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Original Article

Low sodium status in cystic fibrosis—as assessed by calculating fractional Na^+ excretion—is associated with decreased growth parameters

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Abstract

Background: In CF infants, normonatremic Na^+ depletion (NNaD), identified by fractional Na^+ excretion (FE_{Na}) values <0.5%, was recently linked to impaired growth. Our paper investigates the relationship between FE_{Na} and growth in CF children >2 years.
Methods: FE_{Na} values were calculated in 35 CF and 24 control children, and tested for correlations with *z*-scores for weight, height and BMI.
Results: All CF children and controls had normal plasma Na^+ concentrations. A total of 25 of 35 (71.4%) CF patients had decreased FE_{Na} values <0.5% (group I). FE_{Na} results of 10 CF patients (group II) and 23/24 controls (group III) were normal. In Na^+-depleted CF children, compared to normal controls, mean *z*-scores for weight (−0.18 ± 0.87 vs +1.03 ± 0.57, $p < 0.001$), height (−0.06 ± 0.89 vs +0.53 ± 0.72, $p = 0.009$) and BMI (−0.22 ± 0.87 vs +1.00 ± 1.06, $p < 0.001$) were significantly reduced. Also, we found positive correlations between FE_{Na} values and *z*-scores for weight ($r = 0.521$), height ($r = 0.292$) and BMI ($r = 0.468$), respectively.
Conclusion: NNaD may contribute to poor growth in CF.
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Keywords: Cystic fibrosis; Normonatremic sodium depletion; Fractional sodium excretion; Growth retardation

1. Background

CF patients may be at risk for enhanced sodium loss particularly during periods of increased sweating or diarrhea [1–3]. While in hot countries this may manifest as hyponatremia in up to 95% of CF patients [4], plasma sodium concentrations in areas with moderate climates most often remain normal despite an actual state of sodium depletion [5]. Thus, in our institution, we have found a rate of hyponatremia of only 2%–3%. "Normonatremic sodium depletion" (NNaD) may thus not be recognized if sodium concentrations are measured only in blood. NNaD often manifests with only nonspecific symptomatology including a decrease in general well-being, listlessness, chronic fatigue, low blood pressure and anorexia [6–8]. However, it has recently been reported that even moderate states of sodium depletion may be associated with increased risk of morbidity and mortality [9]. Also, initially moderate NNaD may rapidly deteriorate to severe hyponatremia with serious complications including edema, muscle cramps, cerebral seizures, coma and death [10,11].

As an additional sequel, chronic sodium losses, e.g. due to ileostomy or colonic resection have been reported to cause failure to thrive [12,13] while normalization of sodium status was shown to reestablish normal weight gain and linear growth [14].

It thus appears prudent to diagnose sodium depletion as early as possible, i.e. before patients become severely hyponatremic.

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This may be particularly true for subjects with a known risk for enhanced sodium loss such as patients with renal salt-losing disorders, chronic diarrhea, ileostomy and CF. In this situation, and in the light of the limited ability of plasma or urine sodium concentration measurements to accurately assess body sodium balance, calculation of the fractional excretion of sodium which indicates the percentage of filtered sodium excreted in urine may be a useful tool [15,16]. FENa values below 0.5% have been reported to be associated with low sodium status and have been shown to accurately identify states of low sodium balance [15,16]. Moreover, calculation of the FE_{Na} compensates for urine flow rate and thus may reflect sodium status more appropriately than measurement of urine sodium concentrations alone.

The aim of our study was therefore (1) to investigate the incidence of NNaD using the determination of the FE_{Na} in CF patients in comparison with healthy controls, and (2) to evaluate the potential effect of sodium status on growth parameters in CF.

2. Methods

This prospective cross-sectional study included CF patients who were recruited during routine outpatient control visits between November 2013 and February 2014 in the Cystic Fibrosis Center of the Department of Pediatrics III, Medical University of Innsbruck. The study was approved by the ethics committee of the Medical University of Innsbruck. Written informed consent was obtained from a caregiver for each patient. Inclusion criteria were two positive sweat tests (sweat chloride >60 mmol/L), a homozygous CFTR mutation and an age between 2 and 18 years. Patients were excluded from the study if they had one of the following diagnoses: any kind of infectious or inflammatory disease, renal insufficiency (GFR < 60 mL/min/1.73 m^2), Bartter's syndrome, Gitelman's syndrome, diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion (SIADH), diabetes mellitus, edema, cardiac and/or hepatic insufficiency including CF-related liver disease and treatment with diuretics. These exclusion criteria were also applied for controls who were healthy children examined one day prior to minor elective surgery with uneventful patient histories and normal preoperative routine laboratory values.

Patient data were documented in the clinical data information system of the University Hospital of Innsbruck and the Cystic Fibrosis Center data collection system. Measurements of height and weight were performed in accordance with the Anthropometric Standardization Reference Manual [17]. Weight for age, height for age and body mass index (BMI) percentiles for girls and boys as well as the pertaining *z*-scores were determined using the respective CDC/NCHS pediatrics calculators [18]. Concentrations of electrolytes and creatinine in plasma and spot urine were determined using standard laboratory methods. To define sodium balance, the fractional excretion of sodium, i.e. FE_{Na} = urinary Na × plasma creatinine × 100/[plasma Na × urinary creatinine] (with all parameters expressed in mmol/L) was calculated. The normal range for FE_{Na} was chosen to be 0.5%–1.5% according to published literature [15,19].

We compared data on plasma Na, urine Na, FE_{Na} and *z*-scores for weight, height and BMI of children from the following three cohorts: CF-children with FE_{Na} values <0.5% (group I), CF-children with FE_{Na} > 0.5% (group II) and normal control children (group III). The Kolmogorov–Smirnov method was used to investigate if normal distribution of data for all sets of investigated parameters was given in the respective groups. Results were expressed as mean ± 1 SD. The Mann–Whitney *U* test was used to test for differences between the patient groups. A Spearman correlation rank test was performed for each individual patient group to explore the strength of relationship between FE_{Na} values and the *z*-weight, *z*-height and *z*-BMI variables. Spearman's *rho* was used to avoid that outliers as shown in the scatter plots of FE_{Na} versus growth variables exerted an influence on correlation size. A *p*-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 22®.

3. Results

A total of 35 CF patients (17 females, 18 males; age range, 2.5–16.9 years; mean age, 10.1 ± 4.2 years) were examined. Of the 24 healthy control subjects, aged 2.4 to 15.1 years (mean age 8.4 ± 3.5 years, not significantly different from CF children), 12 were females and 12 males.

Laboratory and growth parameters as well as calculated FE_{Na} values are summarized in Table 1 (CF children, groups I and II) and Table 2 (healthy controls, group III). Plasma sodium concentrations were between 135 and 144 mmol/L and thus normal in all CF patients and controls. Sodium concentrations in urine (uNa) were very variable in all three groups (Tables 1 and 2) and were between 10 and 235 mmol/L in group I, 110 and 250 mmol/L in group II and 25 and 245 mmol/L in controls (group III) with a mean uNa being significantly lower in group I (94.0 ± 50.5 mmol/L) as compared to group II (171.1 ± 39.2 mmol/L, $p < 0.01$) and group III (167.4 ± 63.3 mmol/L, $p < 0.01$) (Table 3).

FE_{Na} percentages were below normal (<0.5%) in 25/35 CF patients (group I, Table 1). The mean FE_{Na} value for group I was 0.29% ± 0.11%, which was significantly lower than in the 10 CF patients with normal FE_{Na} values (group II, mean FE_{Na} 0.88% ± 0.43%, $p < 0.01$) and in the 24 normal healthy controls (group III, mean FE_{Na} 1.02% ± 0.26%, $p < 0.01$; Table 3). These data suggest that a large proportion of nearly three quarters of the CF patients in our study had FE_{Na} values below the cutoff point of 0.5% that is thought to indicate low sodium status.

Having characterized the three patient groups with regard to their sodium status, we compared the mean *z*-scores for weight, height and BMI in both groups of CF patients (groups I and II) to those of healthy controls (group III). Table 4 shows significantly decreased mean *z*-scores for weight (−0.18 ± 0.87 vs 1.03 ± 0.57; $p < 0.01$), height (−0.06 ± 0.89 vs 0.53 ± 0.72; $p < 0.01$) and BMI (−0.22 ± 0.87 vs 1.00 ± 1.06; $p < 0.01$), respectively, in the sodium-depleted group of CF patients (group I) as compared to the healthy control group III. Also, the mean *z*-scores for weight (0.52 ± 0.69; $p < 0.05$) and BMI (−0.06 ± 0.83; $p < 0.01$) of the CF patient cohort with FE_{Na} values above 0.5% (group II) were significantly lower than those of the normal control group III,

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