A Renal Cause of Failure to Thrive

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- JB and MC: Wrote the manuscript and approved the final manuscript
- TF, MA and MA: Reviewed the manuscript and approved the final manuscript.

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CASE REPORT

A 6-year-old boy was referred to pediatric nephrology due to symptoms of primary enuresis and polydipsia for a year. His antenatal, natal, postnatal period and first 9 months of life were uneventful, with normal acquisition of early developmental milestones. After this age, he gradually presented failure to thrive (less than the fifth percentile at 4 years old – Fig. 1), but no medical history of fever, fatigue, vomiting, diarrhea, recurrent infections, excessive sweating, low caloric intake, drug intake, behavioral problems or parental neglect. Around 2-year-old a language delay was noticed, without delay of the other development milestones and keeping regular follow up in a development specialist. Any relevant family history and consanguinity were excluded. Physical examination was unremarkable, with normal blood pressure and hydration status. Blood tests showed slightly increased urea with normal creatinine, metabolic alkalosis and electrolyte abnormalities: hypochloremia, hypokalemia, and natremia in lower range of normal (Table 1). No carpopedal spasms were referred.

WHAT ARE THE MOST PROBABLE CAUSES OF METABOLIC ALKALOSIS, HYPOKALEMIA AND NORMAL BLOOD PRESSURE?

In the setting of metabolic alkalosis, we should always evaluate if it is a volume mediated/saline responsive alkalosis (also known as chloride-depletion metabolic alkalosis – CDMA – or “contraction alkalosis”) or if it is a volume independent/saline resistant (also known as sodium-retention metabolic alkalosis – SRMA). In the first case (CDMA), there is volume contraction, leading to secondary hyperaldosteronism and an increase in HCO₃⁻ reabsorption. It can be caused by diuretics use, gastrointestinal fluid losses, renal compensation of respiratory acidosis (“chloride responsive”) or by Bartter and Gitelman syndromes (“chloride resistant”). The second case (SRMA) is associated with hypervolemia, suppression of the renin-angiotensin-aldosterone system and high blood pressure. It may be due to Cushing disease, mineralocorticoid excess, Liddle syndrome, renal arterial stenosis or congenital adrenal hyperplasia. Assessment of patients’ volume status, blood pressure and urine chloride may help to identify the underlying cause.

Our patient had normal blood pressure and increased urinary fractional excretion of chloride. Although he seemed to have a regular hydration state, urea was slightly elevated with normal creatinine, which may indicate some degree of volume depletion. There were no...
WHATS IS THE MOST PROBABLE DIAGNOSIS

The two diagnostic hypotheses at this point were Bartter and Gitelman syndrome. Gitelman syndrome was excluded by normal magnesium level and normal renal calcium excretion. BS types I and II were excluded based on the age of onset, severity and the absence of hypercalciuria and nephrocalcinosis. Lastly, BS type 4 was excluded by normal audiometry.

A next-generation sequencing panel for BS (27 genes) was performed identifying a total CLCNKB gene deletion and a previously described pathogenic CLCNKB missense variant (c.1312C>T – p.(Arg438Cys)) in hemizygosity. The deletion was confirmed by MLPA (with the commercial kit Salsa MLPA P266-B2 CLCNKB) and CGH array (arr[hg19] 1p36.13 (16369552_16385187)): a 1p36.13 deletion with 15-6-Kb involving the entire gene length. Parents testing confirmed the biallelic contribution of the haploinsufficient variant and the copy number variation (CNV).

These results support the diagnosis of classic form of Bartter syndrome (type III).

BARTTER SYNDROME (BS)

BS is a rare autosomal recessive disorder that affects around 1 in 1 000 000 of the population. It is a salt-losing tubulopathy caused by a primary defect in sodium chloride reabsorption in the medullary thick ascending limb of the loop of Henle. It is characterized by hypokalemia, metabolic alkalosis, hyperaldosteronism and hyperplasia of the juxtaglomerular apparatus (IGA) with normal blood pressure. BS is divided into types I to V according to the gene involved. Severity and clinical presentation vary with each type. Nonetheless, there is a poor genotype-phenotype correlation, due to interaction with other cotransporters and different degrees of compensation through alternative pathways.3,3

Types I and II (biallelic pathogenic variants genes in SLC12A1 and KCNJ1 genes, respectively) are usually severe disorders that cause polyhydramnios during pregnancy and prematurity. In these two BS types nephrocalcinosis is common and may lead to late development of kidney dysfunction.3

Type III (classic BS – CLCNKB gene related) is characterized by less severe electrolyte loss and clinical symptoms than type I and II BS. In this type, symptoms usually 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. These patients once treated have normal lives. Nephrocalcinosis may be present but occurs less frequently than in types I and II.3,5 As in cases reported in literature, our patient had neonatal and infant uneventful periods, with clinical manifestations (polydipsia, enuresis, and failure to thrive) starting later, after the second year of life. After establishing diagnosis and optimizing treatment, he is asymptomatic and has a normal quality of life.

Types IVa (BSND gene) and IVb (CLCNKA + CLCNKB genes) are severe diseases, generally with antenatal presentation and congenital hearing loss. Patients with BS types IVa and IVb develop less commonly nephrocalcinosis, but more often evolve to progressive kidney dysfunction.3

Complementary Investigation

The laboratory evaluation is summarized in table I. Urine biochemical analysis showed increased fractional excretion of sodium, potassium and chloride with normal renal excretion of calcium. Glomerular filtration rate (GFR) was normal, with normal plasmatic level of creatinine and a slightly elevated urea nitrogen level. Urinary specific gravity was normal. Both serum magnesium and serum calcium were also normal. Finally, renin and aldosterone levels were increased. Kidney ultrasound showed bilateral hyperechoegenic kidneys, suggestive of nephropathy, but without signs of nephrocalcinosis.

He also had normal levels of thyroid and parathyroid hormones, negative antitransglutaminase antibodies, normal karyotype, bone age consistent with chronological age through hand-wrist radiograph evaluation and normal values of IGF-1 and IGF-BP3. Hearing assessment and audiogram were normal.

WHAT IS THE MOST PROBABLE DIAGNOSIS AT THIS POINT?

Table 1

<table>
<thead>
<tr>
<th>Laboratory results</th>
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<tbody>
<tr>
<td>pH (7.35-7.45)</td>
<td>7.51</td>
</tr>
<tr>
<td>HCO3- (22-25 mmol/L)</td>
<td>28.7</td>
</tr>
<tr>
<td>Base excess (-2 to +2 93 mEq/L)</td>
<td>+4.3</td>
</tr>
<tr>
<td>Plasma sodium (135-145 mEq/L)</td>
<td>136</td>
</tr>
<tr>
<td>Plasma potassium (3,5-5,1 mEq/L)</td>
<td>2.3</td>
</tr>
<tr>
<td>Plasma chloride (98-107 mEq/L)</td>
<td>93</td>
</tr>
<tr>
<td>Plasma magnesium (1.7-2.8 mg/dL)</td>
<td>1.9</td>
</tr>
<tr>
<td>Ionized calcium (1.1-1.3 mmol/L)</td>
<td>1.3</td>
</tr>
<tr>
<td>GFR (&gt; 90 mL/min/1.73m2)</td>
<td>93</td>
</tr>
<tr>
<td>Urinary density (1005-1025)</td>
<td>1.010</td>
</tr>
<tr>
<td>Urinary chloride (20 – 40 mEq/L)</td>
<td>83</td>
</tr>
<tr>
<td>Fractional sodium excretion (&lt;1%)</td>
<td>11</td>
</tr>
<tr>
<td>Fractional potassium excretion (9 ± 4%)</td>
<td>52.5</td>
</tr>
<tr>
<td>Fractional magnesium excretion (&lt;4%)</td>
<td>4.24</td>
</tr>
<tr>
<td>Urinary calcium to creatinine ratio (&lt;0.14)</td>
<td>0.05</td>
</tr>
<tr>
<td>Renin (15.6 – 100.0 uIU/mL)</td>
<td>5640</td>
</tr>
<tr>
<td>Aldosterone (4 – 44 ng/dl)</td>
<td>70.4</td>
</tr>
</tbody>
</table>
Finally, type V (MAGE-D2 gene), also named transient antenatal Bartter syndrome, is an X-linked recessive disorder, although some girls can be affected. It is a severe disease with polyhydramnios and prematurity, but for unclear reasons, the defects improve or resolve over time. In this type of BS hypercalciuria may be observed, but nephrocalcinosis is rare.

An important differential diagnosis is Gitelman syndrome (GS), also a rare recessive salt-losing tubulopathy, characterized by hypokalemia, metabolic alkalosis, hypomagnesemia and hypercalciuria. Usually is not diagnosed until late childhood or adulthood and long-term prognosis is generally excellent. These last two findings can help distinguish between GS and BS, however some patients with BS could have mild phenotypes with late presentation and without hypercalciuria, making genetic evaluation essential to the differential diagnosis.

**TREATMENT AND CASE FOLLOW-UP**

The child’s treatment was started with oral potassium supplements (0.5 mEq/kg/day), indomethacin (0.5 mg/kg/day) along with appropriate dietary advice. On follow-up, higher doses of oral potassium chloride (5.7 mEq/kg/day) and indomethacin (3.5 mg/kg/day) were needed to normalize his electrolyte disturbances. Gradually there was a reduction of polyuria, improvement of growth and normalization of plasmatic levels of potassium, sodium and bicarbonate.

After one year of indomethacin therapy, the patient developed abdominal pain and nausea. A proton pump inhibitor was prescribed, and the patient’s gastric discomfort was significantly relieved.

Patient started to recover weight after first year of treatment and height after two more years. Currently he is above 10th and 5th percentile, respectively. There was no intellectual recovery and he still demonstrates a moderate degree of mental disability.

**WHAT IS THE EXPLANATION FOR THE USE OF INDOMETHACIN IN BARTTER SYNDROME?**

The impaired entry of sodium and chloride into the macula densa increases the expression of cyclooxygenase 2; this stimulates renal production of prostaglandin E2, which results in afferent arteriolar dilatation and activation of renin release by the juxtaglomerular apparatus (JGA). Consequently, the control of filtration becomes uncoupled from volume status. Hypertrophy of JGA is considered a hallmark of the disease. Nonsteroidal anti-inflammatory drugs—NSAID (e.g., indomethacin) inhibit COX2, block prostaglandin synthesis and consequently inhibit the renin-angiotensin-aldosterone system, which normalizes the levels of renin and aldosterone leading to potassium retention. Despite being an efficient therapy, careful monitoring of renal and gastrointestinal side effects of NSAIDs is required. In our patient, a proton pump inhibitor was sufficient to relieve gastrointestinal complaints and no renal function impairment was registered during follow-up.

Nevertheless, in some cases NSAID has to be changed. The use of COX2 selective inhibitor equally suppresses hyperreninemia with less gastric side effects. However, recent evidence about high risk of cardiovascular events in patients receiving this kind of NSAID has limited its use.

High doses of potassium supplementation are often not well tolerated. Complementary use of potassium sparing diuretics (such as spiranolactone and amiloride) may help to raise serum potassium and reverse metabolic alkalosis. Another possible choice is angiotensin-converting enzyme inhibitors, especially if proteinuria is present. Because polyuria and dehydration are common symptoms, caution is necessary due to the potential risk of acute kidney injury in this high-risk group of patients.

**WHAT KIND OF FOLLOW-UP SHOULD BE DONE?**

Due to chronic stimulation of renin-angiotensin system with secondary chronic glomerular hyperfiltration, some cases may develop focal segmental glomerulosclerosis (FSGS) during the course of BS. Thus, renal function and proteinuria should be monitored regularly. FSGS, recurrent episodes of dehydration, long-term use of NSAIDs and presence of nephrocalcinosis are considered risk factors for renal damage.

The hypercalciuric phenotype can lead to osteopenia in some cases. Therefore, bone mineral density must be evaluated and monitored in such patients.

Growth monitoring is essential. Some cases will require administration of growth hormone (GH) for the treatment of short stature. Therefore, if no growth improvement is seen after the implementation of therapy, an endocrinological evaluation must be guided.

Finally, as it is an autosomal recessive disorder, genetic counseling should be offered to the family.

The aim of this case report is to highlight the importance of clinical suspicion of this pathology because with an early diagnosis, correct therapy implementation and regular follow-up, weight and height recover can be achieved.

**References**

Ethical Disclosures

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