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REVIEW

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Bartter syndrome and its neonatal variant

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Key words Tubular disorders · Bartter syndrome · Neonatal Bartter variant · Gitelman syndrome

Abbreviations *FE* fractional excretion · *JGA* juxtaglomerular apparatus · *PAC* plasma aldosterone concentration · PGE_2 prostaglandin E_2 · *PRA* plasma renin activity · *PTH* parathyroid hormone

Introduction

Bartter syndrome is a rare condition. Most textbooks of internal medicine or paediatrics give it no more than half a page, describing it generally as follows: ''Bartter syndrome is a rare metabolic disorder that can be observed in infants, children and adults. Clinical signs and symptoms comprise muscle weakness, growth retardation, polyuria and polydipsia, constipation and a normal blood pressure. Biochemical characteristics are hypokalaemic hypochloraemic alkalosis, hyperkaliuria, isosthenuria, hyperactivity of the renin-angotensin-aldosterone system and increased urinary excretion of prostaglandin E_2. Renal histology shows both hyperplasia of the juxtaglomerular apparatus (JGA) and of the renal medullary interstitial cells.''

In fact, this constellation can be the result of a number of conditions. The first aetiological category is intestinal loss of either potassium or chloride. This occurs in surreptitious vomiting and chronic laxative use, seen mainly in adults, and congenital chloride diarrhoea or feeding a chloride-deficient formula in infants. Second comes the acquired renal loss of chloride or potassium as is the case in chronic diuretic abuse. Finally, in children, the disorder is mainly due to an autosomal recessive renal tubulopathy of which the diagnosis, in most cases, is made in the first 2 years of life when these patients present with failure to thrive, poor appetite and pronounced polydipsia with vasopressin resistant polyuria. We will try to show that this latter tubular disorder deserves to be labelled ''Bartter disease'', the phenotypic expression of which is extremely variable, as it is common in many hereditary disorders.

Most textbooks do not yet mention the fact that, exceptionally, Bartter patients present already in the neonatal period with sometimes life-threatening features. It is the most severe expression of the disease. The onset is during fetal life in the second half of pregnancy. It leads to polyhydramnios and, as a rule, premature delivery.

The purpose of this review is double: first, to clearly define Bartter disease and, second, to describe in detail the special features of the neonatal variant while explaining what prenatal and neonatal observations have taught us about the pathophysiology of this disorder.

History

Bartter et al.'s original observations

In 1962, Frederic Bartter and coworkers published an elegant and elaborate paper on two young patients, a child and an adolescent, with hypokalaemia, hyperkaliuria, hyperaldosteronism, hyperplasia of the JGA and normal blood pressure [1]. It was the time when the renin-angiotensin-aldosterone system was discovered and the JGA rediscovered as the site of renin production. Renin could not be assayed yet but angiotensin could be measured in the serum, and aldosterone in the urine. Also angiotensin II was available for experimental use.

A number of adult patients had been reported with primary hyperaldosteronism due to an adrenal adenoma. They presented with hypokalaemia, hyperkaliuria

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and arterial hypertension. They were cured by partial or total adrenalectomy.

Bartter et al's two patients had profound hypokalaemia, high urinary potassium and aldosterone excretion but normal blood pressure. Since their condition improved with spironolactone (an aldosterone antagonist) and albumin infusion (restoration of volaemia) the authors concluded that the renal potassium loss was caused by excessive exchange of sodium for potassium at the distal tubule, a known effect of aldosterone. They decided to have their younger patient operated. His left adrenal was removed completely as well as 80% of the right. Histology disclosed hypertrophy of the zona glomerulosa, the production site of aldosterone.

Unfortunately, this procedure did not improve the patient's condition. The surgeon had performed, en passant, a renal biopsy the histology of which brought about an interesting new feature namely pronounced hypertrophy of the JGA.

Bartter felt this was a most convincing argument in favour of hypersecretion of renin. How could that be reconciled with a normal blood pressure the more so since the boy's serum contained large amounts of "a pressure agent" with all the characteristics of angiotensin II, the most potent biological vasoconstrictor? Both patients, when given angiotensin intravenously, displayed a remarkably weak pressure answer as compared with healthy controls. Bartter's hypothesis was straightforward: "We suggest that these patients have a primary impairment of the vascular response to angiotensin".

Further important steps in the history

Bartter's hypothesis did not hold for long. The non-responsiveness to angiotensin turned out to be corrected by plasma expanders. Furthermore, new patients were reported in whom a number of key observations were made.

In 1973, Chaimovitz et al. [2], studying a child with Bartter syndrome during hypotonic saline infusion, identified a defect in the sodium reabsorption at the distal tubule. They clearly showed that the proximal tubular sodium handling was normal as well as the patient's reaction to hydrochlorothiazide. They concluded therefore that the defect most likely was at the thick ascending limb of Henle's loop.

In 1976, Verberckmoes et al. [19] and Gill et al. [5] discovered the hypertrophy of the renal medullary interstitial cells and the hyperproduction of renal prostaglandins as a central feature of Bartter syndrome.

These important contributions have led to the widespread succesful use of indomethacin, a potent inhibitor of prostaglandin synthase. At first, many workers in the field believed that hyperprostaglandinism was the primary defect in Bartter syndrome. However, indomethacin did not completely correct all the abnormalities. Furthermore, prostaglandin excretion was increased in a number of other conditions, more specifically in renal tubular disorders such as cystinosis.

In 1978, Gill and Bartter [6] showed that a prostaglandin-independent defect in the renal chloride reabsorption was the most likely explanation for the disease.

This hypothesis is the best one so far and many different observations have confirmed it.

The neonatal variant

In 1982, two groups described in detail patients with neonatal Bartter syndrome. Marlow and Chiswick [7] described a premature baby, the second child of related Asian parents. It died at the age of 18 weeks after having developed necrotizing enterocolitis which was attributed to indomethacin therapy. Rodrigues Pereira and Hasaart [14], in a short report, drew the attention to the occurrence of polyhydramnios as the first sign of Bartter syndrome. Their patient was not a premature baby and presented at the age of 3 months with failure to thrive. These authors acknowledged that the association polyhydramnios-Bartter syndrome had been reported earlier by at least four different groups.

Indeed, as early as 1971, Fanconi et al. [4] describing two children with Bartter syndrome, briefly mention that one of the patients' mother had an unexplained hydramnios. Similar observations were made by authors from Belgium [9], Great Britain [3] and Canada [13] but none of them really understood the link. It was McCredie et al. from Australia [8], who, in 1974, identified the very special constellation of polyhydramnios, prematurity, initial renal sodium and, in a second stage, the emergence of the full features of Bartter syndrome. Moreover, these authors already emphasized the presence of hypercalciuria and nephrocalcinosis which, as became apparent later, really are hallmarks of the neonatal variant of Bartter syndrome.

Prenatal observations in neonatal Bartter disease

Rodrigues Pereira and Hasaart [14] stated that "it might be of great interest to examine amniotic fluid of patients with Bartter syndrome but, as the syndrome is rare and not even 10% of the patients were accompanied by hydramnios, it is almost impossible to obtain such fluid". Yet, nature and the help of a skilful obstetrician (Prof. Kamiel Vandenberghe) allowed us to obtain and examine amniotic fluid in a series of mothers pregnant with suspected Bartter syndrome children [10].

The story of the siblings, patients 2 and 3

Case 2, the first baby of young, unrelated Belgian parents, was born in 1976. At a gestational age of 26 weeks, polyhydramnios was diagnosed. Nine amniocenteses were performed, retrieving some 1500 ml of fluid at each

tap. At 32 weeks, the boy was born. Birth weight was 2350 g (P95) and length 45 cm (P75). The baby fed poorly and vomited. After an radiological investigation for gastro-oesophageal reflux, he collapsed. Plasma and steroids were administered and he was referred to our department. Body weight was 350 g below birth weight, he was pale and dehydrated. Systolic blood pressure was 90 mm Hg. Serum sodium was 128 mmol/l, potassium 7 mmol/l. The urine had 40 mmol/l of sodium. During the first 24 h, the baby passed 520 ml of diluted urine. Plasma 17-α-hydroxyprogesterone and the urinary excretion of 17 hydroxy- and 17 ketosteroids were normal.

Plasma renin activity was 233 ng/ml per hour (normal median value for age 12.0, range 7.1–23.8 ng) and aldosterone 159 ng/dl (normal median value for age 62 ng, range 30–201 ng). There was neither glucosuria, hyperaminoaciduria nor hyperphosphaturia. The diagnosis of pseudohypoaldosteronism was made. However, sodium supplementation as high as 15 mmol/kg per day, while normalizing serum sodium, did not improve the baby's appetite, growth and tendency to dehydrate. At 6 weeks of age, hypokalaemia and hyperkaliuria became obvious. Chaimovitz's test was performed and showed 67% distal tubular sodium reabsorption, far below normal values and comparable to what was found in Chaimovitz's case of Bartter syndrome. The diagnosis of Bartter syndrome was made. The child was given indomethacin at a dose of 1.5 mg/kg per day and the effect was spectacular: the patient started to drink and grow and could be discharged.

Five years later, patient 2's mother was pregnant again. At 23 weeks, her fundus was 33 cm. Ultrasound revealed polyhydramnios and a normal fetus with filled stomach and bladder. It was obvious that this fetus suffered from the same condition as the elder brother. At 24 weeks, 1300 ml of amniotic fluid was removed and analysed. After the 4th amniocentesis, labour ensued and a female baby was born weighing 1400 g (P75) with a length of 42 cm (P90). She is patient 3. The baby did not need ventilatory assistance but after 48 h she had lost 350 g and was dehydrated. Serum sodium dropped to 123 mmol/l at day 5 and chloride to 85 mmol/l. Urinary concentration of both sodium and chloride was around 100 mmol/l. With increasing amounts of i.v. fluid and sodium chloride, birth weight was reached again at day 8. Indomethacin was introduced at very low doses but had to be stopped after 12 days because of necrotizing enterocolitis.

Prenatal observations

This remarkable and instructive experience led our gynaecologist to suspect Bartter syndrome in every fetus with unexplained polyhydramnios. We thus have been able to identify six more similar cases. Each time identical patterns of prenatal abnormalities were present. In total, we have observed nine patients with neonatal Bartter syndrome so far. Their characteristics are summarized in Table 1.

Polyhydramnios

The first striking feature is polyhydramnios in a healthy mother and a morphologically normal fetus. This polyhydramnios is the consequence of fetal polyuria as has been demonstrated by us and others. In case 3 fetal diuresis was estimated by ultrasound according to the technique of Wladimiroff et al. [20]. At 28 weeks, the urinary output was 38 ml/h i.e. 910 ml/24 h, normal values being between 5 and 9 ml/h. The amount of amniotic fluid at the same day was estimated to be in excess of 5 l whereas the normal value is around 1.5 l.

High chloride concentration

More interesting is the composition of the amniotic fluid (Table 2). Sodium concentrations were between 135 and 138 mmol/l, which is in the normal range for 28–30 weeks (136 ± 6.8 mmol/l). Potassium was low: the median figure was 3.2 mmol/l, the range 2.8–4.3 mmol/l; normal values are 4.0 ± 0.2 mmol/l. The most constant and obvious abnormality was the high chloride concentration: median value was 115 mmol/l, range 110–123 mmol, that is to say, with one exception all figures are at or above +2SD of the normal mean of 108 mmol/l. Calcium and creatinine concentrations were all within the normal ranges.

Low prostaglandin E_2 figures

Prostaglandin E_2 concentrations in the amniotic fluid were all very low and, taking into account the dilution factor, probably within the normal range (Table 2).

Table 1 Neonatal Bartter. Patients data

Patients	1	2	3	4	5	6	7	8	9
Sex	F	M	F	F	F	F	M	M	F
Polyhydramnios time of diagnosis (weeks)	30	26	23	28	26	20	20	28	27
Gestational age at birth (weeks)	33	32	29	32	27	32	27	34	35
Body weight (g) (percentile)	1350 (10)	2350 (90)	1400 (75)	2240 (90)	1340 (75)	2260 (90)	1530 (90)	2140 (50)	2250 (25)
Body length (cm) (percentile)	43.5 (50)	45 (75)	42 (75)	47 (90)	39 (75)	45 (75)	41 (90)	47 (75)	47 (75)

Table 2 Neonatal Bartter: amniotic fluid composition

	normal values	Patient	3	4	5	6	7
Na (mmol/l)	136 ± 6.8 (*)		136	138	138	135	136
K (mmol/l)	4.0 ± 0.2 (*)		4.3	3.7	3.0	2.8	3.2
Cl (mmol/l)	**108 ± 3.0** (*)		**112**	**121**	**114**	**110**	**113**
			119	**123**			
Ca (mg/dl)	7.4 ± 2.2 (*)		6.6	6.6	–	13.0	5.9
Creat. (mg/dl)	1.1 ± 0.6 (*)		0.8	0.8	1.5	1.2	0.6
PGE_2 (pg/ml)	82–313		5	44	10	25	12
(pmol/ml)	233–888		14	125	28	71	34

(*) Mean ± 2 SD

When the mother was given indomethacin for 2 weeks, no substantial change in the amniotic fluid was observed [10].

The concurrence of polyhydramnios, intrauterine polyuria and a chloride concentration at or above 112 mmol/l enables prenatal diagnosis of Bartter disease.

Postnatal findings

Polyhydramnios in all our patients, as in many published cases, led to premature delivery at between 27 and 35 weeks. These premature babies immediately have great problems with their water and electrolyte balance. Indeed, and as expected, the intrauterine polyuria continues after birth causing a life-threatening condition characterized by severe renal sodium and chloride loss that can only be compensated for by massive supply of water and sodium chloride. Urinary calcium excretion is also very high from the first day on. Urinary prostaglandins show a rapid increase that is suppressible by adequate volume management.

Polyuria

Urine output in these newborn premature babies is high to massive. Maximal urine output in our patients was between 12 and 50 ml/kg body weight and per hour. Polyuria in this period of life is defined as a urine production of ≥4 ml/kg per hour. Daily urine output has exceeded body weight in three of our patients. Urine output remains very high for between 4 and 6 weeks and then it drops quickly to high-normal values. Patient 7 had a diuresis of 1790 ml per day at 1 week, 1350 ml at 2 weeks, 657 ml at 6 weeks and 411 ml at 10 weeks corresponding to 50, 33, 11 and 5.3 ml/kg per hour respectively. Probably many patients have died due to such cataclysm, most of them without appropriate diagnosis. In four of our cases, a previous sibling died in comparable conditions.

Urinary potassium loss replacing sodium loss

The urinary sodium and chloride concentrations immediately after birth are very high and in the same range as in the amniotic fluid (Table 3). The electrolyte composition of the first postnatal urine sample in seven patients showed the following figures: sodium 93–126 mmol/l, chloride 89–132 mmol/l and potassium 1–15 mmol/l.

Urinary sodium and chloride remain high for a variable period. After 3–6 weeks, their concentrations fall and, concommittantly, the initially very low urinary potassium levels start to rise (Fig. 1). At that stage, the classical Bartter pattern becomes recognizable: hypokalaemia and hyperkaliuria are the main biochemical abnormalities, the urine remains abundant and has a low osmolality. We measured the fractional excretions (FE) of sodium and potassium over time in patient 6. The FENa dropped from 10% to 0.4% in 3 months whereas the FEK increased from 8.5% to 34%. Normal values are $<1\%$ for sodium and $<25\%$ for potassium.

Urinary prostaglandins

Urinary prostaglandin E_2 levels (PGE_2) are within or slightly above the normal range immediately after birth.

Table 3 Neonatal Bartter: urinary electrolytes (*D* day, *M* month)

First urine sample after birth							
Patient	3	4	5	6	7	8	9
Na (mmol/l)	114	125	113	126	97	130	93
K (mmol/l)	15	5	9	1.5	1.0	1.0	1.5
Cl (mmol/l)	120	132	100	132	97	138	89
Urine samples of patient 4 over time							
	D1	D2	D3	D7	D14	M2	M3
Na (mmol/l)	125	130	130	114	113	81	8
K (mmol/l)	5	4	3	4	8	30	67
Cl (mmol/l)	132	138	134	118	120	112	62

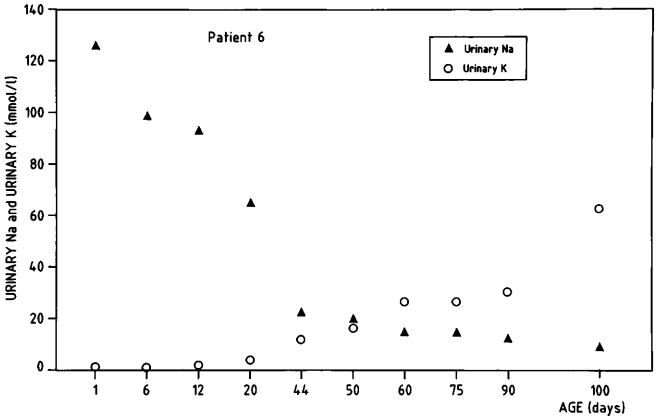


Fig. 1 Course over time of urinary sodium and potassium concentrations in patient 6 with neonatal Bartter disease

Patient 3 excreted 8.9 ng/24 h on day 1. On day 2 the figure was 50.2 ng and on day 3 135.7 ng/24 h. The normal values (mean ± 2SD) for premature babies of 28–32 weeks are 5.5 ± 3.3 ng/24 h. The overproduction of PGE_2 is a secondary, postnatal phenomenon and the explanation is likely the truly tremendous loss of electrolytes and water which were not very well compensated for in patient 3 since she lost 18% of her body weight over that 3 days period. In patients 4 and 8 the increase of urinary PG was no longer seen (Fig. 2). These babies' loss of body weight was around 5% only. In other words, the renal hyperprostaglandinism is not only a postnatal, secondary phenomenon, it is a suppressible one by means of appropriate fluid and electrolyte management. This suppressive effect over a longer period of time is illustrated in Fig. 3.

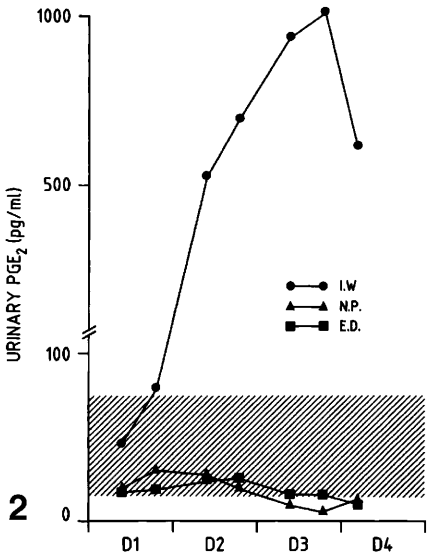
Calcium metabolism

Hypercalciuria and nephrocalcinosis

All our patients had very high urinary calcium/creatinine ratio's (Uca/cr) from the 1st day on. The figures varied from 3 to 6 mg/mg, normal values for premature babies being between 0.60 and 2.06 mg/mg. Our experience clearly shows that this important anomaly is present for weeks and months and remains in most patients. There is a tendency though for the absolute values to decrease but normal levels are exceptional. Patient 6 had a Uca/cr of 4.0 mg/mg at birth, of 4.2 on day 12, 4.4 on day 21 and 1.0 at 2 months of age. The P90 for Uca/cr in infants aged 0–3 months is 0.78 mg/mg. Even when indomethacin is given at doses up to 2.5 mg/kg per day, the hypercalciuria never normalizes, as exemplified by our data in patient 2 (Table 4). This hypercalciuria is part of the neonatal variant of Bartter disease. No

Table 4 Urinary calcium in patient 2 under permanent indomethacin therapy

Age	Uca/cr (mg/mg)	Uca (mg/kg)
2 years	0.77	16.6
4 years	0.50	12.0
6 years	0.38	9.4
8 years	0.60	12.1
10 years	0.49	11.9
12 years	0.37	6.4
14 years	0.38	8.3
16 years	0.30	4.4
18 years	0.37	6.1
20 years	0.35	5.6
Normal values	< 0.32 (P90)	< 4.0



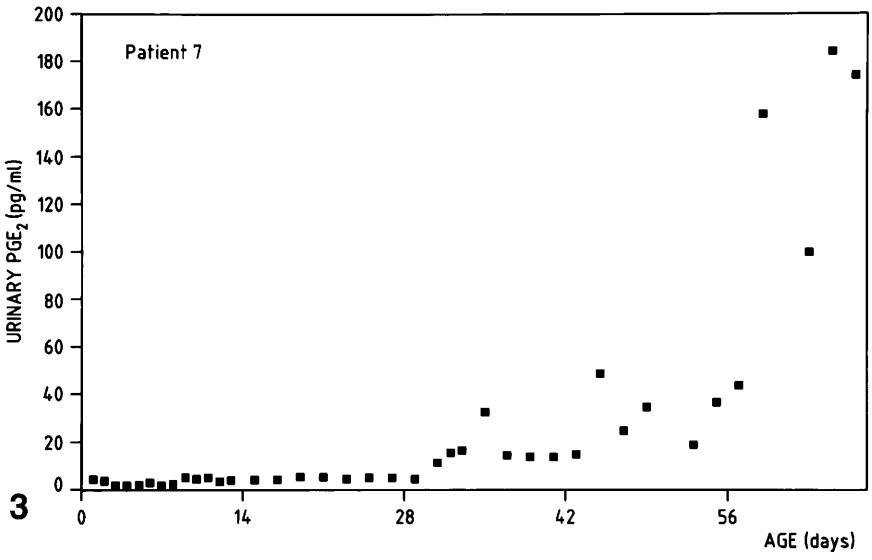


Fig. 2 Urinary PGE_2 levels during the first 4 days of life. A steady and pronounced rise was observed in patient 3 (IW) but not in patients 4 (ED) and 8 (NP) who received appropriate fluid and electrolyte treatment

Fig. 3 Urinary PGE_2 levels in patient 7 remain low while appropriate amounts of sodium chloride and fluid are given intravenously for 40 days

wonder that almost all the patients reported have bilateral medullary nephrocalcinosis on ultrasound.

Serum calcium, parathyroid hormone, and 1,25 dihydroxy vitamin D

The literature often mentions high serum total calcium. This is most probably the consequence of haemoconcentration. Serum total calcium in our patients has always been within the normal range. Ionized calcium, however, was repeatedly low. In contrast, parathyroid hormone (PTH) levels were slightly elevated in most patients. Also, the 1,25 dihydroxy vitamin D levels are elevated and this to a much higher degree than PTH even in the absence of any vitamin D treatment.

This pattern is recognizable from the early days of life and is particularly striking when, at a number of occasions, we measured the three substances concomittantly in our somewhat older patients (Table 5). Restrepo et al. [12] reported high calcitriol levels but normal PTH in four patients with neonatal Bartter disease. The discrepancy is mainly a technical one since we measured intact PTH which they did not.

Table 5 Neonatal Bartter: serum level of ionized calcium, intact PTH and calcitriol

	SCa^{++} (mg/dl)	iPTH (pg/ml)	Calcitriol (pg/ml)
Patient 2	4.84	40	126
	4.56	47	76
	4.16	46	90
	4.52	64	131
	–	55	144
	4.40	83	124
Patient 3	4.48	41	82
	5.16	21	87
	4.96	43	104
	4.12	92	124
Patient 4	5.04	53	148
	4.76	73	153
	4.88	69	136
	4.84	92	164
	4.76	88	154
	4.68	91	183
	4.40	126	116
	4.36	84	92
	4.76	86	134
	4.48	54	114
Normal values	4.56–5.16	0–40	10–80

Plasma renin and aldosterone (Table 6)

High plasma renin activity (PRA) and increased plasma aldosterone concentration (PAC) are hallmarks of Bartter syndrome despite the limited data to be found in the paediatric literature. In our first three patients, PRA was extremely high when the natural course of severe water and electrolyte losses were not counteracted properly. Patient 2 had a PRA of 223 ng/ml per hour at the age of 1 month, 51 at 2 months and 74 at 3 months of age. Once he was put on indomethacin, PRA levels gradually became normal: 12 ng/ml per hour at 1 year, 4 at 2 years and 6 at 3 years of age.

That PRA can be normalized by indomethacin has been documented in many adult and paediatric patients. Yet, our younger patients, when treated properly with fluid and electrolytes, did not have this increase in PRA. PRA in patient 7 was 14.9 ng at day 1, 18.3 at day 7, 12.3 at 1 month and 2.4 at 2 months, in the absence of indomethacin therapy. Once the intravenous administration of sodium and water is withheld, PRA levels increase dramatically to become normal again if indomethacin is given. In patient 6, PRA was 7.3 ng/ml per hour on day 1, 5.7 on day 7, 42 at 2 months and 95 at 3 months of age.

A somewhat similar pattern is observed with PAC. It is high early in life and can be normalized with indomethacin. Yet, normal ranges are not achieved when only appropriate supportive measures are taken. Patient 6 started with 347 ng/dl on day 1, had 145 ng at 1 week, 289 ng at 2 months and 362 ng/dl at the age of 3 months. Comparable data were obtained in patient 7.

Table 6 Neonatal Bartter: plasme renin activity and plasme aldosterone concentration (PAC)

Patient 6	R/i.v. NaCl			R/NaCl and KCl p.o.			R/indomethacin		
	D1	D12	D36		M2	M3	M9	Y1	Y2
P.R.A. (ng/ml/h)	7.3	5.7	–	43	49	95	4.0	3.1	6.0
P.A.C. (ng/dl)	347	115	159	289	362	549	124	104	52
Patient 8	R/i.v. NaCl (no indomethacin)								
	D1	D4	D8	D10	D12	D15			
P.R.A. (ng/ml/h)	1.2	4.7	11.4	–	5.1	7.7			
P.A.C. (ng/dl)	128	274	298	142	112	91			
Patient 7	R/i.v. NaCl (no indomethacin)								
	D1	W1	M1	M3	Y1	Y2			
P.R.A. (ng/ml/h)	15.0	18.3	12.3	2.4	4.0	4.0			
P.A.C. (ng/dl)	225	143	146	44	38	55			

(*D* day, *W* week, *M* month, *Y* year)

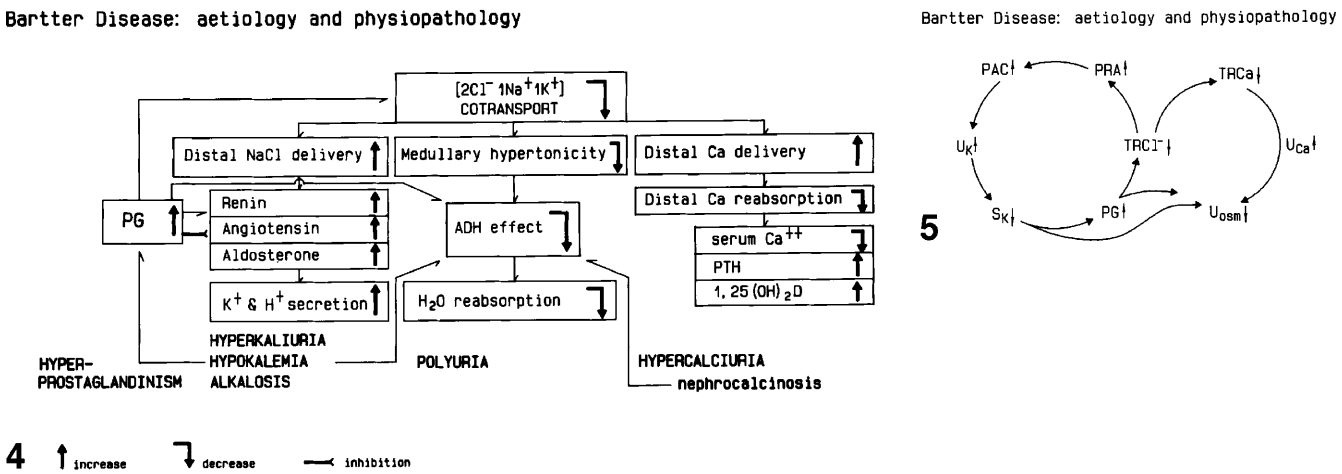


Fig. 4 The complexe and complete weel-work of the pathophysiology of Bartter disease, the starting point being a defect in the chloride-sodium-potassium cotransporter in the thick ascending limb of Henle's loop

Fig. 5 A simplified scheme of the pathophysiology of Bartter disease, the central event being defective tubular chloride reabsorption (TRCl) (PRA plasma renin activity. *PAC* plasma aldosterone concentration, *Uk* urinary potassium, *Sk* serum potassium, *PG* prostaglandins, *TRCa* tubular calcium reabsorption, *Uca* urinary calcium, *Uosm* urinary osmolality)

Physiopathology (Table 4, 5)

In recent years, three main hypotheses have been put forward to explain Bartter syndrome: a primary renal potassium losing nephropathy, primary renal hyperprostaglandinism and defective tubular chloride reabsorption. The ante- and postnatal observations made in our patients point clearly to the last mechanism. Polyuria is the most striking initial feature. The phenomenon is already at work in utero and is responsible for the polyhydramnios. The electrolyte composition of the amniotic fluid and the early postnatal urine point clearly to a major renal defect in sodium and chloride reabsorption and certainly not to a primary potassium loss. The sodium chloride loss is undoubtedly the central and primary cause of the disorder. Some 3–6 weeks after birth, the pattern changes completely to be replaced by a renal potassium loss. The transformation can tentatively be explained by a combined maturation of both the proximal and distal tubule. With improving performance of the reabsorption capacities of the nephron at the proximal tubule and its distal part, the sodium and chloride loss can be compensated for but at the price of marked hyperaldosteronism.

The most likely location of the defect is the thick ascending limb of Henle's loop. At this level, chloride is reabsorbed together with sodium and potassium by virtue of a potent chloride pump, the likely candidate being the chloride-sodium-potassium co-transporter. This active transport realizes an electrical force allowing important amounts of calcium to be absorbed passively somewhat more distally of the segment in question. If this transport system fails, the distal tubule is flooded with large amounts of sodium, chloride and calcium. The reaction at the macula densa is to stimulate renin production and secretion so as to bring into action the mineralocorticoid aldosterone which, at full capacity, is able to completely reabsorb the excessive amounts of sodium presented. The net effect, however, is excessive potassium and hydrogen ion secretion into the lumen, leading to hypokalaemic alkalosis and a pitressin resistant polyuria. The distal tubule is not equipped to do the same with the excessive amounts of calcium offered to this part of the nephron. Hence the presence and persistance of a marked, genuine, renal hypercalciuria. In the case of renal hypercalciuria, a tendency for hypocalcaemia is expected which is counteracted by a mild form of hyperparathyroidism. This secondary hyperparathyroidism could explain the increased synthesis of calcitriol. PRA overproduction as well as renal hyperprostaglandinism clearly are secondary phenomena, the former as a consequence of the chloride pump defect prior to the macula densa region, the latter most likely as a consequence of severe electrolyte loss and hypokalaemia. That acute and chronic furosemide administration results in a Bartter syndrome – including increased urinary calcium and PG excretion – is a strong argument in favour of all this since loop-diuretics act on the thick ascending limb of Henle's loop.

The secondary hyperprostaglandinism has an amplifying effect on the basic features of Bartter syndrome. PGE_2 adds to the defect in sodium reabsorption, further stimulates PRA secretion and enhances the polyuria by counteracting the effect of the antidiuretic hormone in the collecting duct.

Treatment of Bartter disease in childhood

From a historical point of view, the following therapies have been applied to children with Bartter syndrome: (1) potassium supplements, mostly potassium chloride;

(2) potassium sparing diuretics, mainly spironolactone but also amiloride and triamterene; (3) captopril, an inhibitor of the converting enzyme and, (4) inhibitors of prostacyclin synthase, especially indomethacin.

From the early literature and our own experience [11] it is clear that potassium supplementation combined with spironolactone helps improve the general condition and hence the appetite and growth of children with Bartter disease. The main inconvenience is a further increase in hypercalciuria in patients with the neonatal variant. There is little and only short-term experience with amiloride, captopril and aspirin.

In contrast, indomethacin has been largely accepted as the standard therapy for Bartter patients. Indomethacin, by its inhibitory effect on the synthesis of PG's, neutralizes the amplifying effect of PG on the features of Bartter syndrome. It reduces the polyuria, lessens the electrolyte disturbances, normalizes PRA and also reduces PAC and the hypercalciuria. It certainly does not correct the primary chloride reabsorption defect and does not substantially improve the urinary concentrating defect.

As to whether indomethacin should be used in the fetus, the premature baby and the young infant with the neonatal variant of Bartter disease, a differentiated approach is mandatory. Giving indomethacin to the mother whose fetus is thought to have Bartter disease does not make sense. First of all, as we were able to show, there is no hyperprostaglandinism in the fetus. Second, the administration of indomethacin holds many hazards for the baby such as its negative effects on the ductus arteriosus and the developing kidney. In the premature baby with Bartter disease, it is also wise not to administer indomethacin for the same reasons but also because of the risk for necrotizing enterocolitis which has been described by us and others. Apart from that, the administration of indomethacin is meaningless since the appropriate management of the fluid and electrolyte disturbances are most important and prevent secondary hyperprostaglandinism.

The child with Bartter disease, whether or not with neonatal presentation, can certainly profit from indomethacin therapy once growth delay becomes obvious and, whenever possible, after renal maturation is accomplished, that is to say after the age of 18 months. The recommended dosage is between 1.5 and 2.5 mg/kg per day in 2 or 3 doses. Doses above 3 mg/kg are considered nephrotoxic.

Differential diagnosis

Pseudo-Bartter, Bartter syndrome and Bartter disease

There is a case for clearly distinguishing the different types of conditions that can lead to the Bartter constellation. As outlined in the Introduction, mainly three groups of patients should be separated from each other.

For those with congenital or acquired intestinal loss of either potassium or chloride, with very little chloride in the urine, the term "Pseudo-Bartter syndrome" seems appropriate.

Patients with acquired renal potassium and or chloride wasting – most of them being chronic abusers of loop diuretics – the designation "Bartter syndrome" could be reserved.

For infants and children with the inherited tubulopathy, the term "Bartter disease" should be used whether or not the presentation is neonatal, infantile or in childhood.

The latter designation still makes sense after it has been shown recently that Bartter disease is genetically heterogeneous. Indeed, two different defects have already been identified in patients with the neonatal variant of Bartter disease. Simon et al. [17] recently demonstrated linkage of Bartter disease to the renal Na-K-2Cl cotransporter gene NKCC2 in five patients, four of whom were the offspring of consanguineous parents. The same group have identified a second subgroup of patients with the neonatal variant of Bartter disease in whom mutations were found in the K-channel ROMK [18]. Both the NKCC2 transporter and the ROMK channel are located at the thick ascending limb of Henle's loop of the mammalian kidney.

Bartter and Gitelman syndrome (Table 7)

The literature of the last decades has been poisoned by a major confusion between Bartter syndrome and Gitelman syndrome. Gitelman described a disorder in which patients with hypokalaemic alkalosis mainly suffered from carpopedal spasms or total body tetany. These patients have no or minimal increase in PRA and PAC, do concentrate their urine rather well and grow normally. Moreover, they have hypomagnesaemia and hypocalciuria. Recently, Simon et al. [16] demonstrated linkage between Gitelman syndrome and the locus encoding the renal thiazide-sensitive sodium chloride cotransporter located in the distal convoluted tubule.

Neonatal Bartter disease and hyperprostaglandin E syndrome

In the last 10 years, Seyberth and collaborators from Germany [15], have described a series of infants born after a pregnancy complicated by polyhydramnios and premature delivery, who subsequently presented with failure to thrive, hypokalaemia, hypercalciuria, nephrocalcinosis and marked hyperproduction of renal and systemic PGE_2. All the abnormalities improved consistently with indomethacin. These authors felt that this condition with many features in common with Bartter disease, should be differentiated from it, mainly because they could not demonstrate a defect in the tubular reabsorption of chloride. They labelled this inherited disorder "Hyperprostaglandin E syndrome" indicating that the disease was caused by a primary overproduction of PGE in the kidneys.

Table 7 Differential diagnosis: Bartter and Gitelman disease

	Bartter disease	Gitelman disease
Clinical features	**Growth retardation** Muscular weakness	Normal growth **Carpopedal spasm**
Blood biochemistry	**Hypokalaemic alkalosis** Normal magnesium **Markedly elevated P.R.A.** **Elevated P.A.C.**	Hypokalaemia **Hypomagnesaemia** Almost normal P.R.A. Normal P.A.C.
Urinary findings	**Polyuria** **Isothenuria** Hyperkaliuria **Hypercalciuria** Normal magnesuria **Elevated PGE_2**	Normal urine output Mild concentrating defect Hyperkaliuria **Hypocalciuria** **Hypermagnesuria** Slightly elevated PGE_2
Localisation basal defect	**Thick ascending limb of Henle's** loop (frusemide sensitive nephron segment)	**Distal convoluted tubule** (thiazide sensitive nephron segment)

P.R.A.: plasma renin activity; P.A.C.: plasma aldosterone concentration

To us, these patients are identical to the ones described first by McCredie et al., and later by ourselves and many others. In their many papers, the German colleagues emphasize again and again that the chloride reabsorption is normal in their patients. However, it appears that they performed the Chaimovitz test by giving the large amounts of hypotonic fluid by mouth and not by infusion. Apart from this, they have not been able to study either amniotic fluid or urine immediately after birth, as we did. This essential information is needed to find out whether or not the hyperprostaglandinism is just a secondary phenomenon, as we could demonstrate. Here also, molecular genetics will come soon to our rescue for a final judgment.

Short and long-term outcome

Paediatric patients with Bartter disease present mostly with failure to thrive and growth retardation. With adequate treatment as outlined above, many of them display catch-up growth and reach a normal adult height. Yet, there are surprisingly few detailed reports on growth and development in such patients.

We were the first to describe growth from birth to adulthood in a girl with the neonatal variant of Bartter disease [11]. The girl (patient 1) is a good example of what we found afterwards in other similar patients.

The first weeks of life of the premature Bartter patients are very difficult and full of hazards. In our seven families, four couples lost a previous baby with the same condition. Our patient 8 died from severe sepsis at the age of 5 weeks. Yet, once past the critical first months, these children do quite well but normal growth in the first 18 months of life is seldom realized. In childhood, four of our patients have had an impressive catch-up growth with a combined therapy of indomethacin and potassium supplements. As an example, the growth curve of patient 2 is shown (Fig. 6) Bone age has been appropriate for chronological age and pubertal development has been normal. From the intellectual point of view, all our patients have been able to succesfully attend school.

Unsolved problems

Hypercalciuria and nephrocalcinosis

Patients with the neonatal variant of Bartter disease almost invariably have pronounced hypercalciuria and medullary nephrocalcinosis. As we discussed above, hypercalciuria can be explained by the defect in the

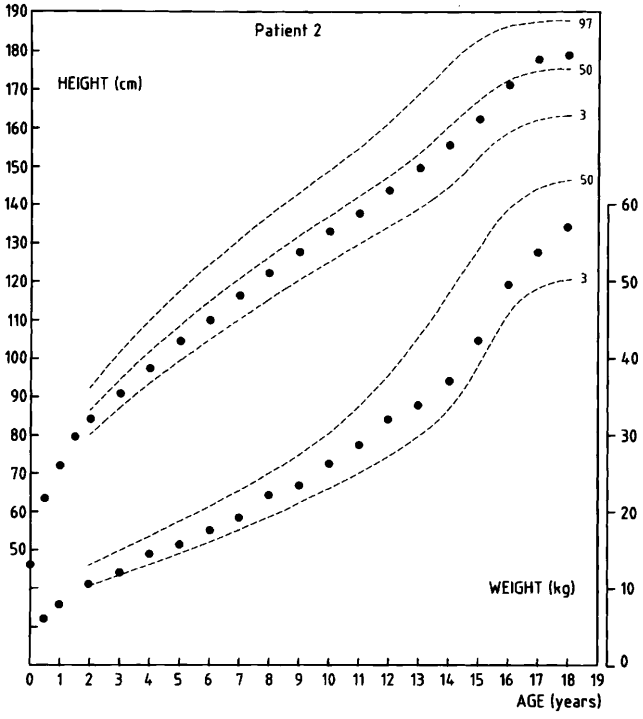


Fig. 6 Growth in height and weight of patient 2 with neontal Bartter disease

chloride transport at the thick ascending limb of Henle's loop. But, the difficult question is, why is it that paediatric patients with the classical early childhood presentation of Bartter disease, as a rule do not have hypercalciuria? Does hypercalciuria only emerge in the most severe forms of the disease or is the neonatal variant a disease in its own right?

More frustrating is the fact that, in our experience, no efficient treatment for hypercalciuria is available. The medullary nephrocalcinosis is of real concern for the future or our patients. We have measured the inulin clearance in a number of our patients and never found normal values. The two patients 1 and 2 who have reached adulthood, had a decreased glomerular filtration rate of 49 and 58 ml/min. per 1.73 m^2 respectively at the age of 18 years. Indomethacin certainly reduces the hypercalciuria but does not normalize it. We have tried a series of measures to further reduce the calciuria. Four patients received amiloride (in addition to indomethacin): only one of them showed an improvement. When indomethacin dosage was increased from 2.5 to 3 and 4 mg/kg per day, patient 2 clearly showed a drop in glomerular filtration rate but only little improvement in urinary calcium excretion. In another experiment, we prescribed potassium phosphate to two of our patients. There was no improvement in calcium excretion. In patient 4 renal biopsy showed definite tubulo-interstitial lesions with deposits of calcium crystals.

Symptomatic hypocalcaemia

Recently, during his pubertal growth spurt, patient 2 developed symptomatic hypocalcaemia. He complained of headache and muscular weakness and suddenly had a general convulsion which resolved spontaneously. Physical examination including blood pressure was normal. Serum electrolytes were within the normal range. Magnesium was low at 1.27 mg/dl where it had been normal before. Total calcium was 7.4 mg/dl and ionized calcium was 1.01 mmol/l. Intact PTH was high (97 pg/ml) and serum calcitriol very high (156 pg/ml). Serum 25 dihydroxyvitamin D was normal. The boy reportedly had not changed his dietary habits recently and his estimated calcium intake was appropriate for age. He also was taking his indomethacin regularly. Calcium supplements, given as calcium gluconaat, at a dose of 500 mg of calcium element three times a day, had only little effect on his serum calcium but PTH and calcitriol came down to normal values. Calcium carbonate was equally ineffective and only with calcitriol, 0.25 μg a day, total and ionized calcium normalized.

Hypomagnesaemia

The above described episode of hypocalcaemia might have something to do with the hypomagnesaemia. Low magnesium levels have frequently been mentioned in paediatric and adult patients with Bartter syndrome. Obviously, many of these have Gitelman disease. Yet, a number of genuine Bartter patients have been found to be mildly hypomagnesaemic, the meaning of which is unclear. To our knowledge, it has never been mentioned in the neonatal variant. Two African siblings we have under our care, who display all classical features of childhood Bartter disease, have marked hypomagnesaemia. It is not excluded that this is another variant of Bartter disease.

Summary and conclusions

Time has come to distinguish Bartter syndrome from Bartter disease. The latter is an autosomal recessive renal tubulopathy which manifests itself during infancy and childhood with variable intensity of clinical and biochemical abnormalities.

Bartter disease is caused neither by a primary renal potassium loss nor by primary renal hyperprostaglandinism. The evidence points to a defect in the sodium-chloride-potassium transport systems located at the thick ascending limb of Henle's loop.

The most severe form of Bartter disease is the neonatal form which is characterized by polyhydramnios, premature delivery and a life-threatening sodium and chloride loss during the early weeks of life. It takes several weeks before sodium wasting turns into renal potassium wasting.

Prenatal diagnosis of this variant is based on three highly specific findings: polyhydramnios not associated with echographically detectable fetal malformation, fetal polyuria and elevated chloride in the amniotic fluid.

In this setting, the administration from the 30th week of gestation of indomethacin is useless and even dangerous. Similarly, this drug should not be given to the newborn Bartter patients for the first months of life. Treatment at this stage consists of administration of large amounts of fluid and sodium chloride.

Hypercalciuria is part of the neonatal variant and leads to nephrocalcinosis for which an efficient treatment is badly needed.

There is no reason to further confuse Bartter disease and Gitelman disease the more so since the gene for the latter has been located and cloned recently. It is as yet not clear whether hypomagnesaemia, a hallmark of Gitelman disease, belongs to the variable phenotypic features of Bartter disease.

We know already that there is not only one gene responsible for the whole spectrum of Bartter disease and further clinical-genetic work-up will surely be fascinating.

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