Osmoregulatory function of the kidneys in children with cystic fibrosis

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"What is known"

- Kidneys are pivotal in water and salt homeostasis, as well as in maintaining cell volume.
- Hyponatremia is not rare in cystic fibrosis.

"What is new"

- Osmoregulatory renal function was compared among children with cystic fibrosis, children with pneumonia and healthy children.
- Renal concentrating and diluting ability was not different between groups.

Abstract

Hyponatremia is not rare in cystic fibrosis, and might be due to several mechanisms. An endocrine and renal imbalance in water and salt homeostasis was suggested. To address this hypothesis, we assessed the urinary concentrating and diluting ability in a group of 12 cystic fibrosis patients (6 females, 6 males), in 14 children with pneumonia (9 females, 5 males) and in 13 healthy children (9 females, 4 males).

Concentrating ability was evaluated following a water deprivation night. Urine osmolality, solute-free and sodium-free water clearances were not significantly different between groups. Renal diluting ability was assessed by means of a water-load test. This provoked a decrease in urine osmolality, as well as an increase in diuresis, solute-free and sodium-free water excretion. These changes were comparable among groups.

Conclusion: Children with cystic fibrosis show a preserved renal concentrating and diluting capacity. A generalized endocrine and renal imbalance in water and salt homeostasis therefore appears unlikely.

Introduction

Hyponatremia is not rare in cystic fibrosis [1-4]. Many mechanisms might underlie this electrolyte disturbance including an enhanced production of sweat rich in salt, a tendency to underestimate fluid and salt needs, excessive intestinal fluid losses, low salt intake or intestinal absorption, non-hypotonic hyponatremia secondary to cystic fibrosis-related diabetes, and inappropriate, i.e. volume independent, antidiuresis [1-5]. Drug-induced dyselectrolytemias have also been observed [6].

The existence of an endocrine and renal imbalance in water and salt homeostasis has also been recently suggested [7]. To address this captivating hypothesis, we performed a pilot study assessing the urinary concentrating and diluting ability in a group of cystic fibrosis patients and in two control groups, the first consisting of patients with pneumonia and the second of healthy children.

Patients and methods

The ability to concentrate and dilute urine was evaluated at Department of Pediatrics, University of Medicine, Saint-Petersburg, Russia, in 12 cystic fibrosis patients with an acute respiratory exacerbation, and in two control groups: 14 previously healthy patients with acute infectious pneumonia and 13 healthy subjects.

The diagnosis of cystic fibrosis was based upon compatible clinical features and elevated sweat chloride (≥60 mmol/L) on two or more occasions [8] as well as on genetic testing, that of acute infectious pneumonia on characteristic symptoms, findings, laboratory data and imaging studies. Healthy subjects had no history of chronic illness, no symptoms of any acute disease and had to have not received any medication within the previous month.

In febrile patients with cystic fibrosis or pneumonia, the urinary concentrating and diluting ability was investigated after relief of fever. To assess the urinary concentration, cystic fibrosis patients, patients with acute pneumonia and the healthy volunteers underwent overnight fluid restriction and the urinary osmolality was measured at each void and the following morning. To investigate the urinary diluting capacity, after their first morning micturition, the participants were given a water load of 10 mL per kilogram body weight and the urinary osmolality was subsequently measured at each void for one hour. Venous blood for the determination of baseline creatinine, sodium, potassium and chloride, and osmolality in serum was also obtained immediately before investigating the urinary diluting capacity.

All measurements were performed in duplicate. Creatinine was measured using the alkaline picrate Jaffe’s method, sodium, potassium, and chloride by direct potentiometry, and osmolality via freezing-point depression with a micro-osmometer.

The results are expressed either as frequency or median and interquartile range. The Fisher exact test and the Kruskal-Wallis test with the Dunn's post hoc test were used for statistical comparisons. Correlation analysis was performed by means of the Pearson correlation coefficient. A $p<0.05$ (two-tailed) was accepted to indicate statistical significance.

Results

Baseline clinical and laboratory data appear in table 1. As compared with the two control groups, cystic fibrosis patients were younger. Furthermore, in cystic fibrosis, potassium and creatinine were slightly lower. Finally, sodium, chloride and osmolality were similar in cystic fibrosis patients and in the two control groups. No patient with cystic fibrosis presented a diabetes mellitus.

Concentrating ability was evaluated following a water deprivation night. Urine osmolality was not significantly different between groups (Table 1). Importantly, no difference in solute-free or in sodium-free water clearances was detected (Table 1). This indicates that the renal concentrating ability in cystic fibrosis patients is comparable to that of healthy children.

The water load, used to assess renal diluting ability, resulted in a significant increase in diuresis in all three groups (Figure 1, panel A). In all groups, enhanced diuresis was

associated with an increase in solute-free and sodium-free water excretion, which were comparable among groups (Figure 1, panel B). Finally, the observed decrease in urine osmolality was similar among the three groups (Figure 1, panel C). Interestingly, in all groups, a positive correlation (r = …, p < … for cystic fibrosis, r = …, p<… for pneumonia and r=…, p<… for healthy children) (please complete) was observed between the baseline urinary osmolality (after the overnight water-deprivation) and the magnitude of its decrease after the water load.

Discussion

The results of the present study indicate that cystic fibrosis patients show a preserved renal concentrating and diluting capacity and argue against the existence of a generalized endocrine and renal imbalance in water and salt homeostasis [7]. The findings of the present study are in line with the results of two seminal reports published in 1970 and in 1982, respectively [9-10].

Circulating creatinine was significantly lower in cystic fibrosis as compared with control groups. Creatinine varies both with glomerular filtration rate and muscle mass, because it is a product of muscle catabolism. Hence, we tentatively assume that, in cystic fibrosis, hypocreatininemia mainly results from a reduced muscle mass caused by the poor nutritional status. On the other hand, an increased glomerular filtration rate has been

sometimes documented in very young cystic fibrosis patients [10].

Circulation potassium was slightly but significantly lower in cystic fibrosis patients. This observation is likely related to the existence of an activated renin-angiotensin-aldosterone system [4].

Of note, to evaluate osmoregulatory renal function, not primarily the absolute values of urine osmolality after night' sleep and water load but the difference between these two values should be considered (Figure 1).

This pilot study has some strengths. 1) In this study, diuresis, urinary osmolality, solute-free and sodium-free water excretions were concurrently assessed. This is important, since the clearance of sodium-free water can be regarded as an indicator of cell volume stabilization. 2) A new, simplified and more practicable water-load test (10mL per kg bodyweight instead of the tradional 20mL per kg bodyweight) was used. Although this method was not validated, the current study demonstrates its feasibility and usefulness. 3) Electrolytes were measured by direct potentiometry, as currently recommended [11].

The study also has some limitations. First, it included a rather small number of patients. Second, patients and controls slightly but significantly differed with respect to some baseline parameters.

In conclusion, this study confirms the widely held view that generally, in cystic fibrosis, disturbances of fluid and electrolyte balance are not of renal origin.

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Figure 1 – Legend

Ability to dilute urine in 12 cystic fibrosis patients and two control groups: 14 previously healthy patients with acute pneumonia and 13 healthy subjects. Results are given as box and whisker plot (boxes are median and interquartile ranges, vertical lines are the 5^{th} and the 95^{th} centiles). No statistical difference was observed among groups.