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Original Article

Risk factors for hypertensive crisis in children with acute glomerulonephritis

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Abstract

Background Hypertensive crisis occurs in 1-4% of the hypertensive pediatric population, mostly due to acute glomerulonephritis (AGN). Some factors have been suggested to affect blood pressure (BP) in children, such as age, sex, race/ethnicity, obesity, and socioeconomic status, but little is known for risk factors for hypertensive crisis in AGN.

Objective To analyze the risk factors for hypertensive crisis in children with AGN.

Methods Retrospectively, we studied possible risk factors for hypertensive crisis in children with AGN at Dr. Soetomo Hospital from 2007 to 2011. Hypertensive crisis was defined as systolic BP ≥180 mmHg or diastolic BP ≥120 mmHg (for children ≥ 6 years of age); and systolic and/or diastolic BP >50% above the 95th percentile (for children aged <6 years). We evaluated the demographic and clinical characteristics as potential risk factors. Statistical analysis was done with Chi-square, Fisher's exact, and logistic regression tests. Variables with P <0.25 in the univariable analysis were further analyzed by the multivariable logistic regression model. A P value of < 0.05 was considered statistically significant.

Results There were 101 children included (mean age 9.7 (SD 2.17) years), with a male-to-female ratio of 2.7:1. Hypertensive crisis occurred in 42 (41.6%) children, of whom 8 had hypertensive urgency and 34 had hypertensive emergency. Proteinuria was seen in 53 children with AGN (52.5%) and was the significant risk factor for hypertensive crisis in our subjects (OR=2.75; 95%CI 1.16 to 6.52; P=0.021). Gender, clinical profiles, ethnicity, nutritional status, blood urea nitrogen (BUN), and glomerular filtration rate (GFR) were not significant risk factors for hypertensive crisis.

Conclusion Proteinuria is the significant risk factor for hypertensive crisis in children with AGN. **[Paediatr Indones. 2016;56:101-6.]**

Keywords: *hypertensive crisis, acute glomerulonephritis, risk factors*

The prevalence of hypertension in children and adolescents was approximately 1-4%.[1-3] Factors known to affect blood pressure (BP) in children include age, sex, body size, race/ethnicity, obesity, and socioeconomic status.[4-6] The etiologies of hypertension in children differ among age groups. Secondary hypertension is generally more severe and likely to occur in younger children, whereas essential or primary hypertension is less severe and likely to occur in older children and adolescents. Renal parenchymal and renovascular diseases are the most common etiologies of hypertension in every age group of children. Acute glomerulonephritis (AGN) is the most common cause of renal parenchymal diseases.[7,8]

Glomerulonephritis is an inflammatory process primarily affecting the glomerulus, with infiltration and proliferation of acute inflammatory cells. Onset of symptoms is usually acute. Symptoms include edema, oliguria, hypertension, hematuria, proteinuria,

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and renal impairment. Acute post-streptococcal glomerulonephritis (APSGN) is the most common type of glomerulonephritis affecting children.[9] Hypertension occurs in around 60-70% of cases, primarily as a result of water and salt retention and some children progress into hypertensive crisis, while the risk factors are still unclear.[10] Therefore, we aimed to investigate risk factors of hypertensive crisis in children with AGN.

Methods

We retrospectively reviewed the medical records of pediatric patients diagnosed with AGN at the Division of Nephrology, Department of Child Health, Airlangga University Medical School, Dr. Soetomo Hospital, Surabaya from 2007 to 2011. We included all children who presented with acute onset of edema, oliguria, and hematuria, with or without hypertension, as well as with or without evidence of antecedent streptococcal infection. Children with a history suggestive of renal and cardiac disease were excluded from the study.

Subjects' BP was measured with a standard clinical sphygmomanometer, with an appropriately-sized cuff, and a stethoscope, after resting for 5 minutes. Subjects' height percentile was determined according to the standard height charts of the Centers for Disease Control and Prevention, National Center for Health Statistics, USA.[11] Subjects older than 1 year were diagnosed to have hypertension based on reference BP values specific to gender, age, and height developed by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents in 2004.[12] Normal BP was defined to be systolic and diastolic BP lower than the 90th percentile for age, gender and height. Prehypertension was defined to be systolic and/or diastolic BP equal or greater than the 90th percentile, but less than the 95th percentile. Stage 1 hypertension was defined to be systolic and/or diastolic BP ranging from the 95th percentile to 5 mm Hg above the 99th percentile. Stage 2 hypertension was defined to be systolic and/or diastolic BP that was higher than 5 mmHg above the 99th percentile. Hypertensive crisis in children aged ≥ 6 years was defined to be systolic BP ≥180 mmHg or diastolic BP ≥120 mmHg, but in children aged < 6 years, it was defined as systolic and/or diastolic BP higher than 50% above the 95th percentile. Hypertensive emergency was defined to be hypertension accompanied by signs and symptoms of end-organ damage, including hypertensive encephalopathy, pulmonary edema, and heart failure. Hypertensive urgency was defined to be hypertensive crisis in the absence of acute target-organ involvement.[13]

Potential risk factors evaluated were age, gender, ethnicity, clinical profiles, nutritional status, BUN, and initial GFR. Regarding nutritional status, obesity was defined to be a weight-for-length greater than 120% of the ideal weight-for-length. Malnutrition was defined to be weight-for-length lower than 90% of the ideal weight-for-length.[14] Clinical profiles included both clinical manifestations and laboratory findings. Clinical manifestations included hematuria (tea- or cola-colored urine), oliguria (urine output ≤1 ml/kg/hour), edema, and hypertension. Laboratory findings consisted of proteinuria (≥ 2+ on dipstick), azotemia (BUN ≥20 mg/dL), positive ß-streptococcus (anti streptolysin O/ASO titer>200 IU) and reduced GFR (GFR ≤ 75 ml/minute/1.73 m^2 by Steward Formula).[15]

Data analysis was performed using the SPSS for Windows Version 16 software. Risk factor analysis was done with Chi-square, Fisher's exact, and logistic regression tests. Variables with P<0.25 in the univariable analysis were further analyzed with the multivariable logistic regression model (P<0.05).

Results

There were 101 children with AGN during the study period, aged 5 to 13 years (**Table 1**). Their mean age was 9.7 (SD 2.1) years and more than two third were boys (male-to-female ratio of 2.7:1). Javanese and Maduranese ethnic groups constituted 84.1% and 13.8% of the study participants, respectively. Approximately one-third of the participants had malnutrition. All patients were hypertensive. Hypertensive crisis occurred in 42 (41.6%) children, of which 8 were hypertensive urgencies and 34 were hypertensive emergencies. Patient characteristics are shown in **Table 1**.

Subjects' clinical manifestations of AGN were hematuria (98%), oliguria (12.9%), edema (87.1%),

Table 1. Subjects' characteristics

Characteristics	(N=101)
Mean age, years (SD)	9.7 (2.1)
Age groups, n (%)	
<10 years	65 (64.4)
≥10 years	36 (35.6)
Gender, n (%)	
Male	74 (73.3)
Female	27 (26.7)
Ethnicity, n (%)	
Javanese	85 (84.1)
Maduranese	14 (13.8)
Other	2 (1.9)
Nutritional status, n (%)	
Obese	4 (3.9)
Normal	68 (67.3)
Malnutrition	29 (28.7)
Severity of hypertension at onset, n (%)	
Prehypertension	3 (2.9)
Stage 1 hypertension	8 (7.9)
Stage 2 hypertension	48 (47.5)
Hypertensive crisis	42 (41.6)
Type of hypertensive crisis, n (%)	
Hypertensive emergency	34 (33.7)
Hypertensive urgency	8 (7.9)

Table 2. Clinical profiles of children with AGN

Clinical profiles	(N= 101)
Clinical manifestations, n (%)	
Hematuria	99 (98)
Oliguria	13 (12.9)
Edema	88 (87.1)
Hypertension	101 (100)
Laboratory findings, n (%)	
Proteinuria	53 (52.5)
Azotemia	44 (43.5)
Positive ASO titre	64 (63.4)
GFR<75 mL/minute/1.73m^2	42 (41.5)

and hypertension (100%). Laboratory findings of proteinuria (52.5%), azotemia (43.5%), positive ASTO (63.4%), and reduced GFR (41.5%) are shown in **Table 2.** Complications included pulmonary edema, cardiac failure, hypertensive retinopathy, and hypertensive encephalopathy in 16 (15.8%), 11 (10.9%), 3 (3%) and 27 (26.7%) patients, respectively.

Of 101 subjects, no deaths occurred. But three patients were discharged on their request because of financial difficulties. The mean duration until improvement of the hypertension was 8.87 (SD 5.52) days. The mean duration of hospital stay was 9 days, but patients with complications needed more time to recover.

Univariate analysis of those with hypertensive crisis (n=42), revealed the following variables to have P values of <0.25: malnutrition (P=0.172), hematuria (P=0.170), proteinuria (p=0.045), azotemia (P=0.210), and ASO (P=0.053) (**Table 3**). These variables were further analyzed with the multivariable logistic regression model.

Table 3. Univariate Chi-square test for risk factors in those with hypertensive crisis

Variables	Category	With hypertensive crisis (n=42)	Without hypertensive crisis (n=59)	P value
Gender, n (%)	Male	30 (71.4)	44 (74.6)	0.725
	Female	12 (28.6)	15 (25.4)	
Age, n (%)	<10 years	28 (66.7)	37 (62.7)	0.453
	≥10 years	14 (33.3)	22 (37.3)	
Ethnicity, n (%)	Javanese	35 (83.3)	50 (84.7)	0.848
	Other	7 (16.7)	9 (15.3)	
Nutritional status, n (%)	Malnutrition	9 (21.4)	20 (33.9)	
	No malnutrition	33 (78.6)	39 (66.1)	0.172*
Hematuria, n (%)	Yes	40 (95.2)	59 (100)	
	No	2 (4.8)	0 (0)	0.170*
Oliguria, n (%)	Yes	4 (9.5)	9 (15.3)	
	No	38 (90.5)	50 (84.7)	0.397
Edema, n (%)	Yes	35 (83.3)	53 (89.8)	
	No	7 (16.7)	6 (10.2)	0.337
Proteinuria, n (%)	Yes	27 (64.3)	26 (44.1)	
	No	15 (35.7)	33 (55.9)	0.045*
Azotemia, n (%)	Yes	7 (16.7)	37 (62.7)	
	No	35 (83.3)	22 (37.3)	0.210*
ASO, n (%)	Yes	22 (52.4)	42 (71.2)	
	No	20 (47.6)	17 (28.8)	0.053*
GFR, n (%)	<75	22 (52.4)	20 (33.9)	
	≥75	20 (47.6)	39 (66.1)	0.299

Table 4. Multivariable logistic regression analysis of risk factors

Parameter	OR	P value	95 % CI	
			Lower	Upper
Azotemia	1.548	0.515	.416	5.768
Malnutrition	0.532	0.205	.201	1.410
Hematuria	0.000	0.999	.000	
ASO	0.386	0.031	.162	0.919
Proteinuria	2.752	0.021	1.161	6.520

On multivariate analysis, proteinuria (OR=2.75; 95%CI 1.16 to 6.52; P=0.021) and positive ASO (OR=0.386; 95%CI 0.162 to 0.919; P=0.031) were the significant risk factors for hypertensive crisis in AGN children (**Table 4**).

Discussion

Glomerulonephritis is an inflammatory process affecting primarily the glomerulus, with infiltration and proliferation of acute inflammatory cells. Acute glomerulonephritis (AGN) is a complex of findings which is marked histologically by generalized glomerular inflammation. Acute glomerulonephritis is heralded by acute onset of edema, hematuria, and hypertension, which is usually associated with oliguria and azotemia. The glomerular inflammation starts with an antigen-antibody reaction, either by direct antigen-antibody binding in the glomerulus, or a localized circulating complex in the kidney. The activated inflammatory mediators include complement cascade, coagulation factors, cytokines, and growth factors which can cause injury to the glomerulus. The glomerular inflammation impairs microcirculation, reducing GFR and increasing BUN and creatinine. Fluid overload follows by the result of GFR reduction that leads to retention of salt and water with varying degrees. In severe situations, it can be manifested by life-threatening hypertension, pulmonary edema, and hypertensive encephalopathy in some children with AGN.[15]

Acute glomerulonephritis is a common renal disease in children. The course and sequelae of an individual patient are unpredictable. In our study, there were 101 pediatric AGN cases admitted over a period of 4 years. We assessed the signs and symptoms for possible correlations to hypertensive crisis. The occurrence of hypertensive crisis was 41.6% of the total pediatric AGN admissions. Subjects' mean age was about 9.7 years. A previous study reported an average age of 8.5 years,[15] while another study reported 7.2 years.[16] In our study, 73.3% were males and 26.7% were females, similar to another report of male predominance in disease occurrence.[16]

Common signs and symptoms in our subjects were edema, hematuria and hypertension. Derakhshan *et al*. noted skin infection in 78%, hypertension in 75%, and sore throat in 4% of cases.[15] Hypertension of variable degrees was present in 100% of patients in our study, primarily as a result of water and salt retention. Hypertensive crisis occurred in 42 (41.6%) children. Physical examination included a careful assessment of vital signs, particularly blood pressure. Blood pressures 5 mmHg above the 99th percentile for the child's age, sex, and height, especially if accompanied by any alteration in mental status, demand prompt attention.[15] Hematuria was the most consistent urinary findings found in all of our subjects. There was no difference in clinical presentation and progress of the disease in those with gross hematuria and those with microscopic hematuria. History-taking included details about changes in urine color. Hematuria in children with AGN is typically described as "coke-," "tea-," or "smoky-"colored. Urine color in AGN is uniform throughout the stream. The gross hematuria of AGN is virtually always painless. Proteinuria is also almost invariably found in AGN, although any cause of gross hematuria can lead to some urinary protein. If the urine is not grossly bloody, however, the combined presence of hematuria and proteinuria virtually always means glomerulonephritis.[15] We found that BUN was significantly high in 44 cases (43.5%). Reduced GFR and proportionately elevated BUN levels were found in 42 cases (41.5%). In our study, 16 patients showed features of pulmonary edema and 11 patients showed features of cardiomegaly.

Pulmonary changes did not bear any relation to proteinuria or blood urea. Clearance of X-ray findings coincided with diuresis and disappearance of edema. In patients with moderate-to-severe AGN, a measurable reduction in volume of glomerular filtrate (GF) is present, and the capacity to excrete salt and water is usually diminished, leading to expansion of the extracellular fluid (ECF) volume. The expanded ECF volume is responsible for edema and, in part, for hypertension.[9] The ASO titre was raised in 64 (63.4%) of our subjects. Derakhshan *et al*. reported elevated ASO in 84% cases. A slight increase in ASO response was noted in patients with skin infections compared to those with sore throats.[15]

In this study, SBP > 95th percentile accounted for nearly all of the cases of BP >95th percentile. The prevalence of BP >95th percentile among children reported in earlier studies ranged from 1.2-13%.[18-20] The results of these studies suggest that BP >95th percentile is not rare in children. Hypertensive crisis occurred in 42 (41.6%) children. Gender, age, ethnicity, nutritional status, BUN, and GFR were not significant as risk factors for hypertensive crisis. A previous study reported obesity to influence hypertension in children.[21] We did not find this to be the case, however, the prevalence of obesity was lower (3.9%) in our sample. On multivariate analysis, proteinuria (OR=2.75; 95%CI 1.16 to 6.52; P=0.021) was the significant risk factor for hypertensive crisis in AGN children. An abnormal excretion of protein in the urine is the hallmark of experimental and clinical glomerular diseases. Proteinuria is an indicator of alterations in glomerular and tubular protein uptake. It can be a good marker of the overall severity of glomerular and tubulointerstitial damage, and therefore, of the prognosis of glomerular diseases. Proteinuria may in itself contribute to ongoing renal injury by causing mesangial and tubulointerstitial damage. In fact, proteinuria is the major determinant of progressive renal failure.[22,23]

In conclusion, proteinuria increases the risk for hypertensive crisis by almost 3-fold in children with AGN.

Conflict of interest

None declared.

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