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Urinary osmolarity in late stage nephritis and nephrosis

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Urinary osmolarity was studied with the DDAVP test in 30 children in the late stage of glomerulonephritis or nephrosis syndrome, and in 12 control children. A restriction of the concentrating ability of the kidney was demonstrated in the cases accompanied by residual symptoms, in comparison to the healthy children and to the patients in lasting remission. In the cases examined histologically, tubular damage corresponding to the functional change could be demonstrated.

In modern paediatric nephrology, one of the most important dilemmas is the assessment of the clinical significance of nephrosis and glomerulonephritis of various origins. This is particularly true in the final stages of the disease, when the patient is in an acceptably good general condition, and the traditional renal function tests are normal or only slightly pathological, but the patient excretes protein with the urine, and may have periodical microscopic haematuria.

We have studied the extent to which urinary osmolarity determination in the DDAVP test may be of assistance in the assessment of such diseases, especially in periods when slight residual symptoms are still exhibited.

Patients and Methods

Examinations were made on 42 children ranging in age from 2 to 17 years. In 30 cases there was glomerulonephritis or a syndrome of nephrosis; they were distributed as follows:

Idiopathic nephrotic syndrome (minimal change): 6 cases.

Diffuse, progressive focal sclerosis in a pre-uraemic state: 1 case.

Membranoproliferative glomerulonephritis: 1 case.

Mesangial proliferative (or sclerotizing) glomerulonephritis: 5 cases.

Hepatorenal syndrome: 2 cases.

Congenital nephrotic syndrome of Finnish type: 1 case.

Schönlein—Henoch nephropathy: 5 cases.

Acute or subacute glomerulonephritis: 8 cases.

Familiar nephropathy (Alport syndrome): 1 case.

At the time of the examination, 22 of these patients were in partial remission, mostly after long-term treatment. Six had manifest oedema (See Table I; children Nos II, III, IV/1, IV/4, VI, VII/1), four had slight azotaemia with urea N values ranging between 20—35 ml/dl (patients IV/2, VI, VIII/1, VIII/5). Six cases were symptom-free one year after treatment. The patients with congenital

nephrotic syndrome of Finnish type and with progressive focal sclerosis were in a moderately severe condition, and in the latter, signs of commencing renal failure (urea N, 65 mg/dl) were observed.

The data for creatinine clearance, haematuria and proteinuria as tested with sulphosalicylic acid are seen in the Tables, Renal biopsy was performed in 16 cases. and evaluated by light-microscopy. Histological examinations were made prior to the present study at the beginning of the active stage of the disease for diagnostic purposes, or later in the event of a failure of corticoid treatment, but even in three cases a long time before the osmolarity studies. In connection with the present study, the biopsy material was reinvestigated for a semiquantitative estimation of the percentage of damaged tubules.

The control group consisted of 12 healthy children.

The DDAVP test was carried out in the following manner: On the previous evening the children received a light supper. On the day of the examination, after emptying of the bladder early in the morning, urine samples were taken at 8 a.m. During the concentration test, free fluid consumption was permitted, solid food was not allowed. After the first urine fraction, 3 drops (21 μg/DDAVP) were administered intranasally, then further urine samples were taken 3 times at 2-hour intervals, made crystal-clear by heating, and osmolarity was determined with a Knauer osmometer.

Results

Table I lists the clinical and biopsy data. In 4 of the 6 children in the reparation stage, osmolarity was higher than 1000 mOsm/kg H_2O. All the other patients had a poorer concentrating ability, proteinuria, and half of them had microscopic haematuria. A certain correlation could be observed between the impairment of concentrating ability and the severity of the basic disease. In the 5 most severe cases urinary osmolarity was less than 600 mOsm/kg H_2O. The correlation was not a strict one, as patient VII/2, who had a normal renal function and no oedema, yielded a value of 581 mOsm/kg H_2O. One patient had severe azotaemia; in the other cases, no marked renal insufficiency could be demonstrated as judged from the serum creatinine, UN or creatinine clearance values.

In all the control children, urinary osmolarity was above 1000 mOsm/kg H_2O; the mean for this group was 1141 ± 72 as compared to $1099 \pm \pm 127$ mOsm/kg/H_2O for the 6 cases in prolonged remission, and 712 ± 143 mOsm/kg H_2O for the 24 patients. With Student's two-sample t test, this group of patients gave significantly lower results than either the controls or the patients in lasting remission ($p < 0.05$).

The histological results are show in Table II.

The amount of kidney tissue available was also taken into account; this is denoted in Table II by the symbols +, ++ and +++. In 3 of the 16 cases, the renal biopsy data are not given, as several years had elapsed between the biopsy and osmolarity examination. With the exception of children I/4, 5, and 6, the biopsy revealed degenerative changes in the proximal tubules and

TABLE I

Data of nephrosis syndrome and glomerulonephritis cases

	Age (years)	Sex	Diagnosis	Proteinuria (g/100ml) during examination	Haematuria during examination	Creatinine clearance (ml/min/1,7 m²) during examination	Osmolarity (mOsm/kg H_2O) maximum urinary value after DDAVP administration
I	Idiopathic nephrotic syndrome						
1	6	♂	N. sy. B.: Minimal change	+	—	116	821
2	14	♂	N. sy.	+	—	117	842
3	5	♀	N. sy.	—	—	84	940
4	10	♂	N. sy. B.: Minimal change	—	—	88	1165
5	5	♀	N. sy. B.: Minimal change	—	—	109	1123
6	5	♂	N. sy. B.: Minimal change	—	—	117	1283
II	9	♀	N. sy. B.: Focal sclerosis	3.0	+	20	290
III	7	♀	N. sy. B.: Membranoproliferative g.n.	1.0	—	78	543
IV.	Mesangial proliferative (or sclerotizing) glomerulonephrities						
1	10	♀	N. sy. B.: Diffuse mesangial proliferative g.n.	0.75	—	80	626
2	14	♂	S.a.g.n.B.:Diffuse mesangial proliferative g.n.	0.22	+	65	659
3	4	♀	N. sy. B.: Diffuse mesangial proliferative g.n.	+	—	126	734
4	5	♂	N. sy. B.: Diffuse Stalk glomerulopathy	3.0	—	104	802
5	14	♂	O.s.g.n.B.: Diffuse mesangial proliferative g.n.	—	—	150	971
V.	Hepatorenal syndrome						
1	17	♂	Autoaggressive hepatitis, N. sy. B.: Diffuse mesangial proliferative g.n.	0.55	—	79	596
2	10	♀	Autoaggressive hepatitis D-penicillamine nephritis	0.46	+	124	729
VI	2	♂	Congenital n. sy. of Finnish type	1.40	—	60	558
VII.	Schönlein-Henoch nephropathies						
1	14	♀	S. H. n.	0.30	—	114	564
2	2	♀	S. H. n.	0.27	+	87	581
3	7	♂	S. H. n. B.: Diffuse glomerular lesion with sclerosis	0.55	+	80	718
4	6	♂	S. H. n.	0.27	+	92	728
5	6	♂	S. H. n.	—	—	127	1113
VIII.	Acute and subacute glomerulonephrities						
1	7	♂	O.s.g.n.B.: Focal segmental g.n.	op.	+	67	671
2	13	♂	S.a.g.n.	op.	+	102	743
3	8	♂	Acute post-streptococcal g.n.	op.	+	78	761
4	14	♂	S.a.g.n.	0.32	+	82	820
5	3	♂	Acute diffuse g.n.	—	+	60	822
6	13	♂	S.a.g.n.	op.	+	112	862
7	3	♂	O.s.g.n.	op.	+	96	872
8	4	♀	O.s.g.n.	op.	+	114	872
IX	10	♂	Alport syndrome B.: Diffuse glomerular lesion	—	+	79	927

Explanation: There was lasting remission in cases I/3, I/4, I/5, I/6, IV/5 and VII/5.

Abbreviations: B.: renal biopsy; N. sy.: nephrotic syndrome; g.n.: glomerulonephritis; S.a.g.n.: subacute g.n.; O.s.g.n.: oligosymptomatic g.n.; S.H.n.: Schönlein—Henoch nephropathy.

TABLE II

Tubular changes in 13 histologically examined cases

Serial number of patients in Table I	Histological diagnosis	Amount of cortical substance examined + − +++	Histologically observed tubular change, expressed in percentage of the tubules examined			Urinary osmolarity mOsm/kg H_2O
			Degeneration	Mild atrophy	Severe atrophy	
II	Focal sclerosis	+++	—	—	100%	294
VII	Focal					
VI	Congenital n. sy. of Finnish type	++	—	80%	below 10%	558
V/1	Diffuse mesangial proliferative g.n.	+++	20%	in a single tubule group	—	596
IV/2	Diffuse mesangial proliferative g.n.	+++	—	15% (15% medulla too)	10%	669
VIII/1	Focal segmental g.n.	+	80%	—	—	671
VII/3	Diffuse glomerular lesion with sclerosis	+++	30%	nephrohydrosis in 50% of the proximal tubules	—	718
IV/3	Diffuse mesangial proliferative g.n.	+++	80%	(20% 10% in the medulla too)	10%	734
IV/4	Diffuse Stalk glomerulopathy	+++	30%	—	—	802
IX	Diffuse glomerular lesion	+ +	—	10%	—	927
IV/5	Diffuse mesangial proliferative g.n.	+++	—	1 tubule	—	971
I/4	Minimal change	+	—	—	—	1165
I/5	Minimal change	+	—	—	—	1123
I/6	Minimal change	+++	—	—	—	1282

Note: Tubular damage in case VI characteristic of the disease; which (disregarding the total atrophy) did not correspond to either the customary degenerative or the atrophio phenomena.

Abbreviations: n.sy.: nephrotic syndrome; g.n.: glomerulonephritis.

atrophy of both types of tubule in the cortical substance.

A certain correlation could be observed between the severity of the changes and the osmolarity values, with the exception of case V/I where, in addition to a marked decrease in concentrating ability, only degenerative changes were found in 20% of the proximal tubules. It was remarkable that no tubular change could be demonstrated in the nephrotic patients.

Discussion

The question of whether, in addition to the well-known glomerular damage, there are tubular changes in nephrosis and glomerulonephritis, has received little attention. From the diagnostic aspect the glomerular change is decisive in the large majority of pathological processes, but in the assessment of the severity and prognosis of the disease one may rely on the degree and extent of the tubular damage [8].

Determination of the concentrating ability of the kidney appears suitable for the demonstration of a functional change occurring in connection with the histological alterations. Specific weight measurement, the limited usefulness of which is generally known, is especially unsuited for this purpose as the protein in the urine has a considerable influence on the result. Depending on the extent of proteinuria, a role is played by the concentration by osmoregulation and by secondary Na reabsorption [3].

Great importance was attached to the urine concentration method developed in patients suffering from various diseases [7], and in healthy children and infants [1]., in prematures and neonates [9]. The drug used was the synthetic ADH preparation, 1-deamino-8-D-arginine-vasopressin (DDAVP). Apart from the absence of pressor-type side-effects, the compound has the advantage over the previously employed lysine-8-vasopressin or pitressin tannate that the children may consume fluids freely during the concentration test. Neither fuid intake nor draining of manifest or latent oedema disturb the test, as in the concentration test after thirsting. We too could confirm the good correlation of the results of the DDAVP test and the pitressin test in 12 healthy children.

Naturally, measurement of the water-reabsorption ability provoked in the distal tubules and collecting tubules is only part of the complex concentration operation of the nephron. According to the model functioning on the principle of the countercurrent multiplier [2, 4], recent data [6] indicate that an essential factor in the ADH effect is the cyclic AMP system; in pyelonephritic experimental animals, the concentrating ability can be enhanced by inhibition of prostaglandin synthesis [5].

In our own material, the DDAVP test was found very suitable for studying the concentrating ability in glomerulonephritis and nephrotic syn-

drome. With the exception of the 6 children in lasting remission, a low osmolarity value was obtained in every case. At the same time, the serum UN, creatinine, and creatinine clearance showed a marked change in one single case only.

In the course of statistical evaluation it had to be taken into account that the material contained cases of heterogeneous aetiology; nevertheless, much was revealed by the simple fact that of the 24 patients only 1 had a urinary osmolarity above 900 mOsm/kg H_2O.

Re-examination of the biopsy material revealed tubular damage in 10 of 13 cases.

The diminished urinary osmolarity measured in the concentration test does not necessarily indicate a damage of the renal tubular system. In the diseases under consideration, a tubular disturbance manifesting itself with a reduction of the concentrating ability may be a direct consequence of the glomerular lesion. The biopsy findings, however, suggested the role of the damage of distal nephron cells.

Urinary osmolarity determination in the DDAVP test is one of the most sensitive means of assessing the extent of renal parenchymal destruction. A further advantage of the method is that DDAVP can be administered intranasally in the form of drops, and no fluid withdrawal is necessary.

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