Late-onset postsurgical hypoparathyroidism following parathyroidectomy for recurrent primary hyperparathyroidism: a case report and literature review

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Concise title: Late-onset postsurgical hypoparathyroidism

Keywords: hyperparathyroidism-jaw tumor syndrome, CDC73, parafibromin, parathyroidectomy

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Abstract

Purpose Previously in 1987, a 21-year-old-male was diagnosed with primary hyperparathyroidism (PHPT) when a right inferior parathyroid adenoma was removed. PHPT recurred after three and six years and on both occasions was cured by resection of parathyroid adenomas. At 52-years-of-age, the patient developed a late-onset hypoparathyroidism (HP), even though postsurgical HP typically occurs as a transient or permanent form soon after neck surgery. The purpose of this work was to report the follow-up of the patient and to review prior cases of late-onset postsurgical HP.

Methods Prior cases of late-onset postsurgical HP were searched and reviewed focusing on clinical and biochemical features.

Results The patient's asymptomatic hypocalcemia with total serum calcium at 8.2 mg/dL was initially documented in September 2018; PTH was inappropriately low at 15 ng/mL. In February 2020, a mild hypocalcemia was confirmed with low-normal PTH at 15 ng/mL. Autoimmune and familial causes of HP were ruled out including the presence of stimulating autoantibodies against calcium-sensing receptor. Instead, a progressive damage or atrophy of the parathyroid gland(s) ensuing years after surgery is believed to have led to the patient's hypocalcemia. All 19 previously reported cases of late-onset postsurgical HP occurred after thyroid surgery, with no examples of the condition being found following parathyroidectomy.

Conclusions The case highlights the rare occurrence of late-onset postsurgical HP in a patient who had had multiple parathyroidectomies for PHPT. Thus, monitoring serum calcium, phosphate and PTH during follow-up of such patients is recommended.

Introduction

Postsurgical hypoparathyroidism (HP) may occur after total thyroidectomy or radical neck dissection and is caused by inadvertent removal of parathyroid glands and/or the irreversible damage of their blood supply [1, 2]. The resulting reduced or absent production of PTH leads to hypocalcemia either because of the lack of mobilization of calcium and phosphate from the skeleton or synthesis of calcitriol due to impaired or absent renal hydroxylation of serum 25-hydroxyvitamin D [1]. In addition, reduced PTH lowers reabsorption of calcium and secretion of phosphate in renal tubular cells. Postsurgical HP may occur transiently when hypocalcemia persists for less than six months or permanently when hypocalcemia persists for more than six and upto 12 months after surgery in the presence of low or inappropriately normal PTH levels [1, 2].

Transient hypocalcemia is not uncommon in the post-operative period after parathyroidectomy in patients with primary hyperparathyroidism (PHPT) caused by the delayed functional recovery of the remaining parathyroid glands and the inhibition of PTH secretion by prior hypercalcemia [2, 3]. The biochemical signature is also characterized by high or elevated serum phopsh**ate** and low or undetectable PTH. Another form of hypocalcemia, the so-called hungry bone syndrome, may follow parathyroidectomy, mainly in patients with severe PHPT and preoperative high bone turnover, **due to rapid remineralization of bone** [4]. Parathyroidectomy usually rapidly decreases bone **resorption**. However, in hungry bone syndrome, the rate of bone formation remains elevated for several weeks, with increased calcium influx in bone and the development of persistent hypocalcemia that requires treatment with calcium and **active** vitamin D [4]. In these patients, the biochemical signature is also characterized by elevated serum PTH associated with hypophosphatemia and hypomagnesemia.

Late-onset postsurgical HP is a rare condition which has been shown to develop several years after thyroid surgery [3, 5–18]. Symptoms of hypocalcemia may be latent and mild and very rarely sever [3, 5, 11–13]. The underlying mechanism of the late-onset postsurgical HP is unclear and may be due to progressive damage or atrophy of the parathyroid glands leading to their insufficiency years after surgery. To our knowledge, no case of late-onset postsurgical HP has been described so far in patients with PHPT after parathyroidectomy.

Herein, the follow-up is described of a patient with apparently sporadic recurrent PHPT carrying a germline mutation of the *CDC73* gene who had undergone **three subsequent parathyroidectomies** with resection of four parathyroid adenomas [19]. Over time, the patient gradually developed a late-onset postsurgical HP. Prior cases of late-onset postsurgical HP, with particular focus on the clinical and biochemical features of this rare condition, are also summarised.

Materials and Methods

Patient history

The detailed medical history of the patient has been reported in a prior publication [19]. The relevant clinical details are briefly reported here. The patient was first diagnosed with PHPT in 1987 at the age of 21 years with a total serum calcium of 17.3 mg/dL (normal range, 8.6-10.2 mg/dL) and a C-PTH level of 3.17 ng/mL (normal, <0.88 ng/mL). In the same year, the patient underwent right inferior parathyroidectomy. In 1990, a relapse of PHPT was diagnosed and successfully cured in 1993 by right superior parathyroidectomy. The patient was referred to our outpatient clinic in 1998 for recurrent PHPT. His total serum calcium and PTH were mildly elevated at 10.6 mg/dL and 72 ng/L (normal range, 10–65 ng/L), respectively. In March 2004, a further relapse of PHPT was evident. The patient's total and ionized serum calcium were 12.2 mg/dL and 1.75 mmol/L (normal range, 1.12-1.32 mmol/L), respectively, and a PTH level of 260 ng/L. The patient underwent surgical neck exploration and subsequent superior and inferior left parathyroidectomy. Histological examination of the excised parathyroids showed chief cell adenomas. Subsequent genetic analysis identified a germline mutation of the *CDC73* gene (encodes the tumor supressor parafibromin) in exon 3 (R91P), and the loss of parafibromin expression was implicated in the development of the benign parathyroid tumors. **Following the identification of the *CDC73* gene mutation which are responsible for hyperparathyroidism-jaw tumor syndrome, a re-evaluation of all parathyroid histological sections was carried out by our pathologist in order to exclude atypical or malignant features that can be present in this setting [20]. However, histology did not reveal the presence of atypical features (i.e solid growth pattern, fibrous bands and cellular atypia) and histologic features suggestive of potential malignancy**.

Furthermore, since patients carrying *CDC73* mutations might develop mandibular/maxillary fibrous tumors and kidney tumors, a radiologic evaluation of the jaw and an abdomen ultrasound were undertaken, but these excluded the presence of tumor lesions. Following the final parathyroidectomy, the patient had a transient hypocalcemia after which ionized serum calcium remained within the normal range until March 2006 (Table 1). PTH also remained within the normal range except for a slight elevation to 68 ng/L in March 2005 (Table 1).

Calcium-sensing receptor (CaSR) immunoprecipitation assays

Immunoprecipitation assays used to detect CaSR antibodies were undertaken as detailed elsewhere [21]. Briefly, HEK293 cells were transiently transfected with pcCaSR-FLAG. GammaBind® Sepharose beads (50-µl samples) (GE Healthcare, Little Chalfont, UK) were mixed with sera at a 1:100 dilution and incubated at 4°C for 1 h. The beads and IgG complexes were collected and incubated with cell extract containing CaSR-FLAG protein for 16 h at 4°C, then collected and subjected to SDS-PAGE and immunoblotting using anti-FLAG® M2-Peroxidase Conjugate (Sigma-Aldrich, Poole, UK) and an ECL™ Western Blotting Analysis System (GE Healthcare). The densitometry of bands was performed in a Bio-Rad GS 690 Scanning Densitometer with Multi-Analyst Software (Bio-Rad Laboratories Ltd., Hemel Hempstead, UK). A CaSR antibody index for each serum sample was calculated as the densitometry value of the tested serum/mean densitometry value of 10 control sera. The upper normal limit for the assay was calculated using the mean CaSR antibody index + 3 SD of 10 controls and was a value of 2.78.

Systematic review of late-onset postsurgical HP cases

A systematic Pubmed search focused on late-onset postsurgical HP was undertaken. The following keywords were used for the search: "late-onset hypoparathyroidism", "late-onset hypocalcemia", "post surgical hypoparathyroidism", "post surgical hypocalcemia", "delayed hypoparathyroidism", "post thyroidectomy hypoparathyroidism", "post parathyroidectomy hypocalcemia", "iatrogenic hypoparathyroidism", and "post thyroidectomy basal ganglia calcifications". The search was made with and without the filter "case reports". All eligible studies were retrieved and their references checked for further relevant articles.

Results

Case follow-up

Since *CDC73* mutation carriers are at risk for recurrence of PHPT or parathyroid cancer, regular follow-up was mandatory in this patient. Frequent surveillance may allow an early detection and cure of PHPT, before a possible development of malignancy [19].

Between March 2006 and July 2008, a relapse of the patient's PHPT was suspected because of the finding that at yearly evaluation there was a slightly elevated ionized serum calcium associated with PTH levels at the upper limit of the normal range (Table 1). No kidney stones or nephrocalcinosis were present. Bone mineral density confirmed a reduced bone mass at one-third distal radius which was comparable with that found in 2004. Neck ultrasound and a sestamibi scan were negative. In May 2009, the patient was further evaluated, and at this time total and ionized serum calcium and PTH, as well as 24-h urinary calcium (normal range, 100-300 mg/24-h), were within the normal ranges. The subsequent follow-ups were notable for the progressive reduction, although still in the normal range, of total and ionized serum calcium and PTH levels (Table 1).

In September 2018, the patient was in good health and asymptomatic. The patient's recent medical history was notable for the presence of arterial hypertension for which he was taking zofenopril. The patient was also taking cholecalciferol (25,000 IU monthly). Physical examination was negative except the presence of neck scars. Chvostek and Trousseau signs were negative. Total serum and ionized calcium were low at 8.2 mg/dL and 1.07 mmol/L, respectively (Figure 1). PTH was inappropriately low-normal at 15 ng/L (Figure 1). Serum phosph**ate** at 2.9 mg/dL (normal range, 2.5-4.5 mg/dL), magnesium at 2.1 mg/dL (normal range, 1.7-2.2 mg/dL), creatinine at 1.11. mg/dL (normal range, 0.5 to 1.2 mg/dL), and urinary calcium at 144 mg/24-h were normal. Serum 25-hydroxyvitamin D level was elevated at 57.4

ng/mL (normal range, 20-50 ng/mL). Alkaline phosphatase and liver function tests were normal. Neck and abdomen ultrasounds did not reveal any tumor lesions. No autoimmune disorders were present. Given that there was no evidence of any other disease contributing to the patient's hypocalcemia, and no family history of HP, a diagnosis of postsurgical HP was made. Since symptoms and signs of hypocalcemia were absent, no treatment was advised.

In February 2020, laboratory tests confirmed a mild hypocalcemia. Total serum and ionized calcium were low at 7.9 mg/dL and 0.98 mmol/L, respectively (Figure 1). PTH levels were inappropriately low-normal at 15 ng/L (Figure 1). Serum phosphate and magnesium were normal at 3.8 mg/dL and 2.0 mg/dL, respectively. Urinary calcium was normal 102 mg/24-h. Renal function was also normal. Serum 25-hydroxyvitamin D was normal at 39 ng/mL while receiving cholecalciferol (25,000 IU monthly). Electrocardiogram (ECG) did not show prolongation of QT interval. Abdomen ultrasound was negative for kidney stones and nephrocalcinosis. Chest x-ray was normal. No hyperparathyroidism-jaw tumor syndrome-related tumors were present. The patient was in good health and had no symptoms or signs of hypocalcemia, thus, no specific treatment was advised.

CaSR autoantibody analysis

Normally, the CaSR controls serum calcium levels via PTH secretion from the parathyroid keeping the calcium concentration within a very tight range. In rare cases autoantibodies against the receptor can cause primary hypoparathyroidism [21]. In such cases, CaSR autoantibodies stimulate the receptor so that even at lower than optimum calcium levels PTH secretion from the parathyroid glands is reduced. However, the patient was negative for CaSR autoantibodies with an antibody index of 0.98.

Review of the literature for postsurgical HP

A total of 19 relevant articles were retrieved for systematic review. Four were excluded due to the lack of a full-text article, so that 15 studies were included and reviewed [3, 5–18]. The results are in Table 2. All cases of late-onset postsurgical HP occurred after thyroid surgery, with no examples of the condition being found following parathyroidectomy.

Discussion

Acquired HP is usually caused by inadvertent removal of the parathyroid glands or damage of their blood supply during thyroid surgery. Indeed, postsurgical HP is the most common complication of total or near-total thyroidectomy [2]. More rarely, it can be caused by the excision of too much parathyroid tissue during surgery for PHPT. Other rare causes include hemochromathosis, sarcoidosis, emosiderosis, Wilson's disease, and metastatic infiltration of the parathyroid gland [1].

Given the clinical history of the patient who carried a germline mutation of the *CDC73* gene leading to recurrent PHPT [19], we unexpectedly observed a late-onset postsurgical HP rather than a possible and foreseeable recurrence of PHPT. Of note, three years after the last parathyroidectomy, **leading to completion of (sub)total parathyroidectomy,** a slight increase of ionized serum calcium and inappropriately normal PTH levels were observed in the absence of enlarged parathyroid gland(s) at neck imaging. This biochemical picture raised the suspicion for a further recurrence of PHPT supporting the concept that, in this setting, all parathyroid tissue may continue to proliferate overtime [1, 19]. However, a subsequent normocalcemia was evident. **The former and latter findings were consistent with the presence of a supernumerary parathyroid gland. Otherwise, it could be speculated that the patient might have a small amount of malignant parathyroid tissue in the site of the first surgery which was carried-out elsewhere and not-re-explored at the last surgery able to maintain normocalcemia. However, the revision of all histological sections of the right-side tumors by our pathologist showed no histological features of malignancy [19]. Thus, we can speculate that the function of the supernumerary parathyroid gland remained almost normal for a given period of time and then progressively decreased due to its damage or atrophy. The question of whether other factors (i.e. environmental) might have contributed to this condition remains unclear.**

However, during follow-up, serum calcium slowly decreased over the years until a mild asymptomatic hypocalcemia with inappropriately low-normal PTH levels was evident.

Potential causes of hypocalcemia **including hypomagnesemia** were ruled out; the patient did not have autoimmune disorders or a family history of autoimmunity [22], family members did not have a history of hypocalcemia ruling out a genetic cause [23], and the patient was negative for autoantibodies to the CaSR [21, 22], a molecule that controls serum calcium levels via PTH secretion from the parathyroid gland. When HP gradually develops, as in non-surgical acquired forms, patients are usually asymptomatic, reflecting a sort of adaptation to a progressive decline of serum calcium [2, 18]. In line with this, our patient did not experience symptoms or signs of hypocalcemia over the years, so we suggest that the residual parathyroid gland, which kept the patient normocalcemic for 14 years, underwent progressive damage until HP developed.

To date, 19 cases of late-onset postsurgical HP have been reported and all occurred after thyroid surgery [3, 5–18]. The first case was described in 1962 by Blanchard et al. who described a 59-year-old male patient presenting with hypocalcemia 33 years after thyroidectomy [5]. This patient was admitted to the University Hospital because of "jerking of his right arm and leg" and a recent history of seizures. Laboratory tests showed a severe hypocalcemia and hyperphosphatemia. ECG showed QT-interval prolongation. At the time of hospital admission focal seizures occurred every 15 minutes and they disappeared after one day of intravenously calcium therapy.

Eighteen patients with late-onset postsurgical HP have since been reported. Four occurred after subtotal thyroidectomy and 15 after total thyroidectomy (Table 2). The age at diagnosis varied considerably from nine months to 41 years with a higher prevalence in females than males (15 *vs* 4), an expected figure considering that thyroid disease is more prevalent in the former. In nine patients, the diagnosis was made more than 20 years after surgery with a mean time of

30.8 ± 5.81 years (range, 23-41 years) [5–8, 10, 12, 13, 15, 18]. In the remaining nine patients, HP was evident within 20 years of surgery with a mean time of 10.1 ± 7.44 years (range, nine months-19 years) [3, 9, 11, 12, 14, 16, 17]. The mean age at diagnosis was 54.5 ± 13.8 years (range, 24-76 years). In female patients, this was 54.5 ± 14.62 years (range, 24-76 years) and, in males, 54.2 ± 12.14 years (range, 42-69 years).

Ten of 19 (52.6%) patients experienced severe symptoms of hypocalcemia that required hospitalization. The medical history of these patients was characterized by seizures which were evident for many years or just a few months [11–14, 17, 18]. Conversely, four of the 19 (21.1%) patients had a history of cramps or tingling in the limbs. In the remaining cases, the medical history was not available. Finally, in six cases (31.6%), computed tomography (CT) scans showed the presence of bilateral and extended brain calcifications, that in HP are located most often in basal ganglia. Patients with brain calcifications usually had a late diagnosis after surgery (range, 10-41 years).

In conclusion, this case highlights the rare occurrence of late-onset postsurgical HP in a patient who had had multiple parathyroidectomies for PHPT as well as in patients with previous thyroidectomy, particularly if total. Although hypocalcemia typically occurs in the immediate postoperative period, progressive damage or atrophy of the parathyroid gland(s) may ensue years after surgery leading to blood calcium and PTH insufficiency. Thus, serum calcium, phosphate and PTH should be monitored during follow-up in patients who have had previous neck surgery to identify and eventually treat such patients.

Acknowledgments The authors wish to thank the patient involved in the study who graciously agreed to collaborate in the study. We also thank Mrs Laura Macrì for her help in searching for the articles for the review of the literature.

Author contributions A.S. and F.C. planned the study. E.H.K. performed the search for calcium-sensing receptor antibodies and revised the manuscript. E.P. and A.D.C. collected the clinical data. C.M. revised the manuscript. A.S and F.C. wrote the manuscript. All authors discussed the results.

Compliance with Ethical Standards

Conflict of interest The authors declare that there is no conflict of interest.

Informed consent Informed consent was obtained from the patient for publication of this case.

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Figure legend

Fig. 1 Time-course of serum calcium and PTH concentrations in the patient. The normal range of serum calcium is 8.6-10.2 mg/dL. The normal range of PTH (2nd generation assay) is 10-65 ng/L from 2012 to 2014, and 8-40 ng/L (3rd generation assay) thereafter.

Figure 1

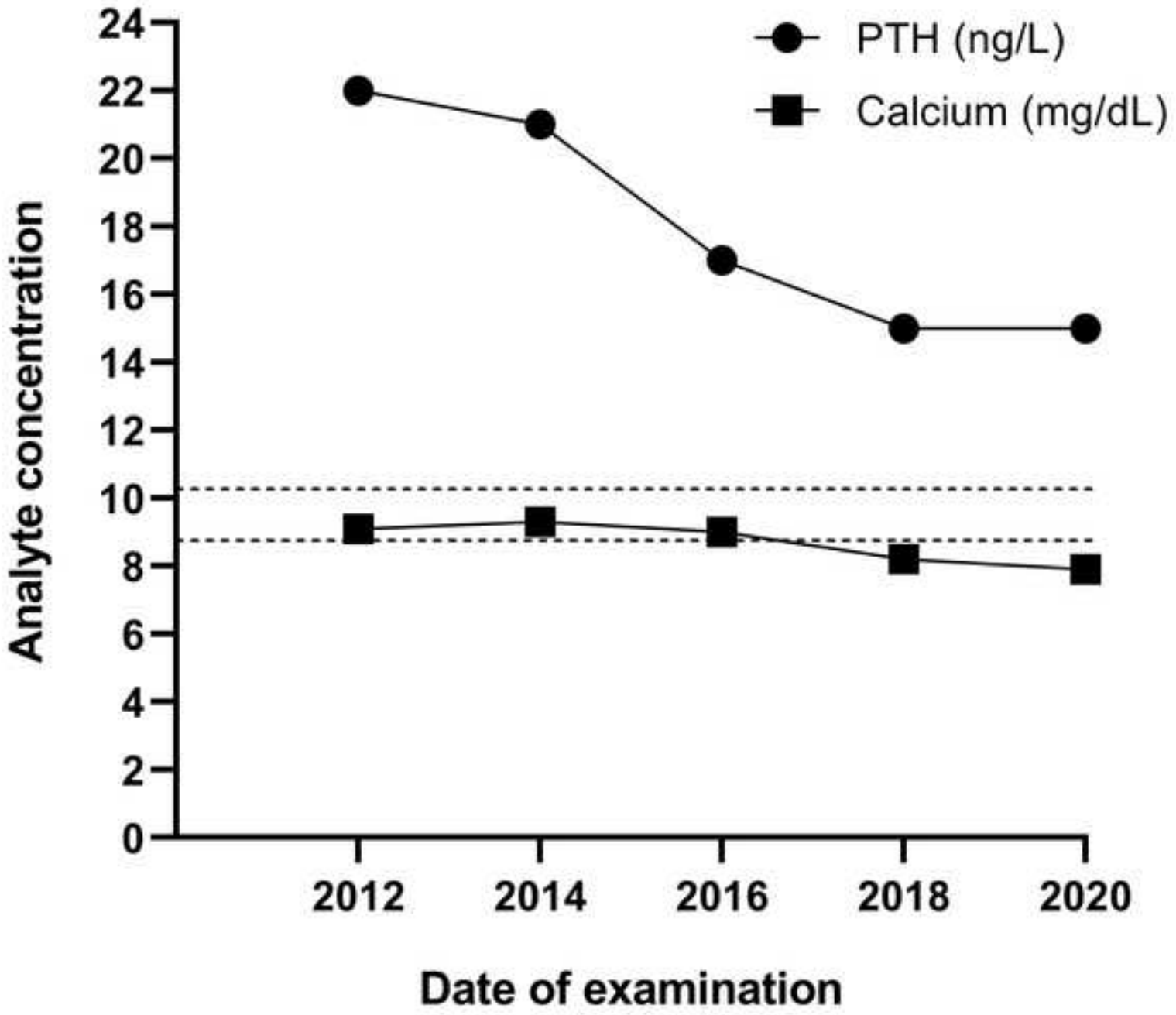

Table 1. Biochemical findings of the patient.

Date	Ionized serum calcium (mmol/L)[1,6]	Total serum calcium (mg/dL)[2,6]	Serum phosphorus (mg/dL)[3,6]	Plasma PTH (ng/L)[4]	Serum 25-hydroxyvitamin D (ng/mL)[5]
June 2004	1.23	na	na	46	27.6
March 2005	1.29	na	na	**68**	21.3
March 2006	**1.34**	na	na	41	23.3
July 2008	**1.38**	na	na	65	31.9
April 2009	na	9.6	2.2	46	20.6
December 2009	1.22	na	na	49	11.1
December 2010	1.30	na	na	47	22.4
June 2012	1.18	9.1	2.8	22	25.1
December 2014	1.19	9.3	3.0	21	43.3
September 2016	1.17	9.0	3.5	17	47.6

[1]Ionized serum calcium normal range: 1.12-1-32 mmol/L

[2]Total serum calcium normal range: 8.6-10.2 mg/dL

[3]Serum phosphorus normal range: 2.5-4.5 mg/dL

[4]Plasma PTH normal range: 10-65 ng/L (2nd generation assay from June 2004 to October 2014); 8-40 ng/L (3rd generation assay from December 2014 to September 2016)

[5]Serum 25-hydroxyvitamin D normal range: 20-50 ng/mL

[6]na, not available

Table 2. Clinical and biochemical features of reported cases of late-onset postsurgical hypoparathyroidism.

Reference	Neck surgery[1]	Clinical presentation	Serum calcium (mg/dL)[2]	Serum phosphorus (mg/dL)[2]	PTH (pg/mL)[2]	Time (years) since surgery
Blanchard et al. (5)	Tx	• Jerking of right arm and leg • Seizures (clonic movements of the right hand that progressed to involve the entire right arm, trunk, and lower extremity) • Pursing and "smacking" of the lips • Tetany: not observed • Chvostek's and Trousseau's signs could not be elicited • Mental obtundation was severe	3.9 (normal range, na)	5.8 (normal range, na)	na	33
Bull et al. (15)	Subtotal Tx	• Generalized seizures (tonic and clonic movements, eye rolling, tongue biting, and unconsciousness) • Frequent headaches and lassitude for years • Chvostek's and Trousseau's signs could not be elicited	6.0 (normal range, na)	5.3 (normal range, na)	na	28
Petch et al. (14)	Tx (two operations)	• Increasing forgetfulness • Loss of interest in her surroundings for several months • Fits • Trousseau's sign was positive	4.5 (normal range, na)	5.4 (normal range, na)	na	27
Cox et al. (6)	Tx	• Episode of unconsciousness • Generalized seizure • Tetany: not observed • Chvostek: negative • Trousseau: another generalized seizure occurred during test	5.8 (normal range, 9-11)	4.1 (normal range, 3-4.8)	162 pgEq/ml (C-terminal; normal range, <150-375)	19
Halperin et al. (7)	Tx	• Case 1: severe paresthesia and muscular spasm • Case 2: paresthesia and muscular spasm • Case 3: generalized seizures • Case 4: paresthesia and psychopathy	6.48 7.08 7.00 8.20	5.26 5.88 6.04 5.60	6 (normal range, 10-60) na 16 pg/mL (N-terminal; normal range, 11-24) 5.3	17 23 5 7

			(normal range, 8.4-10.4)	(normal range, 2.35-4.02)	(normal range, 10-60)	
Lang et al. (18)	Tx	• Tetany • Moderately demented • Bilateral symmetrical calcifications in both cerebellar hemispheres, mid-pons, white matter of the frontal, temporal, parietal and occipital lobes	na	na	na	7 (only tetany) 30
Jorens et al (16)	Subtotal Tx	• History of generalized tonic-clonic seizures • Chvostek's and Trousseau's signs could not be elicited • Bilateral calcifications in the basal ganglia, thalami, frontal periventricular white matter, cerebellar hemispheres and brainstem	4.6 (normal range, 8.01-10.4)	8.01 (normal range, 3.2-5.6)	5 (normal range, 10-55)	35
Bellamy et al. (8)	Tx	• Four-year history of fatigue and musculoskeletal limb pains • History of seizures • Marked bilateral basal ganglia calcification • Increasing pain and stiffness in the neck, shoulders, back, arms and legs • Chvostek's and Trousseau's signs negative	6.16 (normal range, 8.6-9.84)	5.48 (normal range, 2.48-4.46)	< 5 (normal range, 10-65)	36
Garg et al. (17)	Tx	• Generalized tonic-clonic seizure • Chovstek's and Trousseau's sign strongly positive • Extensive intracranial calcification of basal ganglia, cerebellum and cerebral white matter	5.2 (normal range, 9-11)	6.1 (normal range, 2.5-4.5)	1.0 (normal range, 12-72)	19
Mrowka et al. (9)	Subtotal Tx	• Case 1: generalized tonic-clonic seizure • Case 2: generalized tonic-clonic seizure; Chvostek's sign positive	6.0 (normal range, na) 4.0 (normal range, 8.8-10.4)	na na	3 (normal range, na) 5.5 (normal range, 15-70)	9 months 2
Adorni et al. (10)	Tx	• Progressive dementia • Psychosis, agitation and insomnia • Symmetric bilateral brain calcifications.	7.69 (normal range, na)	5.14 (normal range, na)	< 1.0 (normal range, na)	41
Zisimopoulou et al. (11)	Tx	• Loss of consciousness lasting a few seconds • Mild extrapyramidal signs • Extensive bilateral symmetrical brain calcifications in the frontal lobes, basal ganglia, subcortical and periventricular white matter, and cerebellar hemispheres	5.3 (normal range, 8.5-10.5)	5.4 (normal range, 2.5-5)	undetectable	18
Agarwal et al. (12)	Tx	• Generalized tonic-clonic convulsions				

		• Tongue bite • Urinary incontinence • Trousseau and Chvostek signs positive • Truncal ataxia, dysdiadochokinesia, dysynergia, past pointing. Hypotonic limbs; diminished tendon reflexes • Extensive intracranial calcifications	6.1 (normal range, na)	na	na	10
Kamath et al. (13)	Tx	• History of recurrent calf muscle cramps and aches in the legs • History of progressive forgetfulness, jitteriness, difficulty in walking, getting up from squatting position and rising from the chair, tingling and numbness in the hands, toes and around the mouth • Different episodes of generalized tonic-clonic seizures • Trousseau's sign and Chovstek's sign positive • Multiple calcifications in basal ganglia	4.5 (normal range, 9-11)	8.5 (normal range, na)	3.3 (normal range, 9.5-75)	25
Simões et al. (3)	Tx	• Crises of cramps in the upper limbs	3.0 (normal range, 8.6-10.2)	na	3.1 (normal range, 15-65)	3.5
Present study	PTx	• Asymptomatic	7.9 (normal range, 8.6-10.2)	3.8 (normal range, 2.5-4.5)	15 (normal range, 8-40)	14

[1]Tx, total thyroidectomy; PTx, parathyroidectomy

[2]na, not available