Pediatr Nephrol (2006) 21: 1056–1057
DOI 10.1007/s00467-006-0108-4

LETTER TO THE EDITORS

Ferda Ozlu · Hacer Yapicioğlu · Mehmet Satar · Nejat Narli · Kenan Ozcan · Mithat Buyukcelik · Martin Konrad · Osman Demirhan

Barttin mutations in antenatal Bartter syndrome with sensorineural deafness

Received: 1 August 2005 / Revised: 15 January 2006 / Accepted: 20 January 2006 / Published online: 24 May 2006

Sirs,
We have observed two patients with antenatal and postnatal findings pathognomonic for antenatal Bartter syndrome (aBS). In addition, both had sensorineural deafness. This entity is known as aBS with sensorineural deafness (BSND).

Case reports

Case 1 The male patient had been born at 30 weeks of gestation (weight 1,360 g) to consanguineous parents. Pregnancy was complicated by severe polyhydramnios. Findings at his physical examination were normal except for a triangular face, large eyes, protruding ears, tachypnea and retractions. He rapidly developed renal salt wasting, hyper-reninemic hyperaldosteronism, hypokalemic metabolic alkalosis, and impaired renal function [creatinine (Crea) 1.5 mg/dl]. The diagnosis of antenatal Bartter syndrome (aBS) was suspected. On day 49 oral administration of indomethacin was started (2–3 mg/kg per day), which could not help to regulate serum potassium levels. Instead, upon indomethacin treatment, renal function further deteriorated (Crea 2.5 mg/dl). Therefore, indomethacin was stopped, and he was treated with spironolactone. Potassium need declined to 27 mEq/kg, and he was discharged after 140 days. He has unilateral sensorineural deafness detected by impaired brain stem evoked potentials and growth retardation. A homozygous mutation in the Barttin gene (*BSND*) leading to a loss of start codon was detected (Table 1). A similar mutation has been previously described [1].

Case 2 A male child was born at 31 weeks of gestation (weight 1,530 g) after a pregnancy complicated by polyhydramnios. Soon after birth he developed the typical features of aBS. Indomethacin at 1 mg/kg was added to his treatment. He rapidly developed renal insufficiency (Crea 3.3 mg/dl) and indomethacin was stopped. With discontinuation of the drug creatinine levels decreased to normal range. He also had bilateral sensorineural deafness, protruding ears and large eyes, and a triangular face. A new homozygous *BSND* mutation (NtG262T, aaE88-STOP) leading a truncation of the protein at aminoacid position E88 was detected (Table 1).

At least five different molecular defects have been shown to be responsible for either antenatal or classic BS (for review see [2, 3]): mutations in the bumetanide-sensitive Na–K–2Cl co-transporter (NKCC2) (1); the renal potassium channel ROMK (2); and the renal chloride channel ClC–Kb (3). aBS with sensorineural deafness is caused by mutations in the Barttin gene [1] (4). A phenocopy of a Barttin gene defect may also be caused by a defect affecting both renal chloride channel genes (*CLCNKA* and *CLCNKB*) [4] (5).

Genetic analysis in both of our patients revealed a homozygous *BSND* mutation. (Table 1). Both mutations are expected to result in a complete loss of Barttin function, either by the loss of the translation initiation start site or truncation of the protein.

There are few reports of indomethacin use in aBS during the newborn period. It is generally accepted that, in cases of excessive salt and fluid loss, the inhibition of prostaglandin

F. Ozlu (✉) · H. Yapicioğlu · M. Satar · N. Narli · K. Ozcan
Division of Neonatology, Faculty of Medicine,
Çukurova University,
01330 Adana, Turkey
e-mail: ferdaozlu72@yahoo.com
Tel.: +90-322-3386270
Fax: +90-322-3386610

M. Buyukcelik
Division of Pediatric Nephrology, Faculty of Medicine,
Çukurova University,
Adana, Turkey

O. Demirhan
Division of Medical Biology, Faculty of Medicine,
Çukurova University,
Adana, Turkey

M. Konrad
University Children's Hospital,
Berne, Switzerland

Table 1 *BSND* mutations of patients and both parents

Patient	Zygosity	*BSND* mutation
Case 1	homozygous	ntT2A, loss of start codon
Mother of case 1	heterozygous	ntT2A, loss of start codon
Father of case 1	heterozygous	ntT2A, loss of start codon
Case 2	homozygous	NtG262T, aaE88STOP
Mother of case 2	heterozygous	NtG262T, aaE88STOP
Father of case 2	heterozygous	NtG262T, aaE88STOP

synthesis may be life saving. However, it seems that BSND patients are especially vulnerable to the development of renal failure after therapy with non-steroidal anti-inflammatory drug (NSAIDs) such as indomethacin [5]. It might well be that this effect depends on the type of the mutation, since this has not been observed in patients from Israel [6]. Whether the disease itself is a risk for the development of chronic renal failure is still under discussion. Also in these two patients, increases in blood urea nitrogen (BUN) and creatinine levels were detected immediately after indomethacin use. No other nephrotoxic medication had been used.

In conclusion, we present two neonates with aBS, which underlines the need for hearing examinations, on one hand, and caution with early therapy with indomethacin, on the other, especially in BSND patients.

References

1. Birkenhäger R, Otto E, Schurmann MJ, Vollmer M, Ruf EM, Maier-Lutz I, Beekmann F, Fekete A, Omran H, Feldmann D, Milford DV, Jeck N, Konrad M, Landau D, Knoers NV, Antignac C, Sudbrak R, Kispert A, Hildebrandt F (2001) Mutation of BSND causes Bartter syndrome with sensorineural deafness and kidney failure. Nat Genet 29:310–314
2. Hebert SC (2003) Bartter syndrome. Curr Opin Nephrol Hypertens 12:527–532
3. Jeck N, Schlingmann KP, Reinalter SC, Kömhoff M, Peters M, Waldegger S, Seybert HW (2005) Salt handling in the distal nephron: lessons learned from inherited human disorders. Am J Physiol Regul Integr Comp Physiol 288:R785–R795
4. Schlingmann KP, Konrad M, Jeck N, Waldegger P, Reinalter SC, Holder M, Seyberth HW, Waldegger S (2004) Salt wasting and deafness resulting from mutations in two chloride channels. N Engl J Med 350:1314–1319
5. Jeck N, Reinalter SC, Henne T, Marg W, Mallmann R, Pasel K, Vollmer M, Klaus G, Leonhardt A, Seyberth HW, Konrad M (2001) Hypokalemic salt-losing tubulopathy with chronic renal failure and sensorineural deafness. Pediatrics 108:E5
6. Shalev H, Ohali M, Kachko L, Landau D (2003) The neonatal variant of Bartter syndrome and deafness: preservation of renal function. Pediatrics 112:628–633