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Case report: A 10-year-old girl with primary hypoparathyroidism and systemic lupus erythematosus

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Abstract

Hypoparathyroidism is a rare disease in children that occurs as a result of autoimmune destruction of the parathyroid glands, a defect in parathyroid gland development or secondary to physical parathyroid gland disturbance. Typical symptoms of hypoparathyroidism present as hypocalcaemia and hyperphosphatemia due to decreased parathyroid hormone secretion and may lead to nerve and muscles disturbances resulting in clinical manifestation of tetany, arrhythmias and epilepsy. Currently, there is no conventional hormone replacement treatment for hypoparathyroidism and therapeutic approaches include normalising mineral levels using an oral calcium supplement and active forms of vitamin D. We present the case of a 10-year-old girl with primary hypoparathyroidism who had no prior history of autoimmune disorders, but who subsequently developed systemic lupus erythematosus.

Keywords: primary hypoparathyroidism, hypocalcaemia, hyperphosphatemia, parathyroid hormone, systemic lupus erythematosus, autoimmune polyglandular syndrome.

Background

Hypoparathyroidism is a rare endocrine disease in children caused by parathyroid hormone (PTH) deficiency or resistance to PTH [1]. Primary hypoparathyroidism may occur as a result of either autoimmune destruction of the parathyroid glands, a congenital defect of parathyroid gland development as in DiGeorge 22q11.2 deletion syndrome, mutations in the calcium-sensing receptor gene, damage to the parathyroids during surgery, most commonly in the course of thyroidectomy, or following radiation treatment of the neck [2-4]. The typical manifestations of the disease present when all four parathyroid glands are affected and include hypocalcaemia, hyperphosphatemia and low serum PTH concentrations. The serum mineral abnormalities affect nerve and muscle functions leading to tetany, arrhythmias and seizures. There is no conventional hormone replacement therapy and the management of hypocalcaemia and hyperphosphatemia involves an oral calcium supplement and active forms of vitamin D [3].

Here, we present the case of a 10-year-old girl with primary hypoparathyroidism who had no prior history of autoimmune disorders, but who developed systemic lupus erythematosus (SLE) a few months after her diagnosis of hypoparathyroidism. To date, there are only a few reported cases of the coexistence of hypoparathyroidism and SLE [5].

Case presentation

A 10-year-old Polish female initially presented to the Department of Paediatric Neurology and Rehabilitation with convulsions. Following a confirmation of hypocalcaemia she was referred to the Department of Paediatrics, Endocrinology, Diabetology with Cardiology with suspected hypoparathyroidism. The patient had no history of mucocutaneous candidiasis and no history suggesting an endocrine or autoimmune disorder in her family. Her mental development was normal. Her weight was 35 kg (6th percentile of 10-year-old females) and her height was 141 cm (50th percentile of 10-year-old females). She was in early puberty at stage 2 on the Tanner scale, based on breast development.

The patient was admitted to our department severely unwell with drowsiness and confusion. The physical examination revealed a whole body rash that was attributed to an allergic reaction to oxcarbazepine that was being used for the treatment of convulsions. She had no features of ectodermal dystrophy or any signs of primary adrenal insufficiency. Hypoparathyroidism was diagnosed based on very low PTH levels at <3 pg/mL (reference range, 10-69 pg/mL), low total serum calcium levels at 0.80 mmol/L (reference range, 2.19-2.69 mmol/L) (Figure 1) and high plasma phosphate levels at 11.8 mg/dL (reference range, 3.4-6.2 mg/dL) (Figure 1). Alkaline phosphatase levels and serum magnesium concentrations were normal. Total serum vitamin D was low at 35 nmol/L (reference range, 50-150 nmol/L). Urinary calcium levels were lower than normal at admission.

Hormone analysis showed normal thyroid function (thyroid-stimulating hormone at 1.76 IU/L, reference range, 0.28-4.3 IU/L; free T4 at 23 pmol/L, reference range, 14-22 pmol/L). Adrenal function tests were within the normal range (cortisol at 347.3 nmol/L; adrenocorticotropic hormone at 2.8 pmol/L; adequate peak cortisol level of 749.5 nmol/L after 250 μg of tetracosactin by intravenous injection). Markers for specific for autoimmune diseases including antibodies against interferon (IFN)-ω, 21-hydroxylase, 17-α-hydroxylase,

the calcium-sensing receptor, the acetylcholine receptor, and tissue transglutaminase were not detected (Table 1). Autoantibodies associated with autoimmune thyroid disease and type 1 diabetes were also undetectable (Table 1). In blood morphology analysis, there were periodical findings indicating anaemia, leucopaenia and hypoalbuminaemia in biochemical tests.

Ultrasonography revealed a slightly enlarged spleen without any features of nephrocalcinosis and no parathyroid pathology. Echocardiography (ECG) did not reveal any heart defect. However, effusion in the pericardium was observed coinciding with the fever and elevated inflammatory markers. Long QTc (over 0.5 seconds) was recorded in the ECG. A bone densitometry scan showed normal values for bone mass density of the spine L2-L4 (Z-score +0.5) and for total body less head (Z-score +0.1). There was no ectopic calcification observed in magnetic resonance imaging (MRI) of the head. A positron emission tomography-magnetic resonance imaging (PET-MRI) scan of the whole body did not reveal any other pathologies. Electroencephalography was abnormal with pathological changes localised in temporal areas on both sides during activity and generalised paroxysmal patterns during sleep. However, there were no more epileptic seizures during clinical observation.

The patient was started on intravenous calcium gluconate at 5.5 g elemental calcium/day along with oral calcium carbonate (0.8 g elemental calcium/day), vitamin D (2000 IU/day) and the synthetic precursor of the active form of vitamin D3, alfacalcidol (2 µg/day). Hyperphosphatemia was initially treated with a diet low in phosphates. She was also treated with valproic acid for epilepsy, metoprolol for long QTc, and hydrocortisone for the first nine days to reduce her allergy symptoms. The patient's condition improved and her total serum calcium levels increased, although they remained below the normal range (Figure 1).

After fourteen days of hospitalisation, the patient developed a fever with pneumonia and pericardial effusion together with increased inflammatory markers in laboratory tests. C-

reactive protein increased significantly from 30.2 to 1497 nmol/L (reference range, 0-47 nmol/L). She was treated with antibiotics, although the blood cultures returned negative results. There was no evidence of either viral infections including HIV, B19 parvovirus, influenza or of zoonoses or tuberculosis. Furthermore, neoplastic disease was excluded following a bone marrow biopsy. During the course of a chest infection, her total serum calcium levels dropped to below 2 mmol/L. After three weeks of hospitalisation and with a high plasma phosphate level of 9.20 mg/dL, she was given sevelamer (initial dose 2.4 g/day), a phosphate-binding medication, to reduce hyperphosphatemia (Figure 1). Finally, the patient was discharged on regular oral calcium carbonate (3.6 g elemental calcium/day), sevelamer (4.8 g/day) and alphacalcidol (1 µg/day).

Taken together, the clinical symptoms, laboratory test results and the criteria of the American College of Rheumatology for SLE, in particular, epilepsy, leucopaenia, pericardial effusion and anti-nuclear antibodies, the patient was diagnosed with SLE. She was treated subsequently with chloroquine phosphate and oral prednisone (5 mg/day). This treatment unexpectedly improved the patient's calcium and phosphate levels (Figure 1) and allowed a reduction in the doses of calcium, sevelamer and vitamin D. During monthly follow up visits, the patient's serum calcium and phosphate levels continued to normalise (Figure 1), albeit with episodes of hypercalcaemia.

At four months follow-up, the patient was re-evaluated for anti-IFN-ω and anti-21-hydroylase antibodies. She was found positive for IFN-ω antibodies (antibody index 21.4, reference range <5.0) (Table 1). To further investigate the cause of the hypoparathyroidism, we evaluated genetic mutations that are typically connected with the disease. Mutational analysis of genes encoding the calcium-sensing receptor (*CASR*), guanine nucleotide-binding protein subunit alpha-11 (*GNA11*), PTH (*PTH*), glial cells missing transcription factor 2 (*GCM2*), autoimmune regulator (*AIRE*) and GATA binding protein 3 (*GATA3*) were all negative. In

addition, whole exome sequence variants in established disease genes and candidate variants in genes not yet associated with disease were negative. However, it revealed a heterozygous microdeletion in chromosome 15q11.2, inherited from the father and not reported previously to be in association with hypoparathyroidism.

Discussion

The combination of hypoparathyroidism and SLE is extremely rare therefore the underlying causes and significance of these diseases occurring in conjunction is intriguing. Hypoparathyroidism can be caused by several factors including autoimmunity affecting the parathyroid glands, damage to parathyroid glands and genetic mutations such as DiGeorge syndrome or calcium-sensing receptor-activating mutations [6, 7]. In this case, secondary hypoparathyroidism could immediately be discounted as the patient had had no surgery or trauma to the neck or parathyroid glands. The patient did not display symptoms associated with DiGeorge syndrome nor with calcium-sensing receptor-activating mutations. This was supported by mutational analysis, which did not reveal mutations in the *CASR* gene. In view of the above and the association with SLE, it was expected that hypoparathyroidism in this patient had an underlying autoimmune origin.

An autoimmune aetiology of the hypoparathyroidism in our patient was considered after her hypocalcaemia improved with glucocorticoid treatment. Autoimmune hypoparathyroidism is a major component of autoimmune polyglandular syndrome type 1 (APS1) along with chronic mucocutaneous candidiasis and primary adrenal insufficiency (Addison's disease) [8-12]. APS1 commonly manifests in childhood and our patient presents with one of the major components. However, she does not fully adhere to an APS1 diagnosis as she does not display other symptoms currently. In addition, *AIRE* gene analysis in our patient did not identify typical known genetic mutations that cause APS1. However, there may be *AIRE* gene mutations not detected by our analysis and further in-depth mutational analysis is planned. IFN-ω antibodies are highly specific for APS1 [13,14]. Interestingly, our patient initially tested negative for IFN-ω antibodies, but proved positive on re-testing several months after her initial hypoparathyroidism diagnosis. This might suggest that she is progressing towards APS1 and may in time develop another major APS1 autoimmunity. Therefore, monitoring for

chronic mucocutaneous candidiasis and Addison's disease would seem appropriate in the future. Considering an alternative APS diagnosis, there have been occasional reports of hypoparathyroidism occurring in other APS types [10, 11]. The patient does not conform to an APS2 (Addison's disease, thyroid disease and/or type 1 diabetes) or APS3 (thyroid disease plus one other non-Addison's disease autoimmunity) diagnosis. Thus APS4 (two or more autoimmune diseases not in APS types 1, 2 or 3) was considered. Our patient currently has two autoimmune diseases thus fulfils the criteria for APS4, however, as she matures, she may develop additional autoimmune endocrinopathies and her diagnosis might alter accordingly.

In summary, our case report describes the presentation and diagnosis of a 10-year-old girl with hypoparathyroidism who subsequently developed SLE. We suggest that an autoimmune mechanism, potentially associated with an underlying genetic predisposition, is responsible for the disease combination seen in our patient.

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Figure legend

Figure 1. The patient's total serum calcium and plasma phosphate concentrations over time. Shading indicates the reference ranges (total serum calcium, 2.19-2.69 mmol/L; plasma phosphate, 3.4-6.2 mg/dL). The patient's blood calcium levels were initially low (hypocalcaemia) and plasma phosphate levels were initially high (hyperphosphatemia), but both normalised following treatment with calcium and prednisone. The start-points of treatment with sevelamer (4.8 g/day) and prednisone (5 mg/day) are indicated.

242 **Table 1.** Autoantibody screening of the patient

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Antibody target	Positive/negative	Result	Reference range
Diabetes screening (Zinc transporter 8; glutamic acid decarboxylase; islet antigen IA2)	Negative	6.7 (index)	≤30 (index)
Interferon-ω (07.03.2018)	Negative	<5 (index)	<5 (index)
Interferon-ω (27.06.2018)	Positive	21.4 (index)	<5 (index)
21-hydroxylase	Negative	<0.4 u/mL	≤0.4 u/mL
Calcium-sensing receptor	Negative	0.52 (index)	1.37 (index)
Acetylcholine receptor	Negative	<0.45 nmol/L	<0.45 nmol/L
17-α-hydroxylase	Negative	<1 U/mL	<1 U/mL
Tissue transglutaminase	Negative	0.4 U/mL	<4 U/mL
Thyroid peroxidase	Negative	5.9 IU/mL	<34 IU/mL
Thyroglobulin	Negative	13.6 IU/mL	<115 IU/mL
Thyroid-stimulating hormone receptor	Negative	0.35 IU/L	<1.75 IU/L

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Learning points

1. Hypoparathyroidism in children might be caused by an autoimmune process, damage to the parathyroid glands or a genetic disorder.

2. The typical manifestations of the disease are hypocalcaemia and hyperphosphataemia that affect nerve and muscle functions leading to tetany, arrhythmias and seizures.

3. Autoimmune hypoparathyroidism is often associated with other autoimmune diseases to constitute autoimmune polyglandular syndromes, typically APS1.

4. The management of hypocalcaemia and hyperphosphatemia following decreased PTH concentrations involves supplementation with calcium and active forms of vitamin D.

What is new?

- The coexistence of hypoparathyroidism and SLE is extremely rare in children and is not typical for APS1.

- The normalisation of calcium and phosphate blood concentrations after glucocorticoid treatment for SLE, reversed the symptoms of hypoparathyroidism indicating a possible autoimmune basis for the disease.

262 **Figure 1**

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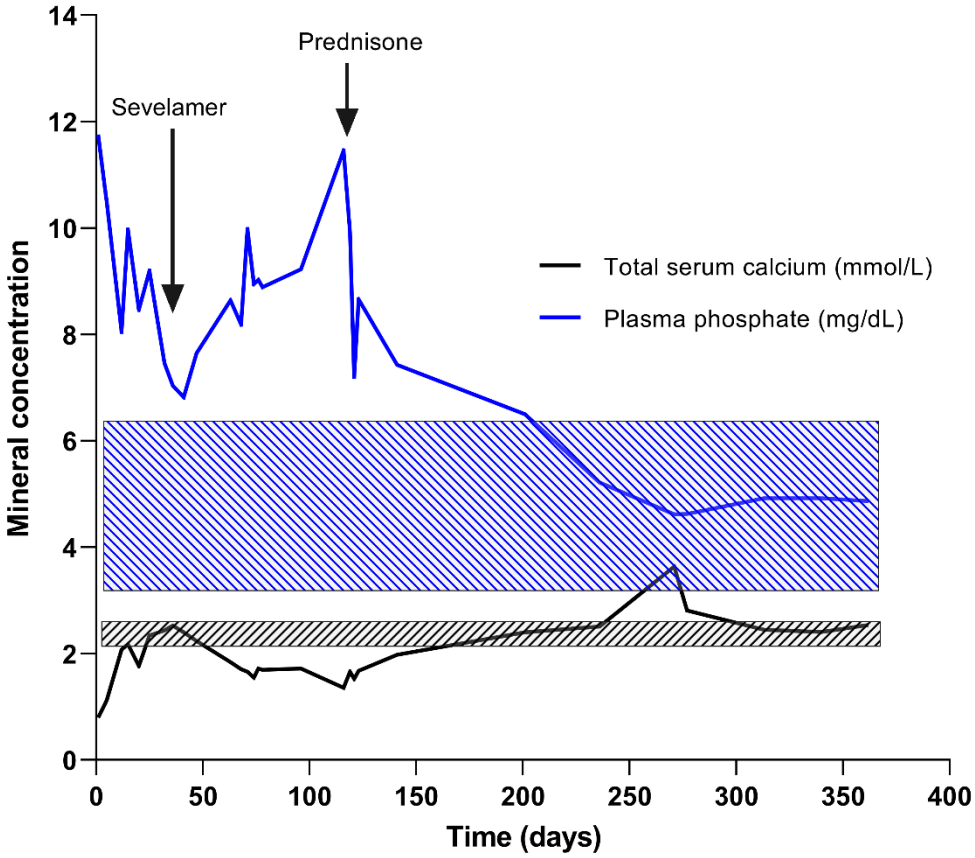

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