Brief Report

Severe syncope and sudden death in children with inborn salt-losing hypokalaemic tubulopathies

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Abstract

Background. Potassium deficiency may cause cardiac arrhythmias culminating in syncope or sudden death.

Methods. An inquiry performed among physicians caring for a total of 249 patients with inborn salt-losing tubulopathies revealed that acute cardiac complications occurred in seven children.

Results. Four patients died suddenly and three had severe syncope. These episodes occurred in the context of severe chronic hypokalaemia (≤2.5 mmol/l) or were precipitated by acute diseases, which exacerbated hypokalaemia (≤2.0 mmol/l).

Conclusions. In conclusion, severe chronic or acute hypokalaemia is hazardous in inborn salt-losing tubulopathies.

Keywords: arrhythmias; Bartter syndrome; Gitelman syndrome; hypokalaemia; sudden death

Introduction

The term inborn salt-losing tubulopathies encompasses a group of closely related clinical disorders of renal electrolyte transport. Recent studies have identified the underlying mutations in various genes [1]. Phenotypically at least five phenotypic variants have been described. The neonatal Bartter syndrome (variant 1), which is sometimes associated with deafness (variant 2), is characterized by polyhydraminos, premature delivery, episodes of fever and dehydration during the early weeks of life, and growth retardation. The classic Bartter syndrome (variant 3) is observed during infancy and childhood and is characterized by polyuria and growth retardation. Finally, Gitelman syndrome (variant 4) is observed in older children and adults with episodes of muscle weakness and tetany but is sometimes asymptomatic. Some cases (variant 5), however, cannot be classified [1].

It is usually difficult to treat potassium deficiency with potassium supplements and cyclooxygenase inhibitors. Furthermore, potassium salts and cyclooxygenase inhibitors sometimes cause severe gastrointestinal complications [2]. Consequently, the overall potassium concentration in the majority of patients with these disorders is low or sometimes even very low. Nonetheless, the majority of patients with low potassium levels do rather well.

Potassium deficiency may cause cardiac arrhythmias culminating in syncope or sudden death. Considering that the likelihood of dangerous arrhythmias in inborn salt-losing tubulopathies is unknown, we performed an inquiry among European paediatric kidney disease specialists with extensive experience in this field.

Subjects and methods

The inquiry was performed between August and November of 2002 among 19 European paediatric kidney disease specialists who care for a total of 249 pediatric patients with inborn salt-losing tubulopathies [3].

Acute cardiac complications were reported in seven children; four patients died suddenly and three had severe syncope. Since we were unable to obtain more information on two patients with severe syncope, we report the remaining five patients (Table 1; patient 4 has been previously reported [4]). In the patient who survived the malignant arrhythmias (patient 5) the diagnosis of Gitelman syndrome was made some weeks after the episode in the context of persisting hypokalaemia of unknown origin [5].
Acute cardiac complications were reported in seven children; in patients 1 (a child with Bartter syndrome linked with deafness), 2 (a child with classic Bartter syndrome) and 5 (the previously mentioned child with Gitelman syndrome) the complications were acutely precipitated by diarrhoea or vomiting, which exacerbated the hypokalaemia (<2.0 mmol/l) [2]. Diarrhoea or vomiting was not noted in patients 3 (a child with a neonatal Bartter syndrome) and 4 (a child with an unclassifiable tubulopathy). Patient 3 (the previously mentioned child with neonatal Bartter syndrome), however, had persisting severe hypokalaemia (<2.5 mmol/l). None of the five patients was on treatment with drugs that have been associated with cardiac arrhythmias.

**Discussion**

The inquiry indicates that in inborn salt-losing tubulopathies, malignant cardiac arrhythmias can occur in the context of severe chronic hypokalaemia (<2.5 mmol/l). This survey also indicates that acute symptoms such as diarrhoea or vomiting that further exacerbate hypokalaemia (<2.0 mmol/l) may precipitate malignant cardiac arrhythmias, as very recently noted in a child with classic Bartter syndrome who developed severe cardiac arrhythmias and prolongation of the electrocardiographic QT interval in the context of severe hypokalaemia that remitted after correction of the electrolyte imbalance [6]. Finally, these tubular disorders may cause malignant arrhythmias before they have been appropriately diagnosed.

The potential of some drugs, including, among others, antiarrhythmic agents, antihistamines, macrolides, antifungals, psychotropics, β2-adrenergic agonists or cisapride, to cause sudden cardiac death or syncope is well recognized, but none of the patients included in these report were on treatment with these agents [7].

In patient 4 the cause of death is undecided considering that on treatment his potassium concentrations approached the normal range and that his death was not triggered by an acute intestinal disease [4]. The multisystemic clinical features of this patient may be related to a mitochondrial cytopathy, which may be complicated by acute cardiac dysfunction or

**Table 1. Cardiac complication in 5 children with inborn normotensive-hypokalemic tubulopathy**

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Renal tubular disorder</th>
<th>Cardiac complication</th>
<th>Trigger</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>Neonatal Bartter syndrome with sensineural deafness</td>
<td>Sudden death at the age of 28 months (hospitala)</td>
<td>Acute, severe diarrhoea (plasma potassium 1.9 mmol/l, creatinine 67 μmol/l)</td>
<td>No molecular biology studies</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>Classic Bartter syndrome with tendency towards persisting hypokalaemia (~2.5 mmol/l)</td>
<td>Sudden death at the age of 5 months (hospitalb)</td>
<td>Severe dehydration in the context of acute vomiting (plasma potassium 1.8 mmol/l, creatinine 44 μmol/l)</td>
<td>No molecular defects identifiedb</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>Severe neonatal Bartter syndrome with refractory hypokalaemia (values ranging between 1.9 and 2.6 mmol/l)</td>
<td>Sudden death during sleep at home at the age of 10 years</td>
<td>Unknown</td>
<td>No molecular biology studies</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>Mild renal tubular hypokalaemic alkalosis with concomitant proximal tubular dysfunction (hypophosphataemia, tubular proteinuria)</td>
<td>Sudden death during sleep at home at the age of 6 years</td>
<td>Unknown</td>
<td>Concurrent severe mental and somatic retardation, hexadactyly, preauricular fistula, triangular face and undescended testes. Potassium level on treatment 3.0–3.3 mmol/l. No molecular defects identified. Case previously reported [4]</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>Gitelman syndrome</td>
<td>Severe ventricular arrhythmias requiring reanimation at the age of 5 months (hospitalc)</td>
<td>Acute, severe diarrhoea (plasma potassium 1.7 mmol/l, creatinine 52 μmol/l)</td>
<td>Cardiac arrhythmias presenting signs of the disease. Heterozygous mutation of the gene encoding the thiazide-sensitive sodium-chloride cotransporter [5]</td>
</tr>
</tbody>
</table>

*Emergency room.

bGene encoding the loop diuretic sensitive sodium-potassium-chloride cotransporter, gene encoding the ATP-sensitive inwardly rectifying potassium channel in the ascending loop, gene encoding the chloride channel mediating the sodium chloride transport, and gene encoding the thiazide-sensitive sodium-chloride cotransporter.
arrhythmias [8]. As a matter of fact, patients with a Bartter-like phenotype have been reported in the context of inborn mitochondrial diseases [9].

Molecular biology studies show that defects in the genes encoding several transporters in the thick ascending limb of the loop of Henlé or in the distal convoluted tubule are responsible for salt-losing tubulopathies. Considering that in clinical practice molecular biology studies, which are very expensive and cumbersome, often fail to disclose significant defects, clinical criteria are mostly used, as in this study, to classify the variants of normotensive hypokalaemic tubulopathy [1–3]. It is tempting to assume that in the future further characterisation of particular genetic mutations might define subgroups at particularly high risk of sudden death.

In Gitelman syndrome, the most frequent salt-losing tubulopathy, hypokalaemia is associated with hypomagnesaemia [1], a further cause of cardiac arrhythmias. The present survey, however, failed to address the possible role of magnesium deficiency in the development of sudden death and syncope. A further possible cause of sudden death or syncope is short-term nonadherence to the recommended regimen of care.

The take-home message of this experience is two-fold. (i) Severe chronic hypokalaemia (≤2.5 mmol/l) is hazardous in inborn normotensive hypokalaemic tubulopathy. Consequently, in addition to potassium salts and nonselective cyclooxygenase inhibitors, potassium sparing diuretics and blockers of the renin-angiotensin II–aldosterone system deserve consideration in patients with refractory hypokalaemia or with gastrointestinal side-effects secondary to potassium supplementation or medication with nonselective anti-inflammatory drugs [2]. A prolonged QT interval on standard electrocardiogram is an estimate of extended ventricular repolarization, imparting an increased risk for development of cardiac arrhythmias culminating in syncope or sudden death that reflects both acquired (including potassium levels) and congenital factors [7]. As a prolonged QT interval has been associated with inborn salt-losing tubulopathies whatever potassium levels [10,11], we speculate that the QT interval has to be systematically measured in inborn salt-losing tubulopathies, and potassium (or magnesium) levels more closely (≥3.0 mmol/l) controlled in those patients with a prolonged interval. (ii) In patients with inborn salt-losing tubulopathies, diarrhoea or vomiting, even if mild, may cause very severe, hazardous hypokalaemia (≤2.0 mmol/l). In this setting early referral and prompt electrolyte and fluid repair is of paramount importance.

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Conflict of interest statement. None declared.

References