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ORIGINAL ARTICLE

Is edema in minimal change disease of childhood really hypovolemic?

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Abstract
Objectives In this study, we aimed to find out whether children with minimal change disease can be classified as hypervolemic by objective measures.
Methods Eighteen children with minimal change disease diagnosed at our department between November 2005 and May 2007 were included in this study. All patients were newly diagnosed or relapsed but were steroid free for at least 6 months. In the first week of edema and when edema resolved (5–7 days after initiation of therapy), weight, height and blood pressure were obtained from all patients. Serum and plasma samples were taken following a starvation period of 12–14 h. The volume load of all patients was evaluated, measuring the inferior vena cava indices in each stage by echocardiography.
Results Average weight at presentation was 8.5% higher than the ideal (dry) weight. There were significant differences between the first and post-treatment body weights, abdomen circumference, and systolic and diastolic blood pressure values ($P < 0.05$ for each). The inferior vena cava index (IVCI) values decreased significantly after diuretic treatment ($P < 0.001$), while inferior vena cava collapsibility index (IVCCI) values increased in the post-treatment period ($P < 0.001$).
Conclusion We believe that a close follow-up of hypervolemic children with MCD, treated solely with easy-to-handle diuretics instead of I.V. albumin and diuretics may properly solve the edematous state in these patients.

Keywords Childhood · Diuretic · Edema · Minimal change disease · Nephrotic syndrome

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Introduction

Interstitial edema is a common clinical expression of nephrotic syndrome (NS). The pathogenesis of edema in NS has not been entirely understood. The historical theory of nephrotic edema generation postulates that stimulation of the renin–aldosterone axis in response to relative hypovolemia mediates sodium retention through the following sequence of events: low serum albumin with decreased plasma oncotic pressure results in an imbalance of Starling forces in capillaries, leading to interstitial leakage of fluid, hypovolemia, and stimulation of the renin–aldosterone system (RAS) [1]. The classical view of edema formation in

childhood NS defines the process as an underfill mechanism [2–4]. However, a large body of clinical and experimental findings is opposed to this theory [5]. In this study, we aimed to find out whether children with late minimal change disease (MCD) can be classified as hypervolemic by objective measures.

Methods

Patients and definitions

Eighteen children with MCD diagnosed at the Department of Pediatric Nephrology, Medical Faculty of Inonu University between November 2005 and May 2007 were included in this study. All patients were newly diagnosed or relapsed but were steroid free for at least 6 months. The informed consent of parents was obtained.

The patients were diagnosed with MCD according to their clinical and laboratory findings: edema, severe proteinuria (over 40 mg/m^2/h), with normal serum creatinine and blood urea nitrogen (BUN) levels, and without macroscopic hematuria, hypertension, and hypocomplementemia. The diagnosis was confirmed by renal biopsy in five children with relapsed nephrotic syndrome who had not received steroid treatment for at least 6 months.

In the study, we took into account the ideal weight of the patients in determining the parameters. In the determination of ideal weight, primarily the age that corresponded to the height of the child was established on first appearance at our clinic. Ideal weight was subsequently taken as the weight that corresponded to the 50th percentile for this age.

In the first week of edema and when edema resolved (5–7 days after initiation of treatment), weight, height, and blood pressure were obtained from all patients. Serum and plasma samples were taken following a starvation period of 12–14 h. Total protein, albumin, BUN, creatinine, sodium, potassium, complement (C_3 and C_4) and 24-h urinary sodium, potassium, urea, creatinine, and protein excretion were also measured at the same time.

The volume load of all patients was evaluated, measuring the inferior vena cava (IVC) in each stage by echocardiography. Echocardiographic examinations were carried out by the same pediatric cardiologist after the patient had taken a 10-min rest in a supine position. IVC diameter during expiration and maximal inspiration was measured from 1–2 cm under the diaphragm by using a Toshiba Powervision 6000 M-mode two-dimensional color Doppler echocardiography with a 3.5–5.5 frequency probe [6, 7]. The inferior vena cava index (IVCI) was measured by the following formula: [(maximal diameter of IVC on expiration + minimal diameter on inspiration)/2]/[the body surface area (m^2)] × 100. The inferior vena cava collapsibility index (IVCCI) was measured by the following formula: [maximal diameter of IVC on expiration − minimal diameter on inspiration]/[maximal diameter on expiration] × 100.

Patients were given diuretics (furosemide and/or amiloride) for treatment during the first week of edema. In only two patients, who had diffuse edema (scrotal edema in a male and pleural-pericardial in a female patient) and hypovolemia signs (hypotension, disturbance of circulation), 1 g/kg human albumin and 1–2 mg/kg furosemide were used.

The procedures were in accordance with the ethical standard for human experimentations established by the Declaration of Helsinki of 1975, revised 1983. The study was approved by the Ethic Committee of Inonu University and detailed consent forms were signed by the families of all patients before participating in the study.

Statistical analysis

The data was expressed as mean ± standard deviation (SD). Pre-treatment and post-treatment data of the patients showed parametric distribution, and paired samples *t*-test was used for the comparison. Statistical significance was accepted as a *P*-value less than 0.05.

Results

Eighteen children (14M/4F), with a mean age of 5.97 ± 2.93 years, diagnosed with minimal change disease were included in the study. Weights, heart rates, systolic and and diastolic blood pressure values both at admission and post-treatment in addition to height and calculated dry weight values are summarized in Table 1. Average weight at presentation was 8.5% higher than the ideal (dry) weight. There were significant differences between the first and post-treatment body weights, abdomen circumferences, and

systolic and diastolic blood pressure values ($P < 0.05$ for each), but not between the heart rates ($P > 0.05$).

Quantitative evaluation of proteinuria at study start showed a nephrotic range proteinuria, and there was a significant decrease after the treatment ($P < 0.001$). Urinary sodium and fractional excretion of sodium (FE_{Na}) were lower than normal in the beginning of the study, and no significant increase was detected in these values after treatment ($P > 0.05$).

IVCI values decreased significantly after diuretic treatment ($P < 0.001$), while IVCCI values increased at post-treatment period ($P < 0.001$). Laboratory data are summarized in Table 2. The alterations in the IVCI and IVCCI values of all patients are detailed in Figs. 1 and 2, respectively.

Discussion

While the pathogenesis of edema in nephrotic syndrome is not well understood, it is usually attributed to an expansion of the interstitial compartment secondary to increased fluid transfer across capillary walls, or accumulation of sodium secondary to an intrarenal defect.

This prospective study was planned to evaluate if edema in children at late phase of edema in MCD is hypervolemic or not, and it was observed that giving only diuretics was enough to resolve the edema of the patients without development of any symptoms or signs of hypovolemia.

According to the classical view, vascular underfill is responsible for the formation of edema. Proteinuria results in hypoalbuminemia and lowers plasma oncotic pressure. This alters Starling forces, determining the distribution of fluid between plasma and interstitium, and results in an increase in interstitial fluid and edema [8]. On the other hand, according to the overfill hypothesis, a primary intrarenal defect in sodium handling is responsible for the occurrence of edema [9]. Studies in animals with experimentally induced nephrotic syndrome suggest that stimulation of tubular sodium reabsorption occurs in the collecting duct [10]. There is increasing evidence that hypoalbuminemia and the inability of the renal distal tubule to excrete sodium are not the only factors responsible for the occurrence of edema. Increased vascular capillary permeability, related to the release of vascular permeability factor and other cytokines, may also play an important role in the pathophysiology of nephrotic edema [11]. The absence or presence of interstitial inflammation may be responsible for whether nephrotic edema is associated with an "underfilled" or "overfilled" plasma volume [12].

First of all, we have to notify that, due to the low socioeconomic status of this region of Turkey, patients admitted or were referred to our hospital a few days after the onset of edema, but not immediately. As a result of admittance of patients at late phase of edema and according to the studies in the literature, we applied only diuretic treatment to all patients during the first week of edema, even to the ones who were at early phase of the edema. Signs of hypervolemia (edema, hypertension, increase in IVCI, decreases in IVCCI and urinary Na and FE_{Na}) were found in 16 (88.8%) patients, in all tests performed to evaluate the volume status before the onset of treatment. On the other hand, we did not

Table 1 Sex, age, height, weight, ideal weight, abdomen circumference, heart rate, and blood pressure data of patients

Clinical data	At presentation (first week of edema) (mean ± SD)	Post-treatment period (5th–7th days) (mean ± SD)	*P*
Sex (male/female)	14/4	–	
Age (years)	5.97 ± 2.93	–	
Height (cm)	111.38 ± 15.68	–	
Ideal weight (kg)	20.80 ± 6.54	–	
Weight (kg)	22.28 ± 5.95	20.86 ± 5.71	<0.05
Abdomen circumference (cm)	59.55 ± 5.67	55.94 ± 6.03	<0.05
Heart rate (beats/min)	108.66 ± 13.09	99.38 ± 9.64	NS
Systolic pressure (mmHg)	106.6 ± 12.9	101.7 ± 9.2	<0.05
Diastolic pressure (mmHg)	74.6 ± 13.6	68.3 ± 10.2	<0.05

Table 2 Total protein, albumin, GFR, urinary protein, Na, FE_{Na}, IVCI, and IVCCI values of patients in the beginning and after treatment

Laboratory data	At presentation (first week of edema), mean ± SD	Post-treatment period (5th–7th days), mean ± SD	*P*
Total protein (g/dl)	4.00 ± 0.65	5.02 ± 0.78	<0.001
Albumin (g/dl)	1.92 ± 1.35	2.60 ± 0.75	NS
GFR (ml/min)	143.44 ± 40.14	142.05 ± 31.83	NS
Urinary protein (mg/m^2/h)	192.05 ± 110.29	16.50 ± 13.71	<0.001
Urinary Na (mEq/l)	35.27 ± 20.73	56.27 ± 42.17	NS
FE_{Na} (%)	0.43 ± 0.44	0.66 ± 0.52	NS
IVCI (%)	94.38 ± 19.13	72.11 ± 18.83	<0.001
IVCCI (%)	25.67 ± 9.87	37.67 ± 11.42	<0.001

GFR: glomerular filtration rate; FE_{Na}: fractional excretion of Na; IVCI: inferior vena cava index; IVCCI: inferior vena cava collapsibility index

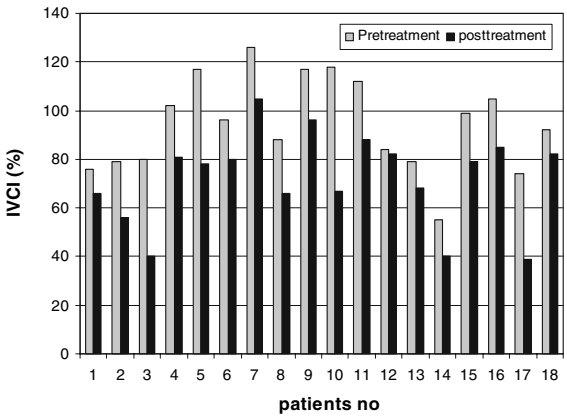

Fig. 1 Alterations of IVCI values of all patients

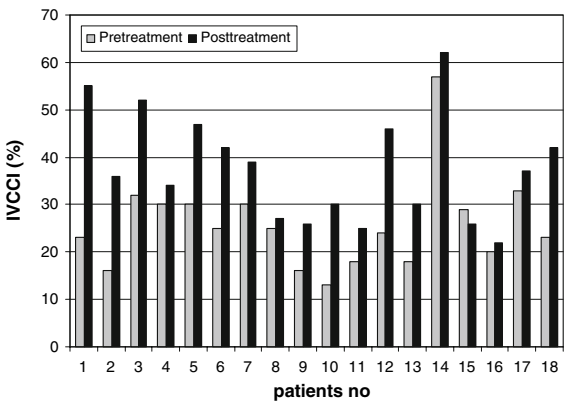

Fig. 2 Alterations of IVCCI values of all patients

observe any of the serious signs or symptoms of hypovolemia (hypotension, postural hypotension, oliguria, and tachycardia) in any of the patients, other than two who were already hypovolemic with diffuse edema at the beginning. Moreover, the systolic and diastolic blood pressures of the patients were found to be significantly higher at the beginning than after treatment ($P < 0.05$). Low urinary Na and FE_{Na} as a result of urinary Na and water reabsorption, which are well-known mechanisms for the compensation of hypovolemia, were found to be unchanged at the end of the study. If the edema was really hypovolemic and water–salt reabsorption had developed secondarily in these relatively late-phase patients, a significant increase at the end of the study would be expected, but this was not so.

On the other hand, variability of plasma and blood volume in nephrotic patients is further illustrated by the following observations: (i) among children with a relapse of minimal change disease, 21% exhibit hypertension but only 4% experienced a hypovolemic shock [13] and (ii) plasma renin activity, aldosterone, and atrial natriuretic peptide (ANP) are correlated with plasma volume in nephrotic patients and vary from low to high values [14, 15]. Therefore, hypovolemia and stimulation of the renin–aldosterone axis are not the primary factors governing sodium retention in nephrotic syndrome. Plasma and blood volume were normal or slightly elevated in several experimental models of nephrotic syndrome [16]. Plasma and blood volume are normal in 84%, low in 2%, and high in 14% of nephrotic patients with edema [17]. Volume expansion by intravenous albumin infusion induces mild natriuresis and fails to potentiate the effect of furosemide [15].

The extracellular volume expansion subsequent to the renal sodium retention of nephrotic syndrome is not symmetrical between the interstitial compartment and the blood volume. Indeed, the blood volume does not increase in proportion to the major enlargement of the interstitial compartment. This asymmetry is accounted for by an abnormal fluid balance between

these two compartments [18]. Moreover, the association of two diuretics (furosemide and amiloride) results in edema removal despite persistent low plasma oncotic pressure and unaltered transcapillary oncotic pressure gradient (6.5 ± 1.5 versus 6.2 ± 1.7 mmHg before and after natriuresis, respectively) [19]. Similarly to the transcapillary oncotic pressure gradient, the transcapillary hydrostatic pressure gradient is not modified in nephrotic patients [20]. This observation relies on the high compliance of subcutaneous and muscle tissues in response to overfilling [21].

Usage of albumin not in all edema patients but only in diuretic-resistant ones has become a more accepted approach after several studies in last few years [22]. As a conclusion, we believe that, instead of using expensive human albumin (which is known to speed up glomerular sclerosis, decrease diuretic response, and cause a modest natriuresis during the hypovolemic early phase) close follow-up of patients for complications and solely administration of diuretics, which are easy to handle in hypervolemic edematous children with MCD. We believe that our findings, which correlate with many experimental studies, must be supported by other clinical studies performed in large series.

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