Idiopathic Hypoparathyroidism: Still a Diagnostic Conundrum – A Tertiary Centre Experience

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ABSTRACT

Idiopathic hypoparathyroidism leads to hypocalcemia and hyperphosphatasemia and usually has a genetic aetiology. The variable but often subtle signs and symptoms usually lead to a misdiagnosis of hypoparathyroidism. Case records of 32 patients of idiopathic hypoparathyroidism admitted over a period of five years were analysed. There was a lag period of 5.94 years from the onset of symptoms to the diagnosis. Carpopedal spasm was the most common indication for admission to the hospital. Trivial symptoms such as fatigue (84 %) and paresthesia (62.5 %) were the most common reported symptoms. A sum of 46.5 % of the patients were on antiepileptic drugs before the correct diagnosis of hypoparathyroidism was made. This observation emphasized that Calcium profile should be obtained in patients with history of paresthesia and seizure to avoid the long delay in diagnosis of hypoparathyroidism.

Introduction

Hypoparathyroidism leads to abnormal calcium metabolism characterised by hypocalcaemia and hyperphosphatemia due to deficient synthesis or secretion of parathyroid hormone [1]. It is a relatively uncommon disorder with prevalence estimated in a large epidemiological population based study to be around 37 per 100 000 person-years [2]. The data on prevalence and incidence of hypoparathyroidism is still lacking in most countries. The aetiology of hypoparathyroidism can be divided into primary hypoparathyroidism, which occurs due to intrinsic defect within the parathyroid gland and the acquired or secondary hypoparathyroidism due to conditions that impair parathyroid gland function. Acquired hypoparathyroidism is more common than primary hypoparathyroidism, with hypoparathyroidism after neck surgery being the most common overall cause of hypoparathyroidism [3]. The aetiology is labelled as idiopathic if no cause is found after exclusion of all possible aetiologies. Idiopathic hypoparathyroidism usually has a genetic aetiology [4].

The clinical signs and symptoms of hypoparathyroidism are broadly related to neuromuscular dysfunction (due to hypocalcaemia) and ectopic mineralisation in various soft tissues (due to hyperphosphatemia) [5]. The quality of life (QOL) is altered in patients leading to a decreased sense of well-being. But still no conclusive evidence of increased mortality has been shown in patients of hypoparathyroidism [6]. The highly variable signs and symptoms often leads to a misdiagnosis in the initial stages of the disease. There is often a latent period of many years from the onset of symptoms to the correct diagnosis of hypoparathyroidism [7]. Only a few case series of hypoparathyroidism have been reported. We describe here the clinical and biochemical profile of patients of hypoparathyroidism admitted over a period of five years.

Patients and Methods

We analysed the case records of 32 consecutive patients of idiopathic hypoparathyroidism admitted between January 2014 to December 2018 at our institute. Demonstration of hypocalcaemia and hyperphosphatemia with low levels of parathyroid hormone (iPTH) were consistent with the diagnosis of hypoparathyroidism. Only cases of idiopathic hypoparathyroidism were included in the study and cases of postoperative hypoparathyroidism, autoimmune hypoparathyroidism (as part of Autoimmune Polyglandular Syndrome), hypoparathyroidism post-radiation exposure, and hypoparathyroidism due to infiltration (likely to metastasis, hemochromatosis, Wilson's disease, etc.) were excluded from analysis.

Detailed clinical history and examination were noted. Age at onset of symptoms, duration of symptoms, presenting complaint, various symptoms and signs related to hypocalcaemia and hyperphosphatemia were recorded for each patient. Treatment history pertaining to the symptoms was also taken. Ophthalmic assessment especially to look for posterior subcapsular cataract was done.

Blood samples for total serum calcium (reference range: 8.6–10.2 mg/dl), inorganic phosphorus (reference range: 2.5–4.5 mg/dl), serum alkaline phosphatase (reference range: 40–130 King IU/l), albumin (reference range: 3.5–5.5 g/dl), and creatinine (reference range: 0.6–1.2 mg/dl) were collected and estimated by automated analyser (model: BS-800; make: Mindray). Ionised calcium values (reference range: 1.1–1.35 mmol/l) were also estimated from a venous blood gas sample. Total serum calcium levels were corrected for respective serum albumin levels. Twenty-four-hour urinary calcium values (with simultaneous detection of 24-h urinary creatinine to assess adequacy of sample collection) were noted. iPTH levels (reference range: 11–67 pg/ml) were measured by immunochemiluminiscence assay (model: Unicel DxI 600; make: Beckman Coulter). Serum 25 hydroxyvitamin D levels were estimated by immunochemiluminiscence (reference range 9–37 ng/ml, model: Unicel DxI 600; make: Beckman Coulter). All patients had ultrasound abdomen to look for nephrolithiasis and nephrocalcinosis. Non-contrast computed tomography of the head was also performed in each patient to look for intracranial calcification.

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Qualitative variables were corelated using Fisher's exact test. A p-value of <0.05 was considered statistically significant. The data were entered in MS Excel spreadsheet and analysis were done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

A total of 32 consecutive patients admitted with idiopathic hypoparathyroidism were studied. Twenty (62 %) patients were males with the mean age at presentation being 27.1 ± 8.52 years (8–45 years). The mean age at the onset of symptoms was 21.2 ± 9.2 years (1–42 years) and there was a lag period of 5.94 ± 4.07 years (3 months to 15 years) from the first reported symptom to the diagnosis (▶ **Table 1**).

Carpopedal spasm was the most common reason for admission to hospital, present in 25 (59.5 %) patients followed by seizures (40.5 % of patients). Overall fatigue was the most common reported symptom (84 %) followed by paraesthesia (62.5 %) followed by carpopedal spasm and seizures each seen in 59.3 % of the patients. Twenty patients (62.5 %) had presence of cataract on ophthalmologic examination. Dental abnormalities were present in 8 (25 %) patients. Only 2 patients had nephrocalcinosis on renal imaging. As many as 15 (46.5 %) patients gave history of treatment with antiepileptic drugs (▶ **Table 2**). One of the patients had brittle nails with transverse grooves and ridging (▶ **Fig. 1**).

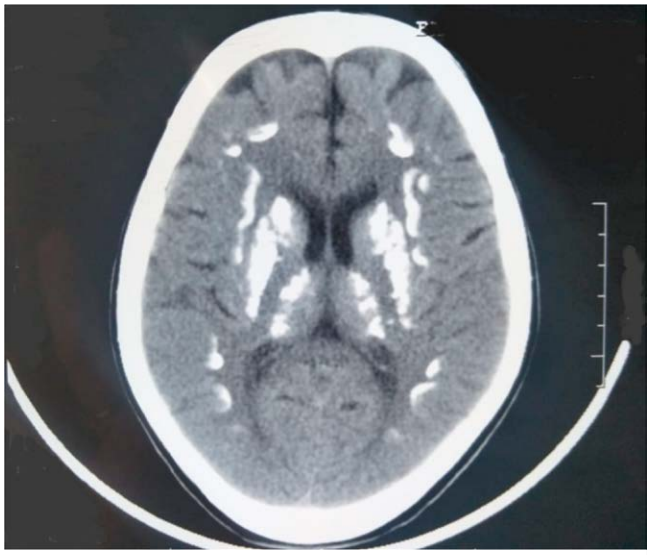
Mean serum total calcium and phosphorus levels at presentation were 5.82 ± 0.77 mg % (2.9–6.9 mg %) and 6.94 ± 0.59 mg % (4.8–7.56) respectively. The mean calcium phosphorus product was 40.23 ± 7.05 (19.14–49.5). Ionised calcium levels ranged between 0.41 to 0.69 with a mean of 0.57 ± 0.08. Basal ganglia calcification was present on imaging in 22 (68.75 %) of the patients (▶ **Fig. 2**). Presence of basal ganglia calcification was corelated with the presence of seizure (89.5 % of patients, p = 0.005).

▶ **Table 1** Demographic and biochemical profile of the patients (n = 32).

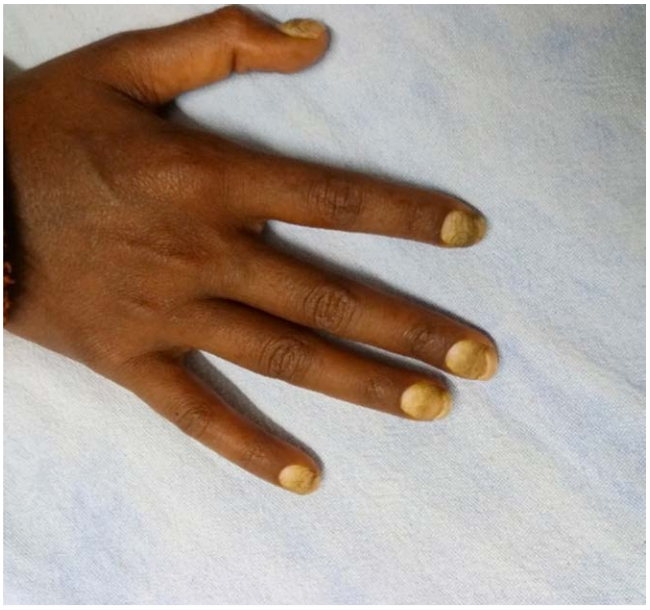
Characteristic	Mean ± SD	Median	Min–Max	Inter quartile Range
Age (years)	27.19 ± 8.52	27.5	10–45	21.500–32.500
Age at onset of symptoms (years)	21.25 ± 9.2	21	1–42	16–25
Duration of symptoms (years)	5.94 ± 4.07	5	0.25–15	3–8
Serum calcium (mg/dl)	5.82 ± 0.77	5.85	2.9–6.9	5.400–6.350
Serum phosphorus (mg/dl)	6.94 ± 0.59	7.05	4.8–7.56	6.800–7.400
Ionized calcium (mmol/l)	0.57 ± 0.08	0.57	0.41–0.69	0.506–0.621
Ca Po4 product	40.23 ± 7.05	41.36	19.14–49.5	36.570–44.970
Serum PTH (pg/ml)	5.75 ± 1.2	5.85	2.5–7.8	5.050–6.700
Serum albumin (g/l)	3.96 ± 0.33	3.9	3.2–4.6	3.800–4.200
Serum ALP (IU/l)	183.25 ± 110.9	135	26–486	112–194
BMI (kg/m^2)	21.56 ± 2.53	21.35	16.6–27.2	19.850–23.100

▶ **Table 2** Clinical profile of the patients (n = 32).

Clinical features	Frequency (n = 32)	Percentage
Fatigue	27	84.37 %
Paraesthesia	20	62.50 %
Seizures	19	59.38 %
Carpopedal spasm	19	59.38 %
Irritability	17	53.13 %
Treatment with Antiepileptic drugs	15	46.88 %
Cataract	20	62.50 %
Dental abnormalities	8	25.00 %
Family history	7	21.88 %
Chovstek sign	11	34.38 %
Trousseau's sign	19	59.38 %
Basal ganglia calcification	22	68.75 %



▶ **Fig. 2** Diffuse cerebral calcification on brain imaging.



▶ **Fig. 1** Characteristic nail changes in a patient of idiopathic hypoparathyoidism.

Discussion

Hypoparathyroidism is a relatively uncommon metabolic disorder, which results from inadequate secretion or synthesis of PTH [1]. Overall postsurgical hypoparathyroidism is the most common aetiology of hypoparathyroidism in clinical practice, accounting for about 75 % of the cases. Idiopathic hypoparathyroidism is generally due to several genetic aetiologies, which result in loss of parathyroid action or function [8].

PTH is the major hormone regulating calcium and phosphate homeostasis in the body via its direct actions on bone and kidney and indirect action on gastrointestinal tract through 1,25-dihydroxyvitamin D production [9]. Thus, the main biochemical hallmarks of hypoparathyroidism are hypocalcaemia and hyperphosphatemia. Hypocalcaemia causes neuromuscular signs and symptoms of hypoparathyroidism while hyperphosphatemia causes mainly ectopic mineralisation in soft tissues (brain, kidney, vasculature, and other tissues). Hypoparathyroidism can involve nearly every organ system of the body over the course of the disease [9].

The mean age of presentation in our study was 27.1 ± 8.52 years, which is quite similar to the 28.7 ± 14.1 years reported in a study done in India by Bhadada et al. [10]. In contrast, in a study done in USA, which included all aetiologies of hypoparathyroidism, the mean age of presentation was 58 ± 20 years [2]. The difference could be due to inclusion of cases of post-surgical hypoparathyroidism as well. Our study showed a time lag of 5.94 ± 4.07 years from the first reported symptom to the diagnosis. As the early manifestations of hypoparathyroidism are highly variable and nonspecific, it is prudent to keep a high index of suspicion for the diagnosis. The delay in diagnosis may lead to poor quality of life.

Fatigue (84 %) and paraesthesia (62.5 %) were the most common reported symptoms in our study, which again highlights the fact that hypoparathyroidism can have nonspecific symptoms in the early stage of the disease. History of previous episode of seizure and carpopedal spasm was present in 60 % of the patients each. Most common indication of admission to hospital was carpopedal spasm. Carpopedal spasm followed by paraesthesia were the most common reported symptoms in a study done by Bhadada et al. [10]. The typical cataract described in patients of hypoparathyroidism is a subcapsular cortical region opacity having a radial spoke like appearance [11]. Since the cataract associated with idiopathic hypoparathyroidism develops slowly and typically do not affect the vision until past middle age, it goes often unrecognised [12]. In our study also, 62.5 % of patients had cataract on presentation. Basal ganglia calcification is also commonly seen in patients of hypoparathyroidism. It is due to hyperphosphatemia leading to high calcium-phosphate product leading to ectopic calcification.

Goswami et al. [13] also hypothesised that inorganic phosphate transporter pit 1 (SLC20A1) may be activated by hyperphosphatemia resulting in the expression of osteogenic molecules in the caudate nucleus and gray matter.

Almost half of the patients were misdiagnosed as seizure disorder and were on antiepileptic drugs. A literature review done by Li et al. [14] reviewing 1020 cases of hypoparathyroidism showed a misdiagnosis rate of 29.51 %. Frequently these patients are misdiagnosed as epilepsy, neurosis, and mental disorders [15]. Patients of idiopathic hypoparathyroidism are also frequently misdiagnosed as Fahr disease based on intracranial calcification if the clinical and biochemical profile of the patients are ignored [15].

Conclusion

The symptoms of presentation of idiopathic hypoparathyroidism were related to the severity of hypocalcaemia. Carpopedal spasm and seizure were the most common presentation for hospital admission. The highly nonspecific and variable presentation of idiopathic hypoparathyroidism often leads to a long lag period of diagnosis as well as high probability of misdiagnosis. A serum calcium profile done in patients with complaint as trivial as that of paraesthesia may avoid the long delay as well as misdiagnosis of patients of idiopathic hypoparathyroidism.

Data Availability Statement information

We state that findings of this study can be taken up from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare that they have no conflict of interest.

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