

## CASE REPORT

## Hypercalcaemia in association with trisomy 21 (Down's syndrome)

I J Ramage, A Durkan, K Walker, T J Beattie

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The combination of hypercalcaemia, hypercalciuria, and nephrocalcinosis with and without renal impairment is rare in paediatric clinical practice. However, this constellation of findings has been reported in three children with trisomy 21, but the absence of detailed nutritional data has failed to clarify the underlying pathogenesis. This report describes a 4 year old girl with trisomy 21 who was found coincidentally to have hypercalcaemia, hypercalciuria, nephrocalcinosis, and renal impairment in the absence of metabolic alkalosis, following a prolonged period of excessive calcium intake.

A 4 year old girl with trisomy 21 and symptomatic gastro-oesophageal reflux was coincidentally found to have hypercalcaemia (3.35 mmol/litre) associated with an increased plasma urea (19.3 mmol/litre) and creatinine (144  $\mu$ mol/litre) and normal plasma bicarbonate (22 mmol/litre) and phosphate (1.6 mmol/litre).

She was born at 33 weeks gestation, with evidence of in-partum asphyxia requiring transient ventilatory and inotropic support. Follow up at age 4 months, while she was receiving standard infant milk formula, revealed a normal plasma creatinine (25  $\mu$ mol/litre), calcium (2.32 mmol/litre), and renal ultrasound. A 99Technetium dimercaptosuccinic acid scan at 6 months was also normal.

Medical management comprising cimetidine, cisapride, and Nestergel to thicken feeds was unsuccessful in controlling her vomiting and because of the persistent confirmed acid reflux, she was referred for fundoplication and gastrostomy insertion.

After the observation of hypercalcaemia, further investigations revealed normal concentrations of alkaline phosphatase (91 U/litre; normal range, 90-850), calcitonin (10 ng/litre; normal value, < 15), and angiotensin converting enzyme (39 U/litre; normal range, 0-88), in addition to normal thyroid function. Her parathyroid hormone (PTH) was suppressed at

1.1 pmol/litre (normal value, < 8) and the PTH related peptide was 0.8 pmol/litre (normal value, < 2.6). Plasma 25 hydroxycholecalciferol was raised at 133 nmol/litre (normal range, 25-125) and 1,25 dihydroxycholecalciferol was reduced at 26 pmol/litre (normal range, 75-120). Chromosome analysis failed to show a deletion at 7q11.23 in 10 analyses, excluding William's syndrome. The spot urine calcium to creatinine ratio was 2.03 mmol/mmol (normal value, < 1.1) and the urate to creatinine ratio was 0.35 mmol/mmol (normal value, < 1.5).

Pronounced medullary nephrocalcinosis was seen on both abdominal ultrasound and x ray. Wrist and hand x ray demonstrated a delayed bone age but no features of hyperparathyroidism.

A detailed nutritional assessment (table 1) demonstrated a calcium intake before diagnosis of 22.7 mmol/day (recommended daily intake of calcium, 8.8 mmol/day), increasing to 24.7 mmol/day with gastrostomy feeding. However, it should be noted that most infants and children on "normal" diets consume significantly more than the recommended daily intake of calcium, and the regimen this child received was considered appropriate for a child with her history of failure to thrive.

Following the fundoplication there was resolution of the vomiting and all anti-reflux treatment was ceased. The hypercalcaemia and hypercalciuria resolved within three months of the introduction of a low calcium and sodium diet, with progressive improvement in renal function (table 1). At this point, an oral calcium loading test (1 g/M<sup>2</sup>) demonstrated an increase in the urinary calcium to creatinine ratio from 0.44 mmol/mmol at baseline to 1.07 mmol/mmol at four hours, with no change in plasma calcium.

The dietary calcium restriction was progressively relaxed and normalised by age 7.6 years. The plasma and urine calcium values have remained normal, with the most recent plasma creatinine being 72  $\mu$ mol/litre (estimated glomerular filtration rate, 47 ml/min/1.73 m<sup>2</sup>). At the age of 8.8 years her PTH was 14.9, with normal concentrations of both 25 hydroxycholecalciferol and 1,25 dihydroxycholecalciferol.

Table 1 Nutritional and biochemical data

Age (years)	Feed	Feed volume ml/kg	Calcium intake (mmol)	Sodium intake (mmol)	Plasma calcium (mmol/l)	Plasma creatinine ( $\mu$ mol/l)	Urinary Ca/Creat (mmol/mmol)
1.33	Cows' milk	110	22.7 (8.8)	15.7 (13-27)	N/A	N/A	N/A
1.85	Nutrison Progress	186	24.7 (8.8)	21.7 (14-28)	N/A	N/A	N/A
4.4	Nutrison Progress	155	20.6 (8.8)	18.1 (14-28)	3.35	144	2.03
4.51	Locasol Nutrison	109	8.6 (11.3)	18.7 (17-34)	3.0	108	1.08
4.7	Locasol	96	2.1 (11.3)	13.9 (21-42)	2.49	94	0.44
5.5	Locasol Nutrison	85	5.5 (11.3)	18.2 (21-42)	2.63	88	0.22
6.0	Locasol	96	10.1 (11.3)	13.9 (21-42)	2.59	92	0.05
7.8	Mixed diet		14.6 (13.8)	22.3 (21-42)	2.54	72	<0.03

Figures in parenthesis for calcium and sodium intake indicate recommended daily nutritional intakes (RDI). Ca/Creat, calcium/creatinine ratio; N/A, not available.

**Take home messages**

- This report describes a case of hypercalcaemia, hypercalciuria, and nephrocalcinosis with renal impairment in a girl with trisomy 21, which resulted from a prolonged period of excessive calcium intake
- The findings support the possible presence of a genetic predisposition to enhanced calcium absorption via the passive route in trisomy 21, despite the presence of hypercalcaemia

**DISCUSSION**

The findings of hypercalcaemia, hypercalciuria, and nephrocalcinosis are rare in childhood and generally occur in the context of William's syndrome, thyrotoxicosis, hyperparathyroidism, sarcoidosis, certain malignancies, vitamin A and D excess, diuretic abuse, or prolonged immobilisation.

There are a small number of reports of hypercalcaemia in Down's syndrome,<sup>1,2</sup> with the findings in these cases attributed to excessive calcium intake. However, evidence for this hypothesis to date is absent and alternative contributory factors such as antacid administration have been proposed.<sup>3</sup>

Our patient was known to consume large volumes of milk but had no antacid treatment prescribed. The diagnosis of classic milk-alkali syndrome is unlikely in our patient<sup>4</sup>; first, because of the absence of metabolic alkalosis, although this may be attenuated by impaired renal function and, second, because of the absence of other associated biochemical abnormalities, including hypokalaemia, hyperphosphataemia, and raised alkaline phosphatase. Finally hypercalciuria is absent in most cases of milk-alkali syndrome because alkalosis compromises urinary calcium excretion.

"The diagnosis of classic milk-alkali syndrome is unlikely in our patient"

Intestinal calcium absorption occurs through both a passive and an active vitamin D dependent mechanism. Increased calcium ingestion results in a compensatory decrease in vitamin D mediated absorption and an increase in faecal calcium excretion. In our patient, there was evidence of suppression of 1,25 vitamin D3 and increased urinary calcium excretion following an oral calcium load. In healthy children, calcium restriction before a calcium loading test resulted in a slightly higher urinary calcium to creatinine ratio compared with those not restricted beforehand, but not to the extent seen in our patient.<sup>5</sup> These findings, along with the biochemical and clinical improvement following dietary calcium restriction, suggest a possible genetic predisposition to enhanced calcium absorption via the passive route in trisomy 21, despite the presence of hypercalcaemia, and suggest that this is an example of "milk drinker's" hypercalcaemia.

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**ECHO****Innocent antigens**

Please visit the Journal of Clinical Pathology website [[www.jclinpath.com](http://www.jclinpath.com)] for link to this full article.

The antigenic trigger for two major inflammatory diseases—rheumatoid arthritis (RA) and ankylosing spondylitis (AS)—has again eluded identification after two more potential culprits failed to elicit an increased immune response in patients.

A small study has shown that human heat shock protein 60 (h-HSP60) and yersinia 19 kDa urease  $\beta$  subunit do not provoke a significantly enhanced immune response in T cells from peripheral blood or synovial fluid from patients with RA and AS when compared with T cells from controls in stimulation tests in vitro.

The tests were conducted on 22 patients with active RA and 45 patients with active AS recruited from an outpatient clinic and 20 healthy controls. CD4+ T cells from peripheral blood and synovial fluid—from a subset—were tested for stimulation by each protein antigen for six hours—the last four with brefeldin A to ensure accumulation of intracellular cytokines—then fixed and stained for CD4+, CD69 cell surface marker, interferon  $\gamma$  (IFN $\gamma$ ) or tumour necrosis factor  $\alpha$  (TNF $\alpha$ ). After gating on CD4+ cells, those cells stained double positive for CD69—indicating early activation by antigen—and INF $\gamma$  or TNF $\alpha$  were scored.

Both potential protein antigens have been linked to inflammatory rheumatic diseases. h-HSP60 has long been suspected, and the 19 kDa urease  $\beta$  subunit of yersinia is the major antigen for T cells and specific antibody stimulant in yersinia reactive arthritis. A notable proportion of HLA-B27 positive patients with this condition develop AK long term.

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