The Diagnostic Approach of Hypercalcaemia in Childhood

An Illustrative Case Report and Narrative Literature Review

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Abstract

In this narrative review, we discuss the case of a 5-month-old girl who presented with feeding difficulties, failure to thrive, and clinical signs of dehydration. Blood examination revealed hypercalcaemia, elevated 1,25-dihydroxyvitamin D levels and suppressed parathyroid hormone. Renal ultrasound revealed nephrocalcinosis. Genetic testing identified two pathogenic variants in the *CYP24A1* gene and confirmed the clinical diagnosis of infantile hypercalcaemia (IH), formerly known as idiopathic infantile hypercalcaemia (IIH). This patient's hypercalcaemia normalised with fluid administration, dietary adjustments, discontinuation of vitamin D supplementation, and adjuvant treatment with fluconazole and intravenous bisphosphonates (pamidronate). Awareness of the symptoms of hypercalcaemia is crucial for an accurate diagnosis, effective treatment, and the prevention of complications. This manuscript highlights the clinical, biochemical, and management aspects of hypercalcaemia in childhood, including a flowchart of the diagnostic approach.

Introduction

Hypercalcaemia is defined as a serum adjusted calcium concentration greater than two standard deviations above the normal mean (1-3). Hypercalcaemia is a rare condition in the paediatric population, affecting approximately 1 in 500 children in a general hospital setting (2, 3).

Although a thorough clinical history and physical examination can provide valuable clues, the diagnosis of hypercalcaemia remains challenging – especially in young children - due to the often variable and non-specific symptomatology (2). Nevertheless, untreated hypercalcaemia can have serious clinical consequences, ranging from vague symptoms like fatigue and nausea to hypercalcaemic crisis, renal complications such as kidney stones and nephrocalcinosis, and severe neurological symptoms such as myoclonus, encephalopathy, hyperreflexia, and proximal muscle weakness (3, 4). The aetiology of hypercalcaemia in children is diverse and the frequency varies between age groups (2, 3). In neonates and infants, genetic or iatrogenic causes are often identified; while in older children, vitamin D intoxication, primary hyperparathyroidism, and immobilisation are more common causes (2, 5, 6).

To illustrate the symptomatology, diagnostic landscape, and initial management of hypercalcaemia in childhood, we describe a clinical case of a 5-month-old infant diagnosed with infantile hypercalcaemia and subsequently provide a narrative overview of the current diagnostic landscape and initial management of hypercalcaemia in children.

Case Report

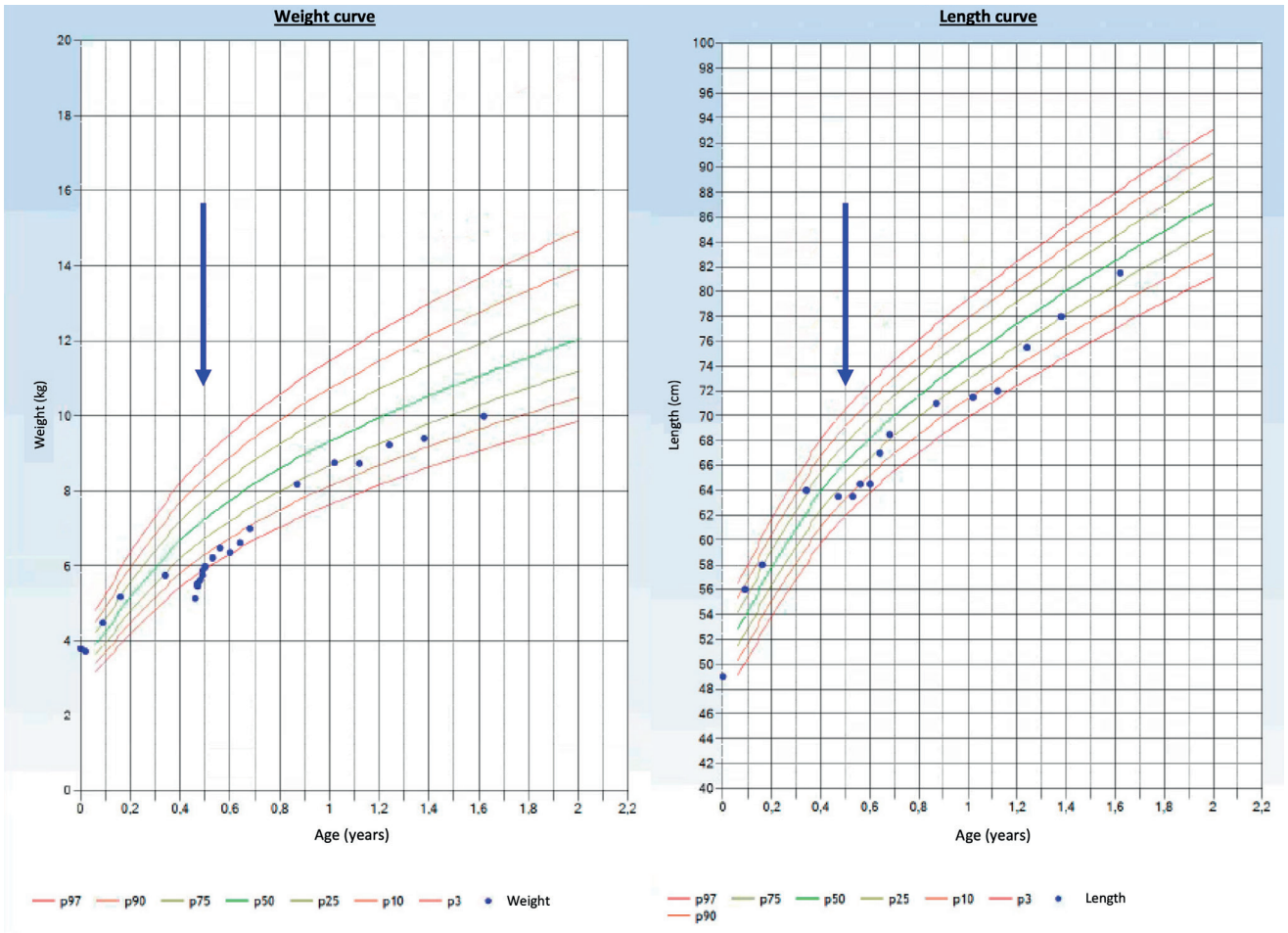
A 5-month-old female infant with an unremarkable medical history was presented to the emergency department because of feeding difficulties (with reported weight loss), being less active than usual and low-grade fever. On physical examination, signs of dehydration were noted, such as dry mucosa and lethargy. As shown in Figure 1, the patient's growth chart showed failure to thrive since the age of 2.5 months, with normal height for age but a weight loss of approximately -2.5 to -3.0 standard deviations over the previous months.

Initial blood tests showed hyponatraemia (sodium 124 mmol/L; reference range (RR) 139 - 146 mmol/L), hypercalcaemia (total serum calcium 3.98 mmol/L, RR 2.20 – 2.84 mmol/L); ionised calcium 2.04 mmol/L (RR 1.20 - 1.38 mmol/L); albumin 40 g/L (RR 30 – 54 g/L) and low bicarbonate of 14.9 mmol/L (RR 16 - 24 mmol/L). Elevated serum creatinine of 44.2 micromol/L (RR 13.3 – 26.5 micromol/L) and urea nitrogen (6.99 mmol/L, RR 1.40 – 6.40 mmol/L) were noted. Serum phosphate, liver and thyroid tests were all within normal limits. A urine sample revealed increased calcium excretion (calcium/creatinine ratio 9.18 mol/mol, 95th percentile for spot urine calcium/creatinine is < 2.2 mol/mol). Renal ultrasound showed bilateral nephrocalcinosis (added in Figure 2). An electrocardiogram was normal.

Her parents were not known to be consanguineous, and both they and the older siblings all had unremarkable medical histories. The patient had not been taking any medication other than the recommended daily dose of 400 IU of vitamin D; intoxication was considered unlikely. Further investigations revealed hypervitaminosis D (elevated serum 25-hydroxyvitamin D: >250 nmol/L, RR 75.5 – 200 nmol/L) and low serum parathyroid hormone (PTH) (< 0.64 pmol/L, RR 1.70 – 9.33 pmol/L). The clinical diagnosis of infantile hypercalcaemia was confirmed with genetic testing: i.e. compound heterozygous variants in *CYP24A1* (the gene encoding 25-hydroxyvitamin D 24-hydroxylase); i.e. c.443T>C (p.Leu148Pro) and c.1186C>T (p.Arg396Trp) (both class 5 pathogenic variants).

Initial management consisted of fluid administration with normal saline (0.9% NaCl), which normalised all electrolytes except for ionised calcium (Figure 2). Vitamin D supplementation was stopped and a

Figure 1: Growth chart. The arrow shows the time of diagnosis.



modified diet was introduced (Nutricia Milupa Basic-CaD formula (<5mg Ca / 100ml) and low calcium solid foods) along with breastfeeding. However, as serum ionised calcium levels remained high despite dietary modification, additional treatment with fluconazole and pamidronate (a bisphosphonate) was initiated. The patient was discharged home after 10 days. At follow-up, the patient showed favourable weight gain (Figure 1) with adequate dietary and medication intake. As shown in Figure 2, maintenance fluconazole was discontinued at 9 months and dietary modifications were slowly tapered and eventually stopped 14 months of age.

Discussion and narrative literature review

Hypercalcaemia is an uncommon entity in childhood with potentially significant morbidity (4). As diagnosis is often challenging and early adequate treatment can change the outcome of these patients, we present an update on the diagnostic and (early) management landscape of hypercalcaemia in childhood, illustrated by a case report of infantile hypercalcaemia due to a compound heterozygous pathogenic variant in *CYP24A1*.

Definition and reference values

The skeleton contains 98% of total body calcium; the remaining 2% circulates throughout the body. Only 1% of circulating calcium is free (ionised) calcium, the only form that has physiological effects (7). Normal serum calcium levels are maintained through the interplay of parathyroid, renal, and skeletal factors (4, 8). Hypercalcaemia is defined as a serum (adjusted for albumin or ionised) calcium concentration greater than two standard deviations above the normal mean. Serum calcium levels must be interpreted according to age, as reference values vary across different age groups (Table 1) (1, 4, 9, 10). There is no formal classification or grading system to define the severity of hypercalcaemia. However, the severity of clinical symptoms is more likely to be associated with greater elevations in serum calcium concentrations, and hypercalcaemia is generally considered to be mild, moderate, and severe for serum adjusted calcium concentrations < 3.0 mmol/L (< 12 mg/dl), between 3.0 to 3.5 mmol/L (12 and 14 mg/dl), and > 3.5 mmol/L (>14 mg/dl), respectively(2). A summary of the reference values of other biochemical markers commonly used in the diagnostic approach to hypercalcaemia in children is provided in Table 1 (10).

Symptomatology

Hypercalcaemia can be an incidental finding without clinical signs or symptoms (5, 11). Clinical manifestations affect the neuromuscular, gastrointestinal, renal, skeletal, and cardiovascular system (7). The most frequent findings are lethargy, hypotonia, anorexia, weight loss or failure to thrive, polydipsia, polyuria, vomiting, bone pain, constipation and abdominal pain (1, 5, 12). The onset is usually insidious over a few weeks (11).

In severe cases, renal failure, marked hypovolaemia, cardiac arrhythmia and reduced consciousness may occur (5, 6, 11). A hypercalcaemic crisis manifests with dehydration, hypertension, and convulsions or coma. It may develop when adjusted serum calcium exceeds 3.5 mmol/l, and such high serum levels must be considered a pending crisis (7).

Epidemiology, aetiology and diagnostic landscape

The prevalence of hypercalcaemia in childhood is inversely related to age, with the highest occurrence in neonates (3, 4). The aetiology of paediatric hypercalcaemia is also age-dependent and includes a broad differential diagnosis (4, 11). Neonates and infants often experience genetic or iatrogenic aetiologies, while in childhood, vitamin D intoxication, primary hyperparathyroidism, and immobilisation are the main causes of hypercalcaemia (2, 5, 6). Hypercalcaemia is observed in less than 1% of children with cancer at the time of diagnosis (5).

Table 1: Reference values of laboratory tests commonly used in the diagnostic approach to hypercalcaemia in children.

CU = Conventional Units. SI = International System of Units. NR = Not Reported. Establishing reference intervals in the paediatric population is particularly challenging due to the necessity of recruiting a large cohort of healthy children and adolescents for accurate stratification by important covariates, including age and sex. The values for serum adjusted calcium, phosphate, albumin, and sodium were adapted from Bohn MK et al(10), where intervals were determined for 32 analytes using Siemens Healthineers Atellica® CH assays in the CALIPER cohort of healthy children and adolescents.

Biochemical markers	Infants (0-1y)	Children and adolescents (1-14y)
Total serum adjusted calcium	Premature: NR Full-term: 2.20 – 2.84 mmol/L (SI) or 8.80 – 11.36 mg/dL (CU)	2.25 – 2.69 mmol/L (SI) or 9.00 – 10.76 mg/dL (CU)
Ionised calcium	< 2 months: 1.05 - 1.37 mmol/L (SI) or 4.20 - 5.48 mg/dL (CU) > 2 months: 1.20 - 1.38 mmol/L (SI) or 4.80 - 5.52 mg/dL (CU)	1.20 - 1.38 mmol/L (SI) or 4.80 - 5.52 mg/dL (CU)
24h urine calcium	< 0,1 mmol/kg/day (SI) or < 4 mg/kg/day (CU)	1.20 - 1.38 mmol/L (SI) or 4.80 - 5.52 mg/dL (CU)
95th percentile for spot urine calcium/creatinine	< 2.20 mol/mol (SI) or < 0.81 mg/mg (CU)	1 – 3 years: < 1.40 mol/mol (SI) or < 0.53 mg/mg (CU) 3 – 5 years: < 1.10 mol/mol (SI) or < 0.41 mg/mg (CU) 5 – 7 years: < 0.80 mol/mol (SI) or < 0.30 mg/mg (CU) > 7 years: < 0.70 mol/mol (SI) or < 0.24 mg/mg (CU)
Phosphate	1.00 – 2.38 mmol/L (SI) or 3.10 – 7.37 mg/dL (CU)	1 - 2 years: 1.03 - 2.09 mmol/L (SI) or 3.19 – 6.47 mg/dL (CU) 2 - 4 years: 1.00 - 1.90 mmol/L (SI) or 3.10 – 5.88 mg/dL (CU) 4 - 10 years: 1.00 - 2.00 mmol/L (SI) or 3.10 – 6.19 mg/dL (CU) > 10 years: 0.80 - 1.80 mmol/L (SI) or 2.48 – 5.57 mg/dL (CU)
Magnesium	0.77 – 1.05 mmol/L (SI) or 1.87 – 2.55 mg/dL (CU)	0.69 – 0.92 mmol/L (SI) or 1.67 – 2.24 mg/dL (CU)
Albumin	Premature infants (until term age): 18 – 30 g/L (SI) or 1.8 – 3.0 g/dL (CU) Full term infants: 30 – 54 g/L (SI) or 3.0 – 5.4 g/dL (CU)	35 – 52 g/L (SI) or 3.5 – 5.2 g/dL (CU)
Sodium	139 – 146 mmol/L (SI) or 139 – 146 mEq/L (CU)	
Parathyroid hormone (PTH)	1.70 – 9.33 pmol/L (SI) or 16 – 88 ng/L (CU)	
25(OH)vitamin D	Reference range: 75.5 – 200 nmol/L (SI) or 30 – 80 ng/mL (CU) Severe deficiency: < 12.5 nmol/L (SI) or < 5 ng/mL (CU) Moderate deficiency: 12.5 – 29 nmol/L (SI) or 5 – 11.6 ng/mL (CU) Mild deficiency: 30 – 49 nmol/L (SI) or 12 – 19.6 ng/mL (CU) Sufficient: > 50 nmol/L (SI) or > 20 ng/mL (CU) Elevated: > 250 nmol/L (SI) or > 100 ng/mL (CU)	

Figure 2: Laboratory data. Data showed on the left Y-axis: 25-hydroxyvitamin D (25(OH)vit D) (orange graph line; reported unit in ng/ml) (deficiency if <20 ng/ml, values >100 ng/ml are not determined in our laboratory); 1,25-dihydroxyvitamin D (1,25(OH)2 vit D) (grey graph line; reported unit in mg/ml) (reference range (RR) 19 - 95 mg/ml in our laboratory); Parathyroid hormone (PTH) (yellow graph line; reported unit in ng/l) (RR 15-65 ng/l in our laboratory) and on the right Y-axis ionised calcium (blue graph line; reported unit in mmol/l) (RR 1.20-1.38 mmol/l). On X-axis the numbers 0 to 10 represent the days hospitalised at initial presentation, and day 38, 52, 80, 241 represent the follow-up consultations with biochemical evaluation. The arrows reflect the administration of Pamidronate (a bisphosphonate). Hyperhydration with intravenous normal saline (0.9% NaCl) from admission to day 8. The modified diet was started on day 3 and slowly tapered to stop at the age of 14 months (day 241). Fluconazole maintenance treatment was started as well on day 3 and discontinued on day 80. The renal ultrasound showing nephrocalcinosis is added.

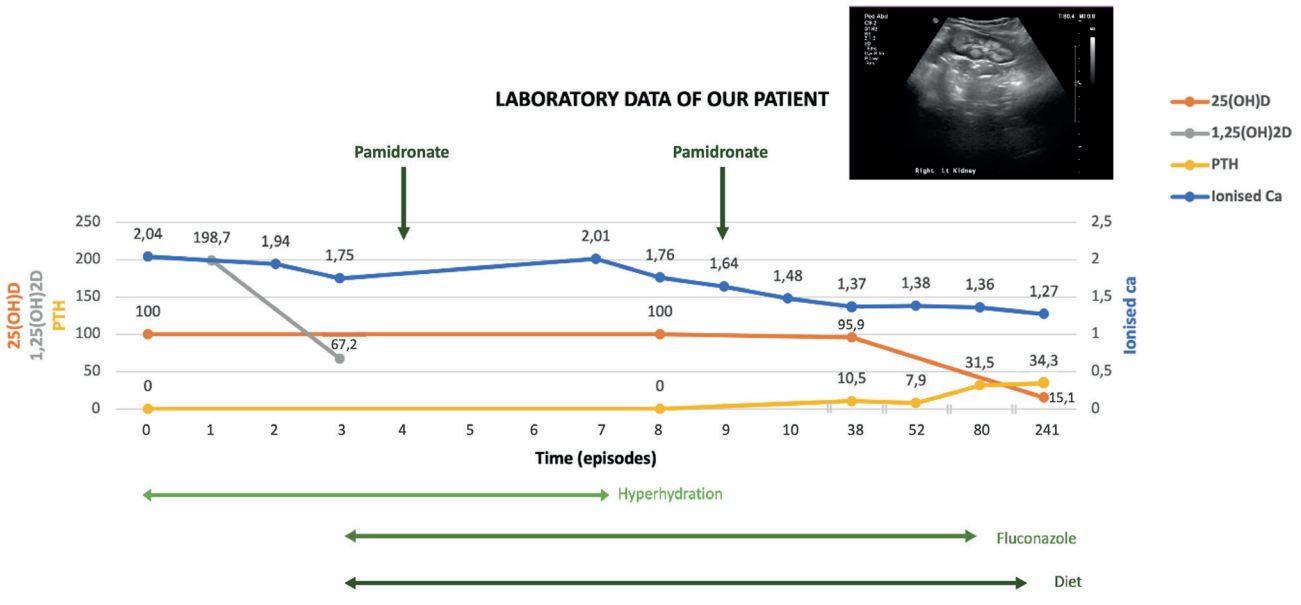


Figure 3: Diagnostic approach to hypercalcaemia in children. The flowchart is adapted from Stokes et al(2). Hypercalcaemia° is defined as a serum (adjusted for albumin or ionised) calcium concentration greater than two standard deviations above the normal mean. See table 1 for reference values of biochemical markers commonly used in the diagnostic approach to hypercalcaemia in children. *Differential diagnoses marked in italic are conditions affecting neonates.* Additional work-up is warranted to identify malignancy. *Some medications associated with hypercalcaemia include thiazide diuretics, lithium, excessive vitamin A, etc. If possible, any medication or supplement that may be causing hypercalcaemia should be discontinued.

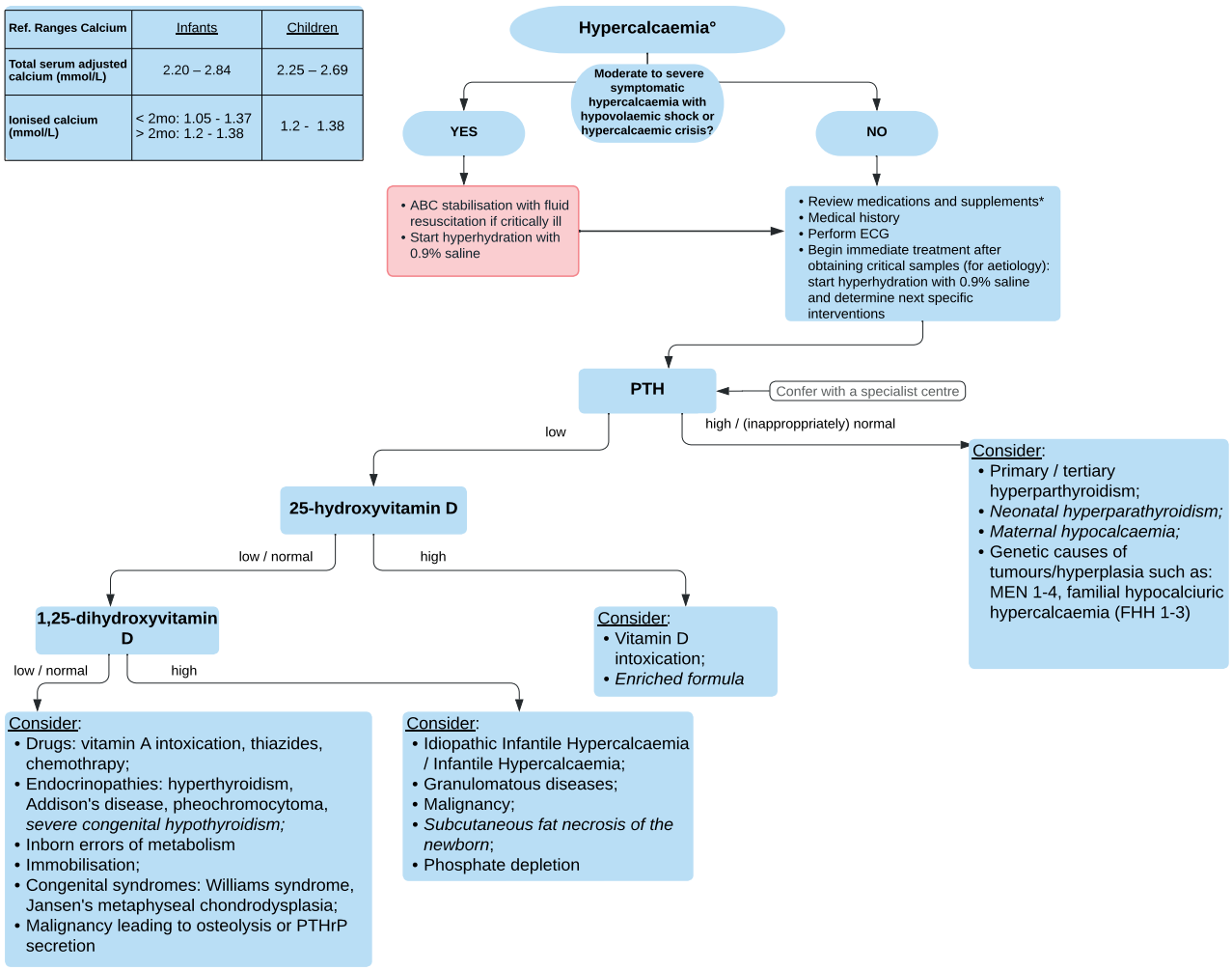


Figure 3 outlines a step-by-step guide for the diagnostic work-up of hypercalcaemia in childhood and is adapted from Stokes et al. (2). Initially, the severity and urgency of the presentation should be assessed. The presence or absence of symptoms of hypercalcaemia may indicate the urgency with which investigations should be pursued (2). If the child presents with a hypovolaemic shock due to a hypercalcaemic crisis, prompt management should be initiated (see treatment section).

Hypercalcaemia can be divided into disorders with inappropriately normal or high PTH and conditions with low or suppressed PTH (8). Primary hyperparathyroidism is rare in childhood (1% of cases), typically presenting with hypercalcaemia and high PTH. It is characterised by autonomous PTH secretion independent of circulating calcium levels, due to a parathyroid adenoma, parathyroid hyperplasia or rarely carcinoma (4, 11). Another disorder presenting with high PTH level is neonatal (severe) hyperparathyroidism. The majority present in the first few weeks of life. There is often severe hypercalcaemia (>4.5mmol/l), low plasma phosphate and very high PTH levels (1, 11). Familial hypocalciuric hypercalcaemia (FHH) (also termed familial benign hypercalcaemia (FBH)) is an autosomal dominant disorder with an inappropriate normal or marginally elevated PTH level despite hypercalcaemia (1, 4, 11). FHH is characterised by lifelong mild hypercalcaemia and very low levels of urinary calcium (4). The hypercalcaemia in FHH is generally benign, usually progresses asymptomatically, and thus does not always require treatment (2). As shown in Figure 3, conditions leading to hypercalcaemia with low or suppressed PTH levels encompass a wide differential diagnosis. In this subgroup, we recommend initiating a comprehensive evaluation, including 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, 24:25-dihydroxyvitamin D3 ratio, serum phosphate, and serum magnesium, ideally prior to initial treatment (1). After collecting critical samples and starting the initial treatment, it is recommended to consult a paediatric specialist centre for further guidance. In addition, we suggest a skeletal survey, urinary tract ultrasound, and urinary spot calcium/creatinine ratio, and genetic evaluation to further guide the differential diagnosis (3, 6, 12). In children with hypercalcaemia and low PTH, it is important to consider secondary causes of hypercalcaemia due to immobilisation or medications like thiazide diuretics, lithium, and excessive vitamin A or vitamin D. If feasible, discontinue any medication or supplements that may contribute. Malignancies, such as leukaemia, lymphoma, rhabdomyosarcoma, Hodgkin and non-Hodgkin lymphoma, brain tumours and neuroblastoma, should also be considered in patients with hypercalcaemia and low PTH (4, 5, 13). Lastly, there are many other rare causes of hypercalcaemia that lead to elevated calcium levels by diverse mechanisms: chronic maternal hypocalcaemia, phosphate depletion, inborn errors of metabolism, infantile hypercalcaemia (see separate section), Williams-Beuren syndrome (deletion on chromosome 7), Jansen's metaphyseal chondrodysplasia, and subcutaneous fat necrosis (4, 11). Full-term newborns that have experienced perinatal stress, such as asphyxia, meconium aspiration, Rhesus incompatibility, hypothermia, or obstetric trauma, are at risk for developing subcutaneous fat necrosis (SCFN). It is

due to excessive 1,25-dihydroxyvitamin D production from over-activity of 1-alpha-hydroxylase. Symptoms of SCFN are often vague, including lethargy, irritability, failure to thrive, hypotonia, vomiting, and constipation (14). It is associated with a significant 15% mortality (4).

Treatment and prognosis

Investigation of the cause of hypercalcaemia and its management are often conducted simultaneously (6). The treatment approach focuses on normalising serum (adjusted) calcium levels and addressing the underlying disorder. Immediate treatment is essential in cases of symptomatic hypercalcaemia to prevent a hypercalcaemic crisis which is associated with significant neurological, cardiac and renal toxicity(6). Treatment should be individually tailored, taking into account the severity of the clinical manifestations, the patient's age, and the expected side effects of the proposed medication (15).

Most children presenting with symptomatic hypercalcaemia are dehydrated, primarily due to reduced fluid intake and the diuretic effect of hypercalcaemia (11). Children with symptomatic hypercalcaemia may present with hypovolaemic shock. ABC stabilisation is then recommended. The main treatment for the critically ill child with hypovolaemic shock is fluid resuscitation. Normal saline (0.9% NaCl) is used in this case because increasing sodium excretion enhances calcium excretion. During fluid administration, special attention should be paid to other electrolytes such as magnesium and potassium (16). Hyperhydration with isotonic sodium chloride is often effective in treating hypercalcaemia, yet is usually insufficient to normalise serum adjusted calcium levels in moderate to severe cases (2, 11). Other treatment options include decreasing calcium absorption from the gut by dietary adjustments, as well as avoiding vitamin D supplementation and prolonged sun exposure. In certain cases, bisphosphonates, loop diuretics, fluconazole (or ketoconazole), and calcitonin have been used (2, 4, 6, 7, 12, 13, 15). Fluconazole, as used in this case, inhibits the activity of vitamin D synthesising enzymes and thereby lowers 1,25-dihydroxyvitamin D levels and reduces calciuria. While fluconazole is not the most potent inhibitor of 1-alpha-hydroxylase, it is far less toxic and more widely available than ketoconazole. However, there is still little research on the use and efficacy of fluconazole in paediatric hypercalcaemia, and we are not convinced that it caused a significant decrease in serum calcium in this case either. Administration of intravenous bisphosphonates leads to a more sustained reduction in serum calcium levels, by suppressing osteoclastic activity and inhibiting 1-alpha-hydroxylase activity as well. Therefore, by decreasing the number of osteoclasts, the rate of calcium release from bone will be reduced. Pamidronate, the drug of choice in children and commonly used in these circumstances, provides a clinical response with a decrease in serum (adjusted) calcium in 2 to 4 days after administration and the effect may last for 2 to 4 weeks (2, 4, 5, 11, 12, 14, 17). Although a wide variety of potential side effects has been described, these appear to be uncommon (18). Comprehensive clinical trials on the safety and efficacy of bisphosphonates in children are lacking; however, several small studies have reported promising results for these agents in the treatment of young patients with hypercalcaemia (4, 12). Specific interventions such as cinacalcet (calcimimetic), denosumab (monoclonal antibody), or surgical intervention, are used depending on the underlying cause, but discussion of these is beyond the scope of this manuscript (2, 6, 11, 15). In a life-threatening crisis (e.g., in patients with renal failure), peritoneal dialysis or haemodialysis has been advocated (6, 11).

Hypercalcaemia in neonates and infants, although uncommon, can have serious long-term consequences, including nephrocalcinosis that may cause permanent kidney damage, bone mineralisation defects and neurodevelopmental impairments (1, 19). There is only limited published information on the natural history of this condition, and the long-term prognosis remains largely unknown (18). The main goal of long-term evaluation is the prevention of renal deterioration and its associated complications (12).

Infantile Hypercalcaemia

Infantile hypercalcaemia (IH), formerly known as idiopathic infantile hypercalcaemia (IIH), was diagnosed in our patient. It is an autosomal recessive disorder caused by inactivating variants in the *CYP24A1* gene encoding for 25-hydroxyvitamin D 24-hydroxylase(2, 6, 15, 17, 19, 20).This enzyme converts active vitamin D metabolites such as 1,25-dihydroxyvitamin D to their inactive form (13). It is expressed in many tissues including the kidney, bone, skin, and intestine (12).

It was first described when symptomatic hypercalcaemia developed in children after receiving high doses of vitamin D for the prevention of rickets in Great Britain in the 1950s (1, 12). However, high variability in the clinical and biochemical phenotypes emerges as a result of genetic and environmental interactions (12). IH is a rare condition and its prevalence in the general population is unknown (13). Its estimated incidence is 1:33 000 to 1:47 000 live births (12, 18). The underlying pathophysiology remained unknown until variants in *CYP24A1* (2011) (type 1) and later *SLC34A1* (type 2) were discovered (13, 15, 21). Despite the term “infantile”, the condition is not confined to infancy as it may also present in later childhood and even adulthood (12). Infants with IH may develop significant hypercalcaemia even when receiving standard vitamin D supplementation (22). Patients typically manifest symptoms between 4 and 12 months of age, have no characteristic dysmorphic features, and show failure to thrive, vomiting, and dehydration. Nephrocalcinosis is commonly detected at presentation (6, 8, 12, 13, 19, 23). Diagnosis of IH is characterised by increased serum (adjusted) calcium, normal or elevated 25-hydroxyvitamin D, elevated 1,25-dihydroxyvitamin D, and suppressed PTH. Particularly, loss-of-function variants in the *CYP24A1* gene result in increased levels of both 25(OH)D3 and 1,25(OH)2D3, which enhance intestinal calcium absorption and bone reabsorption (12). Persistently elevated levels of 1,25-dihydroxyvitamin D lead to increased intestinal calcium absorption and bone resorption (13). This sustained bone resorption could lead to bone mineralisation defects such as osteopenia or osteoporosis; however, this was not present in this case (12).

Although hypercalcaemia in IH usually resolves by age 2 to 3, some individuals may experience persistent hypercalcaemia into adulthood (1, 2, 6). If undiagnosed, IH can cause serious renal complications (13). Regular follow-up and genetic testing in siblings of IH patients are recommended due to the risk of progressive chronic kidney disease and nephrocalcinosis (12, 19, 24). Long-term follow-up through dietary modifications, biochemical evaluations, and renal ultrasound is recommended to prevent complications related to hypercalcaemia and to monitor nephrocalcinosis (12). In the absence of specific guidance in literature, we recommend monitoring these patients at least once every 6 to 12 months, or more frequently if calcium levels are not controlled (25).

Conclusion

In conclusion, we presented the case of a 5-month-old girl with hypercalcaemia due to a compound heterozygous pathogenic variant in the *CYP24A1* gene. This narrative review provides valuable insights into the clinical presentation, diagnostic approach, and differential diagnosis, as well as initial management strategies for hypercalcaemia in childhood. Determining the aetiology of hypercalcaemia is critical for successful treatment, the prevention of (long-term) complications and ensuring favourable outcomes.

The authors declare that they have no conflict of interest.

Informed consent was obtained from the parents of the patient for the publication of this case report and subsequent narrative review.

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