CASE REPORT

Successful pregnancies and reduced treatment requirement while breast feeding in a patient with congenital hypoparathyroidism due to homozygous c.68C>A null parathyroid hormone gene mutation

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SUMMARY

A female patient with consanguineous parents presented at the age of 4 with isolated hypoparathyroidism due to a parathyroid hormone (PTH) gene mutation. She was managed with alfacalcidol and calcium supplements, and developed normally. Her consanguineous parents described symptoms suggestive of hypocalcaemia but had normal serum calcium and low normal PTH levels. A molecular diagnosis obtained in her adulthood revealed the presence of homozygous point mutation (c.68C>A) in exon 2 introducing a premature stop codon resulting in a non-functional precursor protein. This mutation has been reported only once before. Our patient remained on stable doses of alfacalcidol during pregnancy, but stopped all supplementation while breast feeding. This case confirms that alternative mechanisms (likely breast-derived parathyroid hormone-related protein) contribute to calcium homeostasis during breast feeding. Heterozygotes for the c.68C>A mutation may have latent hypoparathyroidism and maintain calcium homeostasis except during prolonged hypocalcaemia. This would suggest incomplete dominance, or a dose effect of the wild-type PTH allele.

BACKGROUND

Idiopathic hypoparathyroidism comprises a rare group of disorders characterised by hypocalcaemia and hyperphosphataemia due to deficient parathyroid hormone (PTH) levels. In familial cases, this can occur in isolation, or as part of a complex autoimmune disorder. Familial isolated hypoparathyroidism (OMIM 146200) is most often caused by an activating mutation of the calcium-sensing receptor; however, mutations involving the PTH, GCM2 and GNA11 gene have also been described.^{1,2}

The human PTH gene consists of three exons and is located on chromosome 11. The first exon is non-coding, and the second exon consists of 25 amino acids of the prepropeptide sequence, as well as part of the propeptide sequence. The third exon encodes the remainder of the propeptide sequence and all 84 amino acids of the mature PTH peptide.³

Six mutations involving the PTH gene, particularly in exon 2, have been described in the literature. The first mutation was reported in 1990 by Arnold *et al* who showed a T→C point mutation at position 18 in the prepropeptide sequence in

a non-consanguineous family.⁴ Sunthornthepvarakul *et al* identified a homozygous T→C substitution at position 23 of the prepropeptide sequence on exon 2.⁵ Both these mutations are thought to lead to ineffective processing of the prepropeptide sequence. Parkinson and Thakker identified a single base substitution (G→C) on the 5' donor splice site causing exon 1 to splice onto exon 3.⁶ The loss of exon 2 resulted in the loss of the ATG initiation codon required for the commencement of PTH mRNA translation.

Lee *et al* identified a homozygous A→C mutation at position 25 of the mature PTH polypeptide which reduces bioactivity of the secreted hormone and also resulted in wide variations in PTH measurements depending on the PTH assay used.⁷ Cinque *et al* recently reported on a heterozygous missense variant in PTH gene exon 2 (c.41T>A) that resulted in the impaired secretion of mutant PTH compared with wild type.⁸

Another homozygous mutation at position 23 of the PTH prepropeptide sequence was reported by Ertl *et al* in 2012. This C→A substitution (c.68C>A) results in the insertion of a premature translational stop codon (p.Ser23X) within the propeptide sequence (figure 1).⁹ Thus, no biologically active PTH can be produced.

Our case is the first adult case to be described of the recently identified c.68C>A PTH mutation, and the first to postulate that heterozygotes may exhibit latent hypoparathyroidism due to a dose effect of the wild-type PTH allele. We also describe our experience managing her through pregnancy and breast feeding. While there are a number of excellent reviews of the management of hypoparathyroidism in pregnancy, it has not been specifically described in patients with a known PTH mutation.

CASE PRESENTATION

The patient is the only child of a consanguineous relationship (figure 2). In 1993, she presented with symptomatic hypocalcaemia at the age of 4 after a 1-week-long illness with gastroenteritis. She had painful carpopedal spasm, increased tone in the lower limbs and was Chvostek's sign positive. Mildly dysmorphic features such as a fine elfin face, unfolded pinnae and hypertelorism were noted. She had irregular dentition with horizontal

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Figure 1 c.68C>A parathyroid hormone (PTH) mutation at the prepropeptide sequence resulting in premature stop codon. aa, amino acids.

striation. Examination was otherwise unremarkable. At presentation, serum corrected calcium was 1.12 mmol/L (2.10–2.55 mmol/L), phosphate 2.71 mmol/L (0.8–1.5 mmol/mol) and PTH undetectable at <0.2 pmol/L (1.7–7.3 pmol/L). Alkaline Phosphatase 407 U/L (40–100 U/L), creatinine 0.05 mmol/L (<0.044 mmol/L), magnesium 0.55 mmol/L (0.7–1.00 mmol/L) and urinary calcium 2.2 mmol/L.

In retrospect, she had presented previously with episodes possibly consistent with stridor, and had a history of muscle cramps. Initial investigations confirmed hypoparathyroidism and she was started on calcium and alfacalcidol with improved serum calcium levels. Chromosomal analysis showed normal 46XX karyotype. She tested negative for 22q11.2 deletion and had normal B and T cell studies excluding DiGeorge syndrome. There were no features to suggest polyendocrinopathy.

Her father reportedly suffered from episodic cramps, had poor dentition and regularly took calcium supplements. Serum corrected calcium levels were normal at 2.11 mmol/L, phosphate 1.08 mmol/L with low PTH at 1.4 pmol/L after stopping calcium for 3 weeks (symptomatic with cramps at the time of testing). Her mother had poor dentition and developed cramping with

exercise but calcium and PTH levels were within normal limits when tested (table 1). They both underwent an EDTA challenge in 1996 (table 2, figure 3) with a 2.5-fold increase in PTH levels from baseline. Both parents had low vitamin D levels, 24 pmol/L and 26 pmol/L (65–175 pmol/L), during the EDTA challenge. The slopes of the regression lines were similar to those of the normal subjects ($r=0.857$) reported by Gidding *et al*. The results of the EDTA challenge indicate both parents had normal secretory PTH reserve.¹⁰

Her mother's siblings died young: one brother died at the age of 21 from suicide, another brother died as neonate and a sister died shortly after birth from possible anencephaly. Her father's siblings are said to have poor dentition but not cramping.

The index patient was treated with alfacalcidol drops and calcium carbonate throughout her childhood with normal physical and cognitive development. She presented intermittently with symptomatic hypocalcaemia associated with intercurrent illness or medication non-adherence. She was followed until the age of 20 (2009) when she relocated.

INVESTIGATIONS

See tables 1 and 2 for details of the investigation.

OUTCOME AND FOLLOW-UP

She re-engaged with medical services in 2012 after presenting with symptomatic hypocalcaemia. Her PTH remained undetectable at <0.3 pmol/L (1.5–7.6 pmol/L). She fell pregnant shortly thereafter and further genetic testing was arranged. She tested negative for a mutation in the calcium sensing receptor gene,

Figure 2 Schematic diagram of family tree.

Table 1 Biochemical findings in analysed family members				
Family member	Calcium (mmol/L)	Phosphate (mmol/L)	PTH (pmol/L)	Magnesium (mmol/L)
Patient (III.II)	1.12	2.71	<0.2	0.55
Mother (II.I)	2.19	1.25	2.8	0.74
Father (I.I)	2.11	1.08	1.4	0.82
Daughter (IV.I)	2.50	2.26	1.3	0.91
Daughter (IV.II)	2.45	2.02	8.1	N/A

Normal ranges: calcium 2.10–2.55 mmol/L, phosphate 0.70–1.50 mmol/L, PTH 1.7–7.3 pmol/L, and magnesium 0.7–1.0 mmol/L. PTH, parathyroid hormone.

Table 2 EDTA challenge in parents

	Ca ²⁺	Ca	PTH	PO ₄	Mg
Father					
Time 0	1.11	2.13	1.8	1.29	0.92
+30 min	1.07	2.02	3.0	1.24	0.73
+60 min	0.98	1.96	3.8	1.17	0.66
+90 min	0.96	1.83	4.6	1.11	0.55
+120 min	0.93	1.81	3.7	1.06	0.53
+150 min	0.88	1.71	4.5	1.00	0.50
Mother					
Time 0	1.15	2.17	1.9	0.83	0.83
+30 min	1.08	2.03	4.0	0.96	0.64
+60 min	1.02	1.89	4.0	0.88	0.56
+90 min	0.95	1.78	4.2	0.81	0.53
+120 min	0.91	1.70	4.7	0.75	0.49
+150 min	0.87	1.65	5.2	0.73	0.47

Normal ranges: ionised calcium 1.15–1.3 mmol/L, calcium 2.10–2.55 mmol/L, phosphate 0.70–1.50 mmol/L, PTH 1.7–7.3 pmol/L, magnesium 0.7–1.0 mmol/L. PTH, parathyroid hormone.

however, was found to be homozygous for C to A nucleotide substitution in exon 2 of PTH. This results in a premature stop codon and no biologically active PTH as previously described.⁹ Unfortunately, neither of her parents are able to be genotyped.

The patient has been followed through two successful pregnancies. During the first pregnancy, she was initially prescribed 1.5 µg calcitriol with 2400 mg elemental calcium daily. At 24/40 gestation, the calcium supplements were stopped and she continued on 1.5 µg of calcitriol alone. She was changed to alfacalcidol 2.0 µg daily at 30/40 gestation and reduced to 1.5 µg 1 month later which she continued until delivery. While on calcitriol, her serum corrected calcium level was between 1.8 and 2.0 mmol/L; this improved during the third trimester on alfacalcidol to 2.1–2.3 mmol/L. She developed gestational diabetes at 35/40 gestation with positive oral glucose tolerance test and was started on low-dose insulin. She delivered a healthy baby girl who was subsequently found to have normal calcium and low PTH levels. Our patient did not require any calcium or vitamin D supplementation while breast feeding until hypocalcaemic symptoms recurred 6 months post partum as the infant started weaning.

During her second pregnancy, she remained on 1.5 µg of alfacalcidol throughout and remained asymptomatic. Infrequent blood tests showed serum corrected calcium between 1.9 and 2.1 mmol/L. Towards the end of pregnancy and during

Figure 3 Parathyroid hormone (PTH)–calcium curve. $r=0.888$ (father) and $r=0.904$ (mother).

the first few months of breast feeding, she reported non-adherence with alfacalcidol, no hypocalcaemic symptoms were noted and there were no presentations to hospital with hypocalcaemia. She was restarted on 0.5 µg alfacalcidol 3 months post partum and continued this until 9 months post partum when her serum corrected calcium fell to 1.70 mmol/mol coincident with weaning. Her alfacalcidol dose was subsequently increased.

Both pregnancies were uncomplicated and she delivered two healthy babies at term. Her children had calcium, phosphate and PTH levels measured at birth and one was found to have low PTH level (table 1). The second child had an elevated PTH level at birth likely due to maternal hypocalcaemia during pregnancy from non-compliance with medications. This result is planned to be repeated but has not yet been done. Neither child has required admissions to hospital with hypocalcaemia thus far.

DISCUSSION

The recommended management of hypoparathyroidism during pregnancy is uncertain, with some case reports suggesting increased calcitriol requirements and some decreased requirements.^{11–13} During pregnancy, multiple physiological adaptations affect calcium homeostasis such as increased calcium absorption in the intestines and increased levels of calcitriol, parathyroid hormone-related protein (PTHrP) and other factors in the circulation. Calcium and calcitriol requirements typically decrease during lactation and this is thought to be due to breast-derived PTHrP levels.¹² Our patient remained on a stable dose of calcitriol throughout pregnancy but stopped exogenous supplementation during breast feeding. On this basis, we suggest that the management of hypoparathyroidism during pregnancy should be individualised based on regular monitoring of calcium levels, aiming for the low normal range.

Our patient was diagnosed with congenital hypoparathyroidism at the age of 4, much later than previously reported cases. Most previous cases were identified as neonates due to tetany or seizures. In the initial case reporting the c.68C>A PTH mutation, intact PTH concentrations were low but detected at 2.1 pg/mL (15–65 pg/mL).⁹ Ertl *et al* postulated that there may have been transcriptional read-through of the premature stop codon resulting in PTH translation but at inadequate levels to maintain normal calcium levels. It is possible our patient had experienced this phenomenon with low levels of PTH initially to remain relatively asymptomatic; however, the undetectable PTH levels observed on multiple occasions throughout her life would suggest this is an unlikely escape mechanism.

Her parents are presumed to be heterozygotes for the c.68C>A mutation and both described symptoms of cramping, particularly at times of physiological stress. Calcium and phosphate levels were within normal limits but PTH levels were low in her father. Her daughters are also heterozygotes for the mutation and one was found to have low but detectable PTH level. In the original case presented by Ertl *et al*, one of the siblings was also noted to have low PTH levels with normal calcium and phosphate levels. This sibling was likely the carrier sibling although this was not evident from the report.

This suggests that the c.68C>A mutation may exhibit a dose effect in the heterozygote state. Normal parathyroid chief cells typically store sufficient preformed PTH to sustain hypocalcaemia-induced PTH release for 60–90 min *in vivo*.³ The normal EDTA challenge in her parents suggests sufficient PTH reserve

with normal secretory rate to respond to acute changes in calcium levels. However, heterozygotes for the c.68C>A mutation may not be able to adequately upregulate the wild-type gene in order to generate sufficient PTH during stress or prolonged episodes of hypocalcaemia.

Our case highlights that congenital hypoparathyroidism may not be diagnosed in infancy, and thus should be considered at any age if there is a strong familial component. Analysis of the family members in this case suggests that the c.68C>A mutation may result in the reduced rate of PTH production, and therefore carriers may only become symptomatic at times of prolonged hypocalcaemia. This however requires further investigation. With this proposed mechanism in mind, patients previously diagnosed with 'idiopathic' hypoparathyroidism may have a PTH mutation as the underlying basis of their disease. As more mutations are discovered and testing increases, we may be able to understand more about the frequency and mechanisms of these rare conditions.

Learning points

- ▶ Management of hypoparathyroidism during pregnancy should be individualised based on regular serum calcium monitoring, aiming for low normal levels.
- ▶ Congenital hypoparathyroidism can present later in life and should be considered at any age particularly if there is a strong familial component.
- ▶ Heterozygotes for the c.68C>A mutation may have latent hypoparathyroidism and become symptomatic at times of prolonged hypocalcaemia; this observation requires more investigation.
- ▶ Patients previously diagnosed with 'idiopathic hypoparathyroidism' may have an underlying parathyroid hormone mutation as the basis of their disease. New mutations are continually being reported and as testing increases, we will gain more understanding about these rare conditions.

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