



SCIENTIFIC LETTERS

Severe systemic type 1 pseudohypoaldosteronism: 5 years of evolution



Seudohipoaldosteronismo sistémico grave de tipo 1: 5 años de evolución

Type 1 pseudohypoaldosteronism (PHA-1) was first described in 1958 by Cheek and Perry.¹ It is a rare syndrome of aldosterone unresponsiveness, expressed in two forms: renal PHA-1 and systemic PHA-1.^{2,3} Renal PHA-1 results from autosomal dominant mutations in the kidney mineralocorticoid receptor. As the mineralocorticoid resistance is limited to one organ, the phenotype is milder and often improves spontaneously due to proximal nephron maturation. Systemic PHA-1 results from autosomal recessive mutations in the genes encoding α , β and γ subunit of epithelial sodium channels (ENaC) that exist in multiple organs (kidney, colon, lung, salivary and sweat glands), and therefore the phenotype is severe. Symptoms manifest during the first week of life and require prolonged hospitalizations. Salt-wasting episodes recur frequently and the patients need lifelong high-salt therapy. The mortality rate is high, especially during the neonatal period.

In both forms, diagnosis is established by the presence of high levels of serum aldosterone and plasma renin activity associated with findings typical of hypoaldosteronism (hyponatremia, hyperkalemia and metabolic acidosis).

Herein we describe the evolution of a previously reported case of systemic PHA-1 due to homozygous mutation in intron 3 of the *SCNN1A* gene (c.1052 + 2dupT)⁴ and our therapeutic approach.

Male child, born at full term with birth weight of 3010 g (10–25th percentile). There was no parental consanguinity. His 11-year-old sister had Chediak–Higashi syndrome. He was admitted in the Emergency Room at the tenth day of life with hypovolemic shock, severe hyponatremia (125 mEq/L), hyperkalemia (>10 mEq/L) and metabolic acidosis (pH 7.28, pCO₂ 48.9 mmHg, HCO₃ 22.6 mmol/L, BE –4 mEq/L). He received normal saline to correct dehydration and calcium gluconate, sodium bicarbonate, nebulized salbutamol, insulin infusion and rectal cation-exchange resin (sodium polystyrene sulfonate) to control hyperkalemia. Initially a clinical diagnosis of congenital adrenal hyperplasia

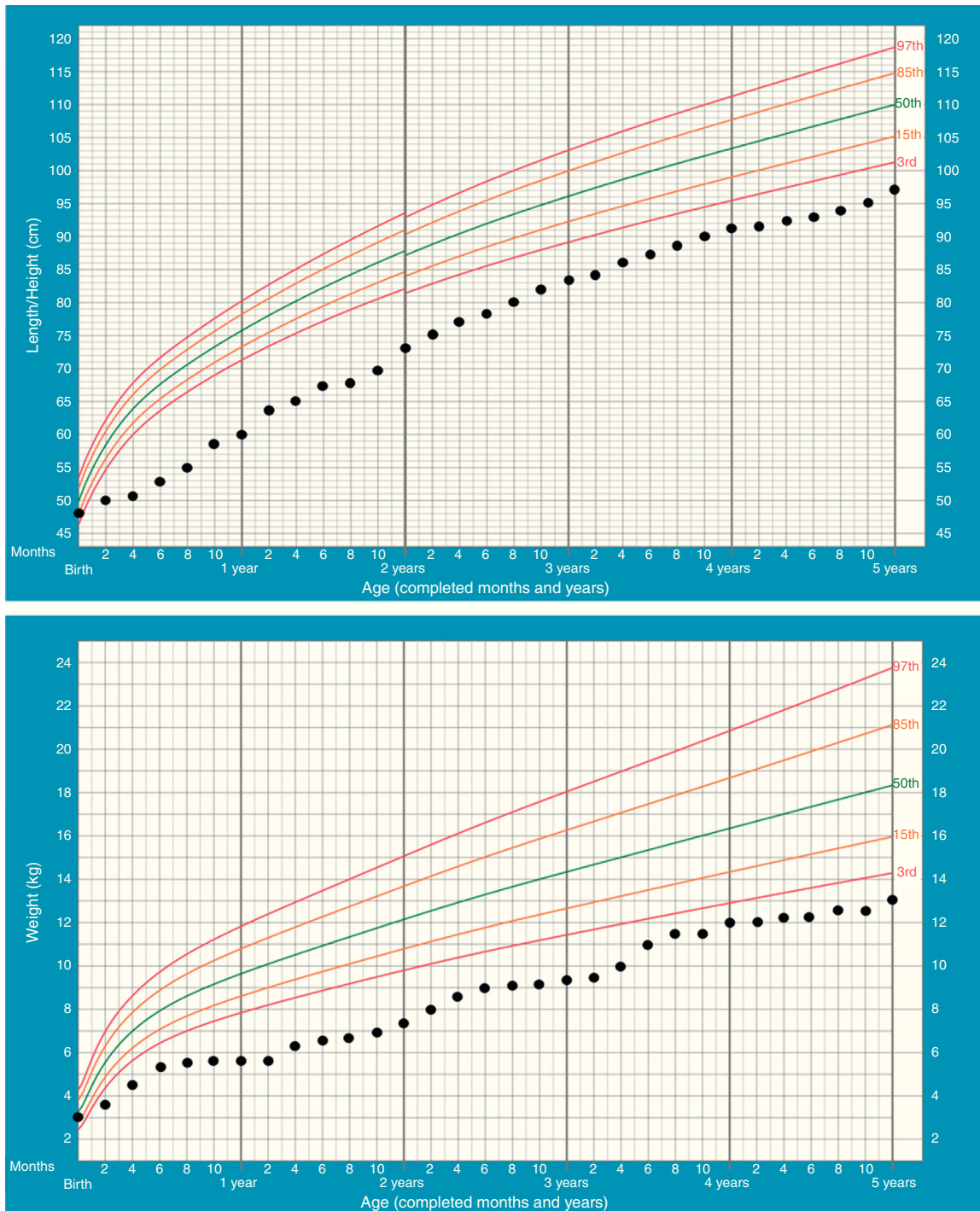
was made and he started hydrocortisone and fludrocortisone. Later, an endocrinological study revealed normal levels of serum cortisol, ACTH, 17-hydroxyprogesterone, DHEAS and thyroid function, but high levels of serum aldosterone (1750 ng/dL: range 7–184 ng/dL) and plasma renin activity (70 ng/ml/h; range 0.4–1.9 ng/ml/h), a diagnosis of PHA-1 was made. Glucose and insulin infusion, calcium gluconate, sodium bicarbonate and nebulized salbutamol were tapered and stopped, and potassium was controlled with high dose of cation-exchange resin. Sodium balance was achieved with 35 mEq/kg/day of sodium chloride. During hospitalization, he presented recurrent episodes of tachypnea and fever mimicking respiratory infections but without identifiable bacterial infection. He was discharged at 5 months of age on oral saline (33 mEq/kg/day) and cation-exchange resin (1 g/kg, six times/day).

He had frequent follow-up pediatric endocrinology consultations with good therapeutic adhesion. Nevertheless recurrences of fluid and electrolyte imbalances appeared (Table 1) and he was admitted several times to the emergency room with hypovolemic shock, requiring intensive treatment, increase of cation-exchange resin and frequent nebulized salbutamol and calcium gluconate. He had several episodes that mimicked recurrent respiratory infections, characterized by cough, tachypnea, fever and wheezing. These respiratory episodes probably occurred due to defective sodium dependent liquid absorption and mucociliary function that increased airway liquid volume and narrowed airways lumen.⁵ These symptoms became less severe and less frequent with increasing age.

He had an atopic dermatitis-like rash that was probably the result of increased salt-loss through the skin.⁶

At 18-months-old, he had his first seizure in apirexia. Other six simple febrile seizures occurred. Electroencephalogram and brain magnetic resonance were normal. Analytical monitoring showed transient subclinical hypothyroidism, asymptomatic hypoglycemia and normal ACTH, cortisol, C-peptide, insulin and IGF-1. ACTH stimulation-test was normal.

Medication was provided by nasogastric tube until 2-years-old. Empirically, hydrochlorothiazide was started from 18 –months old until 4 years old (maximum 2 mg/kg/day). Fludrocortisone was gradually reduced until 3 years, and later, cation-exchange resin was also decreased until 3 years and 8 months old. Sodium supplements ranged from 28 to 55 mEq/kg/day.



WHO Child Growth Standards

Figure 1 Growth charts (longitudinal height and weight) from birth to 5 years of age.

He had a mild development delay and he was under a stimulation program but presently his Griffiths Mental Development Scale is adequate.

In the majority of cases, growth charts show that patients thrive poorly during the first two years. This is also the most critical period of salt-losing crises. Currently our patient, at 5 –years of age, maintains failure to thrive (height

–2.61SDS, weight –3.53SDS) but regular growth velocity (Fig. 1). He only keeps oral sodium supplement.

Management of PHA-1 patients is very challenging since there are no evidence-based recommendations. There is scarce literature about hydrochlorothiazide use but it is used to deliver more sodium to the potassium secretory segment. The dosage of sodium per day to establish salt

Table 1 Amount of salt administration and Na⁺/K⁺ balance during specific periods of admissions.

	Amount of salt (mEq/kg/day)	Na ⁺ (mmol/L)	K ⁺ (mmol/L)
Discharge	33	135	4.8
5 mo.			
URTI	31	120	9.1
5.5 mo.			
Vomiting	33	135	7.7
6 mo.			
URTI	34	129	7.8
7 mo.			
Cough	35	131	5.1
8 mo.			
Vomiting	40	132	6.8
11 mo.			
Vomiting	42	128	6.2
12 mo.			
“Hot day”	47	135	5.8
15 mo.			
Vomiting	51	126	8.0
17 mo.			
Fever	46	135	5.2
2y. 2 mo.			
Vomiting	35	128	8.1
3y.			
Pneumonia	40	135	6.0
3y. 2 mo.			
URTI	45	128	5.6
3y. 3 mo.			
Vomiting	45	127	6.4
3y. 8 mo.			
URTI	40	129	6.4
4y. 2 mo.			
Fever	42	134	4.8
4y. 6 mo.			
“Hot day”	43	124	6.7
5y.			

Mo., months; URTI, upper respiratory tract infections; y., years.

homeostasis varies greatly and has to be readjusted frequently due to changes in body weight. In severe cases this is not enough to prevent salt loss, and death can occur. Moreover, the quality of life of these patients and families is poor: recurrent hospitalizations, large amount of medications, failure to thrive, and susceptibility to infections. An age-dependent trend of amelioration has been reported. The reasons for this improvement are genotype, activity of the truncated ENaC subunit, compensatory increased expression of the NaCl-cotransporter and continued salt supplementation.^{7,8}

The diversity of mutations corresponds to the heterogeneity of clinical phenotypes.³ Mutations are mainly localized on the *SCNN1A* gene. Most of them are nonmissense mutations, leading to abnormal length protein and a severe phenotype, while missense mutations lead to a normal length protein and are associated with milder phenotypes. In our case, there is a splice site mutation not previously described in the literature; therefore, we do

not know its precise effect on the ENaC structure and function. Its location is close to the highly conserved donor splice site of intron 3 and most probably affects the RNA splicing, therefore leading to a grossly abnormal protein.

We would like to share our experience on the difficulties of the management of a patient with genetically proven systemic PHA-1 diagnosed in the newborn period. He fulfilled the criteria listed by Edelheit et al. for severe systemic PHA1: severe salt wasting, frequent hospitalization, recurrent respiratory illness, growth failure, high risk of mortality with requirement of high doses of sodium and cation-exchange resin.⁹ Our patient had a new splicing mutation in intron 3 and presented a severe phenotype. Despite initial poor prognosis, there was a favorable evolution. Severe presentation in the neonatal period does not indicate life-long severity of the disease.

Ethical declarations

The authors state that the procedures followed meet the regulations of the responsible clinical ethical research committee, the World Health Organization and the Declaration of Helsinki.

The authors declare that they have complied the protocols of their workplace for publishing patients' data. The patients included have received sufficient information and have given written informed consent.

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Conflict of interest

There are no conflicts of interest.

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Hipocalcemia autosómica dominante: una nueva mutación



Autosomal dominant hypocalcaemia: A novel mutation

Sr. Editor:

A continuación describimos el hallazgo de una nueva mutación activante en el gen *del sensor de calcio (calcium sensing receptor, CaSR)*. La mutación ha sido identificada en 2 sujetos de la misma familia; ambos presentaban hipocalcemia crónica asintomática con paratohormona (PTH) baja y excreción urinaria de calcio inapropiada.

El CaSR se expresa fundamentalmente en las glándulas paratiroides y el riñón. Está controlado por el calcio extracelular. Permite la regulación de la secreción de la PTH y de la reabsorción tubular de calcio, en función de las variaciones en la concentración de calcio extracelular¹. Los cambios genéticos del CaSR pueden producir alteraciones en la homeostasis del calcio. Se conocen alteraciones en el metabolismo del calcio causadas por mutaciones que pueden ser tanto activantes como inactivantes². Un tercio de los pacientes con hipoparatiroidismo congénito idiopático podrían presentar mutaciones activantes del CaSR. Ello resulta en hipocalcemia autosómica dominante (ADH) que puede presentar un amplio espectro de manifestaciones clínicas^{3,4}. Hasta la actualidad se han identificado más de 50 mutaciones causantes de ADH, caracterizada por hipocalcemia, PTH detectable, pero inapropiadamente baja y calciuria elevada, considerando la hipocalcemia⁵. Muchos de estos pacientes, especialmente los asintomáticos, están infradiagnosticados o diagnosticados de hipoparatiroidismo idiopático⁶. El tratamiento con suplementos de calcio o vitamina D puede exacerbar la hipercalciuria provocando nefrocalcinosis, litiasis e insuficiencia renal.

Presentamos el caso de una mujer de 25 años, derivada a nuestra consulta por hipocalcemia detectada como hallazgo incidental en controles de gestación, 2 años antes. Según la paciente, al ser asintomática no se profundizó en el diagnóstico ni se inició tratamiento.

Se verificaron cifras bajas de calcemia (7,76 mg/dl; rango normal: 8,6-10) junto con niveles de PTH en el rango bajo de la normalidad (20 pg/ml; rango normal: 15-65); la calciuria fue de 34,3 mg/24h (normal: 0-300). Al profundizar

en la historia familiar se descubrió un patrón similar en el padre de la paciente: hipocalcemia con PTH baja. En ambos pacientes se comprobaron los niveles de 25 y 1-25 vitamina D, que fueron normales, y en ambos el tratamiento con calcio oral provocó aumento de la calciuria, sin cambios significativos en la calcemia ni en los niveles de PTH sérico.

Se propuso, a la paciente y a su padre, realizar un test genético.

Tras obtener los consentimientos informados se estudió el gen del CaSR. Se encontró una mutación *missense* en el exón 7: c.2621G>T (p.Cys874Phe); tras una valoración mediante aplicaciones bioinformáticas (MutationTaster y PolyPhen-2) esta mutación se consideró patogénica.

El padre fue derivado para seguimiento en su hospital de referencia. Completamos el estudio de nuestra paciente con una ecografía nefrourológica que no presentó anomalías. En la tomografía axial computarizada (TAC) craneal no se encontraron calcificaciones de los ganglios basales. La densitometría ósea evidenció osteopenia en cabeza de fémur con un *T-score* -1,1.

Se recomendó a la paciente evitar tratamientos con calcio o vitamina D por posibles efectos adversos, dada la ausencia de sintomatología.

Considerando la historia familiar y los hallazgos genéticos se decidió estudiar al hijo de la paciente. Se detectaron niveles de calcio y PTH dentro de la normalidad (9,82 y 22,6 pg/ml, respectivamente). El estudio genético mostró que no era portador de la mutación identificada en la familia.

Describimos una nueva mutación en el gen del CaSR en 2 familiares con hipocalcemia asintomática. Los hallazgos bioquímicos apoyan el diagnóstico de ADH, y corroboran el papel patogénico de la mutación. Prácticamente cada familia con ADH tiene su propia mutación. Frecuentemente se trata de mutaciones *missense* en heterocigosis.

Un hallazgo de hipocalcemia que no se asocia con PTH indetectable o muy disminuida debe plantearnos el diagnóstico de hipocalcemia hipercalciúrica⁷.

Hay un claro consenso en contra de tratar, de forma rutinaria, a pacientes asintomáticos. El tratamiento debe reservarse para pacientes que presentan clínica de hipocalcemia. En estos casos se administrarán suplementos de calcio y/o vitamina D oral en la menor dosis posible. El objetivo será mantener el nivel mínimo de calcemia que permita controlar los síntomas.