Infantile Hypophosphatasia Secondary to a Novel Compound Heterozygous Mutation Presenting with Pyridoxine-Responsive Seizures

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Abstract Hypophosphatasia (HPP) is a rare metabolic disease with the hallmark finding of deficient serum tissue nonspecific alkaline phosphatase (TNSALP) activity. TNSALP is primarily known for its role in mineralization;

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hence, HPP is characterized by defective mineralization of bone and/or teeth. TNSALP is also necessary for proper vitamin B6 metabolism and its participation as a cofactor for neurotransmitters in the central nervous system. Defective TNSALP activity in the brain can result in intractable seizures responsive to pyridoxine. The pathophysiology of pyridoxine-responsive seizures (PRS) in severe HPP remains to be clearly defined. We review the case of a 2-month-old Caucasian boy presenting with seizures refractory to conventional antiepileptic medications. Empiric treatment with favorable response to pyridoxine in conjunction with severe metabolic bone disease, extremely low serum alkaline phosphatase, elevated phosphoethanolamine, hypercalcemia, hypercalciuria, and nephrocalcinosis led to a clinical diagnosis of infantile HPP. Sequence analysis revealed compound heterozygosity of the TNSALP gene with a novel mutation in exon 9 and a previously reported mutation in exon 12. This case reminds the physician that severe infantile HPP can present with PRS as its major initial manifestation and should alert clinicians to consider HPP in their differential of PRS. In addition, despite this severe genotype, the clinical diagnosis of our patient was delayed because of minimal phenotypic features initially. This highlights that the phenotype-genotype correlation could be variable even in severe disease. This case also demonstrates that HPP should be classified as PRS and not a form of pyridoxine-dependent epilepsy (PDE) as our patient was able to stop the pyridoxine supplementation without seizure recurrence once enzyme replacement was initiated. With the advent of enzyme replacement therapy, this once fatal disease may have improved morbidity and mortality.

Abbreviations

ALP	Alkaline phosphatase
CSF	Cerebrospinal fluid
CT	Computerized tomography
EEG	Electroencephalogram
HPP	Hypophosphatasia
HSV	Herpes simplex virus
MRI	Magnetic resonance imaging
PCR	Polymerase chain reaction
PLP	Pyridoxal-5'-phosphate
PRS	Pyridoxine-responsive seizures
PTH	Parathyroid hormone
TNSALP	Tissue nonspecific alkaline phosphatase

Introduction

Hypophosphatasia (HPP) is a rare metabolic disease defined by a deficiency of serum tissue nonspecific alkaline phosphatase (TNSALP). It was first described in 1948 (Rathbun 1948) and has a variable clinical presentation. Seven forms have been reported based primarily on the age at which skeletal lesions are discovered (Whyte 2012).

- Perinatal – usually with clinically apparent skeletal deformities and pathognomonic radiographic changes with rapidly progressive clinical course and early death
- Benign prenatal – gradual improvement of bone disease after birth
- Infantile – symptoms similar to, but typically less severe, than perinatal form and recognized before 6 months of age
- Childhood – diagnosed after 6 months of age, predominantly skeletal manifestations and premature deciduous tooth loss
- Adult – osteopenia, recurrent fractures, and pseudo-fractures with early loss of adult dentition common
- Odontohypophosphatasia – isolated dental manifestations
- Pseudohypophosphatasia – clinical findings similar to infantile HPP but with unremarkable ALP levels

The incidence of HPP has been estimated at 1 per 100,000 births in Canada where HPP was first described (Fraser 1957). In France, infantile and lethal forms have been reported to be less common (1/250,000 births), while milder adult disease is more frequent (approximately 1/6,000 individuals) (Mornet et al. 2011). No race or sex predilection exists, but a Canadian Mennonite isolate has been described with a 1:2,500 incidence (Greenberg et al. 1993). Molecular testing has proven the defect in HPP occurs in the TNSALP gene on chromosome 1p36.1-p34 (Greenberg et al. 1990), with more severe forms having an autosomal recessive

inheritance pattern (Mornet 2008). Milder expressions of disease may be autosomal dominant (Moore et al. 1999).

Alkaline phosphatase (ALP) is a dephosphorylating enzyme found throughout the body. Tissue-specific ALPs are encoded by individual genes and are found in the intestines, placenta, and germ cells (McComb et al. 1979). TNSALP is encoded by a single gene and ubiquitously expressed (Harris 1990). It is primarily known for its role in bone growth by providing inorganic phosphate for hydroxyapatite crystal production (Robison 1923) and by hydrolyzing inorganic pyrophosphate (Whyte 2010; Moss et al. 1967) which is an inhibitor of bone mineralization (Fleisch et al. 1966). TNSALP is also involved in regulation of neurotransmission in the cerebral cortex (Négyessy et al. 2011; Spentchian et al. 2003; Whyte 2010). More than 200 mutations in the TNSALP gene have been described, 80% of these being missense mutations (Mornet 2008). A recurrent point mutation has been described in the Japanese population (Watanabe et al. 2011). Large deletions are rare (The Tissue Nonspecific Alkaline Phosphatase Gene Mutations Database 2011).

In severe HPP, defective TNSALP activity in the cerebral cortex has been associated with “pyridoxine-responsive seizures” (PRS) (Baumgartner-Sigl et al. 2007). TNSALP is necessary for the conversion of pyridoxal 5' phosphate (PLP) to pyridoxal in order to cross the blood–brain barrier. Pyridoxal is then converted back to PLP, where it is a cofactor for over 140 enzymatic reactions, including regulators of GABA synthesis (Gospe 2010). GABA is an inhibitory neurotransmitter, and when reduced, the unopposed excitatory neurotransmitters lead to seizure activity (Plecko and Stöckler 2009; Stockler et al. 2011; Plecko et al. 2007; Smilari et al. 2005; Nunes et al. 2002; Balasubramaniam et al. 2010; Narisawa et al. 2001). The differential diagnosis of PRS includes those that are pyridoxine dependent, such as antiquitin deficiency due to mutations in ALDH7A1 and folinic acid-responsive seizures which are also caused by antiquitin deficiency. The category of pyridoxine-dependent epilepsy (PDE) is reserved for those conditions where a biochemical or molecular defect has been confirmed and removal of pyridoxine leads to return of seizure activity (Baxter 1999; Basura et al. 2009). The moniker PRS is applied when clinical seizures do not recur after the withdrawal of pyridoxine, indicating that the seizure disorder is not dependent upon the vitamin (Basura et al. 2009). Mutational analysis is available for ALDH7A1, and biochemical testing includes the accumulation of α -amino adipic semialdehyde (AASA), piperidine-6-carboxylate (P6C), and pipercolic acid, which serve as diagnostic markers in urine, plasma, and CSF. Other conditions which cause pyridoxine-responsive seizures include hypophosphatasia, familial hyperphosphatasia (PIGV deficiency), and nutritional vitamin B deficiency

(Plecko and Stöckler 2009). Pyridoxal phosphate-dependent seizures result from a deficiency of pyridox(am)ine 5'-phosphate oxidase (PNPO) which is necessary for the conversion of pyridoxine and pyridoxamine to PLP (Mills et al. 2005; Hoffmann et al. 2007). PNPO is not required for the production of PLP from dietary pyridoxal or PLP. Patients with PNPO mutations are responsive to pyridoxal phosphate but not to pyridoxine, and for this reason, as well clinical and biochemical differences, these patients are not classified as having PRS or PDE.

HPP is suggested on the basis of low/absent serum ALP, a constellation of clinical findings as noted previously and is supported by molecular testing of the TNSALP gene. Substrates of ALP are elevated and can be measured in the urine [phosphoethanolamine (PEA)] or serum [inorganic pyrophosphate (PPi) and pyridoxal-5'-phosphate (PLP)]. As previously noted, pyridoxine has been part of the treatment regimen in some children with seizures as a manifestation of HPP. We will discuss below these treatment options and how the advent of these treatments may change our consideration of HPP as a pyridoxine "responsive" rather than pyridoxine "dependent" entity.

Defective mineralization results in rickets and may lead to respiratory compromise and recurrent lung infections due to altered chest wall mechanics of the weakened thoracic cage in those with the most severe disease. Hypomineralized skull bones may be prone to premature fusion of the cranial sutures via an unknown mechanism. Craniosynostosis can lead to increased intracranial pressure and requires close monitoring (Nunes et al. 2002; Béthenod et al. 1967). HPP has also been found to be associated with increased intracranial pressure due to pseudotumor cerebri (Demirbilek et al. 2012). Varying degrees of hypercalcemia are present and may be accompanied by hypercalciuria and resultant nephrocalcinosis. Poor feeding and hypotonia are attributed to hypercalcemia. In severe disease, clinical features of small thorax, limb deformities, and blue sclera are seen.

Patient Presentation

Our patient was born at 35 weeks gestation to a 29-year-old G5P2→3 HSV-positive, previously opioid-dependent mother with a history of buprenorphine/naloxone use during pregnancy. All other serologies were negative. She received routine prenatal care and valacyclovir therapy during gestation. The antenatal course was complicated by preterm contractions beginning at 22 weeks which were treated with bed rest at home and oral terbutaline. Three prenatal ultrasounds were done with no noted fetal abnormalities. Delivery was spontaneous vaginal vertex. APGAR scores at 1 and 5 min were 9 and 10, respectively. Birth weight was

2,585 g (25th percentile), length 45.5 cm (25th–50th percentile), and head circumference 31 cm (5th–10th percentile). Physical examination was normal with no dysmorphic features. Father is of Caucasian-Japanese origin and mother is Caucasian.

At 18 h of life, the patient began to exhibit facial grimacing, flexion of upper extremities, and extension of the lower extremities lasting up to 5 min occurring multiple times a day. Complete blood count and serum electrolytes were normal, including serum calcium and magnesium levels (9.1 and 1.9 mg/dl, respectively). Serum phosphorous was just below the lower limit of normal (5.4 mg/dl, normal range 5.5–9.5 mg/dl). Blood, urine, and cerebrospinal fluid (CSF) cultures were negative. HSV PCR was negative from the CSF. Electroencephalogram (EEG) revealed multifocal sharp waves and mild discontinuity, but was without electrographic seizure activity. Head computerized tomography (CT) and brain magnetic resonance imaging (MRI) were unremarkable. Given maternal opioid use, neonatal abstinence syndrome was suspected and morphine therapy was instituted. He was then transferred to a tertiary care facility. Despite the EEG findings, the clinical suspicion for seizure was still high. These episodes persisted, and 5 mg/kg/day of phenobarbital was initiated. He was discharged at 4 weeks of life when he seemed to be free of further presumed seizures. Once home, he began to have 10–15 clusters of tonic activity, each lasting a few seconds, every two to three days. At 6 weeks of life, he was seen in the outpatient neurology clinic and was admitted for a 24-h video EEG, which showed an electroclinical seizure of right central onset, correlating with left arm jerking. Phenobarbital dose was increased to 7.5 mg/kg/day and he was discharged.

Within 2 weeks, on day of life 63, he presented in status epilepticus. Vitamin-responsive epilepsies were considered and empiric treatment was initiated with 100 mg IV pyridoxine followed by oral pyridoxine (25 mg/kg/day), pyridoxal-5-phosphate (30 mg/kg/day), and folinic acid (1 mg/kg/day) with resolution of seizures. Subsequently, poor feeding, hypercalcemia, and hypercalciuria were noted. Serum calcium was 11.2–12.3 mg/dl (normal range 8.8–10.8 mg/dl) and serum-ionized calcium 1.4 and 1.6 mmol/l (normal range 1.0–1.4 mmol/l). Serum phosphorous was normal. Parathyroid hormone (PTH) was appropriately suppressed for the degree of hypercalcemia at <3 pg/ml (normal range 10–65 pg/ml with a serum calcium in the normal range). Serum total 25-hydroxy vitamin D levels were normal. Renal ultrasound showed bilateral medullary nephrocalcinosis (Fig. 1). Skeletal radiography had changes typical of infantile hypophosphatasia: significant osteopenia of metaphyses with areas of fragmentation of the distal femurs; focal metaphyseal defects in the humeri; and cupping of the distal tibia,

Fig. 1 Renal ultrasound showing bilateral medullary nephrocalcinosis at age 2 months (indicated by *red arrows*)

Fig. 2 Radiograph showing bilateral femoral metaphyseal defects and short right femur with slight curvature at age 2 months

radius, and ulna (Fig. 2). ALP was undetectable (<5 IU/l). On review of old records, ALP was undetectable on the first day of life but had gone unnoticed. In addition, demineralized areas of the skull were retrospectively noted on the bone window of the CT scan obtained at birth with marked worsening over 2 months (Figs. 3, 4).

Infantile HPP was therefore suspected. Supportive laboratory data showed elevated urine phosphoethanolamine (PEA) (9.31 mM/g creatinine; nl: <0.8 mM/g creatinine) and significantly elevated CSF PLP (1999 nmol/l; nl: 30–80) (Dr. Keith Hyland, Medical Neurogenetics, Atlanta, GA). Other forms of PRS and PDE were excluded based on normal testing of CSF neurotransmitters and serum pipecolic acid. PLP deficiency due to PNPO mutations would have shown increased CSF L-DOPA and decreased CSF homovanillic acid and 5-hydroxyindoleacetic acid (Gospe 2010). Serum pipecolic acid is elevated in PDE from antiquitin deficiency.

Definitive diagnosis of HPP was made by sequence analysis of the TNSALP gene (performed at Connective Tissue Gene Tests, Allentown, PA), which revealed compound heterozygosity for a novel mutation in exon 9, c.875_881delCAGGGGinsT, and a previously reported mutation in exon 12, c.1559delT (Orimo et al. 1994).

Discussion

Our patient highlights the wide variability in clinical presentation of HPP. His presentation was dominated by

intractable seizures and many of the common overt phenotypic features of HPP were absent. Given maternal history and clinical findings, the initial diagnosis of neonatal abstinence syndrome (NAS) was made. Treatment with morphine was instituted at appropriate dosing which should have extinguished the seizures, had they been due to NAS. Withdrawal symptoms from buprenorphine often manifest later in neonates than withdrawal from opiates or other opiate agonists such as methadone (Gaalema et al. 2012). The lack of response to appropriate opioid therapy and atypical timing of withdrawal from buprenorphine were indicators that this patient's presentation was not due to NAS.

Neonatal HSV meningitis was also considered until ruled out by evaluation. When seizures became refractory to anticonvulsant therapy, empiric therapy for vitamin-responsive epilepsies and systematic evaluation identified PRS. Subsequently, hypercalcemia, hypercalciuria, and diffuse metabolic bone disease were noted and HPP was suspected. It is important to appreciate that while our patient's initial presentation was apparently isolated PRS, an undetectable level of ALP recorded at the first hospitalization went unnoticed, delaying arrival at the correct diagnosis. In addition, this case highlights the importance of considering vitamin-responsive epilepsies in newborns with refractory seizures and empirically treating with a combination of pyridoxine, pyridoxal-5-phosphate, and folinic acid (Gospe 2010).

Our patient strongly resembles others reported in the literature, including a similar case by Baumgartner-Sigl et al. (2007). Their patient also presented first with PRS in

Fig. 3 Bone window of computerized tomography (CT) scans of the head show progressive widening of the sutures (*thin arrows*) and calvarial bone destruction (*thick arrows*). *Left*: first day of life. *Right*: age 2 months

Fig. 4 Reconstructive head CT showing widened sutures due to poor mineralization at age 2 months

the neonatal period, followed later by skeletal demineralization, hypercalcemia, hypercalciuria, and nephrocalcinosis and died before one year. They suggested that the presence of PRS in HPP was a poor prognostic sign and encouraged the measurement of ALP activity in the evaluation of neonatal seizures. Litmanovitz et al. (2002) also reported a patient with pyridoxine-responsive neonatal seizures, a nearly nondetectable serum ALP and skeletal hypomineralization with early demise due to pneumonia.

Our patient was found to have a novel mutation of the TNSALP gene on exon 9 involving a large deletion predicted to lead to complete lack of protein production. The second mutation on exon 12 has previously been described in Japanese patients with severe infantile HPP (Orimo et al. 1994) and is consistent with his father's ethnicity. These two mutations confer severe disease ultimately observed in our patient. However, a delay in the development of overt phenotypic features of HPP implies that phenotype-genotype correlation could be variable even in severe disease. Ultimately, the patient manifested findings typically associated with HPP, including hypotonia, poor feeding, craniosynostosis, limb shortening, and several episodes of respiratory failure associated with viral illnesses.

Infantile HPP carries a mortality rate of perhaps 50% which further increases in the presence of PRS (Fraser 1957).

PRS in general has a good prognosis. Prior to the introduction of new treatment options for HPP, which will be discussed below, PRS had been associated with increased disease severity of HPP (Baumgartner-Sigl et al. 2007; Litmanovitz et al. 2002).

Variability in severity of disease in patients with HPP is not easily explained. The mutant TNSALP enzymes produced have variable and possibly preferential catalytic activity of substrates, inorganic pyrophosphate, and PLP (Di Mauro et al. 2002). The mutant enzymes are also often found as heterodimers which have variable catalytic activity depending on the combination of monomers composing that particular heterodimeric enzyme (Di Mauro et al. 2002; Zhanhua et al. 2005). These characteristics of TNSALP produced in those with mutations of the TNSALP gene help explain some of the phenotypic variability of disease in HPP. Mouse models of TNSALP deficiency demonstrate a similar seizure phenotype due to defective metabolism of PLP, which can be rescued with pyridoxal (Waymire et al. 1995). Knockout mice have elucidated the role of TNSALP in the central nervous system. TNSALP not only has a role in GABA neurotransmission but was found in the synaptic cleft of primary sensory areas (Fonta et al. 2004).

Several potential therapies to treat HPP have been explored. In 1956, treatment with cortisone showed limited

success (Fraser and Laidlaw 1956). Early enzyme replacement with infusion of ALP-rich plasma from patients with Paget's disease was attempted in the 1980s (Whyte et al. 1982). Calcitonin and chlorothiazide have been used to treat hypercalcemia and hypercalciuria (Barcia et al. 1997). Allogenic mesenchymal stem cell, donor bone fragment, and isolated osteoblast transplantations have been attempted (Tadokoro et al. 2010; Cahill et al. 2007). In adults, teriparatide, a recombinant parathyroid hormone, has had limited success (Gagnon et al. 2010). Adeno-associated virus-8 vectors expressing TNSALP have been used to rescue mice with HPP (Matsumoto et al. 2011). Similarly, treatment using lentiviral vectors expressing a bone-targeted form of TNSALP has led to improved survival in mice with HPP (Yamamoto et al. 2011).

Most recently, enzyme replacement therapy for HPP has been explored with success in animal models and human clinical trials (Millán et al. 2008; McKee et al. 2011; Whyte et al. 2012). This investigational therapy, asfotase alfa (Alexion Pharmaceuticals), a bone-targeted, recombinant TNSALP, has recently been reported to improve survival and clinical outcome in HPP (Whyte et al. 2010). The results of the open-labeled study on 11 patients was recently reported showing improvement in rickets on skeletal radiographs, as well as improved pulmonary function and motor milestones in life-threatening hypophosphatasia (Whyte et al. 2012).

Our patient was started on asfotase alfa at nearly 5 months of age and remains alive at 31 months of age. Once his molecular diagnosis was confirmed and specific treatment with enzyme replacement therapy was made available, our patient was able to wean not only anticonvulsant therapy, but also pyridoxine supplementation, without the return of his seizures. Thus, HPP is truly a pyridoxine-responsive (but not pyridoxine-dependent) form of seizures. Further details on this therapy and long-term outcomes will be reported.

In conclusion, this case illustrates that careful scrutiny of laboratory data and continual revision of differential diagnosis is crucial in reaching the diagnosis of rare entities such as HPP. HPP must be considered in the differential diagnosis of any patient presenting with PRS, and alkaline phosphatase level must be measured. Therapy requires a multidisciplinary approach addressing feeding disorders, respiratory compromise, craniosynostosis and increased intracranial pressure, hypercalcemia, and developmental delay. Close follow-up is critical.

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Synopsis

This case reminds the physician that severe infantile HPP can present with PRS as its major initial manifestation and should alert clinicians to consider HPP in their differential of PRS.

Conflict of Interest

Drs. Belachew, Kazmerski, Libman, Goldstein, Stevens, Sperling, Balest and Ms. DeWard have no financial disclosures. Dr. Vockley discloses research support from Alexion Pharmaceuticals.

The authors attest that this is an original manuscript, and it has never been published. At this time, this manuscript is being submitted only to Journal of Inherited Metabolic Disease Reports and will not be submitted elsewhere while under consideration by this journal.

Contributor's Statement Page

Dr. Belachew drafted the initial draft of this case report and has made a substantial contribution towards the content, outline, background, discussion, revision, editing, and finalization of this manuscript. Dr. Kazmerski has made a substantial contribution to the content, revision, editing, and finalization of this manuscript. Dr. Libman has made a substantial contribution to the diagnosis of this case, revision and editing of this manuscript. Dr. Goldstein has contributed significantly to the neurological aspect of the manuscript content and to revision and editing of this manuscript. Drs. Vockley and Stevens and Ms. Deward have contributed to the genetic discussion of this manuscript and revision and editing. Dr. Sperling has contributed to the background, content, and editing of this manuscript. Dr. Balest has made substantial contributions to the background, revision, editing, and finalization of this manuscript. All of the authors have reviewed this manuscript and given final approval for its submission for publication.

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