Original Article

Phenotypic and Genotypic Spectrum of Indian Patients with Hypophosphatasia

Melkunte S. Dhananjaya, Thrupti S.[1], Hamsa V. Reddy[2], Anusha Nadig, Kenchappa S. Adarsh[3], Swati Jadhav, Parvathy Lalitha[4], Sandhya Nair[5], Shaila Bhattacharyya[3], Anurag Lila[6], Vijaya Sarathi

Department of Endocrinology, Vydehi Institute of Medical Sciences and Research Center, Bengaluru, Karnataka, [1]Kangaroo Care Hospitals, Mysore, Karnataka, [2]Department of Pediatrics, Division of Pediatric Nephrology, M S Ramaiah Medical College, Bengaluru, Karnataka, [3]Manipal Hospitals, Old Airport Road, Bengaluru, Karnataka, [4]Aster Medcity, Kochi, Kerala, [5]Senior Manager - Variant Interpretation, MedGenome Labs Ltd, Bengaluru, Karnataka, [6]Department of Endocrinology, Seth Gordhandas Sunderdas Medical College and King Edward Memorial Hospital, Mumbai, Maharashtra, India

Abstract

Introduction: Hypophosphatasia (HPP) is a rare disorder, with only two genetically proven cases reported from India. Here, We report five Indian patients with genetically proven hypophosphatasia and describe their clinical, biochemical, and genetic profiles. **Methods:** The study included patients with genetically proven hypophosphatasia managed at different healthcare centers in South India. The participants' case records were reviewed, and relevant phenotypic and genotypic information was collected and analyzed. **Results:** Case 1 presented at 4 months of age for failure to thrive, found to have persistent hypercalcemia for which she received bisphosphonate therapy. A low alkaline phosphatase was recognized later. Case 2 presented during adolescence with bilateral genu valgus and delayed dentition with classical tongue-like translucencies on radiology and low alkaline phosphatase. Genetic evaluation in cases 1 and 2 revealed compound heterozygous variants in the *ALPL* gene. Case 1 received asfotase alfa with remarkable improvement in growth. Case 3 presented with multiple vertebral fractures at 33 years of age whereas cases 4 (42 years) and 5 (63 years) presented with musculoskeletal pains with delayed diagnosis for 8 and 13 years, respectively. Cases 3–5 had heterozygous variants in the *ALPL* gene. **Conclusions:** In the largest case series of hypophosphatasia from India, we report five cases of hypophosphatasia with two novel variants. Our study emphasizes the need to increase awareness regarding the disease to improve its early diagnosis and also, the need to form strategies to reduce the challenges in obtaining enzyme replacement therapy for hypophosphatasia in India.

Keywords: *ALPL* gene, hypophosphatasia, India

Introduction

Hypophosphatasia (HPP) is a rare inherited metabolic bone disorder characterized by low serum alkaline phosphatase (ALP) activity and impaired bone and teeth mineralization.[1] The estimated incidence of HPP varies, ranging from approximately 1 in 2,500 to 1 in 300,000 live births.[2] HPP may be inherited as an autosomal recessive or dominant disorder.[3,4] The disease exhibits significant clinical heterogeneity and is categorized into six subtypes: perinatal lethal, perinatal benign, infantile, childhood, adult, and odontoid HPP. The severity of symptoms correlates with the age of onset, with earlier presentations generally associated with more severe skeletal complications. It is not uncommon for HPP patients to be missed or misdiagnosed for a long duration. Varied clinical presentations highlight the need for individualized diagnostic and treatment approaches.[3,4]

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Serum ALP levels are crucial for HPP diagnosis, with patients typically exhibiting decreased ALP levels. However, low ALP levels are not a sine-qua-non for the diagnosis of HPP. Elevated serum pyridoxal-5-phosphate levels or urinary phosphoethanolamine serve as surrogate markers whereas molecular diagnosis is confirmatory.[3,4] Enzyme replacement therapy, utilizing modified human tissue nonspecific alkaline

Address for correspondence: Dr. Vijaya Sarathi, Department of Endocrinology, Vydehi Institute of Medical Sciences and Research Center, Bengaluru, Karnataka - 560 066, India. E-mail: drvijayasarathi@gmail.com

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phosphatase (TNSALP), has shown promising outcomes in life-threatening perinatal and infantile forms, as well as childhood HPP.[4]

The data on patients with HPP from India is limited to single case reports most of which are not genetically confirmed.[5-8] To date, only two patients of genetically confirmed hypophosphatasia have been reported from India.[7,8] Here, we report five Indian patients with genetically proven HPP and describe their clinical, biochemical, and genetic profiles.

Materials and Methods

The study included patients with genetically proven hypophosphatasia managed at different health centers in South India. A written informed consent was obtained from all participants and/or their parents/guardians. Case records were reviewed and relevant phenotypic and genotypic information was collected and analyzed. Genetic analysis was performed using clinical exome sequencing and identified variants were classified per guidelines by the American College of Medical Genetics (ACMG).

Ethical aspect

The study was approved by the Institutional Ethics Committee (VIEC/2024/APP/79). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the study participants.

Results

The clinical and biochemical details of the study participants are summarised in Table 1.

Patient 1

A 4-month-old female infant was referred to the pediatric endocrinology clinic for evaluation of failure to thrive. She was the firstborn of non-consanguineous parents with a birth weight of 3 kg and no history of perinatal depression. She exhibited an isolated delay in gross motor milestones. She was exclusively breastfed and was on 400 IU cholecalciferol supplementation daily. Her weight at 4 months was 3.6 kg. She exhibited a wide anterior fontanelle and generalized hypotonia.

Initial evaluation showed mild hypercalcemia with a calcium level of 12.3 mg/dl, phosphorus of 6.25 mg/dl, and 25-hydroxyvitamin D level of 51 ng/ml. Cholecalciferol supplementation was withheld but a repeat serum calcium a week later was still elevated (12.5 mg/dl) with an intact parathormone level of <1.2 pg/ml. Her repeat serum calcium was 18.1 mg/dl, with a normal 25-hydroxy vitamin D (25OHD) level of 39.8 ng/ml and a suppressed intact parathormone level of 3.74 pg/ml. The spot urinary calcium to creatinine ratio was high (1.01). An ultrasound of the abdomen showed bilateral nephrocalcinosis. She was hospitalized and started on intravenous hydration and diuretics. After 4 days, her weight improved to 4.1 kg, and her calcium dropped to 14.6 mg/dl; she was discharged with a follow-up scheduled in 3 days.

After 5 days, the infant was reviewed in the outpatient department with minimal weight gain (3.9 kg) and persisting hypercalcemia of 14.2 mg/dl. She was started on low-calcium formula milk supplements. Her calcium increased to 15.6 mg/dl, and considering other differential diagnoses of hypercalcemia like idiopathic infantile hypercalcemia, she was treated with intravenous zoledronic acid (0.05 mg) after which her calcium stabilized to 12.8 mg/dl in 2 days and to 9.7 mg/dl in 2 weeks. Meanwhile, a persistently low level of alkaline phosphatase (10.7 to 25 U/L) was striking; hence, X-rays were also ordered. They were suggestive of metaphyseal flaring with an increased gap between metaphyses and epiphyses (hypomineralization) [Figure 1].

After 3 weeks of bisphosphonate therapy, her weight was 4.4 kg, and her calcium levels were 9.7 mg/dl with phosphate at 2.38 mg/dl and alkaline phosphatase levels of 10.7 U/L. The genetic evaluation identified compound heterozygous mutations in *ALPL*, p.Gly491Arg, and p.Asp435His [Table 2]. The variants were classified as pathogenic and variant of

Table 1: Clinical and biochemical details of the study participants

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age/Sex	4 months	13 years	33 years	42 years	63 years
Sex	Female	Male	Male	Male	Female
Clinical Findings	Failure to thrive, delayed milestones, nephrocalcinosis, hypotonia, wide anterior fontanelle.	Knock knees, bony pains, delayed dentition, enamel hypoplasia	Spontaneous multiple vertebral and nontraumatic tibial fractures, recurrent dental issues	Myalgias, bony pains, recurrent minor fractures	Short stature, joint pains, loose teeth, osteopenia with poor response to alendronate
Calcium (mg/dl)	Initial: 12.3, peak: 18.1	9.5	9.5	9.4	8.7–9.4
Phosphorus (mg/dl)	6.25	8.4	3.7	5.5	4.99
Alkaline phosphatase (U/L)	10.7-25	39	28–36	27–45	17–21
Parathormone (pg/ml)	<1.2–3.74	9.6	31.3	24	NA
25-hydroxy vitamin D (ng/ml)	51	75	9.7	53.7	Normal
Pyridoxal-5-phosphate (ng/ml)	---	80.3	44.4	---	---
β-cross laps (pg/ml)	---	263	---	---	358
Follow-up duration	1 year	1.5 years	6 years	2 years	14 years

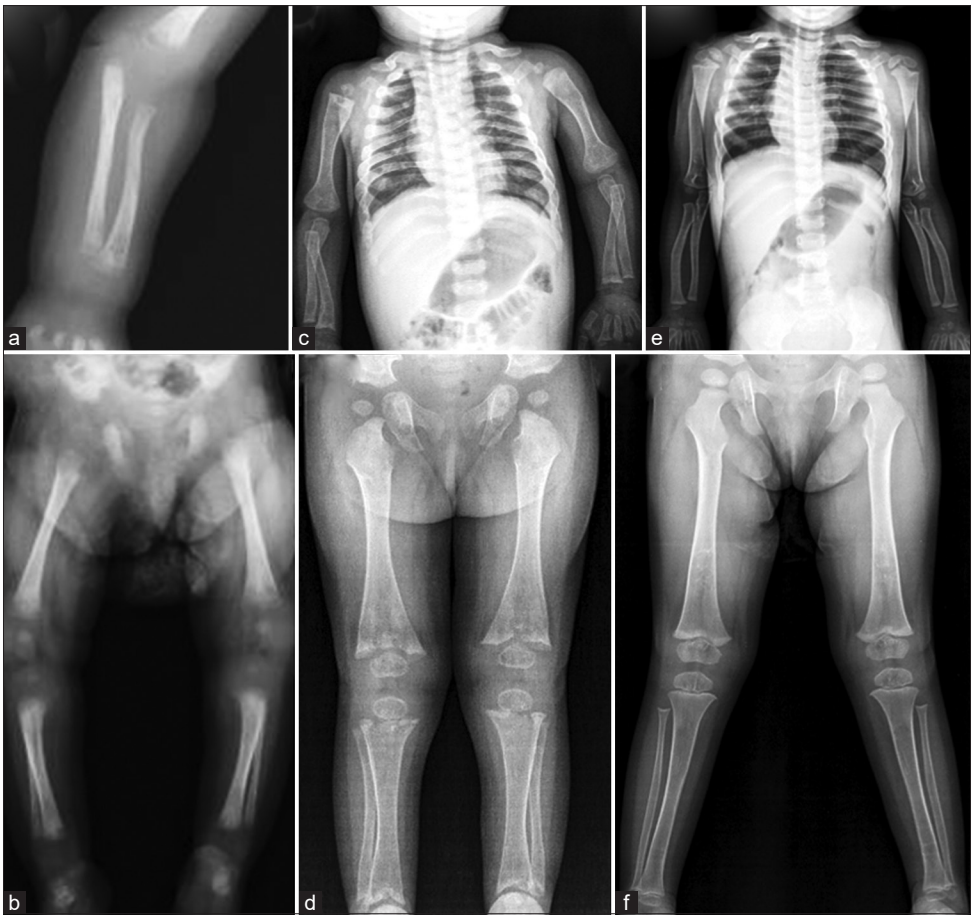

Figure 1: Anteroposterior X-ray images of left forearm and both lower limbs of patient 1 at 5 months of age showing delayed bone maturation (no carpal bone) metaphyseal flaring and increased gap between metaphyses and epiphyses (a and b); Anteroposterior x-ray images of trunk and both upper limbs and both lower limbs at 1 (c and d) and 1.5 (e and f) years of age (after 5 and 9 months of therapy with asfotase alfa, respectively) showing markedly improved mineralization

Table 2: Summary of characteristics of *ALPL* variants observed in our study

Case Number				Genetic Findings	New ACMG classification	Novel	Damaging on	1000G	gnomAD (v3.1),
1	Compound heterozygous	c.1471G>A	p.Gly491Arg	Exon 12	Pathogenic	No	PP2, SIFT, LRT, MT2	NR	NR
		c.1303G>C	p.Asp435His	Exon 11	VUS	Yes	PP2, SIFT, LRT, MT2	NR	NR
2	Compound heterozygous	c.571G>A	p.Glu191Lys	Exon 6	Pathogenic	No	PP2, LRT, MT2	0.10%	0.20%
		c.659G>C	p.Gly220Ala	Exon 7	Pathogenic	No	SIFT, MT2	0.00%	0.00%
3	Heterozygous	c.152C>T	p.Ala51Val	Exon 3	LP	No	SIFT, MT2	0.00040%	0.00500%
4	Heterozygous	c.311A>G	p.Asn104Ser	Exon 5	LP	No	PP2, SIFT, LRT, MT2	NR	NR
5	Heterozygous	c.1336G>T	p.Ala446Ser	Exon 12	VUS	Yes	PP2, SIFT, LRT, MT2	NR	NR

LRT: likelihood ratio test, LP: likely pathogenic, NR: nor reported, PP2: Polyphen 2, MT2: Mutation taster 2, SIFT: Sorting intolerant from tolerant, VUS: variant of unknown significance

unknown significance (VUS), respectively, per the American College of Medical Genetics (ACMG) criteria. Mother (p.Gly491Arg) and father (p.Asp435His) were heterozygous for the variant and serum ALP of 55.6 IU/L and 29.83, respectively.

The infant was started on Asfotase Alfa (AA, Strensiq)) at 8 months of age at a dose of 2 mg/kg SQ on alternate days. At the initiation of treatment, her serum calcium was 10.6 mg/dl with undetectable alkaline phosphatase (ALP). Post-treatment with AA, she had an increase in ALP to 5183 U/L. With the continuation of therapy, there was a striking improvement in all domains including growth, development, and biochemical parameters. She is now 1-year-8-month-old and can sit with support, follows commands, says bisyllables, and socializes with her family. There was a normalization of calcium and parathormone levels and a consistent increase in ALP. There was normalization of urine calcium excretion and resolution

of nephrocalcinosis. A marked improvement in mineralization was also noted [Figure 1].

Patient 2

A 13-year-old boy, borne of a nonconsanguineous marriage, presented with a history of bilateral knock knees from the age of 1.5 years, generalized bony pains, and delayed dentition. Despite multiple courses of vitamin D supplements, there was no significant improvement. There were no similar complaints from the other family members. Upon oral examination, he had delayed dentition, dental caries, and enamel hypoplasia [Figure 2]. He also exhibited bilateral genu valgus and flat feet, accompanied by a waddling gait. Biochemical evaluation revealed normal serum calcium (9.5 mg/dL), and 25OHD (75 ng/ml) but elevated phosphate (8.4 mg/dL), and low ALP (39 U/L) Serum creatinine (0.5 mg/dl) was normal whereas parathormone (9.6 pg/ml) was low. X-ray of the lower limbs displayed bilateral genu valgus with tongue-shaped radiolucency [Figure 2]. Serum pyridoxal-5-phosphate was 80.3 ng/ml. Clinical exome sequencing identified compound heterozygous variants, p.Glu191Lys in exon 6 and p.Gly220Ala in exon 7 of the *ALPL* gene [Table 2]. Both variants were classified as pathogenic per the ACMG criteria. The parents did not consent to their genetic testing.

Patient 3

A 33-year-old male, presented to endocrinology outpatient services with a history of multiple vertebral and tibial fractures following trivial trauma over 2 years. There was no history of short stature or bony deformities in childhood but there was a history of recurrent dental issues and dental loss. Serum calcium (9.5 mg/dL), phosphorus (3.7 mg/dL,) and parathormone (31.3 pg/mL) levels were normal whereas 25-hydroxy vitamin D (9.7 ng/mL) and ALP (28-36 IU/L) levels were low. Serum pyridoxal-5-phosphate (44.4 ng/mL, normal range: 8.7-27.2 ng/ml). At 25OHD level of 28 ng/ml, serum β-cross laps level was 263 pg/ml, and procollagen type I N-terminal propeptide (P1NP) was 60.2 ng/ml. Magnetic resonance imaging of the spine revealed fractures of the right transverse processes of L1, L2, and L3 vertebrae along with compression fractures of D6 and D8 vertebrae. The family screening revealed low ALP (39 IU/L) in the patient's father who was using dentures due to complete loss of teeth and the 3-year-old daughter (44 IU/L). Genetic analysis revealed a heterozygous likely pathogenic missense variant (p.Ala51Val) in exon 3 of the *ALPL* gene [Table 2]. Both the affected family members have been advised of genetic testing.

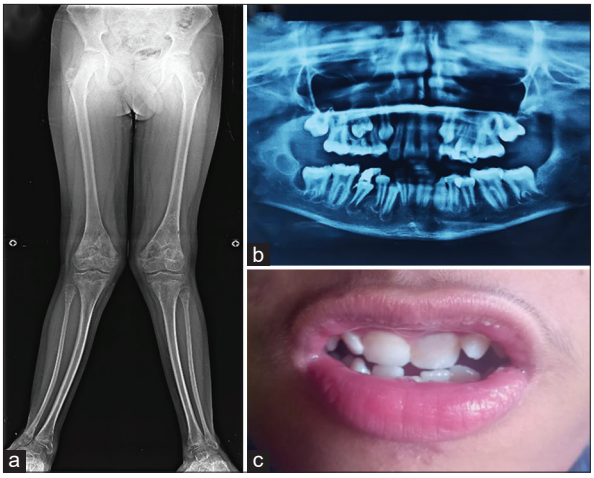

Figure 2: Anteroposterior X-ray images of both lower limbs of patient 2 showing tongue like translucencies of lower ends of femur bones (a), orthopentogram showing persistent deciduous teeth (b) and discoloration of upper incisors (c)

Patient 4

The patient, a 42-year-old male, presented with a range of symptoms including generalized myalgias, and bony pains for 8 years which often resulted in difficulty in daily activities and disturbed sleep. He also exhibited multiple minor peripheral fractures (right wrist, lower end of left tibia, middle phalanx of left little finger) over 2 years. He had visited multiple rheumatologists for his complaints with a provisional diagnosis of fibromyalgia. Evaluation over the years revealed persistent low to low-normal serum ALP levels that ranged from 27 to 45 IU/L. There were no dental concerns. In the presence of normal 25OHD (53.7 ng/ml), serum calcium was 9.4 mg/dl, serum phosphorus level was 5.5 mg/dL, and parathyroid hormone (PTH) was 24 pg/mL. Genetic analysis revealed a novel heterozygous likely pathogenic variant (p.Asn104Ser) in the *ALPL* gene [Table 2]. The patient did not consent to familial screening and segregation analysis.

Patient 5

A 63-year-old female with type 2 diabetes mellitus (T2DM) and hypertension presented with recurrent joint and bony pains, particularly affecting both knee joints, for 13 years. At the age of 50 years, she was evaluated for bone health and diagnosed to have osteopenia at total hip (T-score: -1.2) and treated with oral alendronate (35 mg per week) for 3 years but with poor response (T-score: -1.6). It was noted that her alkaline phosphatase levels were persistently low (17-21 U/L) in all her annual health check reports over the last 8 years. In the presence of normal 25OHD, corrected serum calcium levels ranged from 8.7 to 9.4 mg/dl. On retrospection, she had received multiple dental treatments for loose teeth from the age of 40 years. During the present visit, serum phosphorus was 4.99 mg/dl, β-cross laps were 358 (normal: <1008) pg/ml and osteocalcin was 7.92 (normal: 15-45) ng/ml. Genetic analysis of the patient identified a heterozygous VUS (p.Ala446Ser) in exon 12 of the *ALPL* gene [Table 2]. Subsequently, she was treated with teriparatide for 6 months, which reduced her bony pains within a month of initiation of teriparatide but with no change in serum ALP level.

Discussion

Here, we report five Asian Indian patients with HPP including three patients with adult variants and one patient each of infantile and childhood variants. Two novel variants in the *ALPL* gene were noted in our study, both in the adult form of the disease.

Here we report the first genetically-proven Indian patients with infantile and adolescent variants of hypophosphatasia. Notably, the patient presented with PTH-independent refractory hypercalcemia. Idiopathic infantile hypercalcemia was suspected given hyperphosphatemia, although calcitriol level was not measured. Hypercalcemia occurs in 44% of younger (<6 months) infants with hypophosphatasia.[9] However, hypophosphatasia is a rare cause of hypercalcemia in infants[10]; hence, often not suspected as a cause of infantile hypercalcemia. Notably, the patient had persistently low serum ALP which raised the suspicion of hypophosphatasia. However, leukemia and solid tumors, the most common cause of low ALP in children, may have associated hypercalcemia and may mimic hypophosphatasia.[11] Recently, a patient with hypercalcemia with low ALP after discontinuation of the keto diet mimicking hypophosphatasia has been reported.[12] Hence, in infants and young children with low ALP and hypercalcemia, a high index of suspicion for hypophosphatasia is necessary but should be differentiated from other relatively commoner diseases such as leukemia.

The management of hypercalcemia in hypophosphatasia is challenging, particularly when asfotase alfa is unavailable or unaffordable. In the latter scenario, recommendations for the management of hypercalcemia in hypophosphatasia include intravenous hydration, low-calcium formula, furosemide calcitonin, and thiazide diuretics.[13] However, the initial management of hypercalcemia in our infant was before considering the diagnosis of hypophosphatasia. Withholding of cholecalciferol supplementation, intravenous hydration, and low-calcium formula feeds yielded only marginal or transient effects; hence, intravenous zoledronate was used with early-onset and durable response. Notably, bisphosphonates are contraindicated in hypophosphatasia as they may further reduce the activity of ALP and worsen hypomineralization as bisphosphonate is an analog of pyrophosphate, which accumulates in hypophosphatasia.[14] To the best of our knowledge, this is one of the very few infantile hypophosphatasia patients in whom bisphosphonate is used for the management of hypercalcemia. In a previous report, oral clodronate (10 mg/kg/day) has been reported with no benefit.[15] Ours is the first infantile hypophosphatasia whose hypercalcemia responded promptly to intravenous zoledronate. Although bisphosphonates are contraindicated in hypophosphatasia, our patient demonstrates the efficacy of intravenous bisphosphonate for the management of hypercalcemia. However, the mechanisms underlying need further evaluation.

Patient 1 is the first patient to receive treatment with asfotase alfa in India. Indeed, the parents' perseverance and success in obtaining the standard of care for their infant despite the several unique challenges needs to be applauded. The positive effect of the treatment on growth, development, skeletal abnormalities, and biochemical markers (ALP and urinary phosphoethanolamine) were encouraging to pursue the continuation of treatment amidst the ongoing challenges.

Patient 2 is an adolescent who presented with knock knees and delayed dentition. Poor response to cholecalciferol pointed towards the possibility of vitamin D nonresponsive rickets. An elevated phosphorus was remarkable and initially raised suspicion of renal rickets but a normal creatinine with low ALP suggested the diagnosis of hypophosphatasia. Indeed, the radiological features were characteristic of hypophosphatasia with tongue-like translucencies.[16] Delayed dentition, another chief complaint of patient 2, is indeed a common presentation of childhood hypophosphatasia.[9] Notably, both the reported clinically diagnosed cases of hypophosphatasia from India were based on dental manifestations.[5,6] Hence, there is a need to increase awareness regarding the dental manifestations of and the treatment options for hypophosphatasia.

Recurrent fractures were the presenting manifestation in patient 3 and were also noted in patient 4, although only peripheral fractures in patient 4. Recurrent fractures are often the presenting manifestation of adult hypophosphatasia.[17] However, it is less often considered in the differential diagnosis of recurrent fractures in adults due to its rarity. However, as the disease can be suspected with serum ALP, a simple test, it should be a part of the evaluation of all adults with osteoporosis, with due attention to low to low-normal levels.

The main presenting symptom of patient 4 was generalized myalgia and treated as fibromyalgia for several years by multiple rheumatologists. In a recent study, around half of the patients in a rheumatology clinic with no definitive rheumatological diagnosis and low ALP had a genetically confirmed diagnosis of hypophosphatasia.[18] Hence, there is a need to sensitize rheumatologists to consider hypophosphatasia in adult patients presenting with musculoskeletal pain of unknown origin.

Patient 5 presented with a main complaint of knee joint pain which was diagnosed as osteoarthritis. Chondrocalcinosis in hypophosphatasia is a well-known cause of joint pain but is less well-recognized. Although patient 5 had only mild osteopenia, she received oral alendronate for 3 years with no benefit. Although not observed in patient 5, bisphosphonates increase the risk of atypical femoral fractures; hence, should be avoided in hypophosphatasia.[19] Despite documentation of low ALP over the last 8 years, the diagnosis of hypophosphatasia was not suspected which suggests the lack of awareness regarding the disease among healthcare professionals who provide bone health care. Osteoanabolic agents have shown promising responses to improve bone health in hypophosphatasia, as also noted in patient 5.[20-22] Teriparatide has been shown to reduce pain in hypophosphatasia as also noted in our patient.[22] In a few patients, teriparatide led to a transient and persistent increase in serum ALP but this was not observed in our patient.[22]

This is the first case series of genetically-proven hypophosphatasia from India. Biallelic variants in infantile

and childhood and monoallelic variants in the adult form of hypophosphatasia concur with the severity of the disease. Notably, both the patients with biallelic variants had compound heterozygous ones. p.Gly491Arg variant observed in patient 1 has been reported either as a part of compound heterozygous variants in infantile hypophosphatasia,[23,24] or as a heterozygous variant in adult form,[25] whereas the other variant in P1, p.Asp435His, is novel. p.Glu191Lys, a variant observed in patient 2, is one of the most common variants associated with hypophosphatasia and most often reported as a part of compound heterozygous variants in infantile hypophosphatasia. Functional *in vitro* studies identified p.Glu191Lys as mild (68%) with no dominant-negative effect. The variant is observed at a minor allele frequency (MAF) of 1.6% in the European (Finnish) population.[26] The other variant observed in patient 2 was p.Gly220Ala and has been previously reported in a patient with adult hypophosphatasia as per the CliniVar database.[27]

Per the ClinVar database, p.Ala51Val, a heterozygous variant in patient 3, has been reported in a homozygous state in a patient with perinatal lethal type and a compound heterozygous state in a patient with infantile type of hypophosphatasia.[28] The variant is estimated to diminish the activity of the enzyme to 4% with no dominant effect.[29] p.Asn104Ser, a heterozygous variant observed in patient 4, has been previously reported in an Indian family with adult hypophosphatasia and may be a recurrent variant in India. The variant in patient 5, p.Ala446Ser, is novel.

The study was largely limited by a small number of patients. However, this is the largest case series of hypophosphatasia from India. Besides, low ALP, diagnostic biochemical markers such as pyridoxal-5-phosphate and urinary phosphoethanolamine were not available in some patients. However, the study has some implications. The cases were pooled from multiple healthcare centers in South India and most were missed or misdiagnosed before the diagnosis of hypophosphatasia was attained. Indeed, one patient is a doctor himself whereas another patient is an Endocrinologist's mother which probably led to their diagnosis. These factors emphasize the need for increasing awareness regarding hypophosphatasia in India.

Conclusion

In the largest case series of hypophosphatasia from India, we report five cases of hypophosphatasia with two novel variants. Our study emphasizes the need to increase awareness regarding the disease to improve its early diagnosis and also, the need to form strategies to reduce the challenges in obtaining enzyme replacement therapy for hypophosphatasia in India.

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None.

Author contributions

VS planned the study; ST, VH, AN, KSA, SJ and PL were involved in the diagnosis and management of cases; SN performed the genetic analysis; SB and ARL supervised collection of data; MSD drafted the initial manuscript; VS, SB and ARL further edited and finalized the manuscript; all authors critically reviewed and approved the manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Data availability statement

The raw/processed data required to reproduce the above findings can be shared on reasonable request to the corresponding author.

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