Title:
Renal apnoea: extreme disturbance of homoeostasis in an infant with Bartter syndrome type IV

Short title: Bartter Syndrome Type IV

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Case report:

A two-week old infant was transferred to our renal ward in February 2014 from the neonatal intensive care unit in her local hospital due to polyuria (~200ml/kg/day) and extreme acid-base and electrolyte disturbance from birth. She was born by spontaneous delivery at 32weeks gestation. Severe polyhydramnios was noted antenatally with two amniocenteses procedures removing over 6L fluid. She is the third child of consanguineous parents, with no relevant family history.

Examination at admission was unremarkable; weight: 1.68kg (9^{th}percentile), length: 44cm (25^{th}percentile), head circumference 29cm (5^{th}percentile), BP: 68mmHg systolic (normal).

Initial investigations revealed a marked hypokalaemic (2.1mmol/l), hypochloraemic (59mmol/l) metabolic alkalosis (bicarbonate: 81mmol/l, pH: 7.8), leading to a presumptive diagnosis of Bartter syndrome (BS). Ultrasound showed echogenic kidneys without nephrocalcinosis. She remained polyuric with fragile intravascular volume status, reflected in plasma sodium values between 94-176mmol/L and recurrent episodes of acute kidney injury with creatinine levels between 29-182umol/l. Sodium (14mmol/kg/day) and potassium (13mmol/kg/day) supplementation was provided with 200ml/kg/d of fluid to stabilise volume status, yet she had persistent severe alkalosis (pH 7.56-7.92). Concerns regarding respiration were first raised when she remained apnooeic after general anesthesia for a central line insertion and needed mechanical ventilation for 24hours. She was noted to have repeated desaturations and subsequent polysomnography demonstrated prolonged periods of cyclical dips (73dips/hour; normal <5) in oxygen

saturation (SpO2, see figure 1) with a mean and absolute nadir of 88% and 77%, respectively. Mean transcutaneous pCO2 was raised at 10kPa (75mmHg), maximum 10.64kPa, and a respiratory rate of 10/min in periodic breathing, rising to 48 breaths/minute in Quiet Sleep. The Apnoea-Hypopnoea Index was 68 central events/hour (normal <1, severe >10), with little evidence of obstruction (2/hour).

Over the following year, she demonstrated profound global developmental delay with associated microcephaly, signs of delayed brain maturation on brain MRI and sensorineural hearing loss (SNHL, confirmed by auditory brainstem response). She had evidence of chronic kidney disease (CKD) from birth with an estimated GFR around 30ml/min/1.73m^2. The patient also developed severe hypophosphataemic rickets, with plasma phosphate levels as low as 0.30 mmol/l, alkaline phosphatase levels up to 1226 U/l (normal 80-345) and renal phosphate wasting (TmP/GFR<0.83mmol/l; normal 1.10-2.70).

BS is a genetically heterogeneous condition characterized by failure of renal reabsorption of sodium and chloride in the thick ascending limb of Henle's loop (TAL)[1]. Prenatal onset, SNHL, normocalciuria and CKD are characteristic for BS type IV (BS4)[2] and genetic testing confirmed this diagnosis by identification of a homozygous deletion in *BSND* c.452del; p.(Pro151Leufs*27).

Hypokalaemic alkalosis in BS is secondary to increased aldosterone levels[1], but was extreme in this case. The apneas and hypophosphataemic rickets were considered secondary complications. While respiratory suppression is well recognized as the physiological response to alkalosis[3], hypophosphataemic rickets has to our knowledge not previously been reported. Yet, lower plasma phosphate levels have

been recurrently noted in alkalosis, including in BS, presumably due to the tight pH dependence of renal phosphate transporters[4].

Metabolic alkalosis carries significant risks: an arterial pH >7.55 is associated with a mortality rate of 45%, rising to 80% if >7.65[5]. Most enzyme systems in our body are dependent on tight regulation of acid-base homoeostasis and we presume that besides the rickets, the initial obtunded state of our patient was also related to the extreme alkalosis, as it improved when pH decreased. Complications of prematurity can cause developmental delay in neonatal BS, but in our case the abnormal brain maturation may reflect the severe biochemical disturbance.

Given these serious clinical difficulties, chiefly attributed to alkalosis, discussions were held about potential treatment approaches, including palliative care, bilateral nephrectomies with consequent renal replacement treatment, as well as titration with hydrochloric acid. At 10 months of age, a trial of amiloride was decided with the parents, with sufficient sodium supplementation to maintain volume homoeostasis. The drug was slowly increased to 1mg/kg/day. Within weeks, plasma bicarbonate levels decreased to between 27-47mmol/L with pH levels <7.6. Concurrently, the patient's desaturations became less frequent, plasma phosphate levels normalized without supplementation and an improvement in general alertness was noted. The patient was eventually discharged home after her first birthday. She has shown some development, but remains severely delayed with last follow-up in September 2015.

The treatment of BS with potassium-sparing diuretics, such as amiloride is potentially hazardous, as mineralocorticoid activation is a critical mechanism to maintain euvolaemia. The kidneys regulate volume homoeostasis by tubular salt

handling and the mineralocorticoid-induced sodium reabsorption through the epithelial sodium channel (ENaC), which is coupled to secretion of potassium and protons, reflects the evolutionary importance of volume over acid-base and potassium homoeostasis. Although ENaC blockade by amiloride improves the metabolic alkalosis and hypokalaemia, it carries the risk of hypovolaemia. Yet, hyperaldosteronism may be uncoupled from volume homoeostasis in BS: renal volume sensing involves chloride reabsorption in the macula densa as the critical first step in tubuloglomerular feedback[1]. Decreased chloride transport leads to increased prostaglandin production with consequent renin-aldosterone activation. Since the macula densa is part of TAL, the molecular defect in chloride reabsorption in BS "shortcircuits" tubuloglomerular feedback. Consequently, typical treatment includes prostaglandin synthesis inhibitors. However, neither indomethacin nor celecoxib treatment had resulted in substantial improvement in our patient, as previously reported in BS4[2].

This case highlights the importance of the kidneys in maintaining homoeostasis and the severe consequences for whole body physiology, if the underlying molecular mechanisms are disrupted.

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Contributors:

LAP, WVH, RK, CR, MS and DB provided clinical care; EA performed genetic analysis. All authors contributed to the final manuscript.

Conflict of Interest:

No conflicts of interest to declare

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Figure 1: Selected traces from polysomnography

Shown is a selected 3 min segment (scale bar 30 s) from the patient's polysomnography at 8 months of age, before treatment with amiloride. Shown are traces for oxygen saturation (SpO2), heart rate, thoracic (Thor) and abdominal (Abdo) movement and transcutaneous pCO2 (tcpCO2). The indicated pressure levels of 60 and 90 mmHg are equivalent to 7.98 and 11.97kPa, respectively. Note the persistently elevated tcpCO2 and the cyclical breathing pattern on the thoracic and abdominal movement traces, associated with dips in SpO2.