

Short Communication

Familial Hyperkalemic Hypertension: A New Early-onset Pediatric Case

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Introduction

The Familial hyperkalemic hypertension (FHHt) syndrome (OMIM #145260), first described in 1964, and also known as Gordon's syndrome or pseudohypoaldosteronism type II (PHA II), is a rare autosomal dominant disease characterized by hypertension, hyperkalemia, hyperchloremic metabolic acidosis, and normal renal and adrenal function, with suppressed plasma rennin activity. Thiazides correct the metabolic abnormalities and hypertension (1–3). FHHt syndrome may be due to mutations in the WNK1 and WNK4 genes, encoding the with-no-lysine kinases 1 and 4 respectively. WNK4 mutants fail to inhibit the thiazide-sensitive Na-Cl cotransporter (NCC), increasing reabsorption of chloride in the distal collecting tubule and causing volume expansion and hypertension, and fail to inhibit the ROMK1 channel, causing hyperkalemia. WNK1 mutants also cause an increase in chloride adsorption both through the activation of EnaC and reduced inhibition of NCC through its influence on the WNK4 activity (4–6). Three loci associated with FHHt have been identified (12p13.3 and 17p11-q21 and 1q31-q42), but other loci, not yet

identified, are probably involved, demonstrating the genetic heterogeneity of FHH. The syndrome has been described primarily in adolescents and young adults, and in most cases, hypertension has been the presenting symptom; however, the investigations performed in the relatives of patients with the FHHt syndrome, showed that the metabolic disorders preceded hypertension, and no relationship between the severity of biochemical abnormalities and severity of hypertension was observed (7, 8). Short stature, hypercalciuria with urolithiasis and dental abnormalities have also been reported. The long-term prognosis remains uncertain because follow-up data are still limited.

Case Report

The present case was a male child was born to nonconsanguineous healthy parents with no family history of hypertension or renal or cardiovascular diseases. His birth weight was 2,260 g (<3C), length was 46 cm (3C), head circumference was 31 cm and Apgar index was 7 at 1 min and 9 at 5 min. When he was 9 months old, he was referred to the Pediatric Nephrology Unit of the Meyer Children's Hospital of Florence (Italy) for evaluation of casually detected severe hyperkalemia (7.2–8 mmol/l), hyperchloridemia (109–111 mmol/l) and metabolic acidosis (pH 7.21; bicarbonate 13.3 mmol/l). At that time, his physical examination was unremarkable, and his blood pressure was normal (75/45 mmHg). Biochemical values are illustrated in Table 1.

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Table 1 Physical parameters, biochemical values and therapy during the follow-up

	9 mo	4.3 yr	8.3 yr
Wheight	Kg 9 (>25C)	Kg 16 (25C)	Kg 31.4 (90C)
Length/Height	cm 74 (50C)	cm 104 (25C)	cm 119.5 (>3C)
BP	75/45	180/120	102/58
BUN	12 mg/dl	9 mg/dl	19 mg/dl
Creatinine	0.4 mg/dl	0.5 mg/dl	0.7 mg/dl
Na	136 mmol/l	143 mmol/l	136 mmol/l
K	7.4 mmol/l	4.5 mmol/l	3.5 mmol/l
Cl	111 mmol/l	100 mmol/l	98 mmol/l
HCO ₃ ⁻	16.2 mmol/l	23 mmol/l	23.9 mmol/l
PRA (n. v. for age <16.6 ng/ml/h)	0.22 ng/ml/h		
Aldosterone (n. v. for age 0.14–2.5 nmol/l)	0.26 nmol/l		
Cortisol (n. v. for age 5–25 microg/dl)	8.24 microg/dl		
ACTH (n. v. for age 9–52 ng/l)	40.1 ng/l		
17-OH-progesterone (n.v. for age 0.1–2.7 nmol/l)	0.6 nmol/l		
DHEAS (n.v. for age 80–560 microg/dl)	< 30 microg/dl		
CaU/CrU (mg/mg) (n. V. <0.2)	NA	1.1	0.2
FE Na	NA	2.9 %	
Transtubular potassium gradient (n.v. 8–9)	NA	0.4	
Therapy		Kayexalate 3 g/Kg/d Na bicarbonate 4 mEq/Kg/d	Hydrochlorothiazide 2.4 mg/Kg/d

Renal and adrenal gland sonograms and a renal scan were normal. He was diagnosed with a selective potassium secretory defect (or the hyperkalemic form of renal tubular acidosis or pseudohypoaldosteronism type I) in spite of normal rennin and aldosterone values. He was treated with 2 g/kg/d of sodium polyester sulphate (Kayexalate) and 2 mEq/kg/d of sodium bicarbonate resulting in normalization of the parameters (K 5.7 mmol/l, bicarbonate 19.4 mmol/l and pH 7.37). For the next 3 yr, he was monitored as an outpatient every 6 mo. His physical growth, neurological development and blood pressure were normal up to the age of 4 yr and 3 mo, when measurement of his blood pressure revealed severe arterial hypertension (180/120 mmHg). His electrocardiogram was normal, showing a pulse rate of 96/min; the echocardiogram showed concentric left ventricular hypertrophy consistent with lasting hypertension. At this time, his weight was 16 kg (25C), his height was 104 cm (25C), and his daily

doses of ion-exchange resin and sodium bicarbonate were 3 g/kg/d and 4 mEq/kg/d respectively. Biochemical values are illustrated in Table 1. Antihypertensive therapy was commenced with 1 mg/kg/d of atenolol and 0.4 mg/kg/d of amlodipine, and due to suspecting Gordon's syndrome (pseudohypoaldosteronism type II; OMIM #145260), hydrochlorothiazide was also administered at an initial dose of 1.5 mg/kg/d and gradually increased to 2.5 mg/kg/d. After only a few days, the sodium bicarbonate and ion-exchange resin therapy was discontinued, and he maintained a normal electrolyte and acid-base status. The antihypertensive drugs were at first tapered and finally discontinued after 12 wk, when, with therapy with hydrochlorothiazide only, the boy showed normal blood pressure. His calcium urinary excretion also normalized. During the following 3 yr, the boy showed a growth velocity at 10C (at the age of 8, his stature was 119.5 cm; >3C), but his bone age was in line with his chronologic age. A transient mild

elevation in blood pressure due to excessive dietary salt was resolved with salt restriction. Molecular investigation of both *WNK1* and *WNK4* gene coding regions failed to reveal the presence of mutations.

Discussion

Only a few descriptions of FHHT in infancy and childhood have been reported, and most cases have been diagnosed in the course of clinical and genetic investigations performed in relatives of hypertensive adult patients (9). Two cases, a newborn and her 9-yr-old sister, were found in a family in which the presence of the disease had previously been demonstrated in their mother. In the newborn, laboratory investigations showed hyperkalemia and metabolic acidosis. Besides hyperkalemia and metabolic acidosis, the elder sister also had short stature and hypertension, which was corrected by high doses of chlorothiazide (10). Hyperkalemia, metabolic acidosis and short stature, but not hypertension, were diagnosed in a 9-yr-old boy by Weinstein *et al.* (11). This patient showed a strict clinical analogy with the preadolescent patient previously described by Spitzer *et al.* (12), therefore, this childhood clinical picture, characterized by hyperkalemia, metabolic acidosis, and short stature, but normal blood pressure, has been called Spitzer-Weinstein syndrome. The absence of hypertension in the patients described by Weinstein *et al.* and Spitzer *et al.* might be justified by their prepubertal age. Besides the cases mentioned, Gordon RD *et al.* and Sanjad SA *et al.* described a 10-yr-old girl and a 13-yr-old girl respectively who showed short stature associated with severe hypertension, marked hyperkalemia and renal tubular acidosis (13, 14). The analysis of families with FHH showed that hyperkalemia and metabolic acidosis precede the development of hypertension (8–10, 15). On the other hand, short stature, the origin of which is unknown, is reported in many, but not in all cases with this complex syndrome (9).

In the present patient, the metabolic abnormalities observed since the first months of life and the subsequent appearance of hypertension, which normalized with thiazide therapy, strongly support the diagnosis of FHHT, despite the fact that molecular investigations failed to reveal mutations in both *WNK1* and *WNK4* genes (7). The distinctive aspect of this case is the very early appearance of severe hypertension. A possible explanation of this phenomenon could have been the long-term treatment with sodium bicarbonate and sodium polyesterene sulphonate. Despite the fact that reabsorption of sodium by the proximal tubule decreases in case of expansion of the extracellular fluid, the chronic metabolic acidosis increases the reabsorption of sodium bicarbonate and fluid by the proximal tubule. Consequently, the very high supply of sodium bicarbonate to maintain the acid base and electrolyte balance, in addition to the excessive avidity for chloride, sodium and fluid, typical of this disease, resulted in severe early hypertension. The metabolic sodium disorder could be confirmed by the value of his sodium fractional excretion of 2.9 (n.v.<3), which was therefore normal and did not increase as expected in the circumstance during the extracellular fluid. Another possible explanation could be the association in this child of the mutation in an unrecognized gene involved in FHHT with polymorphisms of other genes associated with essential hypertension, creating a sum of effects on his sodium metabolism (16). The patient showed hypercalciuria, which normalized with thiazide therapy. Hypercalciuria is usually present in patients suffering from FHHT due to some mutations of *WNK4* (9). Even though the mechanism by which the increased activity of NCC causes hypercalciuria has not been clarified, some studies seem to demonstrate that *WNK4* positively regulates TRPV5-mediated Ca^{2+} transport and that the inhibitory effect of NCC on this process may be involved in the pathogenesis of hypercalciuria of FHHT caused by gene mutation in *WNK4* (17). As happens in

hydiopathic hypercalciuria, thiazides are capable of reducing renal excretion of calcium in patients with WNK4 mutations; indeed, hypercalciuria is six times more sensitive to thiazide treatment in these patients than in individuals with wild WNK4 (6). However, despite the fact that many features tend to suggest WNK4 gene mutation, no known molecular defects were detected in this child. On the other hand, in most families with FHHt, the molecular defect has not been identified yet; therefore, it could be a matter of a possible pathogenetic role of abnormalities of either several new components of the same pathway, multiple aldosterone-regulated effectors or direct or indirect partners of the Na-Cl cotransporter.

The case described here, without a familial history of FHHt, suggests caution in diagnosing pseudohypoaldosteronism type 1 and encourages performance of tests with thiazide in children presenting hyperkalemia and metabolic acidosis.

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