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LETTERS TO THE EDITOR

In systemic pseudohypoaldosteronism type 1 skin manifestations are not rare and the disease is not transient

Dear Editor,

We read with interest the recent paper by Turan et al[1] (published online 18 April 2018) on eight patients with hypoaldosteronism resulting from biosynthetic defects of aldosterone secretion (3 cases) or aldosterone insensitivity syndromes named as pseudohypoaldosteronism type 1 (PHA) (5 cases).

In 1991, we described for the first time that PHA type I may appear in two forms with distinct clinical, genetic and endocrine characteristics.[2] These two forms were named as the renal form and the systemic (multisystem) form of PHA. Subsequently, with collaborators, we identified that the systemic form results from mutations in three genes (SCNN1A, SCNN1B, and SCNN1G) that code for the epithelial sodium channel (ENaC).[3,4] Since then, we determined many other mutations in ENaC subunit genes in many patients from many countries.[5,6] With this background and experience on examining the clinical course of these patients, we would like to clarify some aspects of the systemic PHA that has been presented by Turan et al.

The authors mention that three of their patients showed "cutaneous involvement which is a rare feature." In a recent study that mapped the sites of expression of ENaC in the epidermis and epidermal appendages, we presented a list of the skin manifestations observed in PHA patients.[7] Thus, in our experience, the skin manifestations are not rare and, on the opposite, common in multisystem PHA patients.

In discussing the clinical characteristics of two cousins with a homozygous mutation (p.527delPhe in SCNN1A, cases 7 and 8), the authors raise the possibility of "age-dependent amelioration of ENaC function" citing a case reported by Adachi et al.[8] In this patient, salt supplementation was terminated at age 11. He subsequently developed one severe salt-wasting episode requiring hospitalization. At the age of 20, the laboratory examinations showed hyponatremia, hyperkalemia (Na 131 mEq/L, K 5.5 mEq/L) and elevated plasma aldosterone (15 000 pg/mL, normal for age: 15.6-398). Consequently, salt therapy was reinstated (personal communication with Prof. Adachi).

As an additional example for "transient systemic PHA," the authors cite the case of a patient with p.Ser243Pro missense mutation in the SCNN1A gene.[9] Turan et al[1] did not mention that this patient was born prematurely at 32 weeks of gestation and his asymptomatic brother who carried the same mutation was born at term. In the neonatal period, the human kidney is characterized by an impaired ability to regulate water and sodium homeostasis and premature babies are even more susceptible to blood volume and electrolyte changes when ENaC activity is partial. The mention of this patient as a case of "transient" PHA without the information noted here may be misleading regarding the pathogenesis and the course of systemic PHA. Dirlewanger et al[9] noted that missense mutations (such as p.S243P) generally lead to a partial but not to a complete loss of ENaC function. The mild form of systemic PHA observed in this case was a result of the missense mutation.

The in-frame deletion p.527delF reported for the first time by Turan et al[1] is most interesting and instructive about the structure of ENaC. The affected residue, Phe527, is located in the extracellular domain of alpha-ENaC subunit before the TM2.[10] The clinical features of the cases with this mutation resemble the mild symptoms observed in the case of missense mutations. Thus, apparently, the damage to ENaC function is partial as in missense mutations noted above.

We previously expounded on the necessity for lifelong salt therapy in cases of systemic PHA.[11] Although systemic PHA is not a transient disease and salt supplementation should be maintained lifelong, we observed an amelioration in the clinical course (as also noted by Turan et al) in parallel with decreased urinary sodium/potassium ratios despite markedly elevated aldosterone and plasma renin activity in three of four patients followed up for 7-22 years.[6] The only patient with decreased aldosterone and plasma renin activity had a missense mutation. These data suggest a compensatory activation of renin-aldosterone system with age that is attributable to a decrease in urinary salt loss. The study of Adachi et al[8] that showed a compensatory increase in the urinary Na-Cl cotransporter protein level provides a mechanism for age-dependent change in systemic PHA resulting in increased Na reabsorption from kidney tubules.

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The Authors' Reply: In systemic pseudohypoaldosteronism type 1 skin manifestations are not rare and the disease is not transient

Dear Editor,

We appreciate the valuable comments on our article[1] by Hanukoglu and Hanukoglu.[2]

With regard to cutaneous involvement in systemic pseudohypoaldosteronism (sysPHA), we agree with Hanukoglu and Hanukoglu in that these co-occurrences are not rare. Indeed, in our study, 3 of 4 patients with sysPHA1 showed skin manifestations.

As for the clinical improvement with time in some cases of sysPHA, in the article, we discussed the probable reasons for the grandmother being asymptomatic despite possessing the same genotype as the index case in family 7. We believe that the grandmother is still "affected" as her elevated (albeit mildly) plasma aldosterone levels suggest. We disagree with Hanukoglu and Hanukoglu in that the mutation in this family, p.527delF, leads to a milder phenotype, similar to a missense mutation that they cited.[3] As we indicated in our article, an earlier male sibling of the index case died at 10 days of age with vomiting and dehydration, and we reasonably assume that his death was probably due to sysPHA.[1] Additionally, patient 7 and 8 have displayed recurrent episodes of electrolyte imbalances. Therefore, we tend to think that grandmother being asymptomatic is not due to a milder mutation. Rather, it may be a manifestation of milder phenotype due to variability in disease severity within the family and/or age-dependent amelioration. As for the continuation of treatment, we note the clinical experience of Hanukoglu and Hanukoglu, and we do not advocate against the necessity for lifelong salt therapy in cases of systemic PHA.[2,4]

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