CASE REPORT

Subcutaneous fat necrosis causing neonatal hypercalcaemia

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SUMMARY

Hypercalcaemia in neonates is rare and often asymptomatic, but can have significant morbidity. If severe, it can cause symptoms including irritability, vomiting and seizures. We present the case of a baby girl, born at term after a traumatic delivery, who developed severe hypercalcaemia with nephrocalcinosis. She had several large areas of subcutaneous fat necrosis following delivery, with prolonged low-level elevation of C reactive protein. Subcutaneous fat necrosis of the newborn is a rare and underdiagnosed condition, often accompanied by high plasma calcium. Although self-limiting, it is important to recognise and treat this condition to minimise kidney damage, and to avoid unnecessary investigations or treatment with long courses of antibiotics. The infant recovered well, although a degree of nephrocalcinosis remains.

BACKGROUND

Neonatal hypercalcaemia, defined as total calcium >2.70 mmol/L or ionised calcium >1.35 mmol/L, is rare but carries risk of nephrocalcinosis.¹ It is often detected incidentally on routine blood testing. Typically, hypercalcaemic neonates are asymptomatic, but very high calcium levels (>3.2 mmol/L) can cause irritability, poor feeding, vomiting, polyuria, hypertension and seizures. We report the case of a term baby who was born in poor condition after an emergency caesarean section. While on the neonatal unit, large areas of hardened subcutaneous tissue were noted and hospital stay was extended due to prolonged low-level elevation of C reactive protein (CRP). After discharge, at 1 month of age, routine blood testing showed grossly elevated total adjusted calcium of 4.34 mmol/L. Urine calcium excretion was also raised, with ultrasound evidence of nephrocalcinosis.

CASE PRESENTATION

A 4 kg baby girl was born at term to non-consanguineous parents by emergency caesarean section for fetal tachycardia and meconium stained liquor. The baby required ventilation breaths, developed grunting and respiratory distress from 4 to 5 min after birth and required transfer to the neonatal unit. Capillary pH was 7.1 and laboratory plasma glucose was extremely low at 0.6 mmol/L, corrected by intravenous administration of dextrose. She was presumptively treated as septic in a setting of perinatal stress and given intravenous gentamicin and benzylpenicillin. CRP was 54 mg/L on day 2. On day 3, the mother's vaginal swab was positive for group B *Streptococcus*, hence the baby

was continued on intravenous antibiotics, although blood cultures and swabs remained negative.

Over the next few days, the baby was intermittently tachypnoeic and irritable on handling. On day 6, a red lumpy appearance of the left axilla was documented in the patient notes. Similar lumps were noted on the back. The baby was not discharged as CRP levels remained elevated (26 mg/L on day 13) and, due to continuing anxiety about the possibility of an occult source of infection, a lumbar puncture was carried out. Results of this were normal and the baby was clinically well with no signs of infection other than the raised CRP. After a prolonged 2-week stay in hospital, she was discharged on oral amoxicillin, with follow-up CRP measurement every 2–3 days.

INVESTIGATIONS

Ten days after discharge, routine blood testing showed an adjusted total calcium result of 4.03 mmol/L (4.34 mmol/L when repeated the next day; [table 1](#)), with a suppressed parathyroid hormone (PTH) and a replete level of 25-hydroxy vitamin D. 1,25-dihydroxyvitamin D was later measured and was within the normal range. At this stage, large areas of hardened subcutaneous tissue could be palpated over the left arm and scapula, right arm and both buttocks.

On readmission, renal ultrasound showed evidence of nephrocalcinosis, urine calcium:creatinine ratio was elevated² and urea was raised relative to creatinine ([table 1](#)), suggesting a degree of dehydration.

DIFFERENTIAL DIAGNOSIS

Severe hypercalcaemia is rare in newborns. Causes include iatrogenic vitamin D intoxication or excessive calcium supplementation, granulomatous disease, subcutaneous fat necrosis (SCFN) of the newborn and hyperparathyroidism.

Neonatal hyperparathyroidism can occur in maternal hypocalcaemia, congenital parathyroid hyperplasia or with inactivating mutations in the calcium-sensing receptor. The latter, if heterozygous, may cause milder familial hypocalcaemic hypercalcaemia detected in later life, but in homozygous neonates, the severity of the hypercalcaemia means presentation is soon after birth. Williams' syndrome, a multisystem disease caused by deletion of several genes including elastin on chromosome 7, also causes neonatal hypercalcaemia.

Biochemical investigation of neonatal hypercalcaemia should include phosphate, alkaline phosphatase, 25-hydroxy vitamin D and PTH measurement. If the diagnosis remains unclear,

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Table 1 Table of biochemistry results on readmission of the patient

Analyte	Result	Reference range (age related where appropriate)
Calcium	4.06	2.25–2.75 mmol/L
Albumin	31	30–45 g/L
Adjusted calcium	4.34	2.25–2.75 mmol/L
Phosphate	1.64	1.30–2.60 mmol/L
Alkaline phosphatase	104	70–380 U/L
Parathyroid hormone	<0.5	1.6–6.9 pmol/L
25-Hydroxyvitamin D	102	50–250 nmol/L
1,25-Dihydroxy vitamin D	64	40–150 pmol/L
Creatinine	71	31–81 μ mol/L
Urea	9.1	0.8–5.5 mmol/L
Urine calcium:creatinine ratio	7.8	0.09–2.20 ² mmol/mmol

blood samples for 1,25-dihydroxyvitamin D and for DNA analysis (calcium-sensing receptor and elastin genes) should be stored for later testing if necessary. Urine calcium, phosphate and creatinine levels can help determine whether the kidneys are inappropriately retaining calcium, and renal ultrasound should be carried out if hypercalcaemia is persistent and severe.

Given the suppressed PTH level, and the palpable areas of hardened subcutaneous tissue present, a clinical diagnosis of SCFN was made in this patient.

TREATMENT

Intravenous fluid resuscitation was started and a treatment plan developed to lower calcium, in consultation with the endocrine team at Great Ormond Street Hospital, including prednisolone and furosemide. A further option to use the bisphosphonate drug pamidronate was considered, as this has been used to lower calcium in other reported cases of SCFN.³ However, this was not given as no abnormalities were seen on the ECG.

OUTCOME AND FOLLOW-UP

On inpatient treatment, adjusted calcium levels decreased to 2.9 mmol/L after 5 days (figure 1), and furosemide was then stopped. The baby was weaned off intravenous fluids and onto low calcium milk feeds (Locasol). Five days after her readmission to hospital, the baby was discharged, continuing on prednisolone and low calcium feeds with blood tests every 2 days to

Figure 1 Chart showing adjusted calcium levels in this patient, with age.

monitor calcium levels. Prednisolone was stopped when the adjusted calcium was maintained below 3 mmol/L, and a regime of alternate low calcium and normal feeds later started when calcium levels normalised. The child is now 2 years old and thriving but a degree of nephrocalcinosis remains, monitored with regular ultrasounds.

DISCUSSION

SCFN must be considered as part of the differential diagnosis in neonatal hypercalcaemia, particularly in full-term infants who have undergone a traumatic delivery including asphyxia or meconium aspiration.⁴ Other predisposing factors including maternal hypertension and smoking have also been implicated.⁵ A clue is provided by physical examination, as palpable areas of cutaneous or subcutaneous tissue are usually present. Tissue hypoxia during delivery and the perinatal period leads to lobular panniculitis (inflammation of the subcutaneous fat), with necrotic fatty plaques. These plaques have pathognomonic needle-shaped clefts surrounded by an inflammatory infiltrate containing macrophages. The reason for the hypercalcaemia is unclear, although the prevailing theory is that the high concentration of 1- α hydroxylase in macrophages produces excess 1,25-dihydroxyvitamin D, thereby increasing calcium intake from the gut.¹ There are also reports of hypercalcaemia due to increased bone resorption in SCFN, related to increased circulating prostaglandin E levels. Markers of bone resorption were not measured in our patient. 1,25-dihydroxyvitamin D was first measured in this baby at the point when the severe hypercalcaemia was detected, 3–4 weeks after birth. Given a plasma calcium level of 4.34 mmol/L, 1,25-dihydroxyvitamin D should be suppressed, as the 1- α hydroxylase enzyme is regulated by the amount of circulating calcium. However, in this patient it was inappropriately normal. Further, the peak level of 1,25-dihydroxyvitamin D here may have been missed, as it has a much shorter half-life in plasma than 25-hydroxy vitamin D (4–6 h compared with 2–3 weeks). Interestingly, not all babies with SCFN have high levels of 1,25-dihydroxyvitamin D when measured.⁴

In this baby there was concern over the possibility of intra-uterine infection, as the mother's vaginal swab was positive for group B *Streptococcus*. However, the prolonged low-level elevation of CRP may instead merely reflect the underlying inflammation present in SCFN.

Learning points

- Careful clinical examination for subcutaneous fat necrosis (SCFN) should be carried out in neonates with persistent unexplained mild C reactive protein elevation refractory to antibiotic therapy.
- It is also important to check for hypercalcaemia, although not all babies with SCFN will have a raised calcium level.
- Although SCFN will resolve spontaneously within a period of months and is likely to be underdiagnosed, the associated hypercalcaemia has the potential to cause significant kidney damage if left untreated.

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