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ORIGINAL ARTICLE

Acute reversible changes of brachial-ankle pulse wave velocity in children with acute poststreptococcal glomerulonephritis

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Abstract Acute poststreptococcal glomerulonephritis (APSGN) is the most common form of postinfectious nephritis worldwide. The relationship between inflammation and arterial stiffness has been described elsewhere, but there have been no studies that have analyzed the association between arterial compliance and APSGN. The aim of this study is to assess brachial–ankle pulse wave velocity (baPWV) in pediatric patients with APSGN, and the value of baPWV in predicting the outcome. We evaluated 16 children diagnosed with APSGN, 11 children with acute pyelonephritis (APN), and 25 healthy individuals in our hospital. The baPWV of all candidates was measured. In addition, follow-up of the APSGN group was conducted for baPWV, blood pressure and biochemical parameters. Significantly increased baPWV was observed in the APSGN group at initial diagnosis ($P<0.001$), in comparison with the APN group and healthy controls. Of these, 13 patients received sequential measurement of baPWV. Overwhelmingly, baPWV was rapidly normalized in 11 patients, whereas 2 boys presented with persistently higher baPWV. During the follow-up period of 2–3 years, both had consistency of proteinuria, and consequently, they progressed to either chronic renal insufficiency or end-stage renal disease (ESRD). In conclusion, the results demonstrate that APSGN involves not only the kidney, but also the arterials outside the kidney. Acute arterial stiffness might persist in patients who do not recover, but develop chronic kidney disease (CKD).

Keywords Acute poststreptococcal glomerulonephritis · Brachial-ankle pulse wave velocity

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Introduction

Acute poststreptococcal glomerulonephritis (APSGN) most often follows group A streptococcal infections and its manifestations are characterized by acute renal failure, hypertension, glomerular hematuria, mild proteinuria, and edema. Although the incidence has declined considerably over the past four decades, epidemic outbreaks and clusters

of cases of APSGN continue to appear all over the world, in particular in rural and overcrowded communities. The immediate prognosis of childhood APSGN is considered excellent, but the long-term outcome remains variable. There have been reports in the literature that show approximately 1–6% of pediatric patients and about 20% of adults with APSGN experience end-stage renal disease (ESRD) in later life [1–6]. Additionally, many studies have shown the presence of persistent urinary abnormalities (microhematuria, proteinuria, or albuminuria), hypertension, reduction in renal functional reserve, or azotemia several years after APSGN [4–8].

A recent report from Wong et al. [1] described 27 Pacific Islands and Maori (New Zealand) children suffering from severe APSGN. They had a higher tendency (11 out of 27, 41%) toward crescentic PSGN. Of the 27 pediatric patients, 12 needed to receive acute dialysis and eventually, 8 of those (8 out of 12, 67%) presented with either ESRD, chronic renal failure, or significant proteinuria. Many published research reports have proposed that adult patients have a less favorable long-term prognosis, especially in association with nephrotic syndrome, renal insufficiency at the onset, crescentic glomerulonephritis, and alcoholism [2, 4, 7]. However, these risk factors are uncertain for pediatric patients. In Vogl's series of 98 adults with APSGN [2], 21.5% had nephrotic proteinuria and 16% developed chronic renal insufficiency afterward. Conversely, in the series by Wong et al. [1], 18 APSGN children (66%) had nephrotic syndrome and 8 had crescentic glomerulonephritis. Through 4–6 years' follow-up, only 2 progressed to ESRD and 3 out of 12 (4%) developed persistent proteinuria. Little is known about the precise mechanism that initiates this glomerulonephritis, and no useful method of predicting the renal outcome is available today. To our knowledge, there is a high cardiovascular morbidity and mortality in adults and children with CKD. Also, arterial stiffness is important in the pathogenesis of cardiovascular disease. Currently, aortic pulse wave velocity (PWV), obtained using the non-invasive SphygmoCor system (AtCor, Medical, Sydney, Australia), is regarded as a standard method of measuring arterial stiffness and an independent predictor of cardiovascular risk in the general population and patients with hypertension, diabetes and ESRD [9–11]. Nevertheless, along with the introduction of brachial–ankle pulse wave velocity (baPWV), this novel measure seems to possess more practical advantages including technical simplicity and shorter sampling time in comparison to previous methods. Yamashina et al. have further shown that baPWV correlates well with aortic PWV examination by an invasive investigation [12, 13]. To our knowledge, this is the first prospective study to assess the relationship between arterial stiffness and APSGN. Meanwhile, we aim to investigate whether baPWV can be determined to be a predictor of renal survival after APSGN.

Patients and methods

We prospectively investigated 16 children aged 9.1±1.7 years (11 boys and 5 girls) who were diagnosed with APSGN in the outpatient and inpatient departments of Chang Gung Children's Hospital, Link-Kou Medical Center in Taiwan between December 2005 and July 2008. The diagnosis was made on the basis of the following criteria:

1. Evidence of nephritis—macroscopic hematuria with/without proteinuria, hypertension, edema, or reduced renal functions
2. Elevated antistreptolysin (ASLO) titer and hypocomplementemia (low C3±low C4 level)
3. Diffuse proliferative endocapillary nephritis, leukocyte infiltration, and epithelial hump±crescent formation proved by renal biopsy

Children of the APSGN group were apparently initially healthy. The control group comprised 25 children aged 9.0±2.3 years (14 boys and 11 girls) who had no pre-existing renal disease, systemic lupus erythematous, vasculitis (e.g. Henoch–Schönlein purpura or Kawasaki disease), or other chronic illness (e.g. diabetes mellitus, hypertension or hyperlipidemia), and none had abnormal laboratory examinations. Besides, the acute pyelonephritis (APN) group consisted of 11 children aged 10.3±3.9 years (4 boys and 7 girls). The diagnosis of APN was established based on urine culture, renal ultrasound and abdominal computed tomography. All cases had either unilateral or bilateral APN, but were without sepsis. They were admitted for receiving intravenous antibiotic treatments.

All subjects received baPWV examination by non-invasive, volume plethysmographic automatic apparatus (Vascular Profiler-1000; Colin, Komaki, Japan). Body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), and ABI (ankle–brachial index=SBP in the ankle/SBP in the brachial artery) were recorded simultaneously. Patients with APSGN received a 10-day course of antibiotics (penicillin), short-term antihypertensive agent (calcium channel blocker, amlodipine) and diuretics (furosemide) for less than 1 month, with the exception of one boy; he had been treated with long-term antihypertensive medicine, prednisolone, and mycophenolate sodium because of intractable nephrotic syndrome 3 months after the initial diagnosis. Also, the following parameters were studied at baseline and during the follow-up period, nearly every 1–3 months, for the APSGN group: baPWV, blood pressure, ABI, blood urea nitrogen (BUN), creatinine, ASLO, C3, C4, antinuclear antibody, and urinalysis.

Assessment of baPWV

ba PWV was measured using a Colin VP-1000 as previously described. Additionally, personal data (birth date, height, weight, and gender) were entered into the profiler. After at least 10 min of rest, subjects were examined in the supine position and the values of baPWV, BMI, SBP, DBP, ABI, electrocardiogram and phonocardiogram were autocalculated simultaneously. Pneumatic pressure cuffs were placed around the subjects' arms and ankles. Electrocardiographic electrodes were attached to both wrists and a microphone for phonocardiography was placed at the third intercostal space on the left margin of the sternum. baPWV was calculated by the following equation:

$$\text{baPWV} = (\text{D1} - \text{D2})/\Delta t$$

where D1 is the distance between the heart and the ankle, and D2 is the distance between the heart and the brachium. The distance between the arm and the ankle was estimated automatically according to the subject's height and anthropomorphic data for Taiwanese children [14–16]. Δt is the pulse transit time between the brachial and tibial arterial waves determined by the foot-to-foot method. The baPWV of all study subjects was measured by the same operator.

Statistical analysis

Data were expressed as mean ± SD. Differences in the mean values between groups of healthy children, children who had APN, and children with APSGN at initial diagnosis and at follow-up were examined for statistical significance by using the multiple comparison test (one-way analysis of variance, ANOVA). $P<0.05$ was regarded as a statistically significant difference.

Results

At initial diagnosis of APSGN, there were significantly higher SBP (142±19 mmHg vs 104±11 mmHg in the APN group and 104±11 mmHg in healthy controls, $P<0.001$); DBP (85±15 mmHg vs 56±7 mmHg in the APN group and 58±10 mmHg in healthy controls, $P<0.001$); ABI (1.16±0.23 cm/s vs 1.01±0.13 cm/s in the APN group and 1.05±0.08 cm/s in healthy controls, $P<0.005$); and baPWV (1,382±183 cm/s vs 937±88 cm/s in the APN group and 954±120 cm/s in healthy controls, $P<0.001$; Table 1). There were no statistical differences in SBP, DBP, ABI and baPWV among the groups of APN and healthy controls. Also, age and BMI showed no statistical difference among the three groups, but there was a slight male predominance in the APSGN group (male:female=2:1).

The demographics, serological studies, and baPWV of the 16 pediatric patients with APSGN are shown in Table 2. Initial plasma creatinine (Cr), ASLO titer, depressed levels of C3 with or without low C4, and association with nephrotic syndrome did not correlate with the severity of baPWV in the initial phase of APSGN.

Of the 16 APSGN children, 4 (cases 4, 5, 11, and 12) were aboriginal children of Taiwan. Two of them made a full recovery or had persistent microhematuria after a mean follow-up of 2.5 years, but the other 2 were lost to follow-up. Renal biopsy was performed in 3 children (cases 4, 12, and 14) because of developing nephrotic syndrome and oligouric acute renal failure, and all 3 revealed acute proliferative glomerulonephritis with crescents. None required dialysis therapy.

Subsequently, in 11 patients, baPWV rapidly retuned to normal between 0.5 and 2.5 months among the APSGN group (11 out of 13, 85%; 991±149 cm/s vs 954±120 cm/s in healthy controls—no significant difference). In follow-up over periods of 0.5 to 3 years, 4 out of 13 children (31%) were in full recovery and 7 out of 13 (54%) had persistent microhematuria. On the contrary, 2 patients (cases 6 and 14) with persistently high baPWV presented consistency of proteinuria and/or renal function impairment, and they have had normal systolic blood pressure with or without the need for antihypertensive medication. The child (case 14) underwent renal biopsies three times, showing progression to crescentic glomerulonephritis. Eventually, he progressed to ESRD after 3 years' follow-up and another child (case 6) also developed chronic renal insufficiency (Cr 2.10 mg/dl).

Discussion

To our knowledge, this is the first study to demonstrate the relationship between PWV and APSGN. In this study, significantly higher baPWV was detected in the initial stage of APSGN, whereas there was no similar finding in children with APN. These results suggest that APSGN is able to cause increased arterial stiffness that is not restricted to the renal arteries.

To date, the mechanism whereby APSGN increases arterial stiffness is unknown, but may be linked to the renal inflammatory response in APSGN. Previous studies have shown increased production of proinflammatory cytokines, such as IL-6, IL-8, TNF-α, and TNF-β [17, 18]. IL-6 has been reported to not only parallel the clinical course of APSGN, but also to be associated with increased arterial stiffness [19, 20]. In the present study, all children with APSGN developed significant hypertension, and an increase in baPWV. Blood pressure and baPWV normalized rapidly except in case 6 and case 14. Patient 14 presented with persistently higher baPWV, progressive deterioration of renal

Table 1 Comparisons of demographics, body mass index (*BMI*), systolic blood pressure (*SBP*), diastolic blood pressure (*DBP*), ankle–brachial index (*ABI*) and brachial–ankle pulse wave velocity (*baPWV*) among healthy children and children with acute pyelonephritis (*APN*) and acute poststreptococcal glomerulonephritis (*APSGN*)

	Healthy controls (n=25)	APN (n=11)	APSGN (n=16)	
			At initial diagnosis (n=16)	Follow-up (n=13)
Sex				
Male	14	4	11	
Female	11	7	5	
Age (years)	9.0±2.3	10.3±3.9	9.1±1.7	
BMI	18.2±4.1	17.86±1.8	18.3±2.2	
SBP (mmHg)	104±11	104±11	142±19	113±14*
DBP (mmHg)	58±10	56±7	85±15	59±7*
ABI (cm/s)	1.05±0.08	1.01±0.13	1.16±0.23	1.02±0.12**
baPWV (cm/s)	954±120	937±88	1,382±183	991±149*

ABI (ankle–brachial index) is the ratio of SBP in the ankle to that in the brachial artery: its normal criteria are between 0.9 and 1.3. If the value is below 0.9, arterial stenosis is suspected

*P<0.001

**P<0.005

function, and required long-standing antihypertensive therapy. He reached ESRD 3 years later. Patient 6 had persistently elevated baPWV and developed permanent hypertension nearly 2.5 years after acute onset of PSGN. At the present time, he has CKD. In both patients proteinuria and hypertension persisted. It is possible that both these patients had pre-existing renal disease; however, this seems very unlikely in view of the biopsy results in patient 14 and the slow development of hypertension and progression of CKD in patient 6.

Arterial hypertension is very frequent in patients with CKD and 15–80% of patients with chronic glomerular kidney diseases are hypertensive before reaching severe renal failure [21, 22]. More than the severity of renal failure the type of underlying nephropathy deeply influences the development of hypertension [23, 24].

The prognosis for APSGN is dependent on the patient's age. Adult and elderly patients with APSGN have poorer prognoses with approximately 8–20% of patients progressing to chronic renal failure after 5 years [4, 7]. Childhood APSGN is usually considered a benign disease, but Aboriginal patients from Australia and New Zealand have a poor prognosis with a 7-fold higher incidence of progression to chronic renal failure compared with the non-Aboriginal population [1, 3, 6]. In our study, however, aboriginal children of Taiwan had similar prognoses to children from urban areas. Abnormal urinalysis and hypertension might persist in 3.5% of patients after the acute phase of APSGN [4, 5, 25, 26]. Since APSGN might result in CKD and ESRD in a significant percentage of adults and children, there have been many attempts to identify poor prognostic features of APSGN. Nephrotic range proteinuria, impaired renal function, persistent oligouria, and severe crescentic glomerulonephritis have ever been linked with unfavorable outcome, while the reduction in C3 concentration did not correlate with the severity of APSGN [27]. The two patients with chronic kidney disease in this study matched this pattern.

Recently, PWV was considered to be a useful marker reflecting vascular damage. According to the 2007 European Society of Hypertension/European Society of Cardiology hypertension guidelines, carotid-femoral (aortic) PWV of 12 m/s is indicative of end-organ damage in the arterial system [28]. Increased aortic PWV has been shown to be an independent prognostic predictor for all-cause mortality and mainly cardiovascular morbidity in patients with uncomplicated hypertension, impaired glucose intolerance, and renal failure, and in the general population [9–11, 29, 30]. baPWV is a new measure of arterial stiffness that has been widely used in East Asian countries such as Japan, South Korea, and Taiwan [13, 15, 31, 32]. Nowadays, there is evidence that baPWV not only has a similar efficiency to aortic PWV, but it can also examine global arterial stiffness, particularly small-vessel damage in the brain and kidney [31, 33, 34]. Meanwhile, this novel method requires no specialized skills, enabling much easier daily practice for general physicians.

Many studies have shown an increase in baPWV in patients with mild to moderate CKD or proteinuria, regardless of renal functions [35, 36]. In the J-TOPP study [37], it was assumed that high baPWV might predict new-onset microalbuminuria or persistent microalbuminuria despite blood

Table 2 Demographics, serological studies and baPWV (at diagnosis and follow-up) of 16 pediatric patients with APSGN

Case number	Age (years)	Sex	Antecedent infection	Initial plasma Cr (mg/dl)	Antistreptolysin titer (U/ml)	C3 (mg/dl)	Time (months) of low C3 recovery	Nephrotic status	baPWV (cm/s), (BP, mmHg) at initial diagnosis	baPWV (cm/s) at f/u, (BP, mmHg)/duration after initial diagnosis	Current urinalysis/ Cr (mg/dl)	F/u Duration (years)
1	8	Male	Skin	0.5	358	16.1	1.5	No	1,547 (148/4)	1,003 (120/64)/ 0.5 months	Microhematuria/0.6	1
2	7	Female	Upper respiratory	0.6	2,400	<16.4	5	No	1,453 (152/94)	1,066 (102/55)/ 1 month	Microhematuria/0.5	0.5
3	8	Female	Upper respiratory	0.6	3,330	45.70	2	No	1,231 (156/82)	921 (94/48)/ 1 month	Microhematuria/0.5	0.5
4[a, b, c]	11	Male	Skin	1.7	304	<16.4	1.5	Yes	1,468 (147/87)	880 (109/59)/ 2 months	Normal/0.8	2.5
5[a, c]	12	Female	Upper respiratory	1.4	675	23.8	2.5	No	1,201 (127/83)	808 (106/59)/ 1.5 months	Microhematuria/0.8	2.5
6	12	Male	Upper respiratory	1.4	698	24.2	1.5	Yes	1,818 (134/81)	1,260 (121/64)/ 2 years	Proteinuria/2.10	2.5
7[c]	10	Male	Upper respiratory	0.9	1,370	<16.10	2.5	No	1,419 (139/82)	1,021 (125/58)/ 2 months	Normal/0.7	2
8	10	Female	Upper respiratory	1.3	1,690	<16.4	2	No	1,171 (140/90)	1,085 (116/70)/ 2 months	Microhematuria/0.33	3
9	8	Male	Upper respiratory	1.6	3,290	<16.4	1.5	Yes	1,200 (111/62)	1,066 (93/54)/ 2 months	Microhematuria/0.6	0.5
10	10	Female	Upper respiratory	0.6	1,310	24.20	1.5	No	1,497 (168/105)	839 (127/77)/ 2.5 months	Normal/0.6	3
11[a, c]	8	Male	Upper respiratory	0.7	351	17		No	1,200 (110/55)			Lost
12[a, b]	6	Male	Skin	2.3	1,330	<16.10	2.5	Yes	1,560 (139.89)	820 (135/52)/ 1 year	Microhematuria/0.42	3.5
13	9	Male	Upper respiratory	0.8	539	33.5	2	No	1,193 (119/60)			Lost
14[b]	12	Male	Skin	1.0	239	76.8	2	Yes	1,334 (141/82)	1,236 (128/80)/ 3 years	Proteinuria/ESRD	3
15[c]	9	Male	Upper respiratory	0.9	988	8.7	2	No	1,315 (150/92)			Lost
16	8	Male	Upper respiratory	0.7	430	23	2	No	1,513 (176/110)	890 (112/58)/ 2 months	Normal/0.4	1.5

[a] Cases 4, 5, 11, and 12: Aboriginals in Taiwan

[b] Cases 4, 12, and 14 received renal biopsy

[c] Cases 4, 5, 7, 11, and 15 have both depressed C3 and C4

pressure reduction by antihypertensive medications among patients with essential hypertension. Probably, increased baPWV (arterial stiffness) can occur in the early phase before developing renal dysfunction or hypertension. Continuously increasing baPWV might indicate that the inflammatory process is ongoing or severe enough to produce irreversible arterial damage.

In this study, we examined whether acute changes of baPWV were present in acute APSGN and how long those changes might persist. We found a significant increase in baPWV in all patients indicating the participation of vessels outside the kidney in the acute phase of APSGN. Interesting questions for further study are whether baPWV changes are the consequence of vascular changes due to water retention and hypertension or also due to immunological changes, and whether the involvement of extrarenal vessels might contribute to well-known clinical signs like pulmonary edema [38, 39] in patients with APSGN without general water retention [40]. The results of the present study demonstrate how sensitive baPWV is and that even acute reversible vascular involvement can be detected. The significance of this finding is seen from the negative results of the control group with acute pyelonephritis. Whether baPWV investigations can be used as a prognostic indicator needs to be prospectively studied with larger sample sizes.

In conclusion, these observations demonstrate that APSGN acutely induces changes in baPWV. Most likely the pathogenesis and mechanism of the underlying vascular changes are the same as those leading to glomerular changes. This demonstrates that not only renal vessels (glomeruli), but also other (arterial) vessels of the body are involved in the disease process of APSGN. This concept is confirmed by the rapid normalization of baPWV with the healing of APSGN. Patients without healing of acute glomerulonephritis continue to show abnormal baPWV.

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