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Original Article

Growth Failure in an Infant with Congenital Nephrogenic Diabetes Insipidus During Sodium Restriction

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Abstract. Congenital nephrogenic diabetes insipidus (CNDI) is an inherited disorder characterized by renal tubular insensitivity to antidiuretic hormone, resulting in an inability to concentrate urine. We report on an infant boy with CNDI who showed growth failure during treatment with sodium restriction. At the age of 4 mo, he was diagnosed as having CNDI, judging from fever with hypernatremia (serum Na 153 mEq/L), diluted urine (urine osmolarity 193 mOsm/kg), high antidiuretic hormone (plasma antidiuretic hormone 53 pg/mL), and normal renal function (serum creatinine 0.3 mg/dL). His length and weight were mean +0.4 and –1.1 SD, respectively, at that time. He was treated with sodium restriction (sodium intake; 0.53 mEq/kg/day) using low sodium formula in addition to trichlormethiazide, spironolactone, and mefenamic acid. Growth failure developed: his length and weight were mean –2.4 and –3.3 SD, respectively, at the age of 10 mo. After withdrawal of sodium restriction to 1.5 mEq/kg/day of sodium intake without any change of caloric intake and medication, catch-up growth was observed. At the age of 39 mo, the patient's height and weight were mean –0.8 and –0.6 SD, respectively. We conclude that excessive sodium restriction can cause growth failure in infants with CNDI.

Key words: congenital nephrogenic diabetes insipidus, growth failure, sodium restriction

Introduction

Congenital nephrogenic diabetes insipidus (CNDI) is a rare inherited disease, characterized by renal tubular insensitivity to antidiuretic hormone (1). The most common inheritance is X-linked, which is caused by the mutation of vasopressin V2 receptor (OMIM 300538). The less common inheritance is autosomal recessive or dominant, part of which is caused by the mutation of aquaporin-2 (OMIM 107777). The primary clinical features are polyuria and polydipsia. In infancy, other clinical features follow, such as dehydration due to uncompensated polyuria, and growth failure, which is thought to result from insufficient food intake due to obligatory polydipsia. The goals of treatment include adequate calorie intake for growth, prevention of severe dehydration, and reduction of the urinary solute load by sodium restriction (1). Sodium restriction in infancy is usually accomplished by using low sodium formula or human milk. Infants with CNDI sometimes exhibit growth failure even with adequate caloric supplementation and treatment (2). The etiology of this growth failure is not

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fully understood.

We report the case of an infant with CNDI whose growth failure developed after the introduction of treatment of sodium restriction in addition to trichlormethiazide, spironolactone, and mefenamic acid. Catch-up growth was observed after withdrawal of sodium restriction to some extent, leading to the conclusion that the cause of the growth failure was excessive sodium restriction.

Case Report

At the age of 4 mo, a Japanese boy was admitted to another hospital because of fever for the first time. Perinatal history and family history were unremarkable and without consanguinity. Any drug exposure was denied. The patient's length and weight were 49.5 cm and 3.25 kg (mean+0.2 and +0.6 SD) at birth, and 62.2 cm and 5.52 kg (mean+0.4 and –1.1 SD) on admission, respectively. He was diagnosed as having CNDI, based on hypernatremia (serum Na 153 mEq/L), diluted urine (urine osmolarity 193 mOsm/kg), high antidiuretic hormone (ADH) (plasma ADH 53 pg/mL), normal renal function (serum creatinine 0.3 mg/dL), normal urinary tract on ultrasonography (data not shown), together with no response to the aqueous vasopressin test (urine osmolarity with 0.1 μg/kg of aqueous vasopressin administration: before 138 and after 143 mOsm/kg). Informed consent from the patient's parents was not obtained for molecular analyses of vasopressin V2 receptor and aquaporin-2.

The patient was formula-fed and treated with sodium restriction (sodium intake 0.53 mEq/kg/day) using low sodium formula in addition to trichlormethiazide (0.08 mg/kg/day), spironolactone (2 mg/kg/day), and mefenamic acid (20 mg/kg/day) (2–4).

At the age of 10 months, the patient was referred to our service because of growth failure (Fig. 1). He measured 66.6 cm (mean –2.4 SD) and weighed 6.10 kg (mean –3.3 SD). On examination, his general condition was good. No signs of dehydration were noticed. Serum electrolytes were normal. Serum urea nitrogen was high with normal creatinine. Plasma active renin concentration (ARC) and aldosterone were high and fractional excretion of sodium (FENa) was low. Serum insulin-like growth factor-I (IGF-I) was also low (Table 1). Sodium restriction was withdrawn to 1.5 mEq/kg/day using regular formula. All other medications were unchanged in dosage. The patient's caloric intake had been stable (≈90 kCal/kg/day) throughout the clinical course. After withdrawal of sodium restriction, he grew well (catch-up growth to nearly target height SDS) with normal psychomotor development (Fig. 1). At the age of 39 mo, his height and weight were 92.0 cm and 13.3 kg

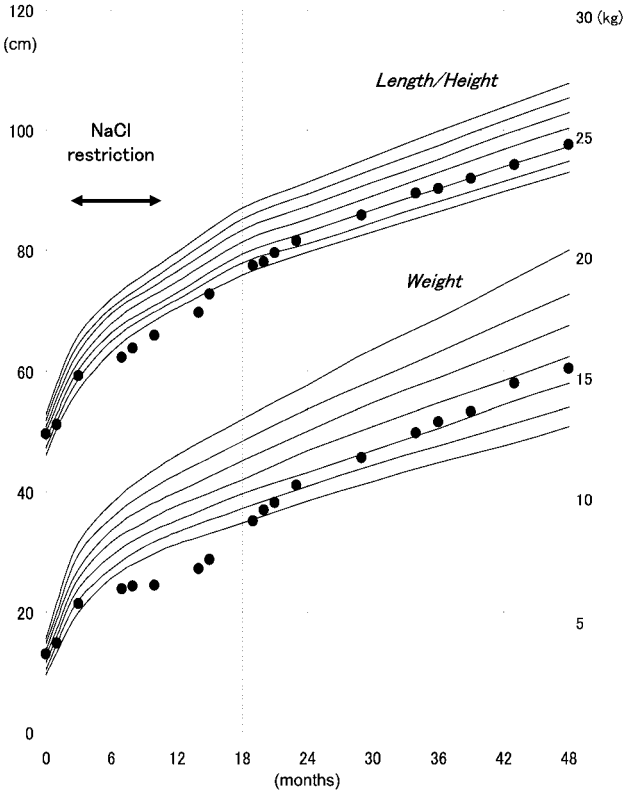

Fig. 1 Growth chart of this case. The duration of sodium restriction (sodium intake; 0.53 mEq/kg/day) is indicated.

Table 1 Laboratory data at the age of 10 mo and 39 mo

age (mo)		10	39	reference value
blood				
Na	(mEq/L)	137.3	140.9	138.0–145.0
K	(mEq/L)	4.4	4.3	3.5–4.7
Cl	(mEq/L)	99	107	99–106
urea nitrogen	(mg/dL)	24.8	7.8	8.0–19.0
creatinine	(mg/dL)	0.4	0.4	0.2–0.6*
active renin concentration	(pg/mL)	141.6	19.7	3.6–36.2
aldosterone	(pg/mL)	1455	119	50–200
IGF-1	(ng/mL)	9.5	109.0	see below**
urine				
FENa		0.02	0.24	

All reference values except creatinine and IGF-1 were for adult. *Reference value for creatinine was for age-matched. **Reference value for IGF-1 for 10 and 39 mo were 18–150 and 29–173 ng/ml, respectively.

(mean –0.8 and –0.5 SD), respectively. Laboratory data at that time showed normal urea nitrogen, ARC, aldosterone, and IGF-I (Table 1).

Discussion

Growth failure in this case was due to excessive sodium restriction. After the introduction of treatment at the age of 4 mo with sodium restriction (Na 0.53 mEq/kg/day), using low sodium formula as well as trichlormethiazide, spironolactone, and mefenamic acid, decreasing growth velocity was evident. At the age of 10 mo, high ARC and aldosterone as well as low FENa indicated excessive sodium restriction. Retrospectively, 1.5 mEq/kg/day of sodium intake was necessary to maintain normal growth velocity in this case. As far as we know, there has been no report describing improved growth velocity after withdrawal of sodium restriction in CNDI. However, we cannot exclude the possibility that other undetermined factors contributed to growth failure in addition to excessive sodium restriction, as the cause(s) of growth failure in CNDI during treatment must be heterogeneous.

The precise mechanism(s) of the growth failure due to excessive sodium restriction remains to be determined. Some plausible explanation is possible judging from low serum IGF-I during excessive sodium restriction. First, volume depletion may cause poor general condition, leading to diminished appetite. However, in the present case, we do not think this possibility is likely. The patient's general condition was good at his first visit to our service. Moreover, the caloric intake did not differ before and after the withdrawal of sodium restriction. Second, volume depletion may cause elevated angiotensin II, which was shown to decrease circulating IGF-I directly in rats (5), leading to growth failure. Third, unknown mechanism(s) might exist. Fourth, any combination of the above is also possible.

We think that the optimal intake of sodium should be determined individually to maintain normal growth velocity in infants with CNDI. Low sodium formula is not mandatory, especially under the use of thiazide diuretics. Although the cause(s) of growth failure in CNDI during treatment must be heterogeneous, every pediatrician should be aware of possible growth

failure by excessive sodium restriction. The measurement of renin and aldosterone in blood as well as FENa may be good parameters to monitor if sodium restriction is adequate.

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