

ORIGINAL ARTICLE

Prevalence of clinical remission in patients with sporadic idiopathic hypoparathyroidism

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Summary

Background Remission of disease activity is a characteristic feature of autoimmune endocrine disorders such as Graves' disease, Addison's disease and occasionally in patients with premature ovarian failure. Autoimmunity is also implicated in sporadic idiopathic hypoparathyroidism (SIH) with clinical remission of disease reported in three cases.

Objective To assess the rate of remission in patients with sporadic idiopathic hypoparathyroidism and review the cases reported so far.

Subjects and methods Subjects included 53 patients (M:F, 24:29) with SIH who had been symptomatic for at least 1 year (range 1–31 years). They were treated with calcium and 1- α -(OH) D_3 /cholecalciferol therapy and had a mean duration of follow up of 5.0 ± 3.2 years. Treatment was withdrawn in two stages in the patients who maintained normal levels of serum total calcium during the preceding year of treatment. In stage-1, the dose of therapy was reduced to half and subsequently all treatment was stopped (stage 2) in those patients who maintained normal serum total calcium levels on the reduced dose. Remission of SIH was defined as maintenance of normal serum total (≥ 2.12 mmol/l) and ionized calcium, inorganic phosphorus and serum intact parathyroid hormone (iPTH) for at least 3 months after withdrawal of calcium and 1- α -(OH) D_3 /cholecalciferol therapy. Calcium sensing receptor autoantibodies (CaSRAb) were determined by Western blot.

Results Two of the 53 patients (3.8%) with SIH stayed in remission for 1 year after complete withdrawal of therapy. CaSRAb was absent in both the cases. The clinical features, age at onset and duration of hypocalcaemic symptoms in cases with remission were comparable to those who did not show remission.

Conclusion Sporadic idiopathic hypoparathyroidism is not irreversible as is widely believed and spontaneous remission of disease may occur in 3.8% of patients.

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Introduction

Remission is a characteristic feature of autoimmune endocrine and nonendocrine disorders such as Graves' disease,^{1,2} adrenal insufficiency,³ premature ovarian failure,^{4,5} vitiligo⁶ and rheumatoid arthritis.⁷ Blizzard *et al.* first identified autoantibodies to parathyroid tissue in sporadic idiopathic hypoparathyroidism (SIH) in 1966 and suggested that this disease may have an autoimmune origin.⁸ Subsequently, four other studies have reported the presence of calcium sensing receptor autoantibodies (CaSRAb) in patients with SIH.^{9–12}

Interestingly, there are three case reports of spontaneous remission in SIH.^{11,13,14} We have a large cohort of patients with SIH on follow up.^{9,15–18} One of them stopped her replacement therapy of calcium and cholecalciferol without medical consultation and returned for follow up after 3 years. She had no symptoms of hypocalcaemia and her serum total calcium, inorganic phosphorus and parathyroid hormone levels were normal. This observation prompted us to systematically assess for the possibility of remission in SIH.

Subjects and methods

Subjects

The study was conducted in the Department of Endocrinology and Metabolism at the All India Institute of Medical Sciences, New Delhi during 2007–2008. The 53 subjects included were part of a larger cohort of 110 patients with SIH who have been treated by us since 1998.^{15–18} The criteria used to diagnose SIH included presence of hypocalcaemia and hyperphosphataemia in association with subnormal or an inappropriately normal level of serum intact PTH (iPTH), normal serum total magnesium and renal function.¹⁹ None of the patients had clinical or biochemical features of haemochromatosis. Patients with postsurgical hypoparathyroidism were excluded. None of them had a family history of hypoparathyroidism

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or features of autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy syndrome.²⁰ Autoimmune adrenal disorders were excluded by demonstrating absence of adrenal cortical autoantibodies by indirect immunofluorescence²¹ and normal plasma ACTH and cortisol (08:00 hours) levels. Six of the 53 (11.3%) subjects had thyroid peroxidase autoantibodies (TPOAb) and one had thyroid dysfunction at presentation. These findings were similar to those reported by us in our larger cohort of patients with SIH.¹⁶

All the subjects were enrolled after ethical clearance of the Institutional ethics committee and written informed consent. They were put on oral calcium carbonate (elemental calcium, 2 g/day, Elder Pharmaceutical, India) and 1- α -(OH) D₃ (0.25–2.0 μ g/day, Cipla Pharmaceutical, India or Panacea Biotech, India) or cholecalciferol (60,000 IU/alternate days, Cadila Pharmaceutical, India) to maintain serum total calcium between 1.99–2.12 mmol/l.¹⁹ Patients were called for follow up at intervals of 3 months.

Assessment of remission of disease

To date, there are no criteria to define remission of disease in SIH. In this study a two-stage protocol involving stepwise withdrawal of therapy was devised to assess remission (Fig. 1).

Patient selection for assessment for remission. After the diagnosis of SIH, a minimum period of 1 year of follow up was considered essential before assessing them for remission. Patients who could not be followed were excluded from the study. In other patients a minimum of three values of serum total calcium, measured at least 1 month apart, while they were on calcium and 1- α -(OH) D₃/cholecalciferol therapy were assessed. Patients with any value <2.12 mmol/l were considered to have persistent disease. Only patients with at least three values of serum total calcium \geq 2.12 mmol/l over 1 year were assessed further.

Stage I: Reduction in the dose of calcium and 1- α -(OH) D₃/cholecalciferol. The dose of oral calcium and 1- α -(OH)D₃/cholecalciferol was reduced to half in patients who maintained serum total calcium values \geq 2.12 mmol/l over 1 year as discussed above. They were followed up every month for the next 3 months. In case of occurrence of symptoms of hypocalcaemia they were asked to contact any of the two authors (RG or SG) by telephone. On follow up visits, the patients were examined clinically for signs and symptoms of hypocalcaemia and blood samples were taken for estimation of serum total calcium, inorganic phosphorus, iPTH and 25(OH)D. Patients with serum total calcium less than 2.12 mmol/l were classified as having persistent disease.

Stage II: Withdrawal of calcium and 1- α -(OH) D₃/cholecalciferol therapy. Patients who maintained serum total calcium levels \geq 2.12 mmol/l on the halved dose of calcium and 1- α -(OH) D₃/cholecalciferol during Stage I were evaluated further. Therapy was stopped completely and they were examined clinically and biochemically every month for the next 3 months. Patients in whom serum total calcium fell below 2.12 mmol/l were classified as having persistent disease.

Patients who did not show any signs and symptoms of hypocalcaemia and maintained normal serum total calcium, inorganic phosphorus and iPTH values on all the three follow up visits after withdrawal of the treatment were categorized as having undergone clinical remission. Normalization of serum calcium was also confirmed by measurement of ionized calcium on their last visit.

Biochemical assays

Serum total calcium, inorganic phosphorus and alkaline phosphatase were measured using an automated analyser (Hitachi 917, Roche, Mannheim, Germany; normal range (NR); 2.12–2.59,

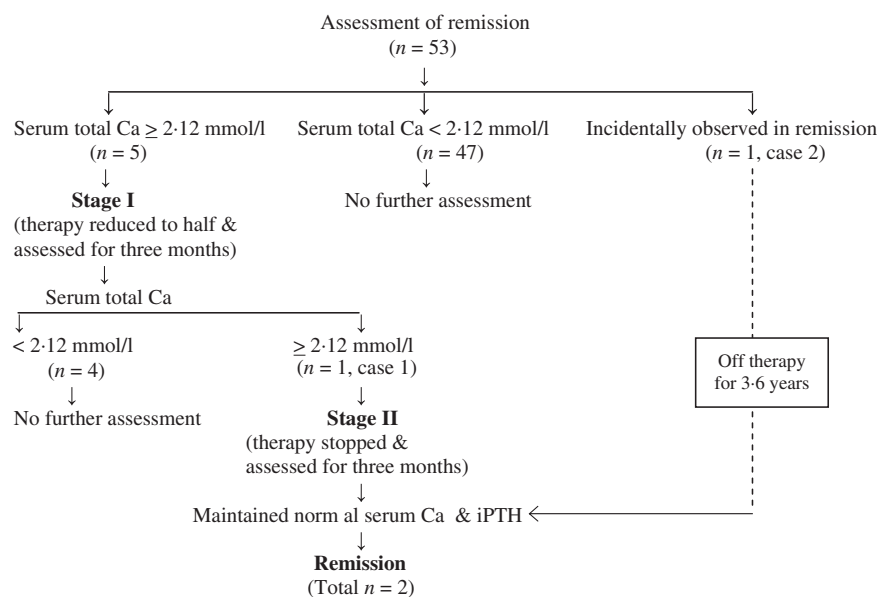


Fig. 1 Summary of the protocol for the assessment of remission in patients with sporadic idiopathic hypoparathyroidism (SIH).

0.81–1.45 mmol/l and 98–279 IU/l respectively). Serum magnesium was measured using Cobas Integra 400 (Roche, NR: 0.70–1.05 mmol/l). Intra-assay and interassay coefficients of variation for these assays ranged from 3.5 to 5.0%. Serum 25(OH)D was measured by radio-immunoassay (Diasorin; NR: 22.5–93.8 nmol/l). Serum iPTH, TPOAb and ferritin were measured by electrochemoluminescence immunoassay (Elecsys-2010, Roche diagnostics, Mannheim Germany; NR, iPTH = 1.6–6.8 pmol/l, ferritin, males = 67–898 and females = 34–337 pmol/l, TPOAb <34.0 IU/ml).

Calcium sensing receptor autoantibodies

Western blot assay was used to detect CaSRAb in the serum of patients showing remission. The assay was performed as described in our earlier study,⁹ except that the antigen used was the recombinant extracellular domain of the calcium sensing receptor. The positive control used consisted of polyclonal antibodies against the N terminal of the extracellular domain of the calcium sensing receptor (CasR-H-100, Santa Cruz Biotechnology, CA, USA) (Fig. 2).

Assessment of *GNAS1* gene

Genomic DNA was obtained from peripheral leucocytes for sequencing *GNAS1* in one of the patients (case 1) to exclude pseudohypoparathyroidism. Sequencing of all the 13 coding exons was performed using a set of 10 pairs of primers as described by Ahrens *et al.*²² and Big Dye[®] v3.1 Cycle Sequencing Chemistry on the ABI PRISM[®] 310 Genetic Analyzer (Applied Biosystems, CA, USA).²¹ The nucleotide sequences were compared with the published sequence of human *GNAS1* gene (GenBank accession no. NT_011362.9).

Statistical analysis

The data is given as mean \pm SD and percentages. Statistical analysis was performed using SPSS statistical software (version 10.0; SPSS Inc, Chicago, IL, USA).

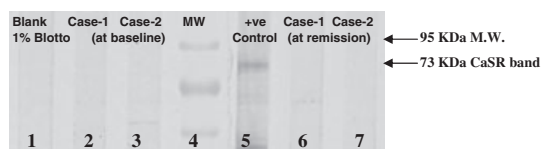


Fig. 2 Western blot for analysis of CaSRAb positivity in two patients with SIH showing clinical remission. A 7% SDS–PAGE performed using minigel electrophoresis apparatus (Hoeffer, San Francisco, CA, USA). Lane 4 contains molecular weight marker. All other lanes contain 20 μ g of extracellular domain of recombinant CaSR protein expressed in *Escherichia coli* C43 (DE3) using pProExHtb vector. Lane 5 is the positive control antibody (1:200 dilution) showing immunoreactivity against CaSR at 73 kDa (CasR-H-100, Santa Cruz Biotechnology, CA, USA). Lane 1 is blank and contained with no primary antibody but only 1% blotting. Lane 2 & 3 and 6 & 7 contained sera of two patients each in dilution of 1:50 at presentation and again at the time of remission respectively, showing absence of CaSRAb. Secondary antibody used was antihuman alkaline phosphates conjugated antibody used in 1:2000 dilution (Dako, Glostrup, Denmark).

Results

The male female ratio (M 23, F 28), body mass index (20.9 ± 3.8 kg/m²), mean age at presentation to the hospital (27.4 ± 3.8 years), total duration of symptoms (9.3 ± 6.7 years), mean duration of follow up (5.0 ± 3.2 years), serum total calcium (1.35 ± 0.24 mmol/l), inorganic phosphorus (2.23 ± 0.48), iPTH (1.21 ± 0.88) values, frequency of basal ganglia calcification (72.2%) and cataract (55.6%) among the 53 study subjects at presentation were comparable to that reported by us in the larger cohort of patients with SIH.^{15–18}

Patient selection for assessment of remission

In the present study the 53 patients with SIH had mean serum total calcium level of 1.85 ± 0.29 mmol/l during 1 year of follow up on therapy. Only six of them (11.3%) had normal serum total calcium on three or more occasions while on therapy with calcium and 1- α -(OH) D₃ (mean value: 2.29 ± 0.13 mmol/l) and were assessed further.

Stage I: Reduction in dose of calcium and 1- α -(OH) D₃/cholecalciferol

Five of the 53 patients fulfilled the criteria for inclusion in stage I. The dose of calcium and 1- α -(OH) D₃ was reduced to half in all of them. Within a month, serum total calcium fell to below <2.12 mmol/l in four of them. Their individual serum total calcium values were 1.79, 1.64, 2.04 and 2.07 mmol/l and corresponding iPTH values were 0.34, 0.70, 4.71 and 0.13 pmol/l respectively. These four patients were put back on the full therapeutic regimen and classified as having persistent disease.

Stage II: Withdrawal of therapy

The patient who had normal serum total calcium on reduction of therapy in stage I maintained normal serum total calcium and ionized calcium levels for three months following complete withdrawal of therapy. This case and the one which was incidentally observed to be in remission were therefore considered to have achieved remission of SIH. They did not have clinical features of sarcoidosis (potential mechanism of reversible hypoparathyroidism) and their X-ray chest, Mantoux test and serum angiotensin converting enzyme levels were normal. The details of these two patients at presentation, during stage I and II are described below and summarized in Table 1.

Case 1, presented to us at the age of 17 years in 2000 with short stature (145 cm, <5th percentile) and absence seizures for 4 years. Slit lamp examination revealed posterior subcapsular cataract and computerized tomography showed bilateral basal ganglia calcification. His serum total calcium and inorganic phosphorus were 1.72 and 2.22 mmol/l respectively and iPTH values were 5.58 and 2.63 pmol/l on two different days. His 24 h urine calcium excretion was 77 mg. Renal and thyroid function tests and serum TPOAb titers were normal and CaSRAb was absent. He was put on oral elemental calcium (2.0 g/day) and cholecalciferol (60,000 IU/

Table 1. Serum biochemical parameters in two cases with sporadic idiopathic hypoparathyroidism who showed remission, at the time of presentation, stage I and II of the study

Patients (case identity)	At presentation			Stage I (Reduction of Ca and vitamin D ₃ therapy)		Stage II (3 months after complete withdrawal of Ca and vitamin D ₃ therapy)				After 1 year of complete withdrawal of therapy			
	Total Ca	PO ₄	iPTH	Total Ca	PO ₄	Total Ca	iCa	PO ₄	iPTH	Total Ca	iCa	PO ₄	iPTH
SD (1)	1.72	2.22	*2.63/5.58	2.50	1.51	2.45	1.10	1.32	2.63	2.39	1.15	1.51	3.72
NI** (2)	1.59	1.99	0.86	NA	NA	2.17	1.19	1.48	2.84	2.14	1.28	1.45	2.35

Normal range for serum calcium (Ca) = 2.12–2.59 mmol/l; inorganic phosphorus (PO₄) = 0.81–1.45 mmol/l; intact parathyroid hormone (iPTH) = 1.6–6.8 pmol/l; ionized calcium (iCa) = 1.10–1.38 mmol/l.

*PTH sample repeated on two different occasions before the start of treatment to confirm PTH values.

**Data not available (NA) for stage I, as the patient came to us after 3 years of withdrawal of therapy.

alternate days) along with carbamazepine (200 mg/day) following which his serum calcium normalized (≥ 2.12 mmol/l). In view of his short stature and normal PTH values, the DNA sequence of coding exons of *GNAS1* gene was also performed to rule out pseudohypoparathyroidism. Coding sequence of all the 13 exons was normal.

His serum total calcium had decreased to 1.99 mmol/l on two occasions in 2001 attributable to poor compliance with therapy. However, since 2006, all of his serum calcium values were ≥ 2.12 mmol/l and serum inorganic phosphorus values were normal. He attained a height of 167 cm (between 50th–90th percentile for Delhi males, http://icmr.nic.in/final/lg_48.html). His treatment was reduced to half the dose in 2007 and was completely withdrawn in 2008. The patient has maintained normal serum calcium, phosphorus and iPTH values for the past 1 year (Table 1). His serum 25(OH)D, assessed at 1 year of complete withdrawal of therapy was, 24.2 nmol/l.

Case 2 (mentioned in the introduction) presented to us at the age of 18 years in 2002 with complaint of cramps for 4 years. Examination revealed positive Chvostek's and Trousseau's signs. Her serum total calcium, inorganic phosphorus and iPTH values were 1.59, 1.99 and 0.86 pmol/l respectively. Baseline renal function and thyroid function tests were normal. There was no cataract or basal ganglia calcification. She was put on oral elemental calcium (2.0 g/day) and cholecalciferol (60,000 IU/alternate days). Her serum total calcium values were in the normal range (≥ 2.12 mmol/l) after 6 months of therapy. While on treatment, her 24 h urine calcium excretion was 120 mg. Her serum total calcium decreased to 1.77 mmol/l in 2004 attributable to poor compliance with therapy. Subsequently she did not report for follow up until we contacted her again in 2008 for assessment of remission. History revealed that she had stopped all the medicines for the past 3 years. Reassessment of her serum total calcium, phosphorus and iPTH revealed normal values (Table 1). However, her repeat thyroid function test showed primary hypothyroidism with serum total T4 of 65.5 nmol/l and TSH of 42.5 mU/l for which she was put on thyroxine therapy. Serum TPOAb titres were normal and CaSRAB could not be detected at presentation and at remission (Fig. 2). Now she is in regular follow up and continues to be in remission

with normal serum calcium, phosphorus and iPTH values (Table 1) and serum 25(OH)D value of 48.7 nmol/l.

Discussion

Sporadic idiopathic hypoparathyroidism is considered to be an irreversible disorder. The results of this study reveal that remission of disease may be possible in patients with SIH. We adopted a careful approach to define remission and observed a remission rate of 3.8% in patients with SIH. Their mean duration of symptoms was 9 years and the mean follow up was of 5 years. Most of our patients with SIH suffered from recurrent attacks of hypocalcaemia during treatment because of noncompliance with the expensive treatment. In fact, 88.7% could not maintain their serum calcium levels ≥ 2.12 mmol/l. The two patients who went into remission had also experienced episodes of hypocalcaemia during the first few years of treatment.

The rate of remission observed in this study can at best be described as modest. However if we had used less strict criteria, it is possible that more patients would have been classified as being in remission. For instance, we graded all patients with serum total calcium levels below 2.12 mmol/l as having active disease. According to the statistical normal distribution serum calcium is below the lower limit of normal in 2.5% of the population. Thus, a minimum of four out of the 53 patients included could realistically be expected to have one value below 2.12 mmol/l even when their disease was in remission.

Spontaneous remission of disease in hypoparathyroidism has been reported only in three cases to date.^{11,13,14} Posillico *et al.* reported a 70-year-old male with history of intermittent hypocalcaemia of a few year duration who showed fall of serum calcium to 1.72 mmol/l following an episode of haemorrhagic cerebrovascular accident.¹³ The patient had normal serum magnesium and C terminal PTH values. After 1 month serum total calcium was 1.99 mmol/l and PTH was low normal. The rise in serum total calcium levels correlated with a decline in levels of PTH secretion inhibiting autoantibodies against the parathyroid cell surface.

In 2004, Kifor *et al.* reported a 25-year-old male with hypothyroidism and primary adrenal insufficiency who had subnormal serum

total and ionized calcium levels (2.0 and 1.0 mmol/l respectively) and activating CaSRab.¹¹ Though serum total magnesium level was mildly decreased (0.62–0.7 mmol/l, NR = 0.74–1.04 mmol/l), serum intact PTH values were normal on two occasions (3.8 and 2.3 pmol/l, NR = 1.05–6.84 pmol/l). When re-evaluated after 3 and 13 months, he had normal serum total calcium levels.

Furuto-Kato *et al.*¹⁴ described a 67-year-old female with numbness of the fingers and low serum total calcium (1.62 mmol/l), inappropriately normal serum intact PTH of 1.4 pmol/l and normal serum magnesium levels. Her serum calcium normalized following treatment with 1,25(OH)₂D₃ (1.5–2.0 µg/day). Treatment was then tapered off over the next 9 months. After 1 year of follow up, her serum calcium and intact PTH levels had risen above the normal range and she underwent parathyroidectomy. The left upper parathyroid gland removed was larger than the other glands and showed lymphocytic infiltration. However, parathyroid specific autoantibodies were not assessed.

In this study we could not identify specific clinical features which correlate with the phenomenon of remission. Interestingly, two of the three previously reported cases^{11,14} and case 1 of this study had normal serum PTH values. While normal serum iPTH values in the presence of hypocalcaemia reflect partial hypoparathyroidism, it can also be regarded as evidence of a sufficient number of viable PTH secreting parathyroid cells. Thus, the presence of normal serum iPTH values at baseline or during therapy could suggest potential for recovery. In these patients and in those who maintain normal serum calcium continuously for at least a year, the physician may attempt reduction of ongoing therapy with monitoring of serum calcium values. The presence of normal serum total calcium and PTH levels on complete withdrawal of therapy indicates remission of the disease. However, more data on SIH and remission would be required to substantiate these guidelines.

Hypomagnesaemia and sarcoidosis (due to expression of 1-alpha-hydroxylase) are possible causes of 'reversible' hypoparathyroidism.^{23,24} Recently, Ebstein *et al.* reported hypomagnesaemia and reversible hypoparathyroidism following use of proton pump inhibitors.²³ In fact, one of our patients (not included in the study) had also used rabeprazole 20 mg/day for 2 months followed by occurrence of hypomagnesaemia and hypocalcaemia, both of which reversed following withdrawal of rabeprazole. Hypomagnesaemia and sarcoidosis were excluded as possible causes of remission in both the patients who showed remission in this study.

The molecular mechanisms involved in the pathogenesis of SIH are under investigation. The hypothesis of an autoimmune origin is favoured because of demonstration of (a) CaSRab in these patients,^{9–12} (b) lymphocyte infiltration observed at autopsy in a few patients with hypoparathyroidism²⁵ and (c) generalized activation of T cells.²⁶ Theoretically, patients with SIH may achieve remission by switching anti CaSRab production from the 'activating' to the 'inactivating' type, akin to that observed in autoimmune thyroid disorders.^{27,28} De Bellis *et al.* have described reversibility of subclinical adrenocortical insufficiency following the disappearance of low titres of antiadrenal autoantibodies.⁴ Similarly Rebar *et al.* have documented spontaneous ovulation and pregnancy in 20% of women with premature ovarian failure.⁵

One of two patients with clinical remission had primary hypothyroidism which can be considered as indirect evidence for the involvement of an autoimmune mechanism. Though CASRab was absent in both patients with remission, they might have other serological markers for parathyroid autoimmunity such as autoantibodies against the new parathyroid auto antigen Human NACHT, leucine-rich-repeat and pyrin domain containing protein 5 (NALP5).²⁹

Thus, this report shows that it is possible for patients with sporadic idiopathic hypoparathyroidism to achieve spontaneous remission following treatment with calcium and vitamin D. Such remissions are rare and observed in only 3.8% of cases. Nevertheless, the observation has clinical relevance when explaining the prognosis of the disease to patients. Besides, it supports the theory of an autoimmune basis for this disease and provides scope for exploring novel immunomodulatory/immunosuppressive therapies to induce remission in these patients.

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Competing interests/financial disclosure

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. This research did not receive any specific grant from any funding agency in the public, commercial or not for profit sector.

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