

Acute glomerulonephritis in Kelantan — a prospective study

Fabiola D'Cruz, MRCP (UK), M.Med. (S'pore)
Lecturer

Me Sepiah Abd. Hamid, MBBS (Mal)
Medical Officer

Ahmad Toha Samsudin, MD (UKM)
Lecturer

Thomas Abraham, * MD
Medical Officer

Departments of Paediatrics, Microbiology, Hospital Universiti Sains Malaysia,
Kubang Kerian, Kelantan*

Summary

A prospective study of acute nephritis in children was conducted at the Universiti Sains Malaysia Hospital, Kubang Kerian between July 1987 and June 1988. One hundred and twenty four children were admitted with acute glomerulonephritis. The aim of the study was to determine the clinical pattern of the nephritis as well as its aetiology. The majority of our patients came from the lower socio-economic group and 54% of the families had incomes below the poverty line. Preceding skin infection was much more common than throat infection. The children showed a high incidence of complications: severe hypertension (43.6%), hypertensive encephalopathy (11.3%), clinical pulmonary oedema (36.3%), severe azotaemia (10.5%), and prolonged gross haematuria (13.7%). By using immunologic indices such as ASOT, anti-DNase B and complement 3, it was concluded that 121 of the 124 patients had post-streptococcal nephritis.

Key words: Acute glomerulonephritis, children, poststreptococcal, Kelantan.

Introduction

Acute nephritis is a common problem in children in Kelantan. Between 1986 and 1990, about 600 cases of acute nephritis were admitted to the Universiti Sains Malaysia Hospital at Kubang Kerian.

In an earlier one-year retrospective study between April 1986 and March 1987, 220 children were admitted with acute nephritis.¹ The study showed that preceding skin infection (56%) was more common than throat infection (21%). There was an unusually severe spectrum of disease during the acute phase: severe hypertension (47%) with hypertensive encephalopathy in 8%, marked azotaemia and renal failure in 15% and prolonged gross haematuria beyond three

weeks in 13% of patients. Laboratory investigations showed that antistreptolysin O titre (ASOT) was positive in only 56% of patients. Acute nephritis in Kelantan has always been assumed to be poststreptococcal.

This prospective study was undertaken primarily to determine the aetiology of the glomerulonephritis – whether it was poststreptococcal as suspected, or otherwise. Although ASOT is an index of preceding streptococcal infection, the ASOT will often not be elevated in pyoderma due to alterations of the streptolysin O by skin lipids. However an elevation in antideoxyribonuclease B (anti-DNase B) titre will be found in more than 90 to 95 per cent of poststreptococcal glomerulonephritis preceded by pyoderma. Hence the combination of both ASOT and anti-DNase B responses should substantiate a preceding streptococcal infection in nearly 100 per cent of cases.²

Patients and Methods

The study was carried out at the Paediatric Department of the Universiti Sains Malaysia Hospital, which served as the only tertiary paediatric referral centre for Kelantan during the period concerned. All children with nephritis admitted to the paediatric ward during the one year period from July 1, 1987 to June 30, 1988 were included. Minimal criteria for diagnosis of acute nephritis were haematuria (macroscopic or microscopic) and/or proteinuria plus at least one of the following clinical features: facial oedema, oliguria, azotaemia, hypertension, pulmonary congestion.

One hundred and twenty four children fulfilled these minimal criteria during the one year period, and were diagnosed as acute glomerulonephritis (AGN). A standard protocol was used for history taking, physical examination and investigations. Preceding skin and throat infections and scabies were elicited in the history. This was counter-checked with physical examination for evidence of healed or fresh impetigo and scabies.

Blood samples were drawn from all cases for biochemical and immunologic investigations. Cultures of throat and suspected skin lesions were obtained routinely. Anti-streptolysin O titres (ASOT), antideoxyribonuclease B (anti-DNase B), Complement 3 (C3) and Complement 4 (C4) were done once in all patients at admission. The ASOT was done using the Latex agglutination technique. The anti-DNase B was done using the precipitation test. Both tests were done using standard kits from Behring, West Germany. The complement levels were determined using radial immunodiffusion technique. A chest X-ray was done on admission in all patients. A fresh specimen of urine was examined by microscopy for red cells and casts. Twenty four hour excretion of urinary protein was determined.

In order to exclude other non-streptococcal causes of post-infectious nephritis, blood film for malaria parasites, Hepatitis B surface antigen and Widal Weil-Felix tests were done in all children with nephritis. Cases which had an atypical or complicated course were screened for Antinuclear Antibody (ANA) and Lupus Erythematosus (L.E.) cells.

Results

Acute nephritis occurs throughout the year in Kelantan. The highest incidence of cases was in August 1987 (23 cases). Impetigo-associated AGN occurs in children of all age groups.³ In our patients, peak incidence was in the age group four to six years which is similar to that described

by Paul in Singapore in the 1960s.⁴ However the ages in our children ranged from two to twelve years. Our paediatric wards are restricted to children up to twelve years, therefore the incidence in the adolescent age group has not been studied. Of the 124 children, there were 67 males and 57 females, that is a ratio of 1.18 : 1. This is unlike the usual male predominance which has been described to be a 2 : 1 ratio.² Kelantan has a population of slightly over one million people. Of the population, 93% are Malays, 6% Chinese and 1% others. In our study, 120 children (96.8%) were Malays and four children (3.2%) Chinese.

The shortest period of hospitalisation was four days, while the longest was 66 days. The majority of children stayed between 10–20 days.

Socio-Economic Status

As can be seen from Table 1, 67 of the 124 families live below the poverty line for Peninsular Malaysia (income less than \$350.00 per month). Only eight families can be considered to fall into the middle-class category.

The average family size was eight members. The largest family consisted of fourteen members while the smallest family had four members. The majority of the families lived in “kampong” (village) houses with electricity but no piped water supply. They used well water and had pour-flush latrines. Due to constraints of time, only one home visit was made.

Table 1
Family income of 124 patients with acute glomerulonephritis

Amount per month	Number of families
< \$350	67
≥ \$350 < \$1000	37
≥ \$1000 < \$2000	7
≥ \$2000	1
(number not elicited = 12)	

Preceding Infections

Table 2 shows that preceding skin infection was much more common than preceding throat infection. Out of the 94 patients with preceding skin infections, 28 had scabies associated with impetigo.

Clinical Features

Table 3 shows the clinical features. Proteinuria was defined as 1+ or more on dipstix or greater than 0.5 gm protein in a 24 hour urine collection. Hypertension was defined as greater than or equal to 130 mm systolic or 90 mm diastolic blood pressure. Azotaemia was defined as a blood urea greater than 7 mmol/L. Pulmonary congestion refers to the chest X-ray findings suggestive

of pulmonary oedema but not all the patients with chest X-ray findings of pulmonary oedema had clinical symptoms and signs. Oliguria was defined as urine output less than 400 ml per 24 hours or a history of very poor urine output.

Table 2
Preceding infections in 124 children with acute glomerulonephritis

Preceding Infections	Number	%
Throat infections	7	5.6
Skin infections	86	69.4
Throat and skin infections	8	6.5
No infections	23	18.5
Total	124	100%

Table 3
Clinical features of acute glomerulonephritis in 124 children

Clinical Features	Number	%
Oliguria	71	57.3
Pulmonary congestion	73	58.9
Azotaemia	80	64.5
Hypertension	101	81.5
Gross haematuria	110	88.7
Proteinuria	111	89.5
Oedema	122	98.4

Complications

The children showed high incidence of complications (Table 4). Severe hypertension was defined as a diastolic blood pressure equal or greater than 110 mm Hg. The presentation of hypertensive encephalopathy ranged from headache, vomiting and visual disturbance to altered consciousness, coma and multiple seizures. One child was diagnosed as presumed meningitis and treated as such for two days before referral to us. Forty five children had clinically overt pulmonary oedema, presenting with cough, dyspnoea, tachypnoea and fine crepitations in the lungs. Out of 73 patients who had chest X-ray evidence of pulmonary oedema, only 45 children had clinically overt pulmonary oedema. Severe azotaemia was defined arbitrarily as a maximum blood urea greater than 15 mmol/L. 2 children required peritoneal dialysis for acute renal failure.

Laboratory Results

The main aim of this study was to determine whether the acute nephritis was poststreptococcal or otherwise. Since our patients had mainly impetigo-associated nephritis, merely doing the

Table 4
Complications in 124 children with acute glomerulonephritis

Complication	Number	Percentage
Hypertensive encephalopathy	14	11.3
Severe hypertension	54	43.6
Clinical pulmonary oedema	45	36.3
Severe azotaemia	13	10.5
Gross haematuria > 3 weeks	17	13.7

ASOT would not be adequate as the ASOT rises little, if any after impetigo.² Therefore the anti-DNase B titres were also done because it rises in over 90% of cases after streptococcal impetigo.⁵ The total serum complement activity is low during the acute stage of poststreptococcal acute glomerulonephritis and this is best reflected by measuring C3 levels.⁶ A depressed C3 has been considered the most pathognomic feature of acute poststreptococcal nephritis.⁷ The C3 usually returns to normal by six to eight weeks, although some may take as long as twelve weeks.⁸ Table 5 shows the results of ASOT, anti-DNase B and C3 levels in our patients.

Table 5
Immunological parameters in 124 children with acute nephritis

Immunological Abnormality	Number tested	Number positive (%)
C3 level < 66mg/100ml	123	116 (94.3%)
ASOT > 200units/ml	124	76 (61.3%)
Anti-DNase B > 200units/ml	118	91 (77.1%)
ASOT and/or Anti-DNase B +ve	118	108 (91.5%)

Normal complement 3 levels in our laboratory were between 66 to 130 mg/100ml. In the method used for anti-DNase B estimation a titre step of 200 was considered the upper limit of normal. A positive ASOT was greater than 200 units per ml. One patient did not have complement 3 levels done due to contamination of specimen. Six children did not have anti-DNase B done due to technical reasons.

Using a combination of depressed C3 and/or raised ASOT and/or raised anti-DNase B, 123 of the 124 patients fulfilled at least one of the immunological parameters. The sole patient who did not fulfil these criteria was probably not poststreptococcal nephritis. Two of the patients were excluded from being poststreptococcal glomerulonephritis because they had a positive antinuclear antibody (ANA). They were both negative for L.E. cells three times.

Only three children had throat swabs positive for group A beta haemolytic streptococci. Twenty children had skin swabs which were positive for group A beta haemolytic streptococci. Ordinary

blood agar was used for culturing and no typing of strains was done. One patient had group A beta haemolytic streptococci isolated from both throat and skin.

Hepatitis B surface antigen was positive in one patient but this was probably a co-incidental finding. All the patients had negative Widal Weil-Felix and no malaria parasites were detected.

Family Studies

Forty eight family members from 15 families were studied. These 48 family members – both adults and children had their blood taken for ASOT and anti-DNase B. Their urines were sent for protein and microscopy. Of the 48 family members, 20 had ASOT positive and 25 had anti-DNase B positive. Three of the family members had mild or subclinical nephritis – two of them had only microscopic haematuria while one had both facial oedema and microscopic haematuria. Complement levels were not checked in them. From the very limited study, it can be concluded that streptococcal infection is very common in family members of AGN patients. Complement levels need to be done as well to absolutely rule out subclinical poststreptococcal nephritis.

Family History of Acute Nephritis

Nine of the 124 patients had siblings who had been previously admitted for acute nephritis. Three families had siblings admitted at the same time during the study period. In one family, two siblings, a brother and a sister were admitted with acute nephritis. All the family members had scabies and impetigo and positive ASOT. The two patients and another brother had positive anti-DNase B. In another family, two siblings were admitted to the Paediatric ward, one sibling to the adult ward and another had mild AGN on screening-facial oedema and microscopic haematuria. Therefore out of five children in the family, four of them had acute nephritis at the same time. The third family had one child admitted to the Paediatric ward and another to the adult ward at the same time. The 15-year old child admitted to the adult ward had a past history of acute nephritis at the age of four years. Thus eight siblings from three families had acute nephritis at the same time during the study period.

Follow-Up

Except for one child who was discharged against medical advice, 123 of the 124 children recovered completely from the acute episode. Two children were re-admitted within the same year with recurrent acute nephritis. They satisfied immunological criteria for preceding streptococcal infection, and depressed C3 returning to normal. Another child with ANA positive nephritis who had recovered from the initial acute episode with prolonged haematuria and azotaemia, was re-admitted a few months later with haematuria, oedema and hypertension. He was no longer ANA positive and is well on follow-up. One child with poststreptococcal nephritis developed mild hypertension after discharge, which resolved spontaneously after several months. She had a past history suggestive of acute nephritis at the age of three years. The majority of the patients defaulted follow-up after a few visits. Some did not come at all for follow-up. Very few are still on follow-up but they are well.

Discussion

The depression of C3 has been found to be the most reliable indicator of acute poststreptococcal glomerulonephritis.^{7,9} All of our patients except one, had C3 levels done at onset, and 94.3% of them had significantly depressed C3 levels. Of the 118 patients who were tested for both ASOT and anti-DNase B 91.5% showed serological evidence of preceding streptococcal infection.

Except for one patient, all the other 123 children showed either depressed C3 levels and/or raised anti-streptococcal antibodies. Even the two children who had positive antinuclear antibody (ANA) had raised ASOT and anti-DNase B. One of them had depressed C3 levels which subsequently returned to normal, suggesting poststreptococcal nephritis. The other child had normal complement levels. Positive antinuclear antibody (ANA), anti-DNA antibodies and DNA-anti-DNA complexes have been reported in biopsy-proven poststreptococcal nephritis¹⁰ although their role is unclear. Since we did not do renal biopsies in the two ANA positive children, we have to exclude them from our analysis as being poststreptococcal glomerulonephritis. Therefore, taking the clinical and laboratory data into account, we believe that 121 of the 124 patients had acute poststreptococcal nephritis.

Clark attributed overcrowding and poverty for the higher incidence of nephritis in children from the lower socio-economic groups.¹¹ The socio-economic status of the families of our children shows that more than half of them live below the poverty line. Large families, overcrowding and poor housing lead to the spread of streptococci among family members through intimate contact. Several families of the nephritic children gave history of impetigo in all the family members. Dillon⁹ in screening 198 siblings of patients with overt AGN, found 18 cases of subclinical nephritis in the siblings. He found that the best index of subclinical nephritis was depressed C3 levels, and that this occurred whether or not there was haematuria. In our family studies, we did not measure C3 levels.

One wonders whether the incidence of endemic acute poststreptococcal nephritis is an inverse index of social progress and development. In Singapore between 1956 to 1960, 200 to 400 cases of acute nephritis were admitted annually to the Paediatric Unit of the Singapore General Hospital.⁴ They were mainly impetigo-associated poststreptococcal nephritis. To-day acute poststreptococcal nephritis is relatively uncommon in Singapore. In the United Kingdom, too, poststreptococcal nephritis is rare in recent years although it was common forty years ago.⁷

Although almost all children recover completely from the acute episode, the long-term prognosis of poststreptococcal glomerulonephritis has been a subject of controversy.¹² Baldwin and co-workers have reported a prevalence of about 50% chronicity in patients younger than 15 years at the time of nephritis.¹³ On long-term follow-up, proteinuria, hypertension or reduction in filtration rate was seen in patients who had apparently recovered fully from their acute episode. Baldwin also suggested that glomerular sclerosis indicated progressive renal damage rather than healing of the acute episode. Progressive renal failure developed in six of their adult patients over periods ranging from two to 12 years, and this was associated with the development of hypertension and glomerular sclerosis.¹⁴ Nissenson et al in Trinidad studied prospectively 722 children and adults, seven to 12 years after 'epidemic' and 'endemic' poststreptococcal nephritis. They found very little evidence of chronic renal disease.¹⁵

Baldwin stressed the probability that many patients with chronic renal failure may have had asymptomatic poststreptococcal nephritis in the past, and that asymptomatic poststreptococcal nephritis may be more common than symptomatic nephritis.¹⁴ This is supported by Dodge et al¹⁶ who found 19 asymptomatic patients in the families of 20 symptomatic patients. Most studies have shown that epidemic poststreptococcal nephritis has a better prognosis than sporadic disease and children have a better prognosis than adults. Pharyngitis related nephritis has been postulated to lead to chronicity more frequently than pyoderma related glomerulonephritis.¹⁵ The difference in prognosis reported by various workers has been attributed to different criteria being used to define chronic renal disease.⁶ Despite this, all studies show at least a small proportion of patients progressing to chronic renal failure. In order to know the prognosis in our local situation,

prospective long-term studies of these children with serologically proven poststreptococcal nephritis are needed. This will be difficult in a community, which does not come even for short-term follow-up.

For the present, we conclude that endemic impetigo-associated acute poststreptococcal glomerulonephritis is the predominant type of nephritis in children in Kelantan. In order to reduce the incidence of acute poststreptococcal nephritis and its possible sequelae of chronic renal disease, socio-economic development of the community has to be accelerated. Short-term measures of reducing streptococcal spread include treatment of all family members of AGN patients with systemic Penicillin and prompt systemic treatment of impetigo and pharyngitis in the community. Health education, family planning and better housing facilities are needed. Acute endemic poststreptococcal nephritis has to be eradicated in this community as it causes considerable morbidity in children during the acute episode, and we do not know its long-term consequences.

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References

1. D'Cruz F, Lau YF. Acute poststreptococcal glomerulonephritis: a review of 220 children. In the abstracts of the 1st International Congress of Tropical Paediatrics, p 28, 1987, Bangkok.
2. Jordan SC, Lemire JM. Acute glomerulonephritis: Diagnosis and treatment. *Paed Clinics N America*, 1982; 29: 857-73.
3. Earle DP, Potter EV. Poststreptococcal glomerulonephritis in the tropics. In *Tropical Nephrology* (Ed. by Kibukamusoke JW) 1984: 287-305, Citforge Pty Ltd.
4. Paul FM. A study of acute nephritis in Singapore children. *Journal Singapore Paediatric Society* 1963; 5:54-60.
5. Schwab TR, Donadio JV Jr. Serology in renal disease: a review. *Seminars in Nephrology* 1985, 5: 179-187.
6. Nissenson AR, Baraff LJ, Fine RN, Knutson DW. Poststreptococcal acute glomerulonephritis: facts and controversy. *Annals of Internal Med* 1979; 91: 76-86.
7. Meadow SR. Poststreptococcal nephritis - a rare disease? *Arch Dis Child* 1975; 50: 379-382.
8. Cameron JS, Vick RM, Ogg CS, Seymour WM, Chantler C, Turner DR. Plasma C3 and C4 concentrations in management of glomerulonephritis. *British Med Journal* 1973; 3: 668-72.
9. Dillon HC, Jr. Streptococcal skin infection and acute glomerulonephritis. *Postgrad Med J* 1970; 46: 641-52.
10. Vilches AR, Williams DG. Persistent anti-DNA antibodies and DNA-anti-DNA complexes in post-streptococcal glomerulonephritis. *Clinical Nephrology* 1984, 22: 97-101.
11. Clark NS. Social factors in the aetiology of nephritis in childhood. *Arch Dis Child* 1956; 31: 53-60.
12. Editorial: Is poststreptococcal glomerulonephritis progressive? *British Med Journal* 1977, 11: 975-6.
13. Baldwin DS, Melvin C, Gluck MC, Schacht RG, Gallo G. The long-term course of post-streptococcal glomerulonephritis. *Ann Intern Med* 1974, 80: 342-58.
14. Baldwin DS. Poststreptococcal glomerulonephritis. A progressive disease? *American Journal of Medicine* 1977, 62: 1-11.
15. Nissenson AR, Mayon-White R, Potter EV, Mayon-White V, Abidh S, Poon-King T, Earle DP. Continued absence of clinical renal disease seven to 12 years after post-streptococcal acute glomerulonephritis in Trinidad. *American Journal of Medicine*. 1979 67: 255-262.
16. Dodge WF, Spargo BH, Travis LB. The occurrence of acute glomerulonephritis in sibling contacts of children with sporadic acute glomerulonephritis. *Paediatrics* 1967, 40: 1028-30.