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Sick kidneys—an insight into post streptococcal glomerulonephritis in Central Australia

James Dowler[1], Angela Wilson[2]
[1]Alice Springs Hospital, [2]Royal Darwin Hospital, NT

Abstract

Aim: This study presents 5 years of admissions data to better understand the clinical course and burden of paediatric Acute Post-streptococcal Glomerulonephritis (APSGN) in Central Australia.

Methods: This retrospective observational descriptive study presents all cases of APSGN diagnosed in children under 14 years of age between 2010 and 2014 inclusive. Cases were confirmed using the Northern Territory Centre of Disease Control case definition guidelines. Case notes and electronic data relating to clinical presentation, management and outcomes were collected. Ethics approval was granted from the Central Australian Human Research Ethics Committee (HREC:16-433)

Results: 69 cases of APSGN were diagnosed in children during the study period and all cases occurred in Indigenous children. Mean hospital stay was 10.5 days. Preceding skin infection was identified in 65.2% of cases. Common complications included renal impairment (81.2%), facial, peripheral or pulmonary oedema (60.9%), hypertension (72.5%) and moderate hyperkalaemia (K≥6mmol/L) (15.9%), .

Patients were commonly managed with diuretics (75.4%,) antihypertensives (53.6%) and fluid restriction (65.2%). Treatment included long acting benzathine penicillin in only 34.8% of cases.

Co-occurring infections were common, including scabies and/or head lice (34.78%), urinary tract infection (21.74%), pneumonia (17.39%) and bacteraemia (8.70%)

There was no evidence of persistent renal impairment in cases at the time of most recent investigation (mean 1621 days following diagnosis).

Conclusion: APSGN is a common presentation in Aboriginal children in Central Australia and often requires prolonged hospital admission.. Children admitted to hospital require close monitoring due to the frequency of renal impairment and associated complications. Skin infection is the major exposure to Group A streptococcus and public health measures to limit Group A streptococcal exposure continues to be a priority in Aboriginal Health.

Introduction

Acute post-streptococcal glomerulonephritis (APSGN) occurs due to an immune mediated glomerular injury following the host's response to infection. Group A streptococcus (GAS).[1] APSGN is the most common form of glomerulonephritis in children and like other diseases caused by GAS infection, it is a disease of poverty and social disadvantage. [1,2]

Although the incidence of APSGN has declined in most parts of Australia and other industrialised and developed countries, the Northern Territory continues to have the highest documented global rate of this disease. The incidence of confirmed APSGN in the Northern Territory is 12.5/100,000 per person years in the general population, and 94.3/100,000 person years in Aboriginal Australians under 15 years of age.[3] There are limited data analysing the acute clinical presentation of APSGN and no studies have described APSGN in Central Australia or Australian Aboriginal communities. [4-10]

The clinical presentation and course of APSGN in Australia has been described in the literature in a cohort cases identified in Sydney.[11] These data were collected from a tertiary referral centre and identified only 37 cases of PSGN over a period of 16 years. The majority were found to have a recent history of upper respiratory tract infection with skin infection occurring much less frequently.[11] The pattern of illness and clinical course of APSGN is not generalisable to endemic areas of Australia, such as Central Australia, due to the population and environmental differences seen in the region.

Alice Springs Hospital services an area of Central Australia covering 900,000 km^2 and a population of 48,000 people, of whom 44% identify as Aboriginal or Torres Strait Islander.[12] As the paediatric referral centre for Central Australia, Alice Springs Hospital sees a large number of children presenting with symptomatic APSGN.

This aim of this study is to present five years of admissions data to better understand and document the clinical course and incidence of paediatric APSGN in Central Australia.

Methods

Retrospective admission data were obtained from Alice Springs Hospital for 174 of children under 14 years of age coded, with International Statistical Classification of Disease and Related Health Problems 10^{th} revision (ICD-10) codes relating to nephritic syndrome or persistent haematuria between 1 January 2010 and 31 December 2014. Cases of APSGN were defined using the Northern Territory Centre of Disease Control case definition guidelines for Post Streptococcal Glomerulonephritis with APSGN, specifically haematuria with low C3 and serological evidence of recent GAS infection or positive GAS culture from skin or throat swabs.[13] Re-presentation within one month was considered part of a single occurrence. Cases were classified as probable APSGN in instances where the diagnostic criteria were fulfilled but without laboratory evidence Group A Streptococcal infection. All six cases of undifferentiated glomerulonephritis had an acute illness with haematuria, low C3 but negative or not completed streptococcal serology and skin or throat culture. All undifferentiated cases had a clear history of streptococcal exposure and a self-resolving clinical course.

Information was collected from case notes as well as electronic hospital data and data from cases' Shared Electronic Health Record. Patient demographic data collected included Aboriginal or Torres Strait Islander status, age at diagnosis, gender, residence at diagnosis, month and year diagnosed.

Clinical information at presentation included; past diagnosis of APSGN, history of recent streptococcal infection, clinical evidence of recent streptococcal infection, clinical signs of fluid

overload, macroscopic haematuria, hypertension, cardiac failure, respiratory failure, hypertensive encephalopathy, admission weight-discharge weight, evidence of comorbid disease.

Laboratory data collected included lowest haemoglobin and mean corpuscular volume (MCV), peak urine albumin to creatinine ratio, peak serum creatinine, urea and potassium, C3 and C4 value, anti-streptolysin O titre (ASOT), antiDNAse B titre and swab culture results. Radiological and management data included renal ultrasound findings, diuretic, antihypertensive and benzathine penicillin treatment, duration of fluid restriction, transfer status and mortality.

Cases were considered to have completed follow up if they had repeat C3 and C4 serology after discharge. Case records were reviewed for evidence of ongoing renal impairment more than 12 months after diagnosis using most recent laboratory values.

Ethics approval was granted from the Central Australian Human Research Ethics Committee (HREC: 16-433). Statistical analysis was conducted using GraphPad software. The investigators retained no identifiable patient data.

69 out of the 174 cases reviewed were identified as either APSGN (63) or probable APSGN (6). All cases identified as being Aboriginal and 50.7% were male. Patients came from 25 towns and communities across central Australia, with the two largest townships, Alice Springs (9) and Tennant Creek (10) accounting for the highest number of cases.

Streptococcal serology (ASOT and/or antiDNAse B) was completed in all patients, with negative serology in eight (12%). Two of these were positive on follow up serology, one remained negative and five had no convalescent serology.

Frusemide was given in 52 patients, with fluid restriction prescribed in 45 cases for a median of 8 days. 37 cases were treated with antihypertensives (*table 2).* Antihypertensives were given for a median of five days, with a range of 1 to 23 days. Three cases continued antihypertensive medication on discharge.

Long acting benzathine penicillin was given in 24 cases. Five required transfer to tertiary centres for further management and investigation (four underwent renal biopsy to confirm diagnosis and one was transferred for concurrent cardiomyopathy).

Admissions ranged from 2-37 days with a median of 9 days.

Follow up ACR (at greater than 12 months) was observed in 42 cases. 2 cases had urine ACR >10g/mol.

No cases had abnormal urea (range 2.3-6.2mmol/L) or creatinine (range 18-85micromol/L) when taken more than 12 months from presentation.

Follow up of complement levels were completed in 42 patients. C3 was normal in 40 cases. The remaining case samples were tested at 5 and 72 days post diagnosis. C3 had increased from 0.06g/L to 0.75g/L and 0.07g/L to 0.8g/L respectively(normal range 0.9-1.6)[14]. Repeat complements were taken over a large spread of with a median of 107 days (range 5-1825)

Table 1 Summary of Investigations: averages given as median (interquartile range)

	Median (Interquartile range)
Haemoglobin	104g/L (96-111)
MCV	77fL (75.4-78.7)
Urine ACR	71.1g/mol (33.4-239.1)
Peak Urea	11.5mmol/L (7.9-17.3)
Peak Creatinine	65 micromol/L(48-88)
Peak Potassium	5.1 mmol/L (IQR 4.6-5.7)
Patients with potassium >6mmol/L	11 (15.9%)
Serology	
C3 value	0.17g/L (0.12-0.29)
Patients with ASOT ≥300 IU	52 (75.4)
antiDNASE B≥400 IU	59 (86.8%)
Positive serology at presentation	61 (88.4%)
Microbiology	
Swabs taken for culture	23 (46.4%)
Throat swab taken for culture	11
Throat swab culture positive	0
Skin swab taken for culture	25
GAS alone	1 (4.0%)
GAS + *Staphylococcus aureus*	13 (52.0%)
Staphylococcus aureus alone	5 (20.0%)
Negative culture	6.0 (24%)
No skin or throat cultures taken	37 (53.6%)
Renal U/S	
Completed	52/69 (75.4%)
Parenchymal changes	13/52 (25.0%)
Kidney size >2SD or >95%ile above mean for age or height	4/52 (7.7%)
Prominence of the renal pelvices	1 (1.9%)

ACR: Albumin to creatinine ratio; ASOT: Anti-streptolysin O titre; GAS: Group A streptococcus; MCV: Mean corpuscular volume.

Table 2 Medical management of hypertension

Nifedipine	29 (78.4%)
Amlodipine	21 (56.8%)
Perindapril	2 (5.4%)
Atenolol	1 (2.7%)

Discussion

Our study showed a number of differences compared to what has previously been reported (Table 3). Age of presentation of APSGN was generally younger in our cohort and there was no male predominance identified.

Table 3 Comparison of previous studies

	Sarkissian et al[4]	Becquet et al[5]	Malla et al[6]	Wong et al[7] ***	Krishnamurthy et al[8]	Loewen et al[9]	Arungirinathan et al[10]	Present study
Location	Armenia	French Polynesia	Pokhara, Nepal (AGN)	New Zealand	Pondicherry, India (PSGN data)	Ontario, Canada (PSGN data)	Pondicherry, India	**Alice Springs**
Time Period	1992–1996	2006–2007	2000–2007	2008	2014	2010–2015	2012–2014	**2010–2014**
Study type	Prospective	Retrospective	Prospective	Retrospective	Prospective	Retrospective	Retrospective	**Retrospective**
Sample size	474	50	92	27	65	10	52	**69**
mean age (years)	7.5	6.7	4 cases< 5years 33 cases 5-10 years 55 cases >10years	9.4	6.8	6.8	1-5 40.3% 5-10 52% >10 7.7%	**5.8**
Male: Female	1.86:1	1.17:1	1.67:1	1.45:1	1.16:1	4:1	1.08:1	**1.03:1**
Hypertension	72%	64%	86.9%	-	92.3%	90%	100%	**72.46%**
Skin source	13%	20%	45.6%	-	89.2%	10%	6.5%	**68%**
Throat source	51%	30%	30.4%	-	6.2%	30%	17%	**10.14%**
Low C3	95%	90%	-	61.5%	100%	40%	100%	**100%**
Cr (mmol/L)	27% 100-299 2% >300	454.36**	59%< 132.6 25% 132.6--142 16%>142	-	70.72 (61.88-88.4)	56umol/L (44-67)*	56.93 (26.52 - 106.08)*	**65 umol/L (48-88)**
Urea (median) mmol/L	-	-	43.5% <14.28 42% 14.29-35.69 10%>35.7	-	7.49 (5.00-11.32)	-	6.78 (0.83-24.62)*	**11.5mmol/L (7.9-17.3)**

*IQ range
** mean
*** - cohort of cases diagnosed by renal biopsy

The prevalence of elevated ASOT titres has been previously reported to be between 4.6% and 46%.[8-10] In our population streptococcal serology titres were much more frequently positive, with elevated titres seen in 88% of cases on presentation. A higher threshold for positivity was also used in our study with cut offs of ≥300IU for ASOT and ≥400IU for Anti-DNAse B compared to ≥200IU and ≥300IU in other studies. This suggests either significantly increased Group A streptococcal exposure in our study cohort or increased response to the exposure.

There was no mortality observed in our study confirming the widespread recognition that the short term prognosis from APSGN is good in patients with access to appropriate medical care.[15] We observed significant morbidity in the form of transfer for biopsy or dialysis. Five cases were transferred for specialised care and four of these cases referred for confirmatory renal biopsy. It is current practice at Alice Springs Hospital to observe patients with APSGN until downward trend in urea and creatinine are observed and proteinuria and hypertension have resolved. The tyranny of distance between Aboriginal communities and Alice Springs Hospital and infrequent transport may lead to prolonged admission for social or logistic reasons and difficulties undertaking clinical review and repeat pathology tests after discharge.

Our study did not look at subclinical cases of APSGN in contacts of population. Previous studies have suggested that sibling contacts have increased risk of clinical and subclinical APSGN, with 22.3% found to have abnormal urinalysis and 9.4% to have active nephritis.[16] To fully appreciate the burden of disease of this condition morbidity of contacts and the cost of the public health response therefore need to be taken into account. The current public health response involves screening and treatment of household contacts, and in outbreaks, screening of all children in a community.[13]

There was significant variability in the medical management of APSGN. The Northern Territory Centre of Disease Control recommends that each case be treated with long acting benzathine penicillin to assist with public health management.[13] Only 37% of cases were observed to fulfil this requirement. This suggests not only poor practice in complying with NT guidelines, but also poor communication between the Centre of Disease Control and practitioners. Time taken until follow up was also variable, indicating that the systems in place for follow up and management of APSGN clients is not robust. Since this time period new APSGN protocols within Alice Springs Hospital have been developed to improve quality and safety of patients and maintain good practice.

Housing and overcrowding play an important role in a number of preventable diseases in Central Australia. Approximately 52% of Aboriginal and Torres Strait Islander people in the Northern Territory lived in overcrowded houses during the study time period, with overcrowding being attributed to a number of physical, behavioural and mental health concerns.[17] These houses often have substandard facilities to maintain hygiene and health, often leading to skin disease and chronic infection.[18]

There has been government recognition of the impact that housing plays in remote wellbeing and health. Efforts to improve housing have led to improvement in overcrowding over the past decade. It is not yet known the effect that this has had on the physical health of the remote population.[19]

It has been demonstrated that type of renal disease and requirement of renal replacement therapy is closely associated with remoteness and socioeconomic status for Aboriginal Australians. This suggests that the environmental factors associated with living remotely is a significant driver in kidney health. There is little evidence of heritability of kidney disease causing significant burden, but combined risk factors such as inter uterine growth restriction and APSGN are strongly associated with renal morbidity. [20]

This study is limited by small patient numbers, retrospective data collection and variable or incomplete documentation of key clinical information such as the presence of macroscopic haematuria, oedema and comorbidities including head lice, scabies and skin sores. Follow up data may not be generalisable to the total study population as it depended on patient engagement with local health centres and paediatric outreach visits, patient mobility and the variable time to follow up.

Conclusion

The study adds further evidence to the known increased burden of streptococcal disease disproportionally affecting Aboriginal Australians and assists in recognising gaps in care and management of this disadvantaged group. Primary care clinicians, paediatricians and public health workers need to ensure that cases are appropriately recognised, managed and followed up. Variability in hospital management and procedure should be reduced and communication between services optimised to improve patient care.

Research focusing on housing development and public health programs and the rate and severity of GAS sequaele, including PSGN is needed to better inform the future directions of program management.

References

1 Balasubramanian R, Marks SD. Post-infectious glomerulonephritis. Paediatr Int Child H. 2017;37(4): 240-7.

2. Carapetis J, Steer A, Mullholland E, Weber M. The global burden of froup A streptococcal diseases. *Lancet Infect Dis.* 2005;5:685-94.

3. Marshall CS, Cheng AC, Markey PG, Towers RJ, Richardson LJ, Fagan LS, et al. Acute Post-Streptococcal Glomerulonephritis in the Northern Territory of Australia: A Review of 16 Years Data and Comparison with Literature. *Am J Trop Med Hyg.*2011; 85: 703-10.

4. Sarkissian A, Papazian M, Azatian G , Arkiants N, Babloyan A, Leumann E. An epidemic of acute postinfectious glomerulonephritis in Armenia. *Arch Dis Child.* 1997;77:342-4.

5. Becquet O, Pasche J, Gatti H, et al. Acute post-streptococcal glomerulonephritis in children of French Polynesia: a 3-year retrospective study. *Pediatr Nephrol.* 2010;25:275-80.

6. Malla K, Sarma M, Malla T, Thaplial A. Varied presentations of acute glomerulonephritis in children. Single centre experience from a developing country. *Sultan Qaboos Univ Med J.* 2008;8:193-9.

7. Wong W, Morris MC, Zwi J. outcome of severe acute post-streptococcal glomerulonephritis in New Zealand CHildren. *Pediatr Nephrol*. 2009;24:1021-6.

8. Krishnamurthy S, Mahadevan S, Harish B. Clinical characteristics and outcome of post-infectious glomerulonephritis in children in southern India: a prospective study. *Indian J Pediatr.* 2015;82:896-903.

9. Loewen K, Kelly L, Olivier C, Kirlew M, Tobe S, Saginur R, Schreiber Y. Acute post-streptococcal glomerulonephritis in northwestern ontario: a six-year retrospective study. *JAMMI*. 2017 Published Online: September 05, 2017 DOI: 10.3138/jammi.1.3.0

10. Arunagirinathan A, Narayanaswamy D, thirunavukaransu B, Raghavan A, Raghavendhran V. Clinical spectrum and outcome of acute post-infectious glomerulonephritis in children: a hospital based study. *IJSS.* 2015; 3:163-166.

11. Blyth CC, Robertson PW, Rosenberg AR. Post-streptococcal glomerulonephritis in Sydney: A 16 year retrospective review. *J Paediatr Child Health*. 2007;43:446-50.

12. Northern Territory Government. NT Health Governance: Central Australia Health Service (CAHS). 2017. [updated 2018 March 27; cited 2018 November 27].Available online: **https://health.nt.gov.au/health-governance/central-australia-health-service**

13. Northern Territory Government, Department Of Health and Families, Centre for Disease Control. Northern Territory Guidelines for Acute Post-streptococcal Glomerulonephritis 2010. Second Edition. June 2010.

14. Royal College of Pathologists of Australia. RCPA Manual. Complement components C3 and C4. 2015 [Updated 2015 June 3; cited 2018 November 28]. Available from **https://www.rcpa.edu.au/Library/Practising-Pathology/RCPA-Manual/Items/Pathology-Tests/C/Complement-components-C3-and-C4/**

15. Kasahara T, Hayakawa H, Okubo S, Okugawa T, Kabuki N, Tomizawa S et al. Prognosis of acute poststreptococcal glomerulonephritis (APSGN) is excellent in children, when adequately diagnosed. *Pediatrics International*. 2001; 43:364-7.

16. Tasic V, Polenakovic M. Occurence of subclinical post-streptococcal glomerulonephritis in family contacts. *J Paediatr Child Health.*2003;30:177-9.

17. Central Australian Aboriginal Congress. Aboriginal Corporation. Discussion Paper: Housing and Health. March 2018.

18. Brewster D, Halpin S, McDonald E, Stevens Matthew R, Bailie Ross S, Robinson G, et al. Skin infection, housing and social circumstances in children living in remote Indigenous communities: testing conceptual and methodological approaches. *BMC Public Health*. 2005;5(1):128

19. Commonwealth of Australia, Department of the Prime Minister and Cabinet, *Remote Housing Review: A review of the National Partnership Agreement on Remote Indigenous Housing and the Remote Housing Strategy* (2008-2018).

20. Hoy W. Kidney disease in Aboriginal Australians: a perspective from the Northern Territory. *Clin Kidney J*. 2014:7;524-30.

Presenter

Dr James Dowler is a consultant paediatrician who has worked at Alice Springs Hospital since 2015. He provides paediatric outreach services to a number of Central Australian communities and is involved in the development of a number of paediatric health-related services in Alice Springs including Diabetes in Youth clinic and Alice Springs Autism Assessment Service. He is passionate about identifying and rectifying barriers to health care in rural and remote locations and the prioritisation of assisting the socially disadvantaged. Dr Dowler studied Medicine at UTAS in Hobart and Launceston, graduating in 2008, and trained in paediatrics through the Women's and Children's Hospital Network in Adelaide and completed a Masters in Public Health through James Cook University in 2016.