah panas tinggi 81%, ruam muka 66,6% dan artritis atau artralgia 44,4%. Sembilan penderita (30%) menunjukkan gambaran klinik sindrom nefrotik, 17 (56,6%) glomerulonefritis, 2 (6,5%) proteinuria dan hematuria, 2 (6,5%) proteinuria saja. Biopsi ginjal dilakukan pada 11 penderita dengan hasil nefropati membranosa pada 1 kasus, glomerulonefritis proliferatif fokal pada 1, glomerulonefritis mesangial pada 2 dan kelainan minimal pada 2 kasus. Jenis terapi yang diberikan adalah prednison oral pada kasus ringan, kombinasi prednison dan siklofosfamid atau azatioprin pada penderita dengan glomerulonefritis atau sindrom nefrotik. Kadang-kadang diberikan bolus metilprednisolon dan pada beberapa kasus terapi puls siklofosfamid. Selama pengamatan, 9 dari 30 penderita meninggal dunia. Semuanya menunjukkan gambaran klinik glomerulonefritis. Dua dari 9 penderita sindrom nefrotik mendapat pengobatan dialisis.

Abstract

Thirty systemic lupus erythematosus (SLE) children with renal involvement treated between 1985-1995 from 7 Pediatric Nephrology Centers throughout Indonesia were reviewed. The mean age of onset of these patients was 11,7 years (range between 8 to 18 years) with a preponderance of female to male ratio 5 to 1. The presenting clinical features were high grade fever 81%, malar rash 66,6% and arthritis or joint pain 44,4%. Nine (30%) patients had nephrotic syndrome, 17 (56,6%) (chronic) glomerulonephritis, 2 (6,6%) proteinuria and hematuria and 2 (6,6%) isolated proteinuria. Renal biopsy done in 11 patients revealed membranous nephropathy in 1, diffuse proliferative glomerulonephritis (GN) in 5, focal proliferative GN in 1, mesangial proliferative GN in 2 and minimal change in 2 cases. The treatment regimen given to these patients was oral prednisone in mild cases, combination of prednison and cyclosphosphamide or azathioprine in patients with glomerulonephritis and nephrotic syndrome, with occational methylprednisolone bolus and in some patients pulse cyclophosphamide. Nine of the 30 patients died of whom all had clinical presentation of glomerulonephritis. Two patients with nephrotic syndrome was on dialysis treatment.

Keywords: systemic lupus erythematosus, lupus nephritis, terminal renal failure

Systemic Lupus Erythematosus (SLE) is an immune complex mediated disorder affecting multiple organs of the body. When the immune complexes are localized in the capillary wall of the glomeruli, lupus nephritis develops.

Renal manifestations are present in nearly two thirds of children with SLE. Renal involvement is a major cause of morbidity in SLE.[1] Although with modern therapy renal failure is becoming less frequent, in many series of patients renal failure eventually developed.[2] In this paper the clinical manifestation, histologic picture and outcome of lupus nephritis was presented. Since the number of cases among children is relatively rare compared with that in the adult population, the data was compiled from 7 pediatric nephrology centers throughout Indonesia between 1985 to 1995.

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MATERIALS AND METHOD

The patients was collected retrospectively from 7 pediatric nephrology centers by distributing questionnaire, namely from Jakarta, Medan, Palembang, Bandung, Yogyakarta, Surabaya and Manado. The number of cases from each center was presented in table 1. The diagnosis of SLE was made using The American Rheumatism Association (ARA) 1982 revised criteria.[3] The patient must have four of the eleven criterias in order to establish the diagnosis of SLE.

All were 18 years o f age or younger. Renal disease (Lupus Nephritis) in these patients was confirmed by the presence of one or more of the following sign : proteinuria, hematuria, acute glomerulonephritis, nephrotic syndrome, renal failure. The results of renal biopsy evaluated by light and immunofluorecent microscopy, were classified according to the WHO criteria:[4]

- Class 1 : normal glomeruli
- Class 2 : mesangial alteration (mesangiopathy)
- Class 3 : focal proliferative glomerulonephritis
- Class 4 : diffuse proliferative glomerulonephritis
- Class 5 : membranous glomerulonephritis

Table 1. Number of cases reported from 7 pediatric nephrology centers

City	Cases
Medan	1
Palembang	4
Jakarta	17
Bandung	1
Yogyakarta	2
Surabaya	4
Manado	1
Total	30

RESULT

Between 1985 and 1995, 30 patients with lupus nephritis were reported from 7 university centres throughout Indonesia (table 1). Seventeen cases came from Jakarta. The age of the patients varied between 8 and 18 years with a mean of 11,7 years and a prepoderance of female to male ratio 5 to 1 (figure 1).

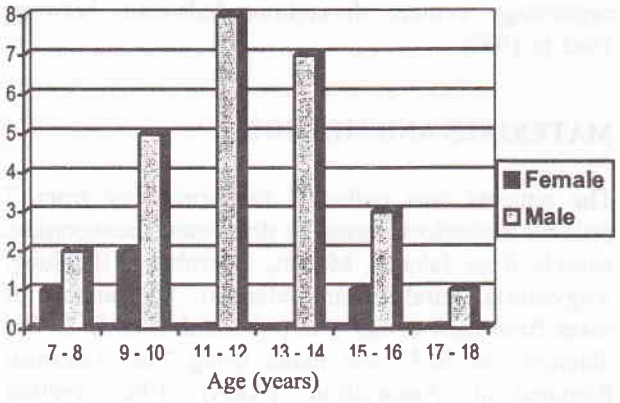

Figure 1. Age and gender of the patients

The dominant clinical feature at the time of initial presentation is shown in table 2. It could be seen that the presenting clinical features were high grade fever in 22 cases (81%), malar rash in 18 (66,6%) and arthritis or arthralgia in 12 cases (44,4%). Hypertension was detected in 10 cases (33,3%).

Table 2. Clinical manifestation on admission

	Cases	%
Fever	22	81,5
Malar rash	18	66,6
Arthritis / arthalgia	12	44,4
Alopecia	7	25,9
Stomatitis	4	13,2
Hyperpigmentation	4	13,2
Pallor	7	25,7
Hypertension	10	33,3

Table 3 showed the result of hematological and immunological pattern of the patients. Anemia was found in 80% of the cases, but hemolytic anemia only 12%; leucopenia in 25% and thrombocytopenia in 20%. Erythrocyte sedimentation rate was found in all cases (100%), low C3 90%, low C4 60%, antinuclear antibody (ANA) 80%, double stranded DNA 75% and LE cell in 40%.

Table 3. Result of hematological and immunological examination

Laboratory finding	%
Anemia (Hb < 10 g%	80
Hemolytic anemia	12
Leucopenia	25
Thrombocytopenia	20
ESR	100
Low C3	90
Low C4	60
ANA (+)	80
Ds DNA (+)	75
LE cells (+)	40

Renal manifestation of the patients are shown in figure 2. Nine patients had nephrotic syndrome (30%), 17 (56,6%) had acute glomerulonephritis, 2 (6,6%) had proteinuria and hematuria while 2 (6,6%) showed isolated proteinuria.

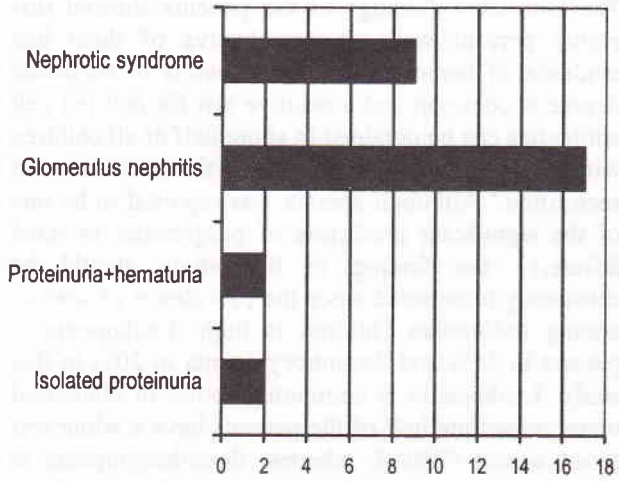

Figure 2. Renal manifestation of the patients

Renal biopsy was done only in 11 patients due to lack of parental permission. Diffuse proliferative glomerulonephritis was the most frequent histologic abnormality in the biopsy specimens, namely in 5 cases. One had membranous nephropathy, 1 focal proliferative glomerulonephritis, 1 with mesangial alteration and 2 with minimal lesion (table 4).

Table 4. Result of renal biopsy in 11 cases

Histopathology	Cases
Class 1 minimal lesion	2
Class 2 mesangial alteration	2
Class 3 focal proliferative glomerulonephritis	1
Class 4 diffuse proliferative glomerulonephritis	5
Class 5 membranous nephropathy	1
Total	11

All patients were treated with prednisone. In patients with clinical presentation of acute or chronic glomerulonephritis or nephrotic syndrome or renal biopsy finding of diffuse proliferative lesion, combination of oral prednisone and cyclophosphamide or azathioprine was given. Some patients received courses of intravenous methylprednisolone bolus (30 mg/kgBW/day in 3 onsecutive days, every other day).

Three patients received pulse cyclophosphamide courses monthly (500-750 mg/m2) in combination with MESNA for 6 months followed by a three month intervals. Beside a moderate degree of leucopenia and nausea, no other side effects was detected.

Table 5. Correlation of clinical presentation and outcome of the patient

Clinical presentation	N	Normal Renal function	Renal failure		Death
			Moderate	Terminal	
Proteinuria	2	2	-	-	-
Proteinuria + hematuria	2	2	-	-	-
Glomerulo-nephritis	20	9	2	-	9
Nephrotic syndrome	6	3	1	2 (D)	-
Total	30	16	3	2	9

Table 5 showed the outcome of the patients related to the clinical presentation. The total number of death during the study period was 9 out of 30 patients (30%). No death was reported in the group of patients with the clinical presentation of only proteinuria and/or hematuria. The renal function of these patients was always within normal limits during the follow up period, while in 11 out of 20 cases with clinical presentation of acute or chronic glomerulonephritis and 3 out of 6 cases with nephrotic syndrome showed moderate to severe impairment of the renal function.

Nine out of 20 patients with acute glomerulonephritis died. In patients with nephrotic syndrome 2 was on dyalisis treatment.

Table 6 showed the correlation of the number of death and the histological presentation. Three out of 5 cases with class IV lupus nephritis died. Two due to terminal renal failure and one due to nonrenal cause. One case with class 1 died due to nonrenal cause (shock of unknown cause) and 1 case of class 3 died due to terminal renal failure.

Table 6. Correlation of renal biopsy and outcome of the patients

Histopathology	N	Death	Cause of death	
		(N)	Renal	Nonrenal
Class 1	2	1	-	1
Class 2	2	-	-	-
Class 3	1	1	1	-
Class 4	5	3	2	1
Class 5	1	-	-	-
Total	11	5	3	2

Table 7. Causes of death in 9 cases

Cause of death	Cases
Terminal renal failure	5
Shock (unknown cause)	1
Cerebral hemorrhage	2
Septicaemia	1
Total	9

In Table 7 it could be seen that the cause of death were mostly due to terminal renal failure namely 5 of 9 cases. One patient died due to shock of unknown cause, 2 due to cerebral hemorrhage and 1 because of septicaemia.

DISCUSSION

Systemic lupus erythematosus (SLE) is an uncommon childhood illness characterized by the formation of autoantibodies and immune complexes which mediate inflammatory responses. Lupus nephritis (LN) is one of the most severe forms of organ involvement in SLE.[5-6] In this study in a period of 10 years only 30 patients was reported from 7 pediatric nephrology centres of which 17 patients was registered in Jakarta. Accurate figures on the incidence of SLE in childhood are difficult to obtain, but estimates in the United States are about 0,6 children in 100.000.[7] Other countries experience much lower rates, possibly reflecting racial factors.[8] Overall incidence of renal disease in childhood SLE is 75%.[9]

The average age of the patients was 11,7 years old (range 8-18 years) with a female to male ratio 5:1, which is in accordance with the literature. The onset of SLE in childhood is observed mostly between the ages of 11 and 15 years, although the disease may present earlier in life.[10] Girls get lupus five times more frequently than boys, although this striking female preponderance is not seen until after puberty, suggesting the role of endocrine factors in the clinical expression of the disease.[11]

The clinical manifestation at the time of diagnosis in this study is mostly fever, malar rash and arthritis. These sign and symptoms are most commonly encountered in the literature. A collaborative study by the French Society of Pediatric Nephrology[12] reported that fever, rash and arthritis was the major clinical features in 62 children with SLE namely 75%, 72% and 64% consecutively.

The laboratory findings of the patients showed that eighty percent were anemic, twelve of them had evidence of hemolytic anemia. Anemia of moderate degree is common and a positive test for anti red cell antibodies can be obtained in about half of all children with lupus. However severe hemolytic anemia are not seen often.[2] Although anemia was reported to be one of the significant predictors of progression to renal failure,13 the finding in this study should be causiously interpreted since the prevalence of anemia among Indonesian children is high. Leukopenia is present in 25% and thrombocytopenia in 20% in this study. Leukopenia is commonly found in childhood lupus, sometime half of the patients have a white cell count below 5000/ul, whereas thrombocytopenia is less common, being found in one fourth of the patients.[2] Leukopenia presumably result from anti white cell antibodies, but the origins of thrombocytopenia are complex. Antibodies directed to dsDNA are commonly considered to be specific for active SLE. Hypocomplementemia is evident in more than three fourth of children with lupus and in a greater proportion of those with evident nephritis. Hypocomplementemia was found along with raised anti-ds DNA. In this study the percentage of positive ANA, dsDNA is found in 80% and 75% of the cases, while low C3 and C4 in 90% and 60% consecutively showing that the disease are still active.

The renal manifestation in this study are mostly acute glomerulonephritis and nephrotic syndrome. Mild presentation like isolated proteinuria and hematuria was only found in 13% of the patients. The mode of clinical presentation of renal disease is mostly related to the histological grade of renal biopsy. Of the patients who presented with nephrotic syndrome, all but one had proliferative glomerulonephritis (class 3 and 4) where as of those who presented with proteinuria had class 1 and 2 histologic feature.[14]

The natural history and overall prognosis of lupus nephritis in childhood as were in adult cases are closely correlated with the nature of the pathological renal lesions.[15] The prognosis are worst in cases with diffuse proliferative glomerulonephritis lesion (class 4).[16] Repeated biopsies showed that minimal lesion of focal and segmental glomerulonephritis may progress to more severe lesion such as diffuse proliferative lesion if not properly treated. On the other hand improvement of renal lesions may be observed and cellular proliferation of diffuse proliferative glomerulonephritis may resolve with adequate treatment. This emphasize the importance of early diagnosis and

prompt treatment in lupus nephritis in children. Five of 11 biopsy finding in this study showed histologic feature of diffuse proliferative lesion. The severity of clinical presentation and high proportion of class 4 renal histology finding could maybe explain the relatively high mortality in this study namely 9 out of 30 cases (30%). Recent publication showed that the mortality rate of SLE in children was only 15% in 10 years and 23% in 15 years period.[17]

The cause of death in this study are mostly due to terminal renal failure (5 of 9 cases). One due to shock of unknown cause, 2 due to cerebral hemorrhage and 1 due to septicaemia. In a compilation of 100 cases from several centres showed that 44 cases died due to renal failure, and 36 cases due to septicaemia, and 4 cases died caused by central nervous system involvement.[2] The importance of extrarenal involvement as a cause of death in children with lupus is evident in these series, particularly central nervous system and pulmonary hemorrhage. However, the main nonrenal cause of death is infection.

In mild cases renal involvement in children with SLE is often well controlled with corticosteroid alone. In children with severe lupus nephritis, intravenous methylprednisolone may provide dramatic anti inflamatory effects as was also experience in our cases. However, intravenous methylprednisolone is not satisfactory for long term control of lupus nephritis since this regimen has been associated with significant complication, including pancreatitis, hypertension, electrolyte abnormalities and death.[18,19] For cases with corticosteroid unresponsive lupus nephritis, combination with cytotoxic drugs are necessary. After the use of cyclophosphamide the prognosis for children with continuing active disease improved significantly.[20] Others reported that combination of prednison and azathioprine to be a satisfactory alternative.[21]

For lupus nephritis with histological lesion of diffuse proliferative glomerulonephritis the use of intermittent intravenous cyclophosphamide has been reported with dramatically improved outcome.[22] In comparison with daily oral therapy, the immunosuppressive effects of this regimen appear to be greater and its toxicity appears to be less.[22,23] In this report three patients received pulse cyclophosphamide. Beside a moderate degree of leucopenia and nausea, no other side effects was detected.

Hemorrhagic cystitis occurs in 15% of patients receiving cyclophosphamide. MESNA inactivates the cyclophosphamide metabolites responsible for bladder irritation.[24] We have used MESNA in our cases together with adequate hydration and no hemorrhagic cystitis was found among them.

Cyclosporine has been proposed as a useful therapy for children with corticosteroid-resistant lupus nephritis.[25] However, more studies of cyclosporine is still necessary before further recommendation of its use in lupus nephritis in children.

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