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Original article

Plasma atrial natriuretic peptide and endothelin levels in acute poststreptococcal glomerulonephritis

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Abstract. Plasma levels of atrial natriuretic peptide (ANP) and of endothelin (ET) were significantly elevated (87.7 ± 13.9 pg/ml and 79.7 ± 10.8pg/ml, respectively) during the acute phase of acute poststreptococcal glomerulonephritis (APSGN). Plasma renin levels were normal, fractional excretion of sodium (FE_{Na}) was 0.5 ± 0.1% and creatinine clearance (C_{Cr}) averaged 82.2 ± 18.3 ml/min per 1.73 m^2. In the recovery phase of the disease (n = 12), levels of ANP (23.6 ± 6.7 pg/ml) and ET (43.1 ± 2.4 pg/ml) fell and were not significantly different from those measured in 11 control subjects. FE_{Na} increased to 1.3 ± 0.1% and C_{Cr} to 113.5 ± 12.1 ml/min per 1.73 m^2 (all values mean ± standard error). ANP did not correlate with PRA, blood pressure, C_{Cr} or FE_{Na}. There was an inverse relationship between the ET level and FE_{Na} in the acute phase of the disease (r = 0.489, P <0.05), but no significant correlation between ET and blood pressure, PRA, C_{Cr} or ANP was found. We suggest that, despite the sodium retention, the increased ANP level in APSGN indicates unresponsiveness of the kidneys to ANP; the increased ET levels may contribute to this.

Key words: Acute poststreptococcal glomerulonephritis – Atrial natriuretic peptide – Endothelin – Sodium retention – Hypertension

Introduction

Acute poststreptococcal glomerulonephritis (APSGN), a not uncommon disease in developing countries [1–3], is characterised by hypertension in 30%–90% of patients [2, 4] and by fluid retention in over 90% of patients [2, 4]. Fractional excretion of sodium (FE_{Na}) is reduced during the acute phase of the disease.

The identification of atrial natriuretic peptide (ANP) and endothelin (ET) has aided our understanding of sodium homeostasis and blood pressure regulation. Levels of ANP, a potent natriuretic and vasodilatory agent [5, 6], increase in response to acute volume expansion [7]. ET, which was isolated by Yanagisawa et al. [8], constricts vascular and non-vascular smooth muscle cells, stimulates ANP secretion and decreases renal blood flow, glomerular filtration rate (GFR), urine volume and urinary sodium excretion [8–11].

In the present study, children were studied in the acute and recovery phases of APSGN in order to determine the roles of ANP and ET in the pathogenesis of the oedema and hypertension observed in this disease.

Patients and methods

The study group consisted of 16 patients with APSGN, 11 of whom were admitted to Hacettepe Children's Hospital until the acute manifestations subsided; the remaining 5 were evaluated as outpatients. Twelve patients were subsequently studied in the recovery phase, 6–12 weeks after presentation of the disease. Eleven age- and sex-matched healthy children were also evaluated.

The diagnosis of APSGN was made following observation of the typical clinical manifestations: the sudden appearance of proteinuria and haematuria associated with hypertension (94% of patients), oedema (94%), azotaemia, hypocomplementaemia and evidence of an antecedent group A β-haemolytic streptococcus infection – either a positive throat culture for β-haemolytic streptococcus and/or elevated titres of anti-streptolysin 0. In 1 patient, the diagnosis was confirmed by renal biopsy. No patient was included who had received diuretics prior to the time of blood sampling for ANP, ET and FE_{Na} measurement. Diuretics were administered to 7 of the 16 patients who met this requirement later in the course of the disease.

Blood samples were drawn from peripheral veins following 15 min rest in the supine position. Routine urinalysis and biochemical analysis of blood were performed in all patients. Urinary sodium excretion was calculated using the urinary sodium value measured in spot urine samples before diuretic administration. Creatinine clearance (C_{Cr}) was calculated from the urine samples collected during the first 24 h. The C_{Cr} could not

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Table 1. The clinical and laboratory characteristics of patients[a]

Patient no.[b]	Age	Sex	Weight (kg)	Blood pressure (mmHg)	Oedema	Proteinuria (mg/kg per day)	Throat culture	ASO (Todd units)	C3 (mg/dl)	C4	S_{Cr} (mg/l)	C_{Cr} (ml/min per 1.73 m^2)	U_{Na} (mEq/l)	FE_{Na} (%)	PRA (ng/ml per min)	ANP (pg/ml)	ET (pg/ml)
1 (1)	10	F	28.0	150/100	+	960	Normal	1250	17	5	2.1	43.3	51	1.0	0.2	98.0	47.5
(2)			25.6	100/70	–	60	Normal	833	71	22	0.8	126.2	107	1.0		19.0	32.3
2 (1)	10	F	32.3	130/85	+	900	βHS	1250	16	22	1.7	60.0	14	0.2	0.1		81.8
(2)			29.0	100/70	–	158	Normal	833	80	20	0.6	156.1	104	1.1		12.7	43.3
3 (1)	9	M	27.0	120/90	+	–	βHS	625	50	30	0.8	ND	34	0.3	4.6	16.2	49.5
(2)			24.9	100/70	–	75	Normal	625	57	27	0.5	131.0	99	1.0		16.0	41.8
4 (1)	9	M	20.0	130/90	+	–	βHS	833	40	26	0.7	ND	31	0.5	0.2	66.8	59.0
(2)			18.2	100/60	–	155	Normal	250	60	60	0.8	101.5	59	2.2		16.0	60.8
5 (1)	14	F	49.6	160/110	+	1269	Normal	250	32	36	2.3	28.2	28	0.4	3.1	58.6	37.5
(2)			45.0	120/80	–	120	Normal	250	67	19	0.7	110.8	112	1.6		15.3	37.0
6 (1)	4.5	M	16.2	135/95	+	–	βHS	1250	12	30	0.9	ND	24	0.1	2.0	213.8	96.8
(2)			15.2	90/60	–	90	Normal	833	42	20	0.7	85.5	101	2.1		91.2	54.0
7 (1)	8	M	26.0	140/100	+	–	Normal	250	16	16	1.0	ND	22	0.2		108.5	196.5
(2)			24.0	90/60	–	147	Normal	166	71	20	0.5	98.3	109	0.7		33.1	36.8
8 (1)	14	M	58.4	145/100	+	6013	βHS	625	52	26	2.4	40.2	17	0.2	2.5	17.0	138.5
(2)			55.1	110/70	–	896	Normal	1250	82	19	0.9	56.7	196	1.2			
9 (1)	14	M	55.0	140/110	+	–	Normal	250	18	10	1.5	ND	91	1.1	2.7	93.0	81.0
(2)			51.2	125/75	–	51	Normal	166	55	21	0.9	40.7	155	1.5		32.9	47.5
10 (1)	9	M	29.0	130/90	+	–	βHS	1250	20	20	1.6	ND	50	0.7	2.0	76.8	47.8
(2)																	
11 (1)	6	F	21.6	140/100	+	–	Normal	833	12	20	0.8	ND	71	0.6	0.1	136.4	46.8
(2)			19.1	120/80	–	135	Normal	625	72	30	0.6	215.4	143	0.7		9.1	34.3
12 (1)	9	F	40.5	180/130	+	150	βHS	1250	26	16	1.3	39.8	32	0.6	0.2	136.3	51.8
(2)			37.0	110/70	–	23	Normal	1250	76	24	0.8	48.0	105	0.9		6.2	42.8
13 (1)	12	M	60.0	135/90	+	325	βHS	625	16	16	0.7	156.7	39	0.2		65.5	95.5
(2)																	
14 (1)	14	F	37.5	140/90	+	196	Normal	833	16	18	0.9	146.5	129	0.5	0.5	68.7	125.5
(2)			36.0	130/85	–	81	Normal	250	66	22	0.9	141.0	160	1.0		14.3	45.5
15 (1)	9	F	37.8	150/110	+	74	βHS	833	136	28	1.1	51.4	71	0.6		139.4	89.3
(2)			35.2	120/70	–	76	Normal	833	76	26	0.7	96.8	98	1.4		11.5	41.3
16 (1)	5	M	17.6	100/70	–	244	βHS	625	16	20	0.7	77.5	38	0.7		21.0	39.8
(2)			17.0	100/65	–	46	Normal	625	52	20	0.6	144.6	130	0.8			
Mean (1)	9.9±0.8			139.1±4.4/97.5±4.6					30.9±7.7	21.2±2.0		82.2±18.3	0.5±0. 1	1.5±0.4		87.7±13.9	79.7±10.8
(2)				119.5±4.8/73.0±3.8					73.2±5.4	23.7±2.2		113.5±12.1	1.3±0.1			23.6±6.7	43.1±2.4

[a] Figures are expressed as mean ± standard error

[b] (1) Acute phase; (2) recovery phase

βHS, β-Haemolytic streptococcus; ND, not determined as patients received diuretics; ASO, anti-streptolysin O; S_{Cr}, serum creatinine; C_{Cr}, creatinine clearance; U_{Na}, urinary sodium; FE_{Na}, fractional excretion of sodium; PRA, plasma renin activity; ANP, atrial natriuretic peptide; ET, endothelin

be calculated in 7 patients because they had to be given diuretics during this period of urine collection.

Plasma renin activity (PRA) was determined by radioimmunoassay (RIA) using Cis Bio International (France) kits. Blood samples for ANP and ET determination were collected in ice-cooled polypropylene tubes containing 5 mmol EDTA and 2,000 units/ml aprotonin for ANP and 7.5 mmol EDTA and 2,500 units/ml aprotonin for ET. Samples were centrifuged immediately and stored at –20° C until assayed.

Plasma concentrations of ET-1 and ANP were measured by RIA. For ANP, a 2-ml aliquot of plasma was acidified with trifluoroacetic acid (TFA) and applied to a Spe-C_8 column (Amprep Amersham International, Buckinghamshire UK) which had been prewashed sequentially with methanol and distilled water. The analyte adsorbed to the cartridge was eluted with 60% acetonitrile 0.1% TFA, following the elution of interfering material with 0.1% TFA. For ET, a 1-ml aliquot of plasma was acidified with 2 M HCl and applied to a Spe-C_2 column which had been prewashed sequentially with methanol and distilled water. The analyte adsorbed to the cartridge was eluted with 80% acetonitrile 0.1% TFA, following the elution of interfering material with 0.1% TFA. Measurement of ANP was carried out using the Incstar ANP (I^{125}) RIA and ET with the Amersham ET 1,2(I^{125}) RPA 535 (intrassay variability 4.1%, interassay variability 12.1%) assay system.

Results were expressed as mean plus or minus standard error. Intragroup and intergroup analysis of statistical significance was performed by Wilcoxon and Mann-Whitney U tests, respectively. Pearson simple regression analysis was used for determining correlations between parameters.

Results

C_{Cr} was significantly lower in the acute than in the recovery period ($P < 0.02$) (Table 1). Values increased in each of the patients who had reduced C_{Cr} levels in the acute phase and who had sequential measurements. FE_{Na} was 0.5±0.1% in the acute phase and increased to 1.3±0.1% in the recovery phase ($P < 0.001$) (Table 1). The levels of both ANP and ET were significantly higher in the acute

Table 2. Serum ANP and ET levels and PRA in patients and controls

	Glomerulonephritis		Control subjects
	Acute	Recovery	
ANP (pg/ml)	87.7±13.9*	23.6±6.7***	16.5±2.2
ET (pg/ml)	79.7±10.8**	43.1±2.4***	40.5±2.7
PRA (ng/ml per min)	1.5±0.4		1.4±0.3

* P <0.001 compared with control and recovery results; ** P <0.005 compared with control and P <0.01 compared with recovery phase values, *** Not different from control values

phase of APSGN than those in the recovery phase or those in the healthy control subjects (Table 2). ANP and ET levels were similar in patients in the recovery period and in the control subjects. PRA was in the normal range in both patients and the control group (Table 2).

There were no significant correlations between either ANP or ET and age, sex, PRA, blood pressure, C_{Cr} or FE_{Na}, in either the acute or the recovery phase of APSGN. No correlations were found for ANP and ET levels in either phase of the disease. There was an inverse relationship between the ET level and FE_{Na} in the acute phase of the disease ($r = 0.489$, $P < 0.05$) (Fig. 1).

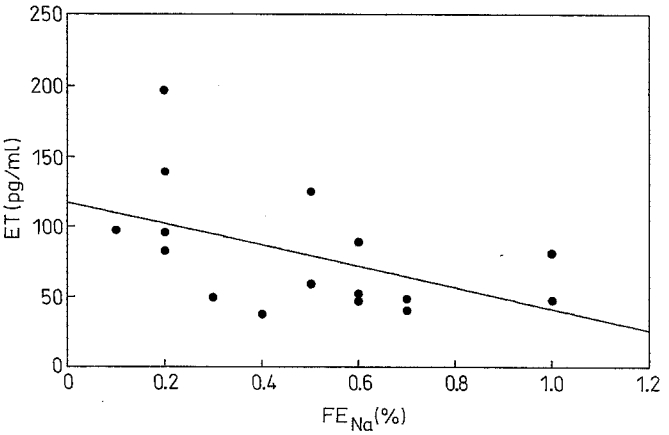

Fig. 1. The correlation between plasma endothelin (*ET*) level and the fractional excretion of sodium (FE_{Na}) in the acute phase of the disease ($n = 16$, $r = 0.489$, $P < 0.05$)

Discussion

As expected both C_{Cr} and FE_{Na} were lower in the early phase than in the recovery phase of APSGN. In recovery, C_{Cr} averaged the normal level observed in the healthy control subjects although it remained low in some patients. There was no relationship between the renal sodium excretion and either blood pressure or C_{Cr}. This suggests that the reduced GFR is not the only factor determining sodium retention.

Most reports on ANP in renal parenchymal disease involve patients with terminal renal failure [12, 13]. We could not find any report on ANP levels in children with APSGN. Levels of ANP are increased in adults who have chronic glomerulonephritis but who have maintained a normal GFR. It has been suggested that the increased level of ANP might represent a compensatory phenomenon in the presence of abnormal sodium and volume homeostasis [14].

The present study demonstrates that in children with APSGN plasma ANP increases during the acute phase of the disease. Since C_{Cr} did not correlate with ANP in patients either in the acute or recovery phase of the disease, we conclude that decreased GFR is not the main factor determining an increased ANP level in APSGN. There was also no correlation between FE_{Na} and ANP. We suggest that the high ANP levels found in the patients may be secondary to the decreased renal sodium excretion, and speculate that the kidneys are insensitive to the natriuretic action of ANP in the acute phase of the disease. However, it is possible that other factors which cause sodium retention may be far more potent than ANP and may overshadow its effects. An alternative possibility is that there is reduced delivery of systemically derived ANP to the renal tissue, secondary to decreased renal blood flow.

Although ANP levels were increased in the patients, PRA was normal (Table 1) and there was no correlation between the ANP and PRA. ET levels are increased in terminal renal failure, but do not correlate with GFR [15–17]. Thus it has been suggested that the elevated levels of ET may be due to hypervolaemia, anoxia and other neuroendocrine disorders. Kanno et al. [18] suggested that injury of the vascular endothelium in vasculitides stimulates ET secretion. It is known that APSGN is an immune-complex disease, and it may cause glomerular endothelial injury. Thus the increased levels of ET that we found in the acute phase of APSGN may be secondary to hypervolaemia and to a possible glomerular endothelial injury.

In both essential hypertension and terminal renal failure no relationship has been found between blood pressure and ET [16, 17]. We could not find any relationship between blood pressure and either ET or ANP, or between ET and ANP levels. ET has been shown to reduce renal sodium excretion [10]. Thus our finding of an inverse correlation between ET levels and renal sodium excretion in the acute phase of APSGN is not unexpected. ET may also inhibit the renal responsiveness to ANP in APSGN.

In conclusion, in APSGN increased ANP levels despite sodium retention suggest a renal unresponsiveness to ANP, perhaps mediated by increased ET levels.

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Ask the expert*

A 3-year-old girl has steroid-responsive nephrotic syndrome, but proteinuria recurs persistently when the dose of prednisolone is reduced to 1.5 mg/kg per day or when she is placed on high-dose alternate-day steroids. The proteinuria is only moderate (Albusti 1+–2+) and there is no oedema. How should this child be managed?

Key word: Nephrotic syndrome

This child has a steroid-responsive and steroid-dependant nephrotic syndrome. She relapses on high-dose alternate-day prednisolone. If this girl has not developed signs of steroid toxicity, prednisolone should be replaced by prednisone. It has been our experience, in some children who do not show cushingoid features despite high doses of prednisolone, that prednisone can be more effective than prednisolone in inducing or maintaining remission. It is not known whether this is due to a decreased intestinal absorption or a faster metabolism of prednisolone than prednisone.

If this girl shows signs of steroid toxicity, particularly statural growth impairment, she should receive a course of alkylating agents (cyclophosphamide or chlorambucil) which often induce long-lasting remissions. As shown by a study from the Arbeitsgemeinschaft für Pädiatrische Nephrologie [1], the duraton of treatment is important: 70% of patients are still in remission 2 years after a 12-week course of cyclophosphamide compared with only 30% after an 8-week course. No study has shown cyclophosphamide to be superior to chlorambucil.

If the patient experiences further relapses despite the course of alkylating agents, she should be treated again with corticosteroids. A prolonged alternate-day prednisone regimen, 15–30 mg/m^2, is proposed, according to the dose at which the relapses occur.

Cyclosporin should be prescribed only if relapses occur with higher doses of prednisone, and if the patient again develops signs of steroid toxicity. This treatment has been shown to be effective in 80% of steroid-dependant children, allowing maintenance of remission despite withdrawal of corticosteroids [2]. As most patients relapse when the cyclosporin dosage is decreased or stopped, cyclosporin may have to be administered for long periods, thus increasing the risk of nephrotoxicity. Therefore, cyclosporin should be given only to those patients who develop further steroid dependency despite a course of alkylating agents.

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* The editors invite questions for this section