Transient Aminoaciduria And Hyperparathyroidism In A Premature Infant With Osteopenia

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Citation


Abstract

Rickets is a common problem in infants of extremely low birth weight. The case of a male infant is reported who received prolonged parenteral nutrition for oesophageal atresia. He developed severe osteopenia with fractures and urine analysis revealed generalised hyperaminoaciduria suggestive of a renal tubular defect. A markedly elevated parathyroid hormone level was seen at the same time. Later a Fanconi renal tubular defect was disproved when the aminoacid leak resolved with treatment and growth, and it now seems that the transient hyperparathyroidism caused the aminoaciduria, leading to diagnostic confusion. This association of hyperparathyroidism and aminoaciduria has been reported before but not in a premature infant.

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CASE REPORT

A 773g male infant was delivered by an emergency Caesarean section at 28 weeks gestation due to fetal distress. There had been intra-uterine growth retardation associated with absent end diastolic flow on umbilical Doppler ultrasound scanning. Apgar scores were 8 at 1 minute and 9 at 5 minutes. Subsequently there were complications in several systems each of which is described separately.

RESPIRATORY

He was intubated at 3 minutes for poor respiratory effort and developed severe respiratory distress syndrome despite artificial surfactant (ALEC). He was initially ventilated conventionally, but on day 2 required high frequency oscillation until day 10. Nasal continuous positive airway pressure and intermittent conventional ventilation were required until day 90 of life. He was then weaned from ventilatory support with a three day course of dexamethasone, and within three weeks no longer needed additional oxygen.

GASTROINTESTINAL

On day 1 it was not possible to pass a nasogastric tube (NGT) due to oesophageal atresia confirmed by a barium swallow, he was therefore started on parenteral nutrition (PN), which continued until day 50. A maximum of 150 ml/kg/day of PN was administered with 1.0 mmol of both calcium and phosphate in each 100 ml of solution. Two episodes of sepsis together with his low weight delayed a gastrostomy until day 45. Expressed breast milk (EBM) was then administered via the gastrostomy and on day 48 reflux of milk into the mouth was noted. It had become possible to pass a nasogastric tube, presumably due to canalisation of the oesophagus and he was given caprilon (a medium chain triglyceride based infant feed), fortifier and EBM. PN was resumed for days 86-96, following an infection of the gastrostomy site, after which time he was fed caprilon via NGT and bottle.

HEPATIC

Elevated serum liver enzymes were noted on day 22. This was thought to be due to sepsis. He subsequently developed chronic cholestasis, with a persistently raised serum gamma gluteryl transferase level, conjugated and total bilirubin levels (figure 1 and 2). These peaked around the 50th day of life. His alkaline phosphatase levels rose gradually (figure 3), and total protein levels were persistently low (figure 4). He was started on the bile acid Ursodeoxycholic acid 10 mgs tds with his caprilon feed on day 55 until day 213. The ALT remained raised for a long time and was still 351 U/L on day 223. Similarly hepatosplenomegaly was evident clinically with a firm liver up until 280 days; and was also evident by ultrasound carried out on day 224. On day 120 tests for hepatitis A, B, and C antigens, galactosemia, immunoreactive trypsin and alpha 1 antitrypsin were all
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Negative.

**Figure 1**  
Figure 1: Serum gamma glutaryl transferase and alanine transferase levels. (Normal GGT level < 60 U/L, Normal ALT level < 50 U/L).

**Figure 2**  
Figure 2: Serum conjugated and total bilirubin levels. (Normal total bilirubin level 17 - 180 micromol/L, normal conjugated level < 20% of total).

**Figure 3**  
Figure 3: Serum Alkaline phosphatase levels. (Normally < 700 U/L until 28 days of life, then < 1000 U/L).

**Figure 4**  
Figure 4: Serum total protein levels. (Normal range 63 - 82 G/L).

**METABOLIC**

Metabolic acidosis. A routine capillary blood test on day 56 revealed a metabolic acidosis with a pH of 7.26, a base deficit of 14.2 mmol/l and a bicarbonate level of 11.4 mmol/l. A serum phosphate level on day 34 was within normal limits at 1.69 mmol/l, but hypophosphataemia occurred over the next fifty days (figure 8). Two days later the chloride was 119 mmol/l, bicarbonate was 15 mmol/l, sodium 135 mmol/l and potassium 5 mmol/l. This resulted in an anion gap of 6 (135 + 5 – 119 – 15). By day 71 the acidosis had resolved on supplements of sodium bicarbonate (1.5 mmol tds) and potassium chloride (5 mmol/day). These supplements were continued until day 86.

Aminoaciduria. On day 68 urinalysis for amino acid composition revealed a generalised hyperaminoaciduria of approximately 3-5 times the upper limit of normal. These levels had improved by day 180. Urinary amino acid
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analysis was normal by day 211.

**BONE DISEASE**

At three months of age fractures of the left upper humerus and hand bones were noted on X ray (figures 5,6 & 7). These were considered to be pathological fractures, a diagnosis of rickets was made and he began vitamin D supplementation with 1 alpha calcitriol. The serum alkaline phosphatase level had been elevated from day 28 of life. A parathormone level was measured on day 137 and was markedly elevated at 87 pmol/l (normal < 6). This responded to treatment with 1 alpha calcidiol being 1.3 pmol/l on day 223. On day 102 for the first time the serum calcium level fell just below the expected range (figure 8). On day 114 oral phosphate supplements were commenced. The osteopenia and rickets completely resolved and the calcitriol and phosphate supplements were stopped on day 217.

**Figure 5**

Figure 5, 6 & 7: Radiographs showing fractures of the left upper humerus, wrist and hand.

**Figure 6**

Figure 8: Serum calcium and phosphate levels. (Normal ranges: corrected calcium 2.1 - 2.6 mmol/L, and phosphate 1.2 - 2.9 mmol/L).

**OUTCOME**

The patient went home on the 184th day of life. He was fed with pre-digested formula milk due to milk allergy from day 209 and thrived. He had an inguinal hernia repair at 6 months. At 18 months he is showing normal neurodevelopment and is on no additional treatment.

**DISCUSSION**

Differentiating the diagnosis in this case was particularly challenging. In view of the acidosis, the hypophosphataemia and the humeral fracture, X linked hypophosphataemic rickets and Renal Fanconi’s syndrome were considered possibilities. Renal tubular acidosis was confirmed due to the presence of a metabolic acidosis, hyperchloraemia and a normal plasma anion gap as indicated above. From day 59 our patient was hypophosphataemic. A urinary phosphate : creatinine ratio whilst on phosphate supplements showed minimal urinary loss of phosphate, making X linked hypophosphataemic rickets highly unlikely.

Urinalysis on day 69 showed a very high generalised hyperaminoaciduria. In the renal Fanconi’s syndrome a generalised proximal tubular dysfunction results in proximal renal tubular acidosis and urinary loss of phosphate. In addition glucose, amino acids and low molecular weight proteins are excreted. However by day 71 the RTA had clinically resolved with bicarbonate and potassium supplements, and after stopping the treatment the acidosis did not recur. The aminoaciduria also proved to be transient (Table 1), so Fanconi’s syndrome was excluded.

**Figure 7**

Table 1: Urine aminoacid composition revealed a generalised hyperaminoaciduria of approximately 3-5 times the upper limit of normal (these aminoacids quantified to demonstrate the magnitude of the generalised aminoaciduria).

<table>
<thead>
<tr>
<th>Day of life</th>
<th>Tyrosine</th>
<th>Glycine</th>
<th>Threonine</th>
<th>Alanine</th>
<th>Histidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>68</td>
<td>255 (50)</td>
<td>1333 (1050)</td>
<td>2256 (300)</td>
<td>1441 (250)</td>
<td>979 (310)</td>
</tr>
<tr>
<td>105</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>569 (224)</td>
<td>652 (310)</td>
</tr>
<tr>
<td>154</td>
<td>158 (30)</td>
<td>2704 (904)</td>
<td>4256 (300)</td>
<td>478 (224)</td>
<td>482 (310)</td>
</tr>
<tr>
<td>180</td>
<td>116 (30)</td>
<td>986 (904)</td>
<td>409 (300)</td>
<td>316 (224)</td>
<td>380 (310)</td>
</tr>
<tr>
<td>211</td>
<td>53 (30)</td>
<td>571 (904)</td>
<td>173 (300)</td>
<td>170 (224)</td>
<td>173 (310)</td>
</tr>
</tbody>
</table>

Figures in brackets are normal maximum values.

The most likely explanation is that the hyperparathyroidism caused the renal tubular pathology. Secondary
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Hyperparathyroidism has been reported as a cause of generalised hyperaminoaciduria in children [1]. A parathyroid hormone (PTH) test on day 137 revealed a very high result of 87 pmol/L, consistent with this diagnosis.

Secondary hyperparathyroidism may occur in the presence of vitamin D deficiency. Hassanein and Patel investigated the effect that injected exogenous PTH had on levels of aminoaciduria in children [2]. Injections of PTH directly caused an increase in the pre-existing aminoaciduria. They proposed that this resulted from an increased glomerular filtration rate in the presence of a proximal tubular amino acid transport defect produced by vitamin-D deficiency. They also concluded that the increased aminoaciduria was not due to changes in serum and urine calcium and phosphate levels. As in our case the principal aminoacids contained in the urine were glycine, histidine and alanine.

Dabbagh et al contradict this theory by suggesting that the mechanism causing aminoaciduria in vitamin D deficiency rickets is independent of parathyroid hormone levels and that it is multifactorial [3]. In a second study Dabbagh et al [4] suggest that the aminoaciduria of vitamin D deficiency may be related to phosphate depletion rather than elevated levels of parathyroid hormone. Yet another explanation is proposed by Van der Jagt et al [5]. They studied 10 rachitic children and concluded that the aminoaciduria was related to their calcium status and not to their vitamin D or parathyroid hormone status.

This metabolic picture of hyperparathyroidism, and calcium and phosphate depletion is the underlying cause of Osteopenia of Prematurity, a significant feature in our case. Many risk factors were present, our patient being premature, having intrauterine growth retardation, prolonged use of PN, hepatobiliary disease, chronic lung disease of prematurity and dexamethasone treatment. Osteopenia of prematurity is very common in extremely low birth weight infants, with as many as 73% of infants with a birth weight of 800g or less suffering from rickets with associated pathologic fractures [6]. Lyon et al found over 70% of infants weighing less than 1000g had defective bone remodelling thereby supporting this hypothesis [7]. Demineralisation occurs because 80% of calcium and phosphate deposition in bone occurs during the exponential intrauterine growth in the third trimester [8]. Following birth, rapid body growth in the very low birth weight premature infant may induce calcium depletion, leading to rickets [9].

In our case the fundamental underlying problem was the need for prolonged parenteral nutrition. This causes rickets by two mechanisms; firstly there is a limit to the concentration of calcium and phosphate in parenteral nutrition because of chalk precipitation [9]. Secondly, prolonged TPN leads to cholestasis, with inadequate bile salt secretion in turn causing decreased absorption of lipid soluble vitamin D from enteral feeds and subsequently poor calcium and phosphate absorption in the small bowel [10,11,12].

Cholestatic jaundice is seen in 10-40% of infants fed with total parenteral nutrition. This incidence is higher the longer the parenteral nutrition is administered for, with 80% of those on it for more than 2 months developing cholestasis[13]. Likely mechanisms by which this occurs include the immaturity of the hepatobiliary system[14], prolonged fasting[15], impaired bile secretion and bile salt formation[16], and the coexistence of sepsis [17]. Commencement of enteral feeding usually results in the resolution of the cholestasis, but progression to biliary cirrhosis and liver failure can occur [18,19].

Minimal enteral feeding during parenteral nutrition helps to prevent these problems. It has physiological effects on gastrointestinal exocrine and endocrine secretion (glucagon, gastrin, motilin) and smooth muscle activity [20]. Glucagon has a role in stimulating bile flow and hepatic enzyme development. Low glucagon levels might therefore explain some of the adverse hepatobiliary changes associated with prolonged parenteral nutrition [11]. Infants who receive early low-volume enteral feeding have improved feeding tolerance, reach full enteral nutrition faster and have less indirect hyperbilirubinaemia, cholestatic jaundice and osteopenia of prematurity [22,23].
CONCLUSION

This case is reported in order to alert paediatricians to the occurrence of aminoaciduria in the presence of hyperparathyroidism.

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