Incidence of Acute Post-Streptococcal Glomerulonephritis in Hawai‘i and Factors Affecting Length of Hospitalization

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Abstract

Acute post-streptococcal glomerulonephritis (APSGN) is a disorder of inflammation in the glomeruli and vasculature of the kidneys that is caused by immune-complex formation after Streptococcus pyogenes infection. Most patients with APSGN present with macroscopic hematuria, edema, and hypertension, however presentation can vary from no symptoms to severe proteinuria, or even acute renal failure. This study sought to estimate the incidence of APSGN among children in Hawai‘i, to identify populations at increased risk for APSGN, and to recognize risk factors correlated with the length of hospitalization by subtype of APSGN (eg, pyoderma-associated, pharyngitis-associated). This retrospective review of 106 patients found that the incidence of APSGN in Hawai‘i is greater than 4 per 100,000 children, which is significantly higher than the incidence of APSGN in high-income countries at 0.3 per 100,000 children. This increased incidence may be due to Hawai‘i’s unique racial group composition and therefore the unique immunologic response of the children of Hawai‘i (particularly Pacific Islanders, who represent 62% of patients with APSGN in this study, but only represent 10% of Hawai‘i’s general population). In addition, there may be increased prevalence of nephritogenic strains of Streptococcus pyogenes in Hawai‘i. The length of hospitalization was significantly increased in children with elevated serum creatinine levels (P <.0001) and lower bicarbonate levels (P =.0003).

Keywords

Acute post-streptococcal glomerulonephritis, Length of hospitalization, Pediatric, Streptococcus, Pacific Islander

Introduction

Acute post-streptococcal glomerulonephritis (APSGN) is a disorder of inflammation in the glomeruli and vasculature of the kidneys, caused by immune-complex formation secondary to *Streptococcus pyogenes* infection.[1] The clinical presentation can vary from no symptoms to acute renal failure; however, most patients present with edema, hypertension, and macroscopic hematuria.[1,2] While APSGN is considered rare in high-income nations (incidence is estimated to be about 0.3 new cases per 100,000 individuals per year),[1] the incidence in low-income countries is estimated to be much higher (between 9.5 and 28.5 new cases per 100,000 individuals per year).[3,4]

By investigating all cases of APSGN in pediatric patients at one local health care facility, we studied children hospitalized with APSGN in Hawai‘i, particularly the incidence, demographic information, and clinical characteristics. Most children with APSGN are hospitalized for severe hypertension or acute renal failure, but there may be other factors (ie, age, sex, level of fluid overload, laboratory results) that affect the length of hospitalization in these patients. To our knowledge, the length of hospitalization in children with APSGN and the risk factors that may prolong hospitalizations have never been investigated in Hawai‘i or elsewhere. A better understanding of these factors could help to predict the severity of APSGN in children.

Methods

This study included all young people hospitalized at Kapi‘olani Medical Center for Women and Children, the only pediatric hospital in Hawai‘i, between January 2008 and December 2014 with the diagnosis of APSGN. We included all patients aged 21 and younger who were hospitalized for APSGN. APSGN was defined by the following criteria: acute onset of glomerulonephritis with hematuria and/or proteinuria, depression of serum C3 levels, and evidence of streptococcal infection.

Medical records of all patients were reviewed by author B.L. Descriptive characteristics (ie, age, sex, race), clinical features (ie, history of streptococcal infection, blood pressure at hospital admission, blood urea nitrogen, creatinine, streptococcal titers), as well as length of hospitalization were obtained for all patients. Estimated glomerular filtration rates were calculated using the Schwartz formula,[5] which includes the patient’s height and serum creatinine level in the calculation.

Demographic and clinical information were summarized using means and standard deviations (SD) for continuous variables and frequencies and percentages for categorical variables. Due to skewed distributions of length of hospitalization ranging from days to weeks, Wilcoxon rank-sum tests were used to evaluate whether significant differences existed between 2 or more groups. Pearson correlation tests were also used to evaluate the association between length of hospitalization and continuous variables. Two-sided $P \leq .05$ were considered statistically significant. Data analysis was conducted using SAS statistical software version 9.3 (SAS Institute Inc.:Cary, NC).

The Hawai‘i Pacific Health Research Institute provided Institutional Review Board (IRB) exemption for this study. This study conforms to the provisions of the Declaration of Helsinki, as revised in 2013.

Results

There were 106 patients aged 21 and younger hospitalized with APSGN at Kapiʻolani Medical Center for Women and Children between 2008 and 2014. Therefore the calculated incidence of APSGN in Hawai'i is 4 new cases per 100,000 people aged 21 and younger per year. This calculated incidence is obtained by using 106 as the numerator, and 372,955 as the denominator (the estimated population of people 21 years and younger in Hawai'i each year during the time period 2008-2014),[6] and then further divided by the duration of 7 years.

In this cohort, the mean age was 8.3 ± 3.8 years (range 2-21 years) and there were more males (64%) than females (Table 1). The majority of patients identified themselves as Pacific Islanders (62%), while 22% identified as Asian, 4% as white, 1% as African American, and 11% as Other. This racial breakdown differs from the general population of Hawai'i because Pacific Islanders comprise only 10% of the general population.[6]

Table 1. Demographic and Clinical Characteristics of the 106 Participants at Time of Admission

Characteristic	Value
Age, mean ± SD	8.3 ± 3.8 years
Sex, n (%)	
Male	68 (64%)
Female	38 (36%)
Race, n (%)	
Pacific Islander	66 (62%)
Asian	23 (22%)
White	4 (4%)
African American	1 (1%)
Hispanic	0 (0%)
Other	12 (11%)
Clinical Manifestations, n (%)	
Adenitis	35 (33%)
Edema	67 (63%)
Hypertension	79 (75%)
Pyoderma	43 (41%)
Pharyngitis	50 (47%)
Laboratory Data, mean ± SD	
Blood Urea Nitrogen, serum (normal range 7-17 mg/dL)	30 ± 23 mg/dL
Creatinine, serum (normal range 0.3-1.1 mg/dL)	1.1 ± 0.8 mg/dL
Potassium, serum (normal range 3.6-5.3 mmol/L)	4.3 ± 0.5 mmol/L
Bicarbonate, serum (normal range 20-30 mmol/L)	21 ± 2.9 mmol/L
C3 level (normal range 87-158 mg/dL)	27 ± 25 mg/dL
C4 level (normal range 12-36 mg/dL)	18.5 ± 6.8 mg/dL
ASO titer (normal range 87-158 IU/mL)	791 ± 805 IU/mL

SD, standard deviation; ASO, antistreptolysin O (antibodies against streptolysin O, a substance produced by *Streptococcus pyogenes*)

Urine microscopy was performed for all 106 patients, and all patients presented with microscopic hematuria and proteinuria. Hypertension was exhibited in 74% of patients, while 63% had edema, and 33% had adenitis. From history, examination, or diagnostic tests, clinicians identified a likely source of infection in 93 patients (88%). Streptococcal pharyngitis was the likely source in 47% of patients, while streptococcal pyoderma (a skin infection) was the likely source of infection in 41% of patients. There was no source identified in the remaining 13 patients. At hospital admission, serum creatinine was elevated in 67% of patients, estimated glomerular filtration rate was elevated in 50% of patients, serum blood urea nitrogen (BUN) was elevated in 58% of patients, serum bicarbonate was depressed in 31%, and serum antistreptolysin O (ASO) titer was elevated in 83% of patients. ASO titers measure antibodies against streptolysin O, a hemolytic toxic substance produced by *Streptococcus pyogenes*.[3,7]

The length of hospitalization ranged from 2 to 21 days, with a mean of 4.7 days (Figure 1). Using correlation analysis, increased length of hospitalization was associated with higher admission serum creatinine ($P < .0001$) (Table 2). Length of hospitalization was inversely associated with admission serum bicarbonate ($P = .0003$). Other factors such as systolic blood pressure, diastolic blood pressure, admission serum BUN, serum potassium, and ASO titers were not associated with the length of hospitalization.

Wilcoxon rank-sum tests were used to determine whether length of hospitalization differed between patients who had pyodema and/or pharyngitis upon admission compared to those who did not have these conditions. No statistically significant difference was found among the groups.

Table 2. Pearson Correlation Coefficients of Characteristics and Length of Hospitalization

Variable	Pearson Correlation Coefficient	*P*-Value
Length of hospitalization (LOH)	1	—
Blood urea nitrogen, serum	0.186	.057
Creatinine, serum	0.382	< .0001
Potassium, serum	0.100	.308
Bicarbonate, serum	-0.349	.0003
ASO titer	0.053	.604
Systolic blood pressure	-0.123	.211
Diastolic blood pressure	-0.090	.361
Percent weight change	0.139	.154

ASO, antistreptolysin O (antibodies against streptolysin O, a substance produced by *Streptococcus pyogenes*)

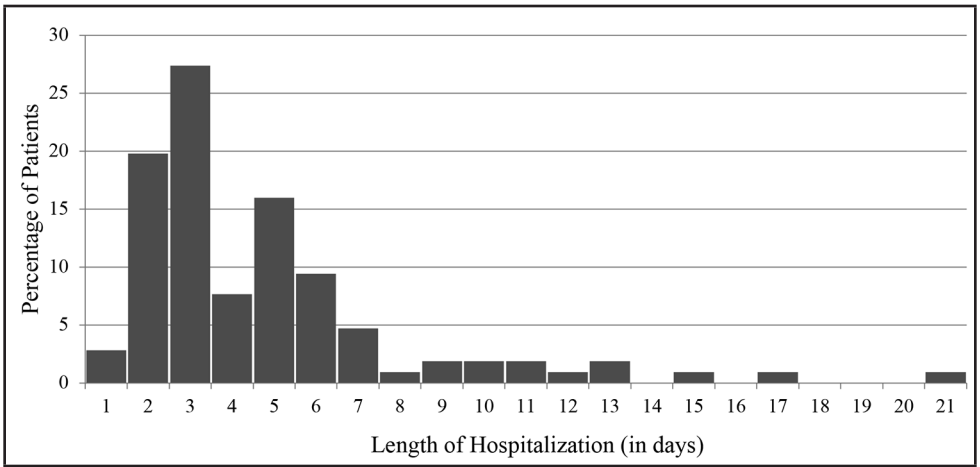

Figure 1. Length of Hospitalization Among APSGN Patients

Discussion

Hawai‘i’s incidence of ASPGN is 4.0 per 100,000 children per year, which is much higher than the reported incidence of 0.3 per 100,000 children per year in high-income countries.[1] Instead, Hawai‘i’s incidence of APSGN approaches the incidence of low-income countries (incidence of 9.5 to 28.5 per 100,000 children).[3,4] Furthermore, our calculated incidence is likely an underestimate of the true incidence because our study did not capture outpatient data (it is possible that some children with APSGN do not require hospitalization) and because our study only captured hospitalizations in 1 hospital in Hawai‘i. The reason for Hawai‘i’s high incidence of APSGN is unclear; it may be due to the unique genetic composition of the residents of this state (in part due to the high influx of people immigrating from low-income countries), as well as the particular strains of *Streptococcus pyogenes* in this environment.

Although Pacific Islanders (including Native Hawaiians, Polynesians, and Micronesians) comprise only 10% of Hawai‘i’s population,[6] Pacific Islanders represent 62% of patients with APSGN in this study. This over-representation of indigenous populations among APSGN cases in Hawai‘i is similarly seen in Australia, where Aboriginal Australians disproportionally represent the patients who develop APSGN. Some of the largest studies conducted on APSGN have been conducted in Australia and have found increased rates in Aboriginal populations compared to non-Aboriginal populations. Blyth, et al, found that Aboriginal Australians represent 30% of patients with APSGN, yet only comprise 2.4% of Australia’s population.[8] Meanwhile, Marshall et al found the rate ratio of cases in Aboriginal Australians to non-Aboriginal Australians was elevated at 53.6 (95% CI =32.6-94.8).[4] This over-representation of APSGN in Pacific Islanders in Hawai‘i and Aboriginal Australians in Australia may suggest that there are immunologic differences between racial groups that may increase the susceptibility of APSGN in these racial groups.

In addition to host factors, the particular strains of *Streptococcus pyogenes* in Hawai‘i may also be contributing to the higher incidence of ASPGN. There are hundreds of strains of *Streptococcus pyogenes*, each with a different cell wall-associated M protein, which is encoded by the *emm* gene.[7] The M protein is an antigenic epitope and virulence factor, and therefore forms the basis for serotyping of *Streptococcus pyogenes*.[7,9] Reports of serotyping in Hawai‘i found that 54% of *Streptococcus pyogenes* serotypes identified in Hawai‘i were not commonly identified elsewhere.[10] The most common *Streptococcus pyogenes emm* serotypes in Hawai‘i were 1, 2, 4, 12, 22, 28, 49, 58, 65, 74, 77, 81, 85, 92, 101.[10] Of these *emm* serotypes, serotypes 1, 2, 4, 12 and 49 are known to be nephritogenic strains of *Streptococcus pyogenes*.[9]

Our study found that length of hospitalization is increased in patients with higher admission serum creatinine levels (Pearson correlation factor: 0.382, $P < .0001$). Length of hospitalization is also increased in patients with lower admission bicarbonate levels (Pearson correlation factor: -0.349, $P = .0003$). Higher creatinine and lower bicarbonate levels indicate a higher severity of kidney injury and disease, which may require longer hospitalization. Patient discharge is often delayed while waiting for improvement of creatinine or signs of acute renal failure. Although a lower bicarbonate level could suggest renal tubular acidosis, the injury of APSGN involves immune complex deposition in the glomeruli; injury of the tubules has not been described.[1] In addition, renal tubular acidosis often results in sodium wasting however the patients in this study had preserved serum sodium levels.

Severity of hypertension and fluid overload (as calculated by percent weight change throughout hospitalization) were not significantly associated with the length of hospitalization. Although APSGN patients are often hospitalized specifically for hypertension and fluid overload, these manifestations can be addressed with intravenous diuretics and antihypertensives. These medications act quickly and rarely delay discharge.

Our study is the first to estimate the incidence of APSGN in Hawai‘i. To our knowledge, no study has looked at risk factors prolonging the length of ASPGN hospitalizations. Although our study provides novel information, our results should be interpreted in the context of some limitations. First, our study has a relatively small sample of patients. Second, our study has a retrospective and uncontrolled study design. Third, we calculated the annual incidence of APSGN for the entire state of Hawai‘i (rather than the island of O‘ahu) despite collecting cases from only 1 O‘ahu hospital. We did this because we found that a significant portion of the 106 patients with ASPGN came from neighboring islands based on their residential zip codes (11 from Hawai‘i, 7 from Maui, 6 from Kaua‘i, and 2 from Moloka‘i).

Conclusion

The incidence of APSGN in Hawai‘i is higher than the typical rates seen in high-income countries, which may be due to the population's unique racial composition, the differences of immunologic response between different racial groups (particularly the Pacific Islanders), or possibly increased nephritogenic strains of *Streptococcus pyogenes* in Hawai‘i. Hospitalizations were longer in patients with higher admission creatinine levels and lower bicarbonate levels. Further studies should be conducted to determine the reasons for the increased incidence in Hawai‘i and the differences between pyoderma-associated and pharyngitis-associated APSGN.

Conflict of Interest

None of the authors identify a conflict of interest.

Disclosure

Author HJA is partially supported by a grant U54MD007584 from the National Institute on Minority Health and Health Disparities, part of the National Institutes of Health (NIH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. No other authors report any financial disclosures.

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