Rare disease

Classic Bartter syndrome: a rare cause of failure to thrive in a child

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Summary

Bartter syndrome is a group of rare autosomal-recessive disorders caused by a defect in distal tubule transport of sodium and chloride. Blood gases and plasma electrolytes raise suspicion of this diagnosis and the definitive diagnosis is made by genetic study. Early treatment improves prognosis. The authors present the case of an 11-month-old child with early failure to thrive and severe regurgitation. Blood gases revealed hypochloraemic metabolic alkalosis, hyponatraemia and hypokalaemia. Blood pressure was normal and polyuria was documented. She began therapy with potassium chloride supplementation and indomethacin. There was clinical improvement and plasma potassium and bicarbonate normalised. The molecular study confirmed it was the classic form of Bartter syndrome. Despite being rare in clinical practice, which may lead to unnecessary medical investigation and diagnosis delay, in a child with failure to thrive, hypochloraemic metabolic alkalosis and hypokalaemia, this diagnosis must be considered.

BACKGROUND

Bartter syndrome is a group of rare autosomal-recessive disorders with a unifying pathophysiology caused by a defect in one of the transporters involved in distal tubule transport of sodium and chloride.¹ Urinary salt and water loss leads to mild volume depletion, resulting in the activation of the renin-angiotensin-aldosterone system and in overproduction of prostaglandin. The combination of hyperaldosteronism and increased distal flow enhances potassium and hydrogen secretion, causing hypokalaemia and metabolic alkalosis.¹⁻³

The term Bartter syndrome does not refer to a single entity. Rather, the expression denotes different variations such as antenatal Bartter syndrome, classic Bartter syndrome and Gitelman syndrome.¹ This classification based on clinical criteria was enriched by clarification of the underlying genetic defects.^{2,3}

Antenatal Bartter syndrome results from disturbed salt reabsorption along the thick ascending limb of Henle (TAL) due to defects either in the NKCC2 sodium-potassium-chloride co-transporter gene, renal outer medullary potassium channel potassium ion channel gene, barttin or both CIC-Ka and CIC-Kb chloride ion channel genes. Classic Bartter syndrome is caused by dysfunction of CIC-Kb chloride ion channel, which impairs salt transport to some extent along the TAL and in particular along the early distal convoluted tubule (DCT1). The CIC-Kb is located in the basolateral membrane of distal tubular cells and allows the passage of chloride from the cell into the bloodstream. Clearly, this channel malfunction will cause an altered transport of sodium and chloride in the distal nephron. A pure defect of salt reabsorption along the DCT1 due to dysfunction of neutral thiazide-sensitive sodium chloride co-transporter finally results in the Gitelman syndrome.¹⁻⁶

Antenatal Bartter syndrome (also called hyperprostaglandin E syndrome), is characterised by the additional features

of maternal polyhydramnios, prematurity, severe polyuria, high urinary calcium excretion, nephrocalcinosis and very elevated levels of prostaglandin E2 in the blood and urine.^{3,6,7} The antenatal form has been associated with a distinctive appearance: thin, with small muscles, triangular face with a prominent forehead, large eyes, protruding pointed ears, and a pouting expression caused by drooping corners of the mouth.¹ Gitelman syndrome is a more benign condition that is often not diagnosed until late childhood or even adulthood.^{8,9} Not uncommonly, patients are diagnosed accidentally while seeking medical consultation because of growth retardation, constipation or enuresis. Laboratory examination shows a typical constellation of metabolic alkalosis, low normal chloride levels, hypokalaemia, and hypomagnesaemia; urine analysis shows hypocalciuria. Between these two extremes, the classic Bartter syndrome presents as a disorder with intermediate severity. Variable extents of extracellular volume depletion and secondary electrolyte disturbances contribute to a rather variable disease phenotype.³

In classic Bartter syndrome symptoms start during the first 2 years of life as polyuria, polydipsia, vomiting, constipation, salt craving, tendency to dehydration, muscular hypotonia, lethargy, developmental delay and failure to thrive. The neonatal period usually passes without major problems. Laboratory examination typically reveals low plasma chloride concentrations, decreased plasma sodium concentration and severe hypokalaemic alkalosis.^{1,2}

We report a case of classic Bartter syndrome with delayed diagnosis, successful treatment and molecular study.

CASE PRESENTATION

An 11-month-old female child was presented. The family history was thalassemia minor and atopy, with no consanguinity. She was the first child, born at 37-week gestation,

Table 1 Laboratory tests on Nephrology Unit admission

pH (7.35–7.45)	7.58↑
HCO ₃ ⁻ (22–26 mmol/l)	41.3↑
Base excess (–2–+2 mmol/l)	18.3↑
Plasma sodium (135–145 mmol/l)	124↓
Plasma potassium (3.5–5.1 mmol/l)	2.2↓
Plasma chloride (98–107 mmol/l)	70↓
Plasma magnesium (1.7–2.28 mg/dl)	2.1
GFR (96±22 ml/min/1.73 m ²)	140
Urinary density (1005–1025)	1005
Urinary chloride (<10 mmol/l)	67↑
Fractional sodium excretion (<1%)	10↑
Fractional potassium excretion (9.2±3.4%)	67↑
Urinary calcium (<6 mg/kg/day)	6.8↑
Renin (2–60 pg/ml)	994↑
Aldosterone (40–310 pg/ml)	2083↑

GFR, glomerular filtration rate.

with mild polyhydramnios diagnosed in the third trimester. The child was born after caesarean delivery, the Apgar score was 9 at 1st min and 10 at 5th min. The birth weight of the infant was 2510 g, which was appropriate for gestational age. Perinatal period was uneventful. The infant was advised exclusive breastfeeding for 2.5 months and food diversification at 4 months. The child presented with early failure to thrive (less than the third percentile) and severe regurgitation. At 5 months, following hospital admission for acute gastroenteritis with mild dehydration with metabolic alkalosis (pH 7.49, HCO₃⁻ 27.2 mmol/l) and mild hypokalaemia (3.2 mmol/l), the child was referred to the gastroenterology unit.

INVESTIGATIONS

The investigation revealed negative allergology study, normal sweat test, negative antitransglutaminase antibody, abdominal and kidney ultrasound without changes, including nephrocalcinosis and endoscopy with incompetent cardia and normal intestinal biopsy. At 11 months, the child was referred to the nephrology unit due to persistence of clinical symptoms associated with metabolic alkalosis (pH 7.58, HCO₃⁻ 41.3 mmol/l, base excess 18.3 mmol/l), hypochloraemia (70 mmol/l), hypokalaemia (2.2 mmol/l) and hyponatraemia (124 mmol/l). At admission, the child's weight and height were below the third percentile, blood pressure was normal and the child presented a mild delay of psychomotor development. Polyuria (6 ml/kg/h) and polydipsia were documented. Laboratory tests revealed (table 1) normal glomerular filtration rate (GFR), increased urinary chloride, increased fractional sodium and potassium excretion, slightly increased urinary calcium, normal plasma magnesium and increased plasma renin and aldosterone.

TREATMENT

With the clinical diagnosis of Bartter syndrome, the child began therapy with increasing supplementation of potassium chloride, in order to normalise plasma potassium levels, to which was later added indomethacin. The molecular study revealed a genetic mutation in CIC-Kb, confirming that it was the classic form of Bartter syndrome.

OUTCOME AND FOLLOW-UP

After a year of follow-up, there was a reduction of polyuria, stable GFR, gradual improvement of psychomotor development and growth, and plasma potassium and bicarbonate levels normalised.

DISCUSSION

Phenotype is very variable in the classic Bartter syndrome, and more than half of the patients are diagnosed within the first year of life.² All the symptoms from the initial presentation are included in this case report, namely failure to thrive, mild delay of psychomotor development, feeding problems, vomiting and dehydration. Blood pressure is typically normal.^{1–3 7} Laboratory evaluation reveals low plasma chloride concentration, decreased plasma sodium concentration and severe hypokalaemic alkalosis.^{2 8} Distal defective chloride transport in the diluting segment of the nephron is thought today to be the prime cause of Bartter syndrome. The increased arrival of fluid to more distal potassium secreting sites will promote kaliuresis. The resulting hypokalaemia will stimulate prostaglandin synthesis, which in turn will induce compensatory increases in the activity of the renin, angiotensin and adrenergic systems to maintain blood pressure. Hyperaldosteronism will also stimulate potassium secretion, thus closing the pathogenic circle.¹

Urinary concentrating ability is preserved at least to a certain extent and a number of patients achieve urinary osmolalities above 700 mosmol/kg in morning urine samples.² Hypercalciuria is not a typical feature of CIC-Kb dysfunction and, if present, occurs only temporarily, which contrasts with the antenatal form. Medullary nephrocalcinosis, a hallmark of pure TAL dysfunction, is rare.^{1–2 5}

Blood gases and plasma electrolytes raise the index of suspicion by revealing hypochloraemic metabolic alkalosis and hypokalaemia. A urinary chloride higher than 10 mmol/l in a patient with metabolic alkalosis and hypokalaemia is important to exclude other extrarenal causes of chloride depletion. The definitive diagnosis is performed with molecular analysis.^{1 8}

Renal biopsy is generally not an indication for the diagnosis of Bartter syndrome. Hyperplasia of the juxtaglomerular apparatus has been observed but can be mild or even absent. Signs of chronic tubulointerstitial nephropathy can occur during evolution.^{1 9}

The tubular defect in Bartter syndrome cannot be corrected. As a result, treatment (which must be life-long) is aimed at minimising the effects of the secondary increases in prostaglandin and aldosterone production.³ Significant fluid and sodium chloride losses need to be replaced, which is a difficult task in younger children.¹⁰ The cornerstones in treating renal salt wasting are long-term potassium chloride supplementation and non-steroidal anti-inflammatory drugs.^{1 2 9–10} There is long-standing experience with the unselective cyclooxygenase inhibitor indomethacin, which is started at 0.5 mg/kg/day and may be gradually increased according to its effects on urinary output, renal prostaglandin synthesis and blood aldosterone levels. Gastrointestinal side effects such as gastritis and peptic ulcers are the main drawbacks of prolonged indomethacin therapy.² In general, the effects of indomethacin treatment are significant:

the general condition improves, polyuria and polydipsia decrease and growth improves with catch-up phenomenon. Chronic hypokalaemia can be addressed pharmacologically with either amiloride or aldosterone antagonists acting in the cortical portion of the collecting duct, but these agents impair important compensatory mechanisms for sodium reabsorption. Furthermore, severe dehydration can occur as a consequence of such a treatment, especially in young children.⁴ Therefore it is essential to, periodically, monitor long-term growth, development, renal function and serum electrolytes.

Early treatment improves prognosis, in particular concerning growth and psychomotor development. Patients poorly managed may develop a progressive tubulointerstitial nephropathy that can lead to terminal chronic renal failure. As Bartter syndrome is an autosomal recessive disorder, genetic counselling should be offered to the families.^{1 10}

Learning points

- ▶ Classic Bartter syndrome is a rare disease, which may lead to unnecessary medical investigation and diagnosis delay.
- ▶ In a child with failure to thrive, hypochloraemic metabolic alkalosis and hypokalaemia, this diagnosis must be considered.
- ▶ The cornerstones in treatment are long-term potassium chloride supplementation and non-steroidal anti-inflammatory drugs.
- ▶ Early treatment improves prognosis, in particular concerning growth and psychomotor development.

Competing interests None.

Patient consent Obtained.

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