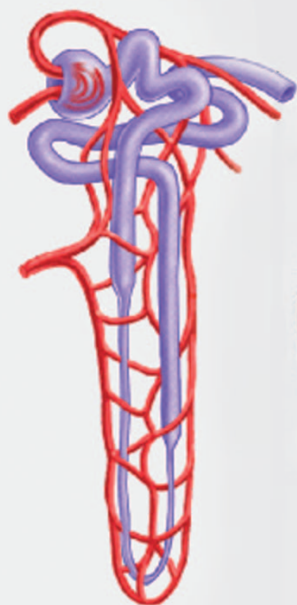


Polyhydramnios caused by
Bartter syndrome type I:
a rare, but typical clinical
condition

SEPTEMBER 2011



This 32-year-old healthy G2/P1 was hospitalized in the 27th week of gestation when extensive polyhydramnios was detected on fetal ultrasound. Following fetal lung maturation, the mother underwent two amniocenteses for symptomatic relief with aspiration of 1600 ml and 2400 ml of amniotic fluid, respectively (Fig. 1). Later in the course of her pregnancy, she developed gestational diabetes mellitus which was controlled with diet only. Routine maternal serologies were normal and there was no vaginal colonization with group B streptococci. CMV PCR of the amniotic fluid was negative. Repeated fetal ultrasound did not show any evidence of intestinal obstruction or other organ malformations. Biochemical analysis of amniotic fluid showed (compared to reference values at corresponding gestational ages) elevated osmolality (275 mosmol/kg) and chloride concentration (116 mmol/l), but a reduced potassium concentration (3.4 mmol/l). Chromosomal analysis revealed a normal fetal karyotype 46, XX.

The infant is the second child of consanguineous Swiss parents having the same great-great-grandparents. The older sister and the parents are in good health. The family history is positive for Bartter syndrome in a female descendant of the same great-great-grandparents (Fig. 2).

The index female infant was born prematurely at 33 5/7 weeks of gestation by vaginal delivery following preterm labor. Apgar scores were 7, 9, 10 at 1, 5 and



Fig. 1

Polyhydramnios at 30 weeks of gestation.

10 minutes, respectively. The female baby was alert and breathing spontaneously. There was asymmetrical intra-uterine growth restriction (IUGR) with a birth weight of 1350 g ($P < 3$), a head circumference of 30.2 cm and a body length of 42 cm (P10-25). Apart from a triangularly shaped face, the girl's clinical examination was normal (Fig. 3).

The leading clinical symptoms immediately postnatally were 1) massive polyuria with a maximum urine output of 20 ml/kg/hour necessitating ongoing replacement to prevent dehydration, 2) general muscular hypotonia with reduced spontaneous movements and 3) feeding problems due to poor sucking. Parenteral nutrition (PEN) was started after birth because of prematurity and IUGR. Blood biochemistry showed compensated hypo-

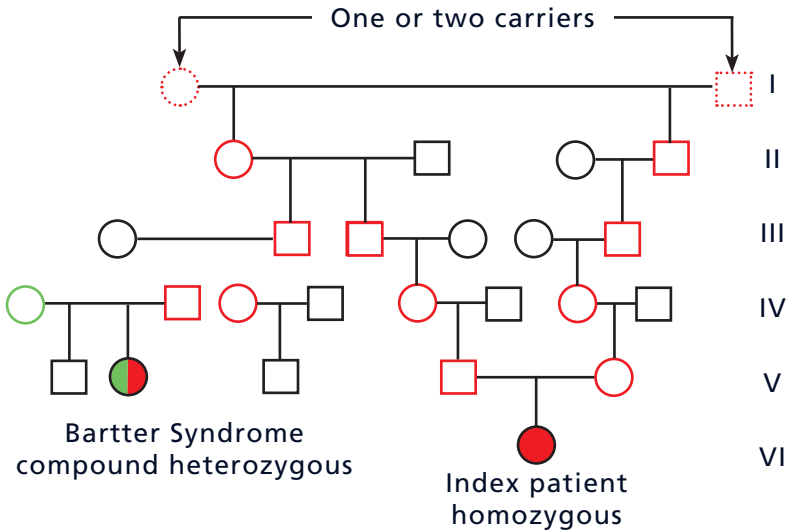


Fig. 2

Pedigree of the family showing the homozygous (c.1685C>T [Ala562Val]) inheritance of the Bartter syndrome in the index patient and the second female descendant with compound heterozygous Bartter syndrome. The filled circles represent the two patients with Bartter syndrome, the outlined circles represent presumptive carriers of the mutation.

kalemic, hypochloremic metabolic alkalosis (minimum chloride concentration 95 mmol/l, maximum pH 7.39, maximum pCO₂ = 7.8 kPa). Potassium levels remained low (lowest value 2.7 mmol/l) despite intravenous potassium replacement up to a daily dose of 6 mmol/kg. In addition, sodium was substituted (maximum daily dose 8.7 mmol/kg). Plasma creatinine was normal or mildly elevated (range 44-67 μmol/l), but urea



Fig. 3

The newborn infant after birth: triangular face and asymmetrical growth restriction.

was transiently increased up to a maximum level of 30 mmol/l on day 8 of life. Urinalysis revealed marked hypercalciuria (maximum calcium/creatinine ratio 6.87 mol/mol), and renal ultrasound showed marked bilateral medullary nephrocalcinosis (Fig. 4).

The patient experienced a significant weight loss in the first days of life despite PEN and intravenous replacement of urine losses (Fig. 5A). After stopping PEN on day 11, oral substitution with NaCl and KCl was required to maintain (low-) normal serum electrolyte levels.

Genetic analysis was performed (Prof. M. Konrad, University Children's Hospital Münster, Germany) revealing a homozygous mutation in the SLC12A1 gene (c.1685C>T (Ala562Val)) leading to an inactivation of the NKCC2 cotransporter in the ascending limb of Henle's loop confirming the diagnosis of neonatal Bartter syndrome type I (1, 2).

Jaundice with conjugated hyperbilirubinemia developed on the second day of life. The conjugated bilirubin increased over time up to a maximum level of 141 $\mu\text{mol/l}$ (normal <5). Liver enzymes were also elevated: ASAT 164 U/l (35-130), ALAT 112 U/l (<50) and γ -GT 251 U/l (15-132). A treatment with ursodeoxycholic acid and substitution of fat soluble vitamins was therefore started. All liver parameters normalised over a period of three months. Routine cerebral ultrasound revealed bilateral small subependymal hemorrhages. The infant was discharged home at six weeks of age (corrected age 39 4/7 weeks) with a nasogastric tube because she was unable to drink the required 160 ml/kg/day of fortified mother's milk (FM 85 5%).

At one year of age, the girl is doing well. She started to feed on her own soon after leaving the hospital. She still needs daily electrolyte substitution with NaCl and KCl to maintain (low-) normal serum electrolyte levels. At the age of nine months, therapy with oral indomethacin (1 mg/kg/day three times a day) was started because of progressive failure to thrive and persistent muscular hypotonia. The clinical effect was immediate with improvement of cognitive performance, motor activity and feeding. In addition, weight and length improved (Fig 5B). Repeat ultrasound examinations showed stable medullary nephrocalcinosis without renal stones and normal liver parenchyma, yet asymptomatic cholelithiasis was detected at the age of 3 months. The etiology of transient postnatal cholestasis and neonatal

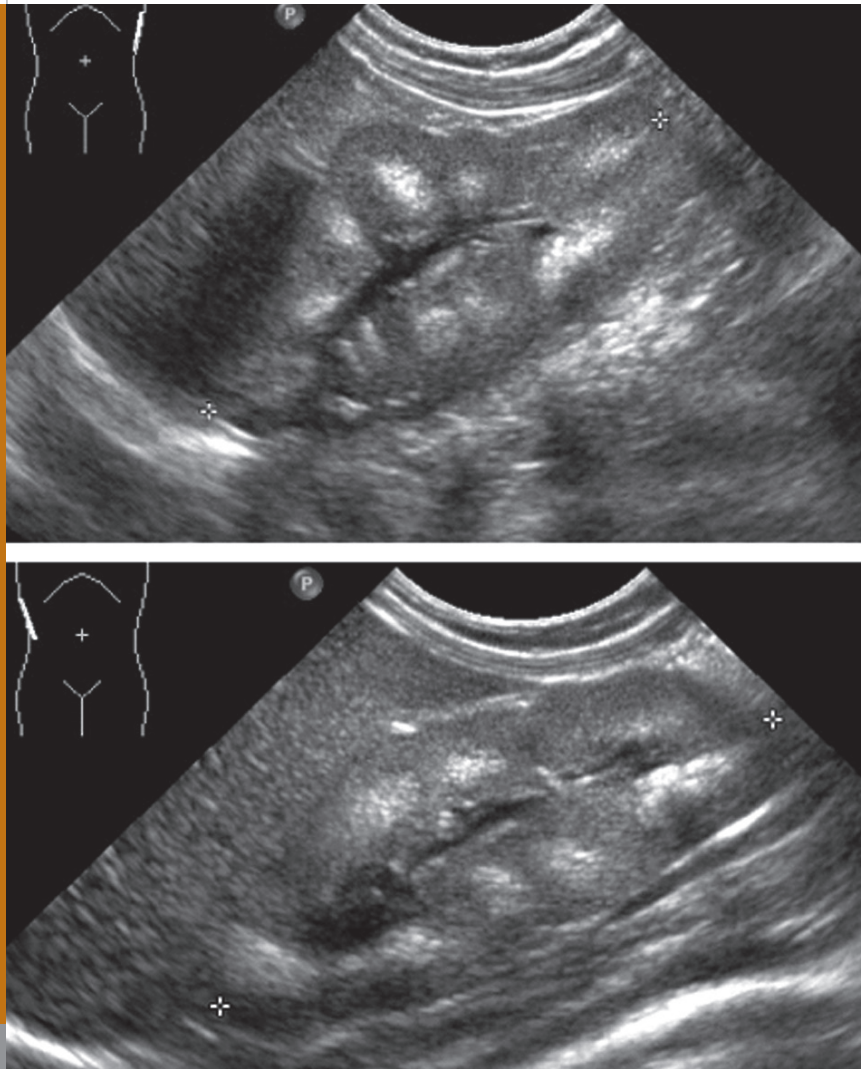


Fig. 4

Renal ultrasound showing bilateral medullary nephrocalcinosis.

hepatitis syndrome remains unclear. However, cholelithiasis seems to be a prominent feature of patients with antenatal Bartter syndrome (3). The girl presented repeatedly in our pediatric emergency department with vomiting and/or viral infections of the respiratory and gastrointestinal tract. All these episodes could be managed in an ambulatory setting because of excellent compliance of the parents. In addition, regular follow-up is provided by the pediatric renal clinic.

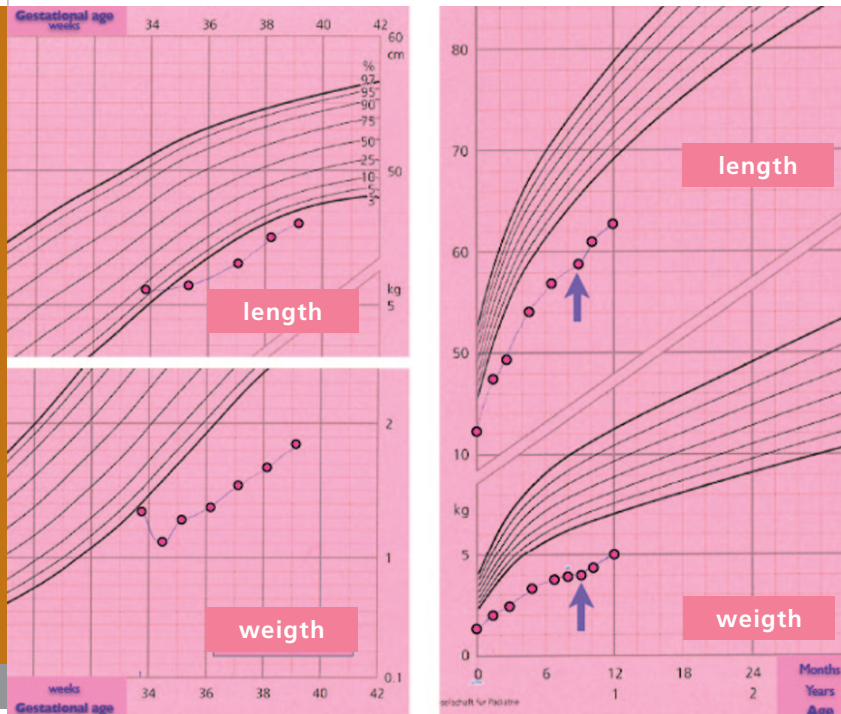


Fig. 5

Growth charts: A) Growth restriction at birth and poor weight gain during hospitalization; B) Improvement of growth after initiation of therapy with indomethacin (arrows) at nine months of age. The percentiles are not corrected for age.

There are various maternal and fetal conditions that can lead to polyhydramnios. In approximately 60% of the cases, pathogenesis remains unclear (i.e., idiopathic polyhydramnios), whereas in 20% of the cases, abnormal fetal conditions are found. Miscellaneous causes, e.g. multiple gestation or maternal (gestational) diabetes mellitus are responsible for the remaining 20% of cases.

Among the subgroup of cases with fetal anomalies, there are either gastrointestinal, cardiovascular, central nervous system or urinary tract malformations (4). In our case, massive polyhydramnios requiring repeated amniocentesis, parental consanguinity, positive family history for Bartter syndrome and normal anatomical findings on fetal and postnatal ultrasound were suggestive of antenatal Bartter syndrome. Garnier et al. suggested a „Bartter Index“ for diagnosing the syndrome antenatally based on amniotic fluid biochemical analysis multiplying total amniotic fluid protein (unit: g/l) with total amniotic fluid AFP (unit: ng/ml). Fetuses with Bartter syndrome had significantly lower values compared to control groups matched for gestational age (5). This index was not determined in our case, but high osmolality and abnormal electrolyte levels in the amniotic fluid were compatible with Bartter syndrome. Polyhydramnios as an early antenatal clinical symptom is a consequence of the defective NKCC2-transporter in the ascending loop of Henle leading to salt and water loss by the fetal kidneys. There

are at least 5 genotypic variants of Bartter syndrome (type I-V: I-IV autosomal recessive, V: autosomal dominant). Type I and II typically present as „antenatal“ variants whereas types III-V are generally diagnosed in infancy or childhood or even in adulthood. The neonatal Bartter syndrome type I is caused by a loss of function mutation in the gene SLC12A1 leading to a defect in the NKCC2 ($\text{Na}^+/\text{K}^+/2\text{Cl}^-$) cotransporter, whereas type II originates from a mutation of the gene KCNJ1 leading to a defect in the renal potassium channel (ROMK). The „classic“ Bartter syndrome type III is caused by a mutation in the gene CLCNKB leading to a defect in the renal chloride channel (ClC-Kb) (1). Type IV (loss of function mutation of the Barttin gene associated with sensorineural deafness and renal failure) and type V (gain of function mutation in the extracellular calcium-ion sensing receptor) are very rare (6).

The presentation of our patient with polyhydramnios and intrauterine growth restriction, the neonatal findings of muscular hypotonia and triangularly shaped face, polyuria with renal salt loss and hypokalemic-hypochloremic metabolic alkalosis and hypercalciuria with medullary nephrocalcinosis are typical for the antenatal/neonatal variants of Bartter syndrome. The genetic analysis revealed a homozygous mutation in the SLC12A1 gene leading to an inactivation of the NKCC2 cotransporter. Historically, the initial clue towards the pathophysiology of Bartter syndrome was

given by the observation that administration of high doses of the loop-diuretic furosemide – whose exact function was unknown until recently (!) – mimicks all clinical and laboratory findings of Bartter syndrome. In fact, furosemide specifically blocks the NKCC2 co-transporter in the ascending loop of Henle (and the NKCC1 in the inner ear) (2).

Therapy of Bartter syndrome consists of fluid and electrolyte supplementation. When there is failure to thrive, non-steroidal anti-inflammatory agents, e.g. indomethacin or ibuprofen, are the gold standard (1,7,8). So far, there is no consensus as to when to initiate indomethacin. Indomethacin has successfully been administered in the first weeks of life to decrease polyuria and prevent dehydration in some cases (9), but serious side effects of prostaglandin inhibitors, e.g. intestinal complications (necrotizing enterocolitis and focal intestinal perforation) must be taken into consideration (10). Vaisbich et al. studied side effects of long-term treatment with indomethacin and potassium supplementation in Bartter syndrome and found relevant gastrointestinal side effects like gastritis, gastric ulcers and even perforated gastric ulceration. They suggested that patients treated with prostaglandin inhibitors for a prolonged period of time should undergo routine endoscopic evaluation (11).

Puricelli and colleagues have reported that patients with antenatal Bartter syndrome type I and II tend to

have satisfactory long-term prognoses. After a median follow-up of ten years, somatic growth (weight and height) was within the normal range and renal function assessed as glomerular filtration rate was normal in the great majority of children (3).

1. Rodriguez-Soriano J. Bartter and related syndromes: the puzzle is almost solved. *Pediatr Nephrol* 1998;12:315-327
2. Haas M. The Na-K-Cl cotransporters. *Am J Physiol* 1994;267:C869-C885
3. Puricelli E, Bettinelli A, Borsa N, et al. Long-term follow-up of patients with Bartter syndrome type I and II. *Nephrol Dial Transplant* 2010;25:2976-2981
4. Moise KJ Jr. Polyhydramnios. *Obstet Gynecol* 1997;40:266-279
5. Garnier A, Dreux S, Vargas-Poussou R, et al. Bartter syndrome prenatal diagnosis based on amniotic fluid biochemical analysis. *Pediatr Res* 2010;67:300-303
6. Hebert SC Bartter syndrome. *Curr Opin Nephrol Hypertens* 2003;12:527-532
7. Proesmans W. Bartter syndrome and its neonatal variant. *Eur J Pediatr* 1997;156:669-679
8. Mackie FE, Hodson EM, Roy LP, Knight JF. Neonatal Bartter syndrome – use of indomethacin in the newborn period and prevention of growth failure. *Pediatr Nephrol* 1996;10:756-758
9. Mourani CC, Sanjad SA, Akatcherian CY. Bartter syndrome in a neonate: early treatment with indomethacin. *Pediatr Nephrol* 2000;14:143-145
10. Cass DL, Brandt ML, Patel DL, Nuchtern JG, Minifee PK, Wesson DE. Peritoneal drainage as definitive treatment for neonates with isolated intestinal perforation. *J Pediatr Surg* 2000;35:1531-1536
11. Vaisbich MH, Fujimura MD, Koch VH. Bartter syndrome: benefits and side effects of long-term treatment. *Pediatr Nephrol* 2004;19:858-863

SUPPORTED BY



CONTACT

Swiss Society of Neonatology

www.neonet.ch

webmaster@neonet.ch