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LETTER TO THE EDITOR

Clinical improvement in patients with autosomal recessive pseudohypoaldosteronism and the necessity for salt supplementation

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To the Editor,

In a recent article Adachi et al. [1] reported clinical improvement with age in one patient with multi-system pseudohypoaldosteronism (PHA) carrying two heterozygous mutations in the γ subunit of epithelial sodium channel (ENaC), noting that this patient "may be the first example of clinical improvement in a molecularly proven AR-PHA1." We would like to draw attention to four major issues of age-dependent amelioration in multi-system PHA raised by this study.

1. Locus of mutation in ENaC genes: The authors comment that the amelioration observed could be due to the presence of an intact α-ENaC subunit. About 2 years ago, we reported clinical improvement in four patients with multi-system PHA starting at 6–10 years of age, although they continue to exhibit salt-losing episodes even in older ages [2]. One of these patients carries a mutation in the α-ENaC gene and another in the β-ENaC gene. Thus, the clinical amelioration is not due to the locus of the mutation in the γ-ENaC gene and can be observed in patients with mutations in any of the three subunits. Moreover, we reported that the degree of the amelioration depends on the genotype, as one patient with a missense mutation showed amelioration after infancy, necessitating relatively smaller amounts of NaCl with only rare salt-wasting episodes after the age of 9 years [2].

2. Activity of truncated ENaC subunit: Adachi et al. [1] note that a mutation that leads to the truncation of an ENaC subunit (without the second trans-membrane domain) should "lead to the complete loss of its function". Recently we showed that a truncated human β-ENaC subunit may support low partial activity of ENaC expressed in Xenopus oocytes [3]. We further noted that this partial activity may be partly responsible for long-term clinical amelioration that we observed.

3. Physiological mechanism of the age-dependent amelioration: The study of Adachi et al. [1] provides the first evidence for a compensatory increased expression of the Na^+–Cl^- cotransporter. This is an important finding to understand the mechanism of age-dependent amelioration in multi-system PHA.

4. Necessity for salt-supplementation: In Adachi's patient, salt supplementation was stopped at the age of 11 [1]. This patient's latest laboratory data (Na 131 mEq/l and K 5.5 mEq/l, with very high aldosterone levels) attest that he still needs salt supplementation. In our experience with severe multi-system PHA patients, dietary salt supplementation is necessary throughout life as we predicted in 1991 and supported with later experience of more than 20 years [4]. One of our patients mentioned in a previous paper [2] had low compliance and eventually stopped taking salt supplementation. Three months ago, this patient at the age of 25 years was hospitalized with severe hyperkalemia, hyponatremia and acidosis (Na 131.9 mEq/l, K 8.7 mEq/l,

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pH 7.2) necessitating i.v. NaCl, fluids, kayexalate therapy and resumption of NaCl supplementation. Mortality has been observed in older patients with multi-system PHA [5]. Thus, despite the clinical improvement in symptoms, we recommend that the multi-system PHA patients should continue with salt supplementation life-long to prevent serious morbidity and even death.

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