Abnormal Calcium, Calcinosis, and Creatinine in Down’s Syndrome

Abstract

The hypercalcaemia in association with trisomy 21 (Down’s syndrome) is often not recognised and therefore underdiagnosed. Patients present with the tetrad of hypercalcaemia, Down’s syndrome, renal impairment, and nephrocalcinosis. ¹-³

A 30-month-old child with Down’s syndrome had a long history of nonspecific symptoms, constipation and feeding difficulties. He was on excessive bottle feeds, taking 14 bottles daily, each with six ounces of milk. He presented with a cardiac arrest having been unwell with an acute illness. Blood tests showed hypercalcaemia, raised urea and creatinine which were not explained by any other aetiologies. Post-mortem analysis showed acute pyelonephritis and nephrocalcinosis.

In children with Down’s syndrome, early detection of hypercalcaemia and introduction of low calcium feeds may prevent morbidity and mortality. Awareness and monitoring of serum calcium levels along with routine thyroid function tests in children with Down syndrome, would be important to prevent such occurrences.

Keywords:

Down syndrome, Hypercalcemia

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Case report

A baby boy was born by normal vaginal delivery with a birth weight of 3.17 kg (50th centile). Down’s syndrome was confirmed by karyotyping postnatally. He was found to have a small atrial septal defect. He lived with his parents and 5 siblings. He had moderate global developmental delay.

Baby A was first reviewed in the clinic at 4.5 months of age. He weighed 6.4 kg (75th centile) and reported to be bottle feeding well. He was seen again at 11 months of age with a weight of 9.29 kg (75th centile). He was bottle feeding at 150 ml/kg/day with a ‘follow on’ formula milk. He was reported to be a ‘fussy eater’ when tried to wean to solids. He was opening his bowels once every 2-3 days with pain for which a stool softener (Movicol®) was commenced. He was referred to the community dietician. Investigations showed mild iron deficiency anaemia which was not considered to be of clinical significance.

At a cardiology clinic review, at 18 months of age, Baby A weighed 10.03 kg (50th centile) and his cardiac examination was normal. When reviewed by a dietitian, at 23 months of age, his carers highlighted constipation and that child A fed better when Movicol® was given. His weight had fallen to 10 kg (25th centile).

At 26 months of age, child A weighed 9.6 kg, (9th centile). He was on excessive formula milk: 14 bottles/day, taking 6 oz/bottle. His carers had noticed that extra cream and butter ingestion caused abdominal pain and unsettled nights. He was advised to use milk free fats, reduce formula feeds by 2 bottles/ week and to try solids.

On review at 28 months of age, his weight was 10.3 kg (9-25th centile). He was eating solid food, although continued on formula milk feeds (four 6oz bottles per 24 hours). Parents had tried to introduce full fat cow’s milk, but this worsened his constipation. Goals were set to have two 6oz formula feeds per day, increase solids, and use milk free fats. An open appointment was given for next 6 months.

At 30 months of age, his weight was 9.9 kgs having fallen to the 9th centile. His carers reported a history of snoring but without significant apnoea. Failure to thrive (9.9 kg, 9th centile) was now evident, therefore further investigations were planned.

Table 1: Summary of feeding history in Community Paediatric and Dietetic clinics:

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Daily Formula milk intake by patient (Cow and Gate 2) (Ca=68mg/100ml)</th>
<th>Milk requirement for age</th>
<th>Calcium requirement/day</th>
<th>Calcium intake/day by our child</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5</td>
<td>Bottle feeding well</td>
<td>Breastfeeding or 130-190ml/kg/day formula</td>
<td>525 mg</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Bottle feeding 150 ml/kg/day</td>
<td>Breastfeeding or 400-600ml/day formula</td>
<td>525 mg</td>
<td>Ca 952 mg</td>
</tr>
<tr>
<td>26</td>
<td>14 bottles/day (6 oz/bottle) 249 ml/kg/day or 2394 mls/day</td>
<td>300-350 ml Cow’s milk (240 mg Ca/200 ml) *</td>
<td>350 mg</td>
<td>Ca 1627 mg</td>
</tr>
<tr>
<td>28</td>
<td>4 bottles/day (6 oz/bottles) / 24 hours (70 ml/kg/day or 682 mls/day)</td>
<td>300-350mls Cow’s milk (240 mg Ca/200 ml) *</td>
<td>350 mg</td>
<td>Ca 428 mg</td>
</tr>
</tbody>
</table>

*After 12 months, there is no guidance/recommendation regarding the amount of milk intake, which should be merely supplementing diets and can differ a lot between children. There is also calcium intake to consider and whether they are having other calcium-containing foods in their diet.

Sources: [https://www.bda.uk.com/foodfacts/Calcium.pdf](https://www.bda.uk.com/foodfacts/Calcium.pdf)

[https://www.firststepsnutrition.org/infant-milks-in-uk](https://www.firststepsnutrition.org/infant-milks-in-uk)
Table 2: Growth chronology compiled from paediatric, cardiology and dietetic reviews (Down syndrome growth chart for boys 6 months-4 years)

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Weight (kg)</th>
<th>Height(cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>3.17 (50th centile)</td>
<td></td>
</tr>
<tr>
<td>4.5 months</td>
<td>6.4 (75th centile)</td>
<td>64.3 (91st centile)</td>
</tr>
<tr>
<td>11 months</td>
<td>9.29 (75th centile)</td>
<td>79.8 (99.6th centile)</td>
</tr>
<tr>
<td>18 months</td>
<td>10.03 (50th centile)</td>
<td>77.6 (50th centile)</td>
</tr>
<tr>
<td>23 months</td>
<td>10 (25th centile)</td>
<td>79.9 (50th centile)</td>
</tr>
<tr>
<td>26 months</td>
<td>9.6 (9th centile)</td>
<td></td>
</tr>
<tr>
<td>28 months</td>
<td>10.3 (9th-25th centile)</td>
<td>80 (25th centile)</td>
</tr>
<tr>
<td>30 months</td>
<td>9.9 (9th centile)</td>
<td>80 (9th-25th centile)</td>
</tr>
</tbody>
</table>

**Terminal events**

Four days later, child A presented to his General Practitioner acutely unwell. He was started on an antibiotic (amoxicillin) for a suspected respiratory infection. On the final morning, Child A woke early, played for an hour, had a feed, then was reported to be crying. A few minutes later his mother, having left him only for a few minutes, noticed that he was floppy, with traces of having just vomited. An ambulance was called for, on arrival the paramedics found the child in pulseless electrical activity. Twenty-five minutes of cardiopulmonary resuscitation was continued while the child was transferred via the local hospital, to the nearest paediatric intensive care unit.

He remained sedated, intubated, and ventilated. He was given antibiotics and was cooled for neuroprotection. On the blood gases, there was evidence of early metabolic acidosis - pH (6.677), severe hyponatraemia (108.8 mmol/L) and hyperkalaemia (10.2 mmol/L) which resolved as the acidosis improved. There was evidence of renal impairment (Urea 23.7 mmol/L, Creatinine 105 umol/L) with both high calcium (3.83 mmol/L) and phosphate (2.53 mmol/L).

Within three hours of admission, he became more unstable with hypotension resistant to fluids, steroids, and vasopressin. He suffered a further bradycardic cardiac arrest, progressed to asystole.

A multi-agency response visit was carried out by a Consultant Community Paediatrician and police team. The home visit did not raise safeguarding concerns relating to the deceased, or his sibling’s welfare. A Coroner’s post-mortem found acute pyelonephritis and nephrocalcinosis.

**Discussion:**

Abnormal calcium, calcinosis, and creatinine in Down syndrome (ABCD syndrome) is under-recognised and consequently under-diagnosed.

The constellation of hypercalcaemia, renal impairment and nephrocalcinosis is seen in hyperparathyroidism, sarcoidosis, excessive intake of vitamin D or A, milk alkali syndrome, Williams syndrome, certain malignancies, and renal tubular acidosis.

Although our patient received small doses of multi-vitamin supplement, and excessive milk, the haematological findings were not in keeping with milk alkali syndrome or vitamin D toxicity as the haemoglobin was normal (Hb 123 g/L) and there was no evidence of iron deficiency (MCV 77.8 fl) at the time of terminal events. Similarly, there was no evidence of any of the above-mentioned aetiologies.
Baby A was consuming significant amounts of calcium. At 11 months, he was consuming 952 mg (recommended 525 mg) and at 26 months 1627 mg (recommended 350 mg). We hypothesise that hypercalcaemia over months gradually became deposited in kidneys causing nephrocalcinosis, which in turn resulted in a degree of renal insufficiency. In our case it is postulated that the calcified renal parenchyma made the patient at risk of acute pyelonephritis which resulted in severe acute illness and eventually death.

Another hypothesis for hypercalcaemia in Down's syndrome is related to an increase in intestinal absorption of calcium. This may well explain hypercalcaemia in children with Down's syndrome who are taking normal amounts of milk, as described in few other case reports.

While chromosome 21 carries no gene that is definitively involved in the calcium regulation, the recent discovery of the "transient receptor potential" or TRP channels V and M provides a possible mechanism. These channels are proposed to be heavily involved in calcium metabolism in the small intestine, duodenum, and kidneys.

Child A was reviewed by a different community paediatrician and dietician at each clinic visit. Failure to thrive became evident when serial weights were reviewed from three different medical records for the Child death Review. It was not picked up in individual clinics until his last visit, a week prior to his hospital admission.

There is no guidance to check serum calcium level as part of Down's syndrome surveillance investigations. Because of the insidious nature of the tetrad, which presents with non-specific symptoms, we suggest that checking serum calcium levels at the same time as the routine thyroid function surveillance in pre-school children can help identify ABCD syndrome early. Hypercalcaemia associated with Down's syndrome responds to restriction of calcium intake and high creatinine often improves with restoration to normocalcaemia.

Summary

1. This report describes a case of hypercalcaemia and nephrocalcinosis in a toddler with trisomy 21, resulting in acute pyelonephritis and renal failure leading to cardiac arrest.

2. Having a single digital medical record when multiple professionals are involved may improve morbidity and mortality.

3. There is an opportunity to check serum calcium level at the same time as the thyroid function test surveillance for pre-school children with Down syndrome.

References


