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Bartter syndrome in Costa Rica: a description of 20 cases

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Abstract. Bartter syndrome involves an overlapping set of closely related renal tubular disorders which can be subdivided into at least three clinical phenotypes: (1) classic Bartter syndrome (2) Gitelman syndrome, and (3) a neonatal variant of Bartter syndrome. In contrast to classic Bartter syndrome and Gitelman syndrome, the neonatal variant of Bartter syndrome has both the features of renal tubular hypokalemic alkalosis as well as profound systemic manifestations. Specifically, neonatal Bartter syndrome is characterized by intrauterine polyhydramnios, premature delivery, and life-threatening episodes of fever and dehydration. Most of these infants also have severe hypercalciuria with associated nephrocalcinosis and osteopenia. Over a 22-year period, 20 Costa Rican patients with a congenital syndrome that resembles neonatal Bartter syndrome have been identified and characterized. While these patients exhibit some of the clinical characteristics previously described for neonatal Bartter syndrome, this cohort also has a set of distinct features. They are predominantly female, have a later age of diagnosis, manifest a relatively unique set of physical traits, and appear to have milder clinical disease. Given these differences, it will be important to apply the emerging molecular tools to determine whether the phenotypic variability indicates genetic heterogeneity in neonatal-onset Bartter syndrome.

Key words: Neonatal Bartter syndrome – Costa Rica

Introduction

Bartter syndrome is characterized by a constellation of clinical symptoms and laboratory abnormalities. Most notable among these are profound hypokalemic metabolic alkalosis, increased urinary excretion of potassium and prostaglandins, normotension despite elevated plasma renin and aldosterone levels, a relative vascular resistance to the pressor effects of exogenous angiotensin II, and hyperplasia of the juxtaglomerular apparatus [1]. Most patients are diagnosed in childhood or early adolescence. While the disease prevalence is unknown, there appears to be a significant familial incidence of Bartter syndrome. Specifically, the occurrence in siblings and in the children of consanguineous marriages suggests an autosomal recessive mode of inheritance [2].

Based on numerous clinical studies, it now appears that Bartter syndrome involves an overlapping set of closely related renal tubular disorders. In the simplest formulation, primary renal tubular hypokalemic metabolic alkalosis can be subdivided into at least three clinical phenotypes: (1) classic Bartter syndrome, (2) Gitelman syndrome, and (3) a neonatal variant of Bartter syndrome.

In classic Bartter syndrome, the clinical presentation generally occurs in the first 2 years of life, with polyuria, polydipsia, vomiting, a tendency for dehydration, and failure to thrive. Biochemically, these patients are distinguished by hypokalemic metabolic alkalosis, increased potassium excretion, and normal to elevated levels of urinary calcium excretion [1, 3]. Clinical data demonstrating defective chloride transport in the distal nephron and decreased concentrating capacity suggest that the primary defect in classic Bartter syndrome involves transport processes in the medullary thick ascending limb [1, 4, 5]. In addition to these biochemical perturbations, a small subset of patients have developed progressive renal insufficiency due to severe tubulo-interstital nephritis [6, 7]. It is not clear whether the loss of renal function in these patients was a direct consequence of their primary molecular defect or a secondary phenomenon related to their chronic hypokalemia [8].

Gitelman syndrome is characterized by a milder and later clinical presentation, notable for fatigue, muscle weakness, and recurrent episodes of carpopedal spasm. Hypocalciuria and hypomagnesemia are prominent features of this subtype [1, 3]. Recently, Simon et al. [9] have demonstrated that Gitelman syndrome results from mutations in the thiazide-sensitive sodium-chloride cotransporter (*NCCT*) of the distal nephron.

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In contrast to classic Bartter syndrome and Gitelman syndrome, the neonatal variant of Bartter syndrome has both the features of renal tubular hypokalemic alkalosis and profound systemic manifestations [10, 11]. Neonatal Bartter syndrome is characterized by polyhydramnios due to intrauterine polyuria and, typically, this results in premature delivery [10, 12, 13]. After birth, life-threatening episodes of fever and dehydration occur secondary to profound polyuria, vomiting, and diarrhea. Most of these infants also have severe hypercalciuria with associated nephrocalcinosis and osteopenia [14]. Seyberth et al. [10, 11] and Leonhardt et al. [14] have reported marked stimulation of renal and systemic prostaglandin E_2 production in their cohorts of neonatal Bartter syndrome patients and have coined the term hyperprostaglandin E syndrome. In addition, as initially described by James et al. [15] and later confirmed by Ohlsson et al. [16] and Landau et al. [17], some of these infants have a peculiar facies characterized by a triangular-shaped face, prominent forehead, large eyes, protruding ears, and a drooping mouth. Recently, Landau et al. [17] have described an extended consanguineous Bedouin family in which neonatal Bartter syndrome is also associated with sensorineural deafness in five affected children.

The pathogenesis of neonatal Bartter syndrome is not well understood. Based on clinical studies, investigators have proposed that the primary defect involves decreased renal tubular chloride reabsorption, increased renal tubular potassium loss, or abnormalities in prostaglandin metabolism [11, 12, 18–20]. Recently, Simon et al. [21] have analyzed a cohort of neonatal Bartter syndrome patients from six families and identified mutations in the bumetanide-sensitive, sodium-potassium-chloride cotransporter (*NKCC2*) of the medullary thick ascending limb. These findings are not consistent with the normal distal chloride reabsorption previously described in some subsets of neonatal Bartter patients [10] and may indicate that neonatal Bartter syndrome is genetically heterogeneous.

In this report, the clinical characteristics of 20 Costa Rican patients with a congenital syndrome that resembles neonatal Bartter syndrome are presented. These patients were identified over a 22-year period at the Hospital Nacional de Niños of Costa Rica, a 350-bed pediatric teaching hospital for a referral population of 3.3 million people.

Patients and methods

Patients. The charts of all patients who were diagnosed between June 1972 and June 1994 with primary renal tubular hypokalemic alkalosis were reviewed. Patients who had an immediately antecedent history of diarrhea and/or vomiting, arterial hypertension, cystic fibrosis, use of diuretics, laxatives, or steroids were excluded from further consideration. Twenty patients, 15 females and 5 males, fulfilled our diagnostic criteria and were more extensively analyzed. For each patient, a clinical questionnaire was completed jointly by the parents and one of the investigators. This questionnaire included information regarding pregnancy and delivery, birth weight and length, mental and motor development, clinical symptoms, i.e., fever, vomiting, diarrhea, dehydration, and tetany, as well as their temporal onset, therapeutic interventions, family history, parental consanguinity, and the number of affected siblings. Physical features such as facial characteristics, and height and body weight at initial presentation, as well as 2 or more years after institution of medical therapy were recorded. Laboratory data from the initial evaluation, including venous blood acid-base values, serum sodium, potassium, chloride, calcium, magnesium, phosphate, urea, and creatinine, were recorded.

Study protocol. The study protocol was approved by the Ethics Committee of the Hospital Nacional de Niños. The purpose of the studies and the nature of all the procedures were explained in detail to the parents, and written parental consent was obtained for each patient. For these studies, all patients were admitted to the nephrology ward between June 1994 and January 1995. Two weeks prior to admission, potassium supplementation and all drugs were discontinued.

On the 1st hospital day, the baseline evaluation included venous blood gases, serum sodium, potassium, chloride, calcium, magnesium, phosphate, urea, creatinine, and aldosterone levels. On the 2nd hospital day, clearance studies were performed according to previously described protocols [10, 22]. Briefly, in fasting patients, a stable urine flow rate was established under conditions of maximal free water clearance by intravenous infusion of 5% dextrose. In three consecutive 20-minute intervals, blood and urine samples were collected from an indwelling venous needle and an indwelling Foley catheter, respectively. For each set of samples, creatinine, chloride, and osmolality were determined and the values were averaged. Free water clearance (C_{H2O}) was calculated from the formula $C_{H2O} = V - (U_{osm} \times V/P_{osm})$ where V = urine flow rate, U_{osm} = urinary osmolality, and P_{osm} = plasma osmolality. The chloride clearance (C_{Cl}) was determined and the distal fractional chloride reabsorption was calculated from the formula ($C_{H2O}/C_{H2O}+C_{Cl}$). A sonographic evaluation of the kidneys and bladder was performed in each patient at some point following the diagnosis of neonatal Bartter syndrome.

Analytical methods. Serum and urine electrolytes, serum calcium, magnesium, urea, and creatinine and venous blood gases were determined using routine laboratory methods. Plasma and urine osmolalities were measured by an Digimatic Osmometer (Advanced Instruments, Needham Heights Mass., USA). Plasma aldosterone levels were measured in all patients using a solid-phase radioimmunoassay (Coat-A-Count Aldosterone, Diagnostic Products, Los Angeles Calif., USA). When the radioimmunoassay for plasma renin activity (PRA) (INCSTAR, Stellwater Minn., USA) became available at the Hospital Nacional de Niños in 1995, ambulatory PRA levels were determined for 18 of the 20 patients. Urinary prostaglandins were not measured.

Results

Over a 22-year period, 20 patients with neonatal Bartter syndrome were identified. The clinical characteristics of each patient are presented in Table 1. Pregnancy was complicated by polyhydramnios in 18 patients (90%) and 18 (90%) were delivered prematurely as defined by a gestational age ≈35 weeks. Two families had 2 affected siblings, while the mothers of 4 other study patients had one or more additional pregnancies complicated by polyhydramnios, premature delivery, and perinatal death. No history of consanguinity was elicited from any of the parents. However, in one family a maternal aunt had a pregnancy complicated by polyhydramnios and premature fetal demise. While the index mother, her sister, and their respective spouses all lived in the same region of the country, no relationship could be established between the spouses.

Eleven patients presented for evaluation in the 1st year of life and were diagnosed with Bartter syndrome. However, based on retrospective data from the clinical questionnaire, all 20 patients had had recurrent episodes of vomiting and dehydration dating to the first few weeks of life. The phenotype in this cohort of children was most

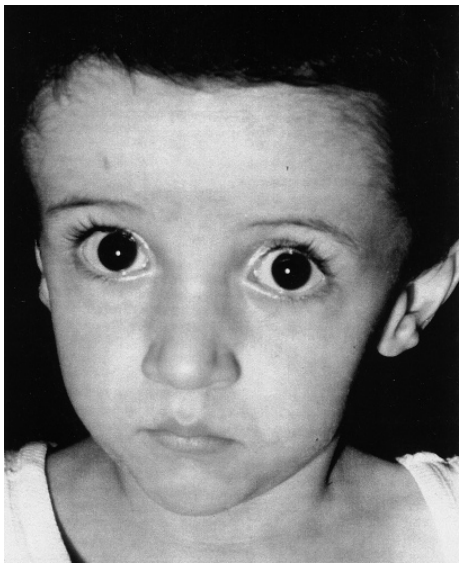

Fig. 1. Characteristic facies in a Costa Rican child with neonatal-onset Bartter syndrome. The face is triangularly shaped with large eyes and protrouding ears. The drooping mouth gives the child a pouting expression

remarkable for a peculiar facies, distinguished by a triangularly shaped face, large eyes, and protruding ears (Fig. 1). This characteristic facies was evident in 16 (80%) patients, including 2 sisters with the disease. There was no correlation between the presence of this facies and the age of diagnosis. In addition, of the patients tested, 9 (47%) had strabismus and 8 (57%) had evidence of sensorineural hearing loss by audiogram testing (Table 1).

At presentation, failure to thrive was evident in all of these patients as defined by lengths and weights significantly less than the third percentile for age (based on United States normative data). From a clinical perspective, all patients have some evidence of developmental delay. Twelve patients were formally tested within the first 3 years of life using the revised Gesell Developmental Schedule (Gesell Developmental Test Materials, Houston, Tex., USA). All 12 patients had abnormal developmental coefficients (DC), i.e., <75, and the mean score for this cohort was 60.0 ± 9.7. In those patients who had undergone evaluations for both hearing and psychomotor development, there was no correlation between the sensorineural hearing loss and the DC. These findings suggest that factors other than hearing impairment contributed to the developmental delay in this patient cohort.

The data from the in-hospital studies are shown in Table 2. Hypokalemia was present in 18 (90%) patients, but interestingly only 12 (60%) patients had evidence of metabolic alkalosis. In comparison, all 20 children had had significant hypokalemia (mean serum potassium 2.8 ± 0.4 mg/dl) and metabolic alkalosis (mean serum bicarbonate 29 ± 3 mg/dl, normal range 19–22 mg/dl [23]) at the time of diagnosis (data not shown). While 2 children were both hypocalcemic and hypomagnesemic, no episodes of tetany were observed. As expected, the PRA levels and plasma aldosterone levels were significantly elevated for age in most of those patients. Renal function, as assessed by creatinine clearance, was well preserved in all but 1 patient (patient 10) who developed renal insufficiency and progressed to end-stage renal disease (ESRD) by 16 years of age. Seventeen (85%) patients had

Table 1. Clinical phenotype data

Patient no.	Gender	Gestational age (weeks)	Age at diagnosis (months)	Polyhydramnios	Peculiar facies	Strabismus[a]	Developmental delay[b]	Sensorineural hearing loss[c]
1	F	30	5	+	+	1	69.0	1
2	F	30	1	?	+	2	–	1
3	F	33	25	+	+	2	60.0	3
4	F	28	72	+	+	1	40.0	3
5	F	31	36	+	+	1	–	3
6	F	34	9	+	–	1	60.0	2
7	F	30	6	+	+	2	–	3
8	F	32	5	+	–	1	–	2
9	F	35	27	+	+	1	61.0	1
10	F	34	53	+	+	2	–	2
11	M	34	48	–	+	2	70.0	1
12	M	29	8	+	+	1	–	1
13	F	39	4	+	+	2	60.0	3
14	F	29	120	+	–	1	43.0	1
15	M	32	6	+	–	3	60.0	1
16	F	29	6	+	+	2	72.0	3
17	F	35	39	+	+	2	–	2
18	F	34	9	+	+	2	65.0	2
19	M	40	118	+	+	1	60.0	2
20	M	32	12	+	+	2	–	1
Mean		32.5±3.2	–				60.0±9.7	
Median		32	10.5				60	

[a] Strabismus coded as either (1) present, (2) absent, or (3) unknown
[b] Developmental status assessed by Gesell Schedule
[c] Sensorineural hearing loss diagnosed by audiogram testing and coded as either (1) present, (2) absent, or (3) unknown

Table 2. Laboratory data

Patient no.	S_{Na} (mg/dl)	S_K (mg/dl)	S_{Cl} (mg/dl)	S_{HCO_3} (mg/dl)	S_{Ca} (mg/dl)	S_{Mg} (mg/dl)	PRA[a] (ng AI/ml per hour)	S_{Aldo} (ng/dl)	C_{Cr}[b] (ml/min per 1.73 m^2)	$U_{Ca/Cr}$[c]	Renal sonogram[d]	$C_{H_2O}/C_{H_2O}+C_{Cl}$[e]
1	154	2.3	110	29.0	9.7	2.1	50.0	120.0	110	0.30	3	0.05
2	135	2.9	88	20.0	8.9	2.0	40.0	120.0	110	0.60	2	0.10
3	132	2.6	103	21.5	9.8	1.9	50.0	120.0	124	1.30	2	0.11
4	138	3.3	104	25.0	8.3	1.2	50.0	69.4	115	0.54	3	0.17
5	139	3.2	103	24.0	7.8	1.5	22.6	75.2	120	0.58	3	0.20
6	144	3.0	105	28.0	9.0	2.3	27.5	109.8	111	0.72	3	0.22
7	139	2.0	103	33.0	10.0	1.7	30.2	120.0	125	0.42	2	0.27
8	139	3.7	100	31.0	9.9	1.3	32.6	120.0	120	0.30	3	0.36
9	135	3.5	103	26.0	9.9	1.4	11.5	120.0	86	0.45	2	0.43
10	140	3.4	110	19.0	6.0	2.0	50.0	–	27	0.10	2	0.50
11	133	3.4	105	25.0	10.0	1.3	17.6	3.2	131	0.02	1	0.52
12	140	3.3	98	28.0	11.4	1.0	21.1	–	143	0.40	2	0.53
13	144	3.0	–	21.0	9.0	1.2	36.8	21.5	88	0.26	3	0.54
14	146	2.6	106	21.0	8.0	1.7	27.4	120.0	96	0.80	3	0.56
15	131	3.0	104	21.0	11.0	1.4	50.0	120.0	151	0.69	1	0.56
16	136	2.6	103	22.0	9.0	1.6	50.0	–	110	0.10	3	0.60
17	167	2.8	115	26.0	11.0	1.9	30.0	–	120	0.45	3	0.60
18	139	3.1	98	31.0	9.3	2.0	50.0	120.0	90	0.60	3	0.60
19	150	4.1	103	19.0	9.2	1.1	–	–	80	0.50	3	0.60
20	141	3.3	102	24.0	8.4	–	–	120.0	113	0.55	2	0.17
Mean	141 ± 8.6	3.0 ± 0.5	103 ± 5.6	24.8 ± 4.3	9.3 ± 1.3	1.6 ± 0.1	32.1 ± 15.2	108 ± 28	104 ± 31	0.48 ± 0.33		0.40 ± 0.20
Normal	135 – 145	3.5 – 5.0	98 – 107	1 – 22	8.8 – 10.5	1.7 – 2.4	0.84 – 2.5	1 – 16	80 – 120			0.86 ± 0.04

S, Serum; Na, sodium; K, potassium; Cl, chloride; HCO_3, bicarbonate; Ca, calcium; Mg, magnesium; PRA, peripheral plasma renin activity; Aldo, aldosterone; C_{Cr}, creatinine clearance

[a] Normal values listed for children 1–4 years of age [24]

[b] Normal values for males (1.5 years to adolescent) = 124.0 ± 25.8 ml/min per 1.73 m^2 and for females (1.5 years to adolescent) = 108.8 ± 13.5 ml/min per 1.73 m^2

[c] Normal values for age taken from [25]

[d] Renal sonographic findings coded as (1) normal, (2) loss of corticomedullary differentiation, or (3) nephrocalcinosis

[e] Distal tubular chloride reabsorption ($C_{H_2O}/C_{H_2O}+C_{Cl}$) was determined as previously described [22]

Table 3. Review of the literature

	Total no. of patient	Patients diagnosed at ≤1 year[a]	Females/total patients ≤1 year	Polyhydramnios and prematurity	Hypercalciuria/ nephrocalcinosis	Typical facies
Camacho and Blizzard [28]	2	1	1/1	0	No data	No data
James et al. [15]	2	2	2/2	0	No data	2
Dillon et al. [29]	10	6	3/6	3	4	No data
Robson et al. [30]	9	2	2/2	1	No data	No data
Simopoulos [31]	9	4	No data	0	No data	No data
Ohlsson et al. [16]	1	1	1/1	1	1	1
Seyberth et al. [10]	5	5	3/5	4	5	No data
Restrepo de Rovetto et al. [27]	6	3	No data	3	3	No data
Schroter et al. [32]	7	7	4/7	7	7	No data
Landau et al. [17][b]	5	5	2/5	5	2	4

[a] Number of patients diagnosed with Bartter syndrome in the 1st year of life. The patient presentation is most consistent with the neonatal Bartter variant

[b] All patients from a single consanguineous pedigree

hypercalciuria, as defined by an elevated ratio of urinary calcium to creatinine [25]. Renal sonograms were performed in all patients and abnormalities were detected in 18 (90%), with loss of the corticomedullary junction in 7 patients and distinct evidence of nephrocalcinosis in 11. The lack of correlation between the urine calcium to creatine ratios and the presence of nephrocalcinosis may be due to a change in urinary calcium excretion over time that could not be detected with the current study design. Alternatively, the urinary calcium to creatine ratio may be a crude indicator of pathologically significant hypercalciuria.

Following the initial diagnosis of Bartter syndrome, all patients were treated with oral potassium supplementation using a solution of 5% potassium chloride (KCl). For those patients with a particularly severe hypokalemia, indomethacin or spironolactone was also added to the medical regimen. The effect of KCl supplementation alone versus KCl supplementation combined with either indomethacin or spironolactone on growth velocity and serum potassium was not rigorously evaluated in this patient cohort. Follow-up 2 years or more after initiation of treatment revealed that linear growth and body weight had

increased substantially in all 20 patients, irrespective of the treatment regimen. However, none of the patients achieved a height greater than the third percentile for age. Three female patients have progressed through normal pubertal development and are currently 20, 18, and 16 years of age. Each has attained a post-pubescent height that is at the third percentile and all are shorter than their mothers.

Discussion

Over 22 years, 20 children with neonatal-onset Bartter syndrome have been identified and characterized at the Hospital Nacional de Niños. This Costa Rican study adds to the previous reports of neonatal-onset Bartter syndrome from Australia [25], Europe [3, 10, 13, 16], the United States [15, 27], and the Middle East [17, 21]. Although the world-wide prevalence of neonatal Bartter syndrome has not been established, the case frequency appears to be relatively high in the Costa Rican population. The Hospital Nacional de Niños is the only pediatric tertiary referral center in Costa Rica, for a population of 3.3 million people. If the number of neonatal-onset Bartter syndrome cases is compared with the total number of live births during this interval, the incidence would be 1.2 cases per 100,000 live births per year. However, if only preterm births are taken into account, the incidence would be 25.4 cases per 100,000 births per year. This relatively high incidence can not be easily explained because consanguinity is not prevalent in Costa Rica and there is no evidence to suggest that these patients were the product of consanguineous relationships. While this cohort includes only two pairs of siblings, the mothers of 4 other patients had one or more additional pregnancies complicated by polyhydramnios, premature delivery, and perinatal death. All of the parents are completely asymptomatic. These data support the autosomal recessive mode of inheritance proposed by others [2, 14, 16, 27].

The patient cohort described in this report share a number of characteristics with the neonatal-onset Bartter syndrome patients reported previously in the literature (Table 3). Almost unanimously, these patients were born prematurely after pregnancies complicated by polyhydramnios. All had episodes of vomiting and dehydration in the 1st year of life and all have failed to thrive. Most of the patients had significantly elevated PRA and aldosterone levels. Hypercalciuria was documented in 85% of the patients and there was a high incidence of nephrocalcinosis. The physical phenotype in these patients was most remarkable for the peculiar facies initially described by James et al. [15]. Indeed, this facies is so characteristic, that its presence in a Costa Rican child with failure to thrive strongly suggests the diagnosis of neonatal Bartter syndrome.

Compared with previous reports, the Costa Rican cohort also has a number of features that are relatively unique. In contrast to the reports of Seyberth et al. [10] and Landau et al. [17], only 1 (5%) patient had a stormy neonatal course. Of note, this patient survived without the benefit of indomethacin treatment. In all patients, KCl supplementation was the intial therapeutic intervention. In 10 (50%) patients, marked hypokalemia prompted the addition of indomethacin alone or in combination with spironolactone. While a rigorously controlled study was not performed, follow-up data obtained in 1994 suggest that the disease severity in some patients may have attentuated over time. Following a 2-week suspension of all therapy, 3 patients (15%) were normokalemic and 8 (40%) had normal serum bicarbonate levels. Regardless of the treatment regimen, growth velocity appeared to improve in all patients, but none achieved a height greater than the third percentile for age. In previous reports, more severely affected children had achieved significant catch-up growth with indomethacin treatment [11, 13]. While the effect of prostaglandin synthase inhibitors on growth is not well understood, it is important to note that only 1 patient in the current study was treated with indomethacin.

Strabismus and sensorineural hearing loss were prevalent in this patient cohort. Nine (47%) patients had strabismus, including a pair of affected sisters. The association of strabismus and neonatal Bartter syndrome has not been previously reported. Eight of the patients tested (57%) had sensorineural hearing loss. Landau et al. [17] noted an association between neonatal Bartter syndrome and sensorineural deafness in their cohort of five consanguineous patients. They propose that this association results from the pleiotropic effect of a single recessive gene defect. However, given that two sibling pairs in the present study (patients 6 and 9, patients 10 and 13) are discordant for hearing loss while presumably sharing the same recessive mutation, this seems to be a less-likely explanation in the Costa Rican patients.

Hypomagnesemia, a typical feature of Gitelman syndrome [5], was evident in 52% of the Costa Rican patients. Of note, Landau et al. [17] reported normal or elevated serum magnesium levels in their five patients. In previous reports, chloride clearance studies have demonstrated defective distal tubular chloride reabsorption in classic Bartter syndrome patients but not in a cohort of neonatal Bartter syndrome patients [5, 10, 22]. All of the patients in the present study had markedly decreased distal tubular chloride reabsorption. In their original publication, Gill and Bartter [22] applied the same method to evaluate distal chloride reabsorption and reported values in their patients that are comparable to those found in the Costa Rican patients. While renal function was generally well preserved in the Costa Rican cohort, 1 patient developed renal insufficiency and progressed to ESRD. The development of tubulointerstitial disease leading to a progressive decline in renal function has been described both in patients treated with long-term indomethacin and in patients with classic Bartter syndrome. The patient presented in this study was not treated with indomethacin.

In summary, a cohort of 20 Costa Rican patients with neonatal-onset Bartter syndrome is described. These patients share numerous clinical characteristics with neonatal Bartter syndrome patients reported previously in the literature. However, they are predominantly female and have a relatively unique set of physical features. In addition, these Costa Rican patients appear to have a somewhat milder clinical phenotype than the patients described by Seyberth et al. [10] and Landau et. al. [17]. The median age of di-

agnosis was 10 months of life and indomethacin was not required as a life-saving therapeutic intervention. While the molecular defect in these patients remains to be determined, the clinical data suggest that the Costa Rican patients may have a defect in medullary thick ascending limb chloride transport. As noted, Simon et al. [21] have identified mutations in the (Na-K-Cl) cotransporter (NKCC2) in a cohort of primarily Saudi Arabian children with neonatal-onset Bartter syndrome. It will be important to evaluate whether, despite the phenotypic differences, all patients with neonatal-onset Bartter syndrome have defects in the NKCC2 or whether these phenotypic differences indicate genetic heterogeneity in this disorder.

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