

Pseudo-Bartter Syndrome in an Infant with Congenital Chloride Diarrhoea

Zoran Igrutinović^{1,2}, Amira Peco-Antić^{3,4}, Nedeljko Radlović^{3,4}, Biljana Vuletić^{1,2}, Slavica Marković^{1,2}, Ana Vujić^{1,2}, Zorica Rašković¹

¹Paediatric Clinic, Clinical Centre Kragujevac, Kragujevac, Serbia;

²Medical School, University of Kragujevac, Serbia;

³Faculty of Medicine, University of Belgrade, Serbia;

⁴University Children's Hospital, Belgrade, Serbia

SUMMARY

Introduction Pseudo-Bartter syndrome encompasses a heterogeneous group of disorders similar to Bartter syndrome. We are presenting an infant with pseudo-Bartter syndrome caused by congenital chloride diarrhoea.

Case Outline A male newborn born in the 37th gestational week (GW) to young healthy and non-consanguineous parents. In the 35th GW a polyhydramnios with bowel dilatation was verified by ultrasonography. After birth he manifested several episodes of hyponatremic dehydration with hypochloreaemia, hypokalaemia and metabolic alkalosis, so as Bartter syndrome was suspected treatment with indomethacin, spironolactone and additional intake of NaCl was initiated. However, this therapy gave no results, so that at age six months he was rehospitalized under the features of persistent watery diarrhoea, vomiting, dehydration and acute renal failure (serum creatinine 123 µmol/L). The laboratory results showed hyponatraemia (123 mmol/L), hypokalaemia (3.1 mmol/L), severe hypochloreaemia (43 mmol/L), alkalosis (blood pH 7.64, bicarbonate 50.6 mmol/L), high plasma renin (20.6 ng/ml) and aldosterone (232.9 ng/ml), but a low urinary chloride concentration (2.1 mmol/L). Based on these findings, as well as the stool chloride concentration of 110 mmol/L, the patient was diagnosed congenital chloride diarrhoea. In further course, the patient was treated by intensive fluid, sodium and potassium supplementation which resulted in the normalization of serum electrolytes, renal function, as well as his mental and physical development during 10 months of follow-up.

Conclusion Persistent watery diarrhoea with a high concentration of chloride in stool is the key finding in the differentiation of congenital chloride diarrhoea from Bartter syndrome. The treatment of congenital chloride diarrhoea consists primarily of adequate water and electrolytes replacement.

Keywords: pseudo-Bartter syndrome; congenital chloride diarrhoea; diagnostics

INTRODUCTION

Bartter syndrome was originally described by Bartter et al. [1] in 1962 presenting autosomal recessive renal disorder characterized by hypokalaemic, hypochloreaemic metabolic alkalosis and hyperreninaemia associated with normal blood pressure. This renal abnormality results in excessive sodium, chloride and potassium loss by urine. The similar clinical hallmarks and biochemical profile are indicated in the newborns and children suffering from disorders, such as cystic fibrosis, congenital chloride diarrhoea, pyloric stenosis or neonates on prostaglandin infusion [2, 3].

Congenital chloride diarrhoea is a disorder characterized by polyhydramnios, premature delivery, failure to thrive, dehydration and hypokalaemic, hypochloreaemic metabolic alkalosis, with excessive chloride loss by stools [3, 4]. We describe an infant with clinical hallmarks and laboratory parameters which are similar to Bartter syndrome caused by congenital chloride diarrhoea.

CASE REPORT

A male child born in the 37th gestational week (GW) from young healthy and non-consanguineous parents. Intestinal loops dilatation and maternal polyhydramnios were noticed in the 35th GW by ultrasonography. Birth weight was 2800 g, birth length 54 cm, head circumference 32 cm and Apgar score 8. On the second day of life he developed frequent watery stools, abdominal distension and dehydration. On the fifth day of life his body weight was 2530 g. Abdominal distension and dehydration persisted. A plain abdominal X-ray showed distended small intestinal loops and colon, but irrigography and transanal rectal biopsy were not conclusive. Over the next few days the dehydration with a low level of serum sodium, potassium and chloride were intravenously regulated and the newborn was discharged with normal laboratory results. In the third month the patient was hospitalized, because of failure to thrive, dehydration, vomiting and watery diarrhoea. The body weight

Correspondence to:

Zoran IGRUTINOVIĆ
Paediatric Clinic
Clinical Centre
Zmaj Jovina 30, 34000 Kragujevac
Serbia
zigrutinovic1@sbb.rs

was 2900 g (<3th percentile), the body length 55 cm (<3th percentile) and blood pressure was normal. The laboratory results showed metabolic alkalosis (pH 7.61, bicarbonate 45 mmol/L, base excess of +18.5 mmol/L, pCO₂ 49.5 mmHg), hyponatraemia (120 mmol/L), hypokalaemia (2.84 mmol/L) and hypochloraemia (60 mmol/L). Serum creatinine, urea nitrogen, calcium, magnesium, phosphorus, albumin, glucose and liver function tests were within normal limits. The level of chloride in sweat was 25 mmol/L. Urine had a specific gravity of 1005, pH 7.0, without the presence of glucose, proteins, blood and ketones. Considering the diagnosis of Bartter syndrome, he was treated from the third to sixth months of life with indometacin, spirinolactone and sodium chloride supplementation. However, his condition did not improve. When aged sixth months the patient was hospitalized because of failure to thrive, dehydration, vomiting, watery stools and acute renal failure (123 µmol/L). At presentation the patient was dehydrated, normotensive, with low body length (60 cm) and body weight (4100 g) for age. Laboratory results showed hyponatraemia (123 mmol/L), hypokalaemia (3.1 mmol/L), severe hypochloraemia (43 mmol/L), alkalosis (blood pH 7.64, bicarbonate 50.6 mmol/L), high plasma renin (20.6 ng/ml) and aldosterone (232.9 g/ml). Chloride concentration in urine was low (2.1 mmol/L), and in stool very high (110 mmol/L). On the basis of persistent watery stools (6-8 times per day), low urinary, but high stool chloride excretion (six times more than urinary chloride concentration), Bartter syndrome was excluded and congenital chloride diarrhoea was diagnosed. Indomethacin was stopped and further on the patient was treated with intensive fluid, sodium and potassium supplementation, which resulted in the normalization of serum electrolytes, renal function, as well as his mental and physical development during 10 months of follow-up.

DISCUSSION

Bartter syndrome is a renal disorder characterized by hypokalaemic, hypochloraemic metabolic alkalosis and hyperreninemia associated with normal blood pressure. The renal abnormality results in excessive sodium, chloride and potassium loss by urine [1]. According to the molecular genetic classification, Bartter syndrome is characterized by four variants; Bartter syndrome type I (BSI) refers to a defect of NKCC2 (gene name SLC12A1), BS II of ROMK (KCNJ1), BS III of ClC-Kb (CLCNKB), and BS IV of barttin (BSND). Accordingly, genetic defects associated with antenatal Bartter syndrome affect NKCC2, ROMK, barttin, and both ClC-K isoforms. Gitelman syndrome, owing to disturbed NCCT (SLC12A3) function despite its apparent relatedness to this group of disorders, was not included in this classification [4, 5, 6].

Until recently, the cause of the neonatal variant was controversial. A defect in chloride transport in the medullary diluting segment of the ascending limb of Henle's loop has been the most plausible hypothesis [4]. The diagnosis of neonatal Bartter syndrome has been supported by the pres-

ence of a history of polyhydramnios, premature delivery and hypercalciuria in these patients [7]. The basic defects in tubular channels as mentioned above causes increased loss of salts in urine, which leads to activation of renin-angiotensin-aldosterone axis leading to hyperaldosteronism and hyperreninemia. The exact mechanism of increased prostaglandin level in blood and urine is still not known but it appears to be secondary to underlying defect in the transport of sodium chloride in thick ascending limb [4, 7].

The clinical neonatal Bartter syndrome features are vomiting, failure to thrive, dehydration, triangle face, large eyes, prominent forehead, protruding ears, drooping mouth, strabismus, convulsions and in type IV sensorineural deafness [8]. Hyponatraemia, hypochloremia, hypokalaemia, metabolic alkalosis and hypocalcaemia have been found in the laboratory results in the neonatal Bartter syndrome. Hypercalciuria, nephrocalcinosis, higher chloride, potassium and prostraglandine E₁ levels have been found in the urine. There are also higher renin and aldosterone values in the patient's serum [7-9]. There might be transient hyperkalaemia with Bartter syndrome in the early neonatal period in BS II of ROMK [9]. Unlike patients with loss-of-function mutation of ROMK and NKCC2, barttin deficient patients exhibit only transitory hypercalciuria and therefore medullary nephrocalcinosis is absent [10]. Cases of Bartter syndrome without nephrocalcinosis have been described [11].

Certain disorders in newborns can have clinical features and biochemical parameters similar to Bartter syndrome. Cyclic vomiting, congenital chloride diarrhoea (CCD), pyloric stenosis, disorders with primary excessive mineralocorticoid production and Guller syndrome (family hypokalaemic alkalosis with primary tubulopathy) can cause dehydration, failure to thrive, hypokalaemia, hypochloraemia and metabolic alkalosis [2, 4]. Also, pseudo-Bartter syndrome has been described in the patient suffering from cystic fibrosis, surreptitious diuretic use and laxatives abuse [4, 12, 13]. Iatrogenic caused pseudo-Bartter syndromes have been described with the newborns being injected prostaglandine infusions because of ductus-dependent heart defects [14, 15].

We have come across the data about polyhydramnios, premature delivery, failure to thrive, dehydration and hypokalaemic, hypochloraemic metabolic alkalosis, with excessive chloride loss by stools in the infant suffering from CCD [3, 4, 16]. CCD is an uncommon autosomal recessive hereditary disorder characterized by severe watery diarrhoea and metabolic alkalosis [16]. It is caused by a defect in sodium independent Cl⁻/HCO₃⁻ exchanger [17]. The basic defect in CCD is the impairment of Cl⁻/HCO₃⁻ exchange in an otherwise normal distal ileum and colon. Active of Cl⁻ re-absorption occurs when defective massive amounts of Cl⁻ are lost in stools and hypochloraemia develops. The respective defect in HCO₃⁻ secretion leads to metabolic alkalosis and the acidification of intestinal content, which further inhibit the absorption of Na⁺ through the Na⁺/H⁺ exchanger. In the intestine, the high luminal electrolyte content leads to diarrhoea by osmotic mechanisms. Na⁺ and water losses cause secondary hyper-

aldosteronism and K⁺ wastage, resulting in both hyponatraemia and hypokalaemia [18]. With adequate salt substitution and compliance with the medical regimen, CCD children develop normally, and a normal life is expected. Without treatment, most children die in infancy, but some will achieve a spontaneous electrolyte balance and survive with retarded psychomotor development. Without adequate therapy, chronic intravascular contraction is known to lead to hyperaldosteronism, hyperreninism and reduced renal function [19].

Our patient had maternal polyhydramnios which was found much later (35th GW) than in children suffering from Bartter syndrome (26th-30th GW), and at the same time the intestinal dilatation was diagnosed by ultrasonography. Antenatally, due to chronic watery diarrhoea, the patients developed hypokalaemic, hypochlorhaemic metabolic alkalosis with failure to thrive and dehydration, which is distinctive for Bartter syndrome. However, unlike neonatal Bartter syndrome, he did not have high

chloride, sodium and prostaglandine E₁ values in urine. He had no either hypercalciuria or nephrocalcinosis. Patients with Bartter syndrome without nephrocalcinosis have been described in the literature [11]. Unlike Gitelman syndrome he did not have hypomagnesaemia. We found higher chloride values in the stool, referring to chloride diarrhoea with excessive chloride loss by stool and to secondary higher renin and angiotensin values leading to higher potassium loss by urine. Our patient had normal blood pressure leaving out the possibility of pseudohyperaldosteronism accompanied by hypertension.

In conclusion, clinical and biochemical picture of congenital chloride diarrhoea may be very similar to Bartter syndrome, especially in infants, because watery stools can be easily mistaken for urine. The basis of the clinical diagnosis of chloride diarrhoea features a low ratio of urine and stool chloride concentrations, and therapy adequate water and electrolytes replacement.

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Псеудо-Бартеров синдром код одојчета с конгениталном хлорном дијарејом

Зоран Игрутиновић^{1,2}, Амира Пецо-Антић^{3,4}, Недељко Радловић^{3,4}, Биљана Вулетић^{1,2}, Славица Марковић^{1,2}, Ана Вујић^{1,2}, Зорица Рашковић¹

¹Педијатријска клиника, Клинички центар, Крагујевац, Србија;

²Медицински факултет, Универзитет у Крагујевцу, Крагујевац, Србија;

³Медицински факултет, Универзитет у Београду, Београд, Србија;

⁴Универзитетска дечја клиника, Београд, Србија

КРАТАК САДРЖАЈ

Увод Псеудо-Бартеров (*Bartter*) синдром чини хетерогена група поремећаја која је клинички и лабораторијски слична Бартеровом синдрому. Приказујемо одојче са псеудо-Бартеровим синдромом узрокованим конгениталном хлорном дијарејом.

Приказ болесника Мушко дете рођено је у 37. гестационој недељи (ГН) од младих, здравих и неконсангиних родитеља. Ултразвучним прегледом је у 35. ГН потврђен полихидрамнион са дилатацијом црева. По рођењу се манифестовало неколико појава хипонатријемичке дехидратације с хипохлоремичким, хипокалијемичким и метаболичком алкалозом, те је, због сумње на Бартеров синдром, започето лечење новорођенчета индометацином, спиронолактоном и додатним уносом соли. Међутим, ова терапија није дала резултате, па је дете у узрасту од шест месеци, због упорне водене дијареје, повраћања, дехидратације и акутне инсуфицијенције бубрега (ниво креатинина у серуму био је 123 $\mu\text{mol/l}$), поново хоспитализовано. Резултати лабораториј-

ских анализа су указали на хипонатријемичку (123 mmol/l), хипокалијемичку (3,1 mmol/l), тешку хипохлоремичку (43 mmol/l), алкалозу (pH крви 7,64, бикарбонати 50,6 mmol/l), висок ниво ренина (20,6 ng/ml) и алдостерона (232,9 ng/ml) у плазми и малу концентрацију хлора у урину (2,1 mmol/l). На основу ових налаза, као и високог нивоа хлора у столици (110 mmol/l), постављена је дијагноза конгениталне хлорне дијареје и започета интензивна надокнада фекалног губитка воде, натријума и калијума, која је током десет месеци клиничког праћења довела до нормализације нивоа електролита у серуму и функције бубрега, те оптималног менталног и физичког развоја детета.

Закључак Упорна водена дијареја с високом концентрацијом хлора у столици кључни је налаз у диференцирању конгениталне хлорне дијареје од Бартеровог синдрома. Терапија хлорне дијареје је прилично једноставна и превасходно заснована на одговарајућој надокнади воде и електролита.

Кључне речи: псеудо-Бартеров синдром; конгенитална хлорна дијареја; дијагностика