Idiopathic Infantile Hypercalcaemia in 5-month Old Girl

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Abstract: Idiopathic infantile hypercalcaemia (IIH) is a mineral metabolism disorder of unknown origin. It is characterized by high levels of serum calcium resulting in parathyroid hormone (PTH) suppression, muscle hypotonia, thirst, anorexia, failure to thrive, psychomotor retardation, constipation, nephrocalcinosis. Treatment consists of low calcium diet, glucocorticoids, furosemide. We present a case of 5-month old girl with IIH, where total calcaemia peaked to 4.25 mmol/l. The leading symptoms were failure to thrive, constipation, muscle hypotonia, dehydration. Rehydration, low calcium diet, and application of glucocorticoids and furosemide resulted in a drop in calcaemia to normal values and an overall clinical improvement within two weeks. Williams-Beuren syndrome (WBS), benign familial hypocalciuric hypercalcaemia (FHH), neonatal severe primary hyperparathyroidism (NSHPT), Jansen’s metaphyseal dysplasia, primary hyperparathyroidism, vitamin D intoxication, granulomatous diseases, thyroid disease, malignancy were all ruled out. In conclusion, infants with failure to thrive should have their serum levels of minerals, especially, calcium, checked. In case of hypercalcaemia, treatment with corticosteroids and furosemide should be initiated, together with further diagnostic steps in order to elucidate its origin.

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Introduction
Idiopathic infantile hypercalcaemia (IIH) is a very rare mineral metabolism disorder of unknown origin. It is characterized by high levels of serum calcium resulting in parathyroid hormone (PTH) suppression, muscle hypotonia, thirst, anorexia, failure to thrive, psychomotor retardation, constipation, nephrocalcinosis (McTaggart et al., 1999). We present a female patient with this rare disorder.

Case report
A 5-month old girl with uneventful neonatal history was referred because of failure to thrive, as her weight dropped from 6,010 g at the age of three months (+0.25 SD) to 5,450 g at month 5 (–1.95 SD). She was breastfed and receiving additional formula. She was taking 666 units of cholecalciferol per day as antirachitic prophylaxis since second week of age, and she never received a higher dose of vitamin D. The parents reported her as being tired and sleepy with constipation in the course of previous month. Upon physical examination she had signs of dehydration and muscle hypotonia. Urinalysis revealed leukocyturia (high power field full of leukocytes), with *E. coli* concentration of 10^6/ml in urine obtained by bladder catheterization. Therefore, diagnosis of urinary tract infection was established and she received cefuroxime for seven consecutive days, resulting in negative culture of bacteria in spontaneously voided urine. In addition, the serum level of creatinine was elevated for age (68 µmol/l; normal 18–35), same as blood urea nitrogen (10.8 mmol/l; normal 1.8–6.4), suggesting dehydration. Creatinine clearance based on Schwartz formula was 36 ml/min per 1.73 m², i.e. 0.6 ml/s per 1.73 m², suggesting renal failure due to dehydration. The following were normal: serum concentrations of sodium (S-Na), chloride (S-Cl), potassium (S-K), phosphorus (S-P), magnesium (S-Mg), bilirubin, total serum protein and albumin, serum activities of aspartate-aminotransferase (S-AST), alanin-aminotransferase (S-ALT), alkaline phosphatase (S-ALP), glutamyltransferase (S-GMT), serum and urinary pH. The serum level of calcium (S-Ca) was high (3.93 mmol/l; normal 2.2–2.7), same as serum ionized Ca (S-Ca²⁺; 1.99 mmol/l; normal 1.1–1.3) and urinary calcium/creatinine ratio (11.9 mmol/l:mmol/l; normal age related upper reference range 1.5). Bilateral nephrocalcinosis and a single cholecystolithiasis were apparent on abdominal ultrasonography. Markers of bone turnover (S-osteocalcin and S-Crosslaps) were within age related reference ranges. Serum parathyroid hormone level (S-PTH) was low (6.4 pg/ml, normal 15–65). There were normal levels of serum free thyroxine and thyrotropin, respectively. Concerning serum vitamin D levels, serum concentration of calcitriol (1,25-dihydroxyvitamin D) was only mildly elevated (68.8 pg/ml; normal range 19.9–67) while calcidiol (25-hydroxyvitamin D) was close to the upper reference range (44.5 ng/ml; normal 8.9–46.7), respectively. Chest and spinal X-ray, together with X-rays of the extremities were all normal, without any signs of osteolysis. ⁹⁹Tc bone scan was normal. Echocardiography was repeatedly normal, with no signs of aortic or...
pulmonary artery stenosis. Treatment consisting of intravenous rehydration with 0.9% saline solution, application of glucocorticoids (dexamethasone 0.4 mg/kg/day) and furosemide (0.6 mg/kg/day) was initiated immediately after obtaining the high S-Ca results. Low-calcium diet was started following the intravenous rehydration and vitamin D prophylaxis was stopped. First, the S-Ca levels transiently peaked up to 4.25 mmol/l, but within one day a gradual decrease was apparent, resulting in normal S-Ca values (Figure 1). The S-Ca\(^{2+}\) followed a similar trend (Figure 2). The U-Ca/U-creatinine ratio also dropped (Figure 3) and serum levels of blood urea nitrogen and creatinine decreased to 2.8 mmol/l and 51 µmol/l, respectively in the course of rehydration. Creatinine clearance improved to 50 ml/min per 1.73 m\(^2\), i.e. 0.8 ml/s per 1.73 m\(^2\). The S-PTH level, which was initially suppressed, increased to normal value of 31 pg/ml, once the S-Ca and S-Ca\(^{2+}\) approached physiological levels. The American Academy of Pediatrics Committee on Genetics Score for Williams-Beuren syndrome (Cunniff et al., 2001) was just 2 points, thus ruling out this diagnosis.

![Figure 1](image1.png)

**Figure 1** – The serum levels of Ca (mmol/l) assessed on a daily basis in the course of hospitalization.

![Figure 2](image2.png)

**Figure 2** – The serum levels of Ca\(^{2+}\) (mmol/l) assessed every other day in the course of hospitalization.
The diagnosis of IIH was established and the girl was dismissed after 15 days with S-Ca 2.73 mmol/l, S-Ca\(^{2+}\) 1.4 mmol/l, body weight of 6,580 g (−0.64 SD). There were no signs of cholecystolithiasis on the abdominal ultrasound one month later. Due to calcaemia approaching the upper reference range, furosemide (0.5 mg/kg/day) was applied for a total of 4 months, with U-Ca/U-creatinine ratio being carefully monitored and having the results consistently within the age-related reference values. One year after dismissal the U-Ca/U-creatinine ratio was 0.8 (normal below 1.2). The steroids were administered for a total of 4 months, their dose being gradually tapered to 2.5 mg/day of prednisone. Following the dismissal, the serum concentrations of calcidiol were within normal ranges, while calcitriol was mildly elevated after three and five months (78 and 75 pg/ml), respectively. Eight and twelve months after dismissal the serum calcitriol levels were within reference ranges. The girl is still closely followed up. The serum levels of calcium have been within the reference ranges since the dismissal. Currently, at the age of five years the girl’s basic anthropometric parameters are within normal reference ranges.
ranges of ±2 SD (body weight 16.5 kg, i.e. –1.2 SD; body height 106 cm, i.e. –1.6 SD, body mass index 14.7, i.e. –0.4 SD), with normal values of S-Ca (2.55 mmol/l), S-P (1.79 mmol/l), S-ALP (3.2 µkat/l), urinary calcium level (below 0.1 mmol/kg/24 h), and without any signs of impaired health. Nephrocalcinosis still persists (Figure 4), with renal functions being normal (S-creatinine 41 µmol/l; creatinine clearance according to Schwartz formula 121 ml/min/1.73 m², i.e. 2 ml/s/1.73 m². The S-Ca, S-P, S-ALP, S-PTH in patient’s parents and sister were within normal reference ranges.

Discussion
Idiopathic infantile hypercalcemia is a very rare cause of hypercalcemia in the 1st year of life and has an estimated incidence of approximately 1 in 47,000 live births (Martin et al., 1984; Huang et al., 2006). IIH was originally described during a period of high-dose vitamin D fortification in England in the 1952 (Lightwood, 1952) and at the same time by Fanconi in Switzerland (Fanconi et al., 1952). The diagnosis of IIH can be established only after the exclusion of other conditions that cause hypercalcaemia in infancy, such as Williams-Beuren syndrome (WBS), benign familial hypocalciuric hypercalcaemia (FHH), neonatal severe primary hyperparathyroidism (NSHPT), Jansen’s metaphyseal dysplasia, primary hyperparathyroidism, vitamin D intoxication, granulomatous diseases, thyroid disease, malignancy (Table 1).

Excessive hypercalcaemia with hypercalciuria, low-to-normal S-PTH, normal serum free thyroxine and thyrotropin, normal wrist X-ray, absence of any dysmorphic features characteristic of WBS or Jansen metaphyseal dysplasia, only two points on Genetics Score for WBS, absence of neoplasm and of granulomatous tissue together with negative history of vitamin D overdose and normal serum level of calcidiol ruled out the above mentioned diagnoses in our patient. Nephrocalcinosis and transient cholecystolithiasis in our patient should be considered among signs of IIH. The body height in our patient is –1.6 SD, this is still within ±2 SD, however it is difficult to estimate whether episode of hypercalcaemia or genetically predicted height (mother’s body height is 160 cm, i.e. –1 SD) could have contributed to girl’s slightly stunted growth.

The exact cause of IIH remains unknown; increased sensitivity to vitamin D or slow/impaired elimination of vitamin D and its metabolites has been proposed (Aarskog et al., 1981; Martin et al., 1984, 1985; Siani et al., 1985; McGraw, 1986; Pronicka et al., 1997; Rodd and Goodyer, 1999). The upper reference range values of calcidiol and calcitriol in our patient and mildly increased levels of calcitriol in the 5 months’ follow-up seem to favor this hypothesis. Furthermore, it seems very likely that IIH can be triggered by administration of high vitamin D doses (Fanconi et al., 1952; Lightwood, 1952; Hrdličková and Kutílek, 1990). A combination of IIH and renal tubular acidosis with nephrocalcinosis has also been reported (Sakallioglu et al., 2008). The inheritance of IIH remains largely unknown. Familial occurrence has been documented, as IIH occurred in two siblings, while another
Table 1 – Differential diagnosis of hypercalcaemia throughout the first year of life

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Cause</th>
<th>S-Ca</th>
<th>S-P</th>
<th>U-Ca</th>
<th>U-P</th>
<th>S-PTH</th>
<th>S-25OHD</th>
<th>S-1,25(OH)₂D</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIH</td>
<td>unknown</td>
<td>high</td>
<td>normal</td>
<td>high</td>
<td>normal</td>
<td>low</td>
<td>normal to high</td>
<td>normal to high</td>
</tr>
<tr>
<td>WBS</td>
<td>elastin gene deletion</td>
<td>high in 15% of patients</td>
<td>normal to high</td>
<td>high in 30% of patients</td>
<td>normal</td>
<td>low</td>
<td>normal to high</td>
<td>normal to high</td>
</tr>
<tr>
<td>NSHPT</td>
<td>CaSR homozygous inactivating mutation</td>
<td>very high</td>
<td>low</td>
<td>high</td>
<td>normal to high</td>
<td>high</td>
<td>normal to low</td>
<td>high</td>
</tr>
<tr>
<td>FHH</td>
<td>CaSR heterozygous inactivating mutation</td>
<td>normal to high</td>
<td>normal to low</td>
<td>low</td>
<td>normal to high</td>
<td>normal to high</td>
<td>normal</td>
<td>high</td>
</tr>
<tr>
<td>JMD</td>
<td>PTH receptor activating mutation</td>
<td>high</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>normal</td>
<td>normal</td>
<td>high</td>
</tr>
<tr>
<td>HPT I</td>
<td>increased PTH secretion</td>
<td>high</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>normal</td>
<td>high</td>
</tr>
<tr>
<td>vitamin D</td>
<td>overdose</td>
<td>high vitamin D intake</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>subcutaneous fat necrosis</td>
<td>high calcitriol production</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>low</td>
<td>normal</td>
<td>very high</td>
</tr>
<tr>
<td>granulomatous disease</td>
<td>high calcitriol production</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>low</td>
<td>normal</td>
<td>very high</td>
</tr>
<tr>
<td>malignancy</td>
<td>humoral or osteolytic malignancy</td>
<td>high</td>
<td>high (osteolytic) low (humoral)</td>
<td>normal or high</td>
<td>high</td>
<td>low</td>
<td>normal</td>
<td>high (humoral) low (osteolytic)</td>
</tr>
</tbody>
</table>

S-Ca – serum calcium level; S-P – serum phosphate level; U-Ca – urinary calcium level; U-P – urinary phosphate level; S-PTH – serum parathyroid hormone level; S-25OHD – serum calcidiol level; S-1,25(OH)₂D – serum calcitriol level; CaSR – calcium-sensing receptor; PTH – parathyroid hormone; IIH – idiopathic infantile hypercalcaemia; WBS – Williams-Beuren syndrome; NSHPT – neonatal severe hyperparathyroidism; FHH – familial hypocalciuric hypercalcaemia; JMD – Jansen metaphyseal dysplasia; HPT I – primary hyperparathyroidism
five relatives within one family presented with hypercalciuria (McTaggart et al., 1999). IIH presents between the ages of one and seven months with nonspecific signs and symptoms such as lethargy, thirst, hypotonia, poor feeding, failure to thrive, dehydration, constipation and respiratory distress, all due to hypercalcaemia (Siani et al., 1985; Hrdličková and Kutílek, 1990; Kooh and Binet, 1990; Pronicka et al., 1997; McTaggart et al., 1999; Rodd and Goodyer, 1999; Huang et al., 2006; Sakallioglu et al., 2008). Hypercalciuria with nephrocalcinosis is also common finding in IIH (Pronicka et al., 1997; McTaggart et al., 1999; Huang et al., 2006; Sakallioglu et al., 2008). Urinary tract infection might occur in presence of hypercalciuria (Huang et al., 2006), as evidenced in our patient. Only limited published data exist on the natural history of IIH, with case reports suggesting that hypercalcaemia spontaneously resolves when the child is approximately 12 months of age, however, hypercalcaemia can persist up to two or even three years (Pronicka et al., 1997; McTaggart et al., 1999; Huang et al., 2006). Prompt treatment is necessary in patients having S-Ca 3.0 mmol/l with clinical symptoms and in all subjects with S-Ca ≥ 3.5 mmol/l (Carroll and Schade, 2003). Vitamin D supplementation must be stopped immediately and low calcium diet should be started. Treatment of hypercalcaemia in infancy consists of furosemide 1–2 mg/kg (given only after rehydration), glucocorticoids (mostly prednisone 1–3 mg/kg/day), and eventually calcitonin and pamidronate (Goodyer et al., 1984; Alon et al., 1992; Rodd and Goodyer, 1999; Huang et al., 2006; Sakallioglu et al., 2008; Assadi, 2009; Lietman et al., 2010). Pamidronate has been so far used in WBS and NSHPT (Cagle et al., 2004; Shiva et al., 2008), but not in IIH. Phosphate cellulose has been also reported as efficient in the treatment of IIH (Mizusawa and Burke, 1996; Huang et al., 2006). In our patient the application of corticosteroids and furosemide resulted in decrease of calcaemia within four days, but the corticosteroids had to be maintained and gradually tapered for additional three months. Persistence of nephrocalcinosis with otherwise normal renal function is consistent with previous reports of patients with IIH, where nephrocalcinosis was noted even up to 12 years of age (Pronicka et al., 1997). Due to the fact that children with IIH should be on low-calcium diet without vitamin D supplementation, special attention must be paid to the S-ALP levels, this in order to prevent development of rickets.

In conclusion, infants with failure to thrive should have their serum levels of minerals, especially, calcium, checked. In case of hypercalcaemia, treatment with corticosteroids and furosemide should be initiated, together with further diagnostic steps in order to elucidate its origin.

References

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