McBride Lucy (Orcid ID: 0000-0002-5947-9373)

Introduction:

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Case report:

A 27-year-old Caucasian female and her newborn infant both presented with symptomatic hypercalcaemia post-partum.

Significant maternal medical history included nephrolithiasis and a family history of renal disease. Her father developed end stage renal failure of unclear aetiology, requiring renal transplantation, and her brother had recurrent nephrolithiasis.

She and her non-consanguineous partner were both Australian-born, of Maltese and Greek ethnicity respectively. The paternal family history was non-contributory.

This was our patient's first pregnancy. Antenatal ultrasonography demonstrated fetal renal tract abnormalities. Pregnancy was complicated by polyhydramnios and term pre-eclampsia. A male infant was born weighing 2.86kg via Caesarean section due to breech presentation.

Maternal acute kidney injury was identified day three post-partum, attributed to hypercalcaemia.

Constipation during pregnancy was described, however no other symptoms of hypercalcaemia were reported. She consumed approximately 1 litre of milk and a prenatal multivitamin containing cholecalciferol 250IU daily throughout pregnancy. Antenatal 25-hydroxyvitamin D concentration was 64nmol/L (deficiency < 30, insufficiency 30-50, sufficiency >50, toxicity>250 with additional biochemical features (2)).

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jpc.14219

Postnatally, she was clinically well, with mildly elevated blood pressure and peripheral oedema. Examination was otherwise unremarkable.

Further investigation revealed parathyroid hormone (PTH) suppression, sufficient 25-hydroxyvitamin D, normal twenty-four-hour urine calcium/creatinine ratio and an elevated urinary albumin/creatinine ratio (10 mg/mmol, normal <3.5). 1,25-dihydroxyvitamin D level was 250 pmol/L (normal 78-190), parathyroid hormone related peptide (PTHrP) was undetectable 15 days post-partum while lactating (<0.6pmol/L, normal <2.0). See Table 1. Renal tract ultrasound was consistent with medullary nephrocalcinosis. Maternal causes of hypervitaminosis D and hypercalcaemia were systematically excluded on extensive testing.

The Infant

Meanwhile, her newborn had become unwell. He was breast-fed and received a single dose of oral ergocalciferol 50,000iu day one postnatally (given contra to hospital guidelines due to inaccurate documentation of maternal vitamin D status). Increasing lethargy and poor feeding prompted serum biochemistry testing on day 5 of life demonstrating hypercalcaemia with PTH suppression. Urine biochemistry demonstrated an elevated calcium/creatinine ratio at $2.17\ \mathrm{mmol/mmol}\ (\mathrm{normal} < 0.7)$, 25-hydroxyvitamin D (>250nmol/L, sufficiency >50, toxicity > 250 with additional biochemical features(2)), and 1,25-dihydroxyvitamin D (200pmol/L, normal 78-190) were elevated.

Micturating cystourethrogram was normal. Renal tract ultrasonography and mercaptoacetyltriglycine studies demonstrated bilateral hydroureters and hydronephrosis, without evidence of obstruction, and normal renal function.

Following 5 weeks of breastfeeding, exclusive use of a low calcium, vitamin D free formula (Locosol ©) was commenced with gradual improvement in serum calcium.

Repeat ultrasound scanning of the infant at 4 months demonstrated nephrocalcinosis. Serum uric acid and urinary oxalate/creatinine ratio were normal. Hypercalcaemia with PTH suppression, elevation of 1,25-dihydroxyvitamin D, and hypercalciuria persisted. When trialled off low calcium formula, hypercalcaemia and hypercalciuria increased. Low calcium

formula was recommenced, and potassium citrate introduced. By 10 months of age, serum calcium and urinary calcium/creatinine ratio normalized, although the 1,25-dihydroxyvitamin D remained elevated (440pmol/L). The infant was developmentally normal with a normal chromosomal analysis.

It was hypothesized that this infant and his mother were likely to have inactivating 24-hydroxylase mutations. *CYP24A1* sequencing identified two variants in the affected infant: NM_000782.4: c. 427_429del, p.Glu143del and c.1186C>T, p.Arg396Trp. Both have previously been reported in the literature (2) and were classified as pathogenic. Subsequent maternal testing demonstrated the c. 1186C>T, p.Arg396Trp mutation in a homozygous state, consistent with affected status, and paternal testing revealed the c. 427_429del, p.Glu143del mutation, consistent with carrier status. (Figure 1). Unfortunately, paternal biochemistry was not available.

Genetic counseling highlighted future offspring would have 1 in 2 chance of being affected and 1 in 2 chance of being heterozygous carriers of the c.1186C>T, p.Arg396Trp mutation. Consequently, bolus vitamin D dosing was contraindicated in future offspring.

Discussion

Idiopathic infantile hypercalcaemia (IIH) is a rare condition, characteristically occurring within the first year of life. Affected infants present with failure to thrive, hypotonia, vomiting, dehydration, hypercalcaemia and nephrocalcinosis. A spike in incidence occurred in the United Kingdom in the 1950s(3) following the fortification of milk products with vitamin D. In affected children, hypercalcaemia was noted to improve with conservative measures, and the condition was considered transient. However, data from 11 children with IIH between 1993 and 2004 demonstrated that although serum calcium at 3 years-of-age was usually normal, persisting hypercalciuria and nephrocalcinosis was common(4).

Schlingmann *et al*(5) studied a cohort of familial cases of typical IIH with suspected autosomal recessive inheritance. The sequence analysis of *CYP24A1*, encoding 25-hydroxyvitamin D 24-hydroxylase (responsible for 1,25-dihydroxyvitamin D3 degradation, see Figure 2), revealed recessive mutations in all. A second cohort of children,

hypercalcaemic following bolus vitamin D supplementation, revealed similar results. Functional characterization demonstrated loss of function in these *CYP24A1* mutations.

Since this report of *CYP24A1* mutations was published, multiple cases of the condition outside the recognized phenotype have been published, including during pregnancy. Pregnancy is associated with altered calcium metabolism, and hypercalcaemia is exacerbated in pregnant women with *CYP24A1* mutations, due to up-regulation of renal and placental 1-α-hydroxylase, which occurs during normal pregnancy(6). Hypercalcaemia in these women is further exacerbated by supplementation of vitamin D and calcium. Routine testing of 25-hydroxyvitamin D (which may be low-normal in this condition), may prompt increased vitamin D supplementation. Significant pregnancy complications have been described(7).

This is the first case report describing both maternal and neonatal hypercalcaemia secondary to *CYP24A1* mutations, raising the possibility of genotype/phenotype variations in 24-hydroxylase activity as a result of *CYP24A1* mutations, which may be exacerbated by pregnancy. Furthermore, both heterozygous males and females may be mildly affected by more severe *CYP24A1* mutations, as suggested by the maternal family history in our case. The infant in our case is a compound heterozygote, and future genetic counseling should include precautionary avoidance of large, single vitamin D dosing in all offspring.

International guidelines published by *Munns et al.* in 2016 recommend daily vitamin D dosing of 400iu for all infants from birth to 12 months of age, independent of their mode of feeding(2). Recent data published in this journal(1) compares bolus dosing with daily dosing of vitamin D in infants of vitamin D insufficient mothers with the intention to exclusively breastfeed. Although this approach was demonstrated to be safe in the 70 infants studied, infants with *CYP24A1* mutations are at risk of clinical disease in the setting of single high dose vitamin D supplementation, much like the conditions that lead to the initial description of the disorder and in this case report. Therefore, caution should be used when considering bolus vitamin D dosing, and the apparent safety of this approach in vitamin D deficient mothers who exclusively breastfeed should not be extrapolated to the general infant population.

Although *CYP24A1* mutations are considered uncommon, available data estimate a frequency of *CYP24A1* mutations leading to 24-hydroxylase deficiency as 420 per 100 000 (1 in 238) of the general population(8). Consequently, it is likely that this disorder is under-recognized.

In conclusion, our case illustrates that caution must be used when administering single high dose vitamin D, and we strongly recommend that single, large dose vitamin D dosing should only be considered for term infants of vitamin D deficient mothers with 25-hydroxyvitamin D less than 50mmol/l and who intend to exclusively breastfeed. Furthermore, if any family history of nephrolithiasis/calcinosis or related concerns is known, we recommend that daily vitamin D dosing is the safer option.

Learning points

- Single bolus dosing of Vitamin D needs to be given cautiously, and we recommend that this approach should be contraindicated in the setting of a family history of disordered calcium metabolism or nephrolithiasis/calcinosis.
- Autosomal recessive inheritance of *CYP24A1* gene mutations needs to be considered when the investigation of hypercalcaemia reveals a vitamin D-dependent mechanism
- Acute and long-term complications occur in children and adults, including symptomatic hypercalcaemia, nephrocalcinosis, nephrolithiasis and kidney disease
- Vitamin D and calcium supplementation poses a risk to affected individuals, particularly pregnant women and affected infants.

Multiple choice questions

1. Vitamin D deficiency rickets:
    a. Is more likely to occur in breast fed infants
    b. Is commonly associated with inactivating *CYP24A1* mutations
    c. Is unlikely to cause hypocalcaemia in infants
    d. Is better treated with parenteral rather than oral vitamin D
    e. Is less common in infants than older children

    Correct answer (a)
    Vitamin D deficiency is more likely to occur in breast fed infants than in formula fed infants or older children as breastmilk is lower in vitamin D, especially if maternal vitamin D is low.
    Inactivating CYP24A1 pathological variants cause a deficiency of 24-hydroxylase, which reduces breakdown of 1,25-hydroxyvitamin D to less active metabolites. Therefore, it is unlikely to be associated with vitamin D deficiency rickets.
    Vitamin D increases intestinal absorption and renal reabsorption of calcium. Hypocalcaemia and consequences (seizures, tetany) can be caused by vitamin D deficiency.

Oral vitamin D is the treatment of choice, rather than intramuscular, as it more rapidly restores 25-OHD levels.

2. Which of the following is a disorder of vitamin D excess in infants:
    a. Embryonal renal tumours
    b. Subcutaneous fat necrosis
    c. Hypophosphatasia
    d. Jansen's Hereditary Metaphyseal Dysplasia
    e. Familial hypocalciuric hypercalcaemia (FHH)

    Correct answer (b)
    Subcutaneous fat necrosis of the newborn is an uncommon disorder usually affecting full term infants in the first weeks of life. It is a form of panniculitis of unclear pathophysiology. Granulomatous inflammatory cells express high levels of 1-alpha-hydroxylase, which is the mechanism of hypervitaminosis D and hypercalcaemia.
    Hypophosphatasia is a rare genetic disorder characterized by mutations in tissue non-specific alkaline phosphatase gene, leading to reduced activity of TNSALP enzyme and accumulation of substrates that inhibit mineralization of bone.
    Jansen's Hereditary Metaphyseal Dysplasia is a severe dysplasia caused by mutations in the parathyroid hormone receptor 1 gene, which leads to independent activation of the PTH receptor in chondrocytes.
    Familial hypocalciuric hypercalcaemia is a genetic condition caused by inactivating mutations of the calcium sensing receptor gene, resulting in altered calcium-sensing and inappropriate PTH release.

3. Which of the following is contraindicated in severe vitamin D dependent hypercalcaemia in infancy
    a. Calcium free formula
    b. Vitamin D free formula
    c. Sun avoidance
    d. Breast feeding

e. Glucocorticoids

Correct answer (d)

Vitamin D dependent hypercalcaemia (such as CYP24A1 mutations) necessitates close monitoring of calcium and vitamin D intake, and modified formulas are required.

Sunlight exposure also needs to be controlled, to avoid excessive synthesis in the skin from 7-dehydrocholesterol (pre-cursor to active vitamin D) in the presence of ultraviolet light.

Breastmilk is contra-indicated if hypercalcaemia is severe, as amounts of vitamin D and calcium need to be restricted.

Glucocorticoids are used successfully to treat some forms of vitamin D dependent hypercalcaemia, mechanisms of action include reduction of calcium absorption from the gut and reduction of calcitriol production in activated mononuclear cells (ie in granulomatous disease).

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Learning points

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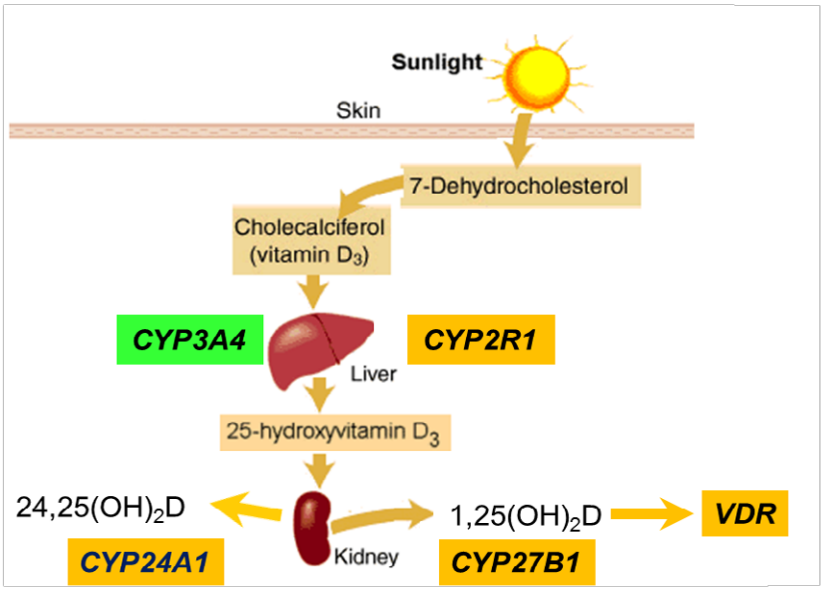

Title:

Instructive case: A rare cause of maternal and neonatal hypercalcaemia

Authors:

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Dr Betty Messazos, Paediatric Endocrinologist, Royal Children's Hospital, Melbourne

Figure 1 reproduced with permission of Professor Michael Levine

No financial disclosures

Table 1. Maternal and infant biochemistry

	Maternal			Infant			
Parameter units	**Normal range**	**Post-natal**	**2 months PP**	**Normal range**	**5-6 days**	**3 months**	**24 months**
Ionized Ca mmol/L	1.13 - 1.32	1.77	1.32	1.13 - 1.32	1.5		
Calcium (corr) mmol/L	2.15 - 2.55	3.63	2.53	1.8 - 2.65	3.06	3.03	2.64
PTH pmol/L	1.6 - 6.9	0.6	2.4 / 1.5	1.6 - 6.9	0.6	1	1
Urinary Ca/Cr mmol/mmol	<0.7	0.22		<0.7	2.17	4.38	0.75
25-OH Vit D nmol/L	50 - 250	77	96	50-250	>250		
1,25-OH Vit D pmol/L	78 - 190	250	79	78 - 190	200	350	210
Sodium mmol/L	135 - 145	136	135	135 - 145	137		
Potassium mmol/L	3.5 - 5.0	4.5	3.7	4.0 – 6.4	6.4		
Chloride mmol/L	100 - 110	103	103	100 - 110	104		
Bicarbonate mmol/L	23 - 31	27	27	18-27	24		
Creatinine umol/L	30 - 97	133	91	10-60	21		
Urea mmol/L	2.6 - 6.7	8.7	6.2	2.9 - 10	1.0		
Magnesium mmol/L	0.70 - 1.00	0.60	0.74	0.76 - 0.90	0.69		
Phosphate	0.87 - 1.45	0.95	1.17	1.30 - 2.36	1.97		

mmol/L					
Albumin	35-52	23	40	28 - 44	31
g/L					