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BARTTER'S AND BARTTER-LIKE SYNDROMES

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Introduction

Several major developments in the understanding of disorders influencing sodium homeostasis particularly associated with hypokalaemic alkalosis have occurred in the recent past and have helped in our understanding of Bartter's syndrome and Bartter like syndromes in childhood.

Bartter's syndrome

Bartter's syndrome comprises hypokalaemia, hypochloraemia and metabolic alkalosis with increased urinary Na^+, K^+, and Cl^- losses (1). There is an increase in plasma renin and aldosterone levels but blood pressure is normal. Children with Bartter's syndrome on clinical grounds are subdivided into the "classic" and "neonatal" forms. These conditions are inherited on an autosomal recessive basis. Gitelman's syndrome which has similarities with Bartter's syndrome, is biochemically and genetically distinct and hence is now differentiated (2).

Pathogenesis

Bartter's syndrome results from Na^+ and Cl^- wasting in the thick ascending limb of the loop of Henle (3). Abnormalities in the frusemide-sensitive Na^+ / K^+/ $2Cl^-$ (NKCC2) cotransporter, the renal outer medullary K^+ channel (ROMK), the chloride channel (CIC-Kb) involved in Cl^- reabsorption from tubular cell into blood and recently barttin (BSNB) a chloride channel subunit, have all been reported in patients with a Bartter's phenotype (Table 1) (4-6).

NKCC2 mutations

Bartter's syndrome can be caused by mutations of NKCC2 in the thick ascending limb of the loop of Henle (4). Various mutations (frameshift, nonsense, or missense) of the gene for NKCC2 have been found in affected patients. These mutant alleles cause loss of NKCC2 function resulting in salt wasting from the loop of Henle.

The salt wasting coupled with volume contraction leads to renin-angiotensin-aldosterone system activation and with increased Na^+ reabsorption by ENaC in the distal nephron. This Na^+ reabsorption in the distal nephron is linked to both K^+ and H^+ secretion with resulting hypokalaemic alkalosis. Increased fluid delivery to the distal nephron as well as direct loss of K^+ in the loop of Henle also contributes to hyperkaliuria.

Increased systemic production of prostaglandin E_2 (PGE_2) which is seen in these patients is not specific to Bartter's syndrome as was once thought but secondary to chronic hypokalaemia, volume contraction, and elevated levels of angiotensin ll. However, elevated levels of systemic and urinary PGE_2 activate the renin-aldosterone axis and inhibit ROMK activity with disruption of K^+ recycling and NKCC2 function. This elevation of prostaglandin coupled with activation of the kallikrein-kinin system as well as chronic volume contraction together contribute to the lack of hypertension in spite of the high plasma renin levels.

In addition there is impairment of urine concentration and dilution as well as reduced distal Cl^- reabsorption. Increased urinary ammonium ion excretion impairs the decrease in urine pH during ammonium chloride loading. Reduction of Cl^- absorption in the loop of Henle interferes with the voltage-driven paracellular reabsorption of Ca^{2+} and Mg^{2+}, resulting in hypercalciuria and hypermagnesuria. There is also a contribution by prostaglandins to urinary Ca^{2+} and Mg^2 losses by increase of bone resorption. The hypercalciuria of Bartter's syndrome is associated with the development of nephrocalcinosis. Enhanced distal nephron Mg^2 reabsorption probably compensates for proximal hypermagnesuria, reducing Mg^2 losses and preventing significant hypomagnesaemia.

ROMK and CIC-Kb mutations

Another group of Bartter's syndrome patients have mutations in ROMK (5,6). Loss of ROMK function interferes with K^+ recycling and as a result inhibits NKCC2 function. Mutations that inactivate the gene for CIC-Kb result in Cl^- wasting and features of Bartter's syndrome.

Most but not all children with "neonatal" Bartter's syndrome have mutati-

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Table 1
Single gene defects causing Bartter's and Giteman's syndromes

Tablica 1.
Barterov i Gitemanov sindrom zbog defekta jednog gena

Syndrome	Inheritence	Gene localization	Gene produce
Neonatal Bartter's syndrome	AR	15q	$Na^+/K^+/2C1^-$ co-transporter NKCC2
Neonatal Bartter's syndrome	AR	11q	Renal potassium channel ROMK
Neonatal Bartter's syndrome	AR	1p	Barttin-βsubunit for CIC-Kb in renal tubule and inner ear
Classic Bartter's syndrome	AR	1p	Renal chloride channel CIC-Kb
Gitelman's syndrome	AR	16q	$Na^+/C1^-$ co-transporter NCCT

ons of the genes encoding NKCC2 or ROMK, whilst those with late-onset or "classic" type Bartter's syndrome have abnormalities of the gene for CIC-Kb (7). However, correlation between genotype and phenotype is not perfect and some patients with Bartter's syndrome do not show any of the above abnormalities and some of these have the BSND mutation. It is likely that other unrecognized gene mutations may also be responsible.

Renal biopsy in "neonatal" and "classic" cases shows juxtaglomerular cell hyperplasia, vacuolar changes in proximal tubular cells, tubular atrophy with cystic dilatation, and interstitial fibrosis as a consequence of chronic hypokalaemia and hypercalciuria.

Mutations affecting BSND

Recently a fourth variant of Bartter's syndrome has been described with mutation of BSND encoding for the integral membrane protein barttin (8). This is an essential subunit for the chloride channel ClC-Kb in the loop of Henle but also is important in K^+ recycling in the inner ear. Clinically affected patients have sensorineural deafness.

Neonatal Bartter's syndrome clinical features

Clinical features of neonatal Bartter's syndrome include polyhydramnios (caused by intrauterine polyuria), premature delivery, postnatal polyuria, vomiting, failure to thrive, hypercalciuria and nephrocalcinosis. Salt craving is sometimes present and most affected individuals have hypokalaemia, metabolic alkalosis plus hyperreninaemia and hyperaldosteronsim. Occasionally aldosterone concentration may be inappropriately low because of the severe hypokalaemia but increases after treatment with K^+ supplements has started. Urinary Cl^- excretion is markedly increased and prenatal diagnosis of Bartter's syndrome may be made by showing high amniotic fluid levels of Cl^-. Increased urinary excretion of PGE_2 is said to be a characteristic feature of neonatal Bartter's syndrome but may not be present in all patients especially during early neonatal period. The Bartter patients with the BSND mutation also present in the neonatal period and congenital deafness is a feature.

"Classic" Bartter's syndrome clinical features

In "classic" Bartter's syndrome, symptoms begin during the first 2-3 years of life. They are generally milder than in the neonatal form and include polyuria, polydipsia and vomiting, episodic dehydration, constipation, and failure to thrive. Blood pressure is normal. Subsequently fatigue, recurrent carpopedal spasms, and developmental delay may be seen but nephrocalcinosis is usually absent.

Diagnosis and differential diagnosis

Biochemically the findings in neonatal and classic forms of Bartter's syndrome are similar. The most obvious laboratory feature is hypokalaemia, with plasma K^+ levels of 1.5-2.5 mmol/L. Increased levels of renin and aldosterone are characteristic reflecting extracellular fluid volume depletion. There is increased fractional excretion of K^+, Na^+, and Cl^-. Hyperuricaemia is reported due to extracellular fluid depletion and hypomagnesaemia is seen in some patients. Defective urine concentration, dilution, and acidification are present. The glomerular filtration rate is usually normal initially but may decline with time.

The distinction between Bartter's syndrome and other conditions associated with persistent hypokalaemic metabolic alkalosis can be made on blood pressure and urinary Cl^- excretion. The absence of hypertension distinguishes Bartter's syndrome from renal artery stenosis, renin-secreting tumours, and low-renin causes of hypertension (primary hyperaldosteronism, Liddle's syndrome, apparent mineralocorticoid excess, glucocorticoid responsive aldosteronism as well as salt retaining forms of congenital adrenal hyperplasia). Chloride depletion may occur as a result of laxative abuse, cyclical vomiting, colonic adenoma, and congenital chloridorrhoea. Excessive loss of Cl^- in sweat, for example, in cystic fibrosis, and dietary Cl^- deficiency may also lead to Cl^- depletion but urinary Cl^- in all these cases is low at less than 10 mmol/L.

Presence of high urinary Cl^- (more than 20mmol/L), with hypokalaemic metabolic alkalosis suggests Bartter's or Gitelman's syndrome or diuretic use or abuse. The essential findings distinguishing Bartter's from Gitelman's syndrome are the presence of significant hypomagnesaemia, hypermagnesuria, and hypocalciuria in the latter. Most patients with the onset of symptoms in late childhood or adult life will turn out to have Gitelman's syndrome. Diuretics, other than potassium-sparing agents and carbonic anhydrase inhibitors, can cause hypokalaemic metabolic alkalosis. The metabolic disturbances as a result of administration of loop diuretics, however, mimics Bartter's syndrome quite

precisely. Diuretics and their metabolites should be measured in urine whenever diuretic consumption is suspected (occasionally as a form of Münchausen by proxy syndrome) and testing may be necessary on several occasions to exclude this with certainty.

Patients with NKCC2 mutations commonly have more severe clinical and biochemical abnormalities. The disease can be initially less severe in patients with ROMK mutations who might manifest milder salt wasting and sometimes a biochemical picture akin to pseudohypoaldosteronism type 1 (hyponatraemia, hyperkalaemia, and metabolic acidosis) with hypokalaemia and metabolic alkalosis developing some weeks later.

Erythrocytes from patients with Bartter's syndrome show increased intracellular Na^+ associated with a reduced Na^+ efflux (9). These abnormalities may represent a widespread defect in membrane electrolyte transport or be a secondary phenomenon to longstanding hypokalaemia. The changes can be reversed by treatment with indomethacin with correction of hypokalaemia. Measurement of erythrocyte intracellular Na^+ levels have diagnostic value in Bartter's syndrome as well as being useful in assessing response to therapy.

Treatment

In the neonatal form of Bartter's syndrome there are markedly abnormal fluid and electrolyte changes that need often aggressive correction. Saline infusions may be needed and potassium chloride supplementation is always necessary. Spironolactone or triamterene can be useful in helping with the correction of the hypokalaemia. In the past angiotensin-converting enzyme (ACE) inhibitors have been used for correction of hypokalaemia but results were conflicting and these are not recommended. Magnesium deficiency may aggravate renal K^+ wasting and, if present, should be corrected.

The efficacy of long-term treatment with prostaglandin synthase inhibitors, such as indomethacin or ibuprofen, is well established (10). These drugs have no direct effect on the inherited renal tubular abnormalities but act predominantly by reducing cortical perfusion and decreasing delivery of Na^+ and Cl^- to the distal nephron. Additionally the effects of prostaglandins on the renal tubules are neutralized. Treatment results in correction of the hypokalaemia plus reduction of polyuria and polydipsia, restitution of normal growth, and improved activity. Plasma levels of renin and aldosterone reduce to the normal range but inspite of these benefits the plasma potassium levels rarely exceed 3.5 mmol/L.

Prognosis

Untreated, patients may succumb to dehydration, electrolyte disturbance, or intercurrent infection. With appropriate therapy, the majority of children show clinical improvement with catch-up growth. Pubertal and mental development are usually normal although early reports did describe developmental delay. Chronic tubulo-interstitial nephropathy secondary to hypokalemia, hypercalciuria, and nephrocalcinosis may lead to progressive reduction in GFR. The patients with the BSND mutation seem to be especially prone to develop renal failure. There are occasional reports of renal transplantation in patients with end-stage renal disease (ESRD) following which the biochemical abnormalities are reported to return to normal.

Gitelman's syndrome

Gitelman syndrome is an autosomal recessive condition also characterized by hypokalaemic metabolic alkalosis associated with hypocalciuria and hypomagnesaemia.

Pathogenesis

The similarity between features caused by thiazide administration and those of Gitelman's syndrome suggested that the defect might be situated in the distal convoluted tubule. It has now been shown to be due to inactivating mutations of the gene involved in the thiazide sensitive apical Na^+/Cl^- cotransporter (NCCT) (Table 1). Loss of NCCT function causes Na^+ and Cl^- wasting from this segment, leading to hypovolaemia and secondary activation of the renin-angiotensin-aldosterone system. This results in an increase in collecting tubule Na^+ reabsorption but is counterbalanced by K^+ and H^+ excretion resulting in hypokalaemic alkalosis.

The mechanisms causing the increased urinary Mg^{2+} and reduced urinary Ca^{2+} are not clearly understood. It has been proposed that efflux of intracellular Cl^- through basolateral CIC-Kb might promote Ca^{2+} reabsorption in the distal convoluted tubule cells resulting in hypocalciuria. This nephron segment also reabsorbs about 5% of filtered Mg^{2+} and loss of NCCT function might inhibit Mg^{2+} absorption by an Na^+ - dependent mechanism.

Clinical features and diagnosis

Patients with Gitelman's syndrome present with hypokalaemia at a later stage than those with "classic" Bartter's syndrome and are frequently asymptomatic. They sometimes have features of muscular weakness and tetany (2, 3). Polyuria and growth retardation are not major manifestations but some individuals are shown to have chondrocalcinosis. There is no history of maternal hydramnios or prematurity. The findings that allow distinction from Bartter's syndrome are marked hypomagnesaemia, increased urine magnesium losses and hypocalciuria. Plasma renin and aldosterone are increased but not to the degree seen in Bartter's syndrome. Urine prostaglandins are not increased.

Treatment

Magnesium supplements, either in the form of magnesium chloride or magnesium glycerophosphate are recommended, the latter being useful in patients intolerant of magnesium chloride. Mg^{2+} supplements correct hypomagnesaemia and prevent tetany and also usually correct the hypokalaemia. However, K^+ supplements may be required in some patients. Prostaglandin synthase inhibitors are usually not thought to be useful, but some patients do show improvement of clinical and biochemical abnormalities following the addition of indomethacin. The long-term prognosis for renal function and growth is good but therapy with Mg^{2+} supplements is required lifelong.

Conclusion

As can be seen in the space of the past 6 years remarkable developments have occurred in the understanding of the aetiopathogenesis of Bartter-like syndromes in childhood. The ability to elucidate the distinct genetic subgroups by molecular genetic technology has revolutionized our view on such conditions and it is anticipated that even more precise classifications will be possible in the future. A number of review articles concerning this topic exist to which the reader is referred if more detail is required (3, 12, 13).

REFERENCES

1. Bartter FC, Pronove P, Gill J, MacCardle R. Hyperplasia of the juxtaglomerular complex with hyperaldosteronism and hypokalemic alkalosis. Am J Med 1962; 33: 811-28.
2. Gitelman HJ, Graham JB, Welt LG. A new familial disorder characterized by hypokalemia and hypomagnesemia. Trans Assoc Am Physic 1966; 79: 221-35.
3. Rodriguez-Soriano J. Bartter and related syndromes: the puzzle is almost solved. Pediatr Nephrol 1998; 12: 315-27.
4. Simon DB, Karet FE, Hamblan JM et al. Bartter syndrome, hypokalemic alkalosis with hypercalciuria, is caused by mutations in the Na^+- K^+ - $2Cl^-$ co-transporter NKCC2. Nat Genet 1996; 13: 183-8.
5. Simon DB, Karet FE, Hamdan JM et al. Genetic heterogeneity of Bartter's syndrome revealed by mutations of the K^+ channel, ROMK. Nat Genet 1996; 14: 152-6.
6. International Collaborative Study Group for Bartter-like Syndromes. Mutations in the gene encoding the inwardly-rectifying renal potassium channel, ROMK, cause the antenatal variant of Bartter syndrome: evidence for genetic heterogeneity. Hum Mol Genet 1997; 6: 17-26.
7. Simon DB, Bindra RS, Mansfield TA et al. Mutations in the chloride gene, CLNNKB, cause Bartter's syndrome type III. Nat Genet 1997; 17: 171-8.
8. Birkenhäger R, Otto E, Schürmann MJ et al. Mutation of BSND causes Bartter syndrome with sensorineural deafness and kidney failure. Nat Genet 2001; 29: 310-4.
9. Uchiyama M, Shah V, Daman-Willems C, Dillon MJ. Erythrocyte sodium transport in Bartter's syndrome. Acta Paediatr Scand 1988; 77: 873-8.
10. Dillon MJ, Shah V, Mitchell MD, Bartter syndrome: 10 cases in childhood. Results of long term indomethacin therapy. Q J Med 1979; 48: 429-46.
11. Simon DB, Nelson-Williams C, Bia MJ et al. Gitelman variant of Bartter syndrome, inherited hypokalemic alkalosis, is caused by mutations in the thiazide-sensitive Na^+ - Cl^- co-transporter. Nat Genet 1996; 12: 24-30.
12. Simon DB, Lifton RP. Ion transporter mutations in Gitelman's and Bartter's syndromes. Curr Opin Nephrol Hypertens 1998; 7: 43-7.
13. Bagga A, Dillon MJ. Inherited disorders of sodium and water handling. In: Johnson RJ, Feehally J (eds). Comprehensive Clinical Nephrology. London, Mosby 2000; 52.1-52.11.