Chapter 14
Neurological Symptoms of Hypophosphatasia

Takeshi Taketani

Abstract Hypophosphatasia (HPP) is a bone metabolic disorder caused by mutations in the liver/bone/kidney alkaline phosphatase gene (*ALPL*), which encodes tissue-nonspecific alkaline phosphatase (TNAP). This disease is characterized by disrupted bone and tooth mineralization, and reduced serum AP activity. Along with bone and tooth symptoms, many neurological symptoms, seizure, encephalopathy, intracranial hypertension, mental retardation, deafness, and growth hormone deficiency (GHD), are frequently found in HPP patients. Seizure occurs in severe HPP types soon after birth, and responds to pyridoxine, but is an indicator of lethal prognosis. Encephalopathy rarely presents in severe HPP types, but has severe sequelae. Intracranial hypertension complicated in mild HPP types develops after the age of 1 year and sometimes need neurosurgical intervention. Mental retardation, deafness and GHD are more frequently found in Japanese HPP patients. Mental retardation occurs in all HPP types. Deafness in perinatal lethal type is both conductive and sensorineural. GHD develops in all but perinatal lethal type and the diagnosis tends to delay. The pathogenesis of these neural features of HPP might be due to impairment of both vitamin B6 metabolism and central nervous system development by *ALPL* mutations.

Keywords Seizure · Mental retardation · Deafness · Encephalopathy · Growth hormone deficiency

T. Taketani (✉)
Department of Pediatrics, Shimane University Faculty of Medicine,
89-1, Enya, Izumo, Shimane 693-8501, Japan
e-mail: ttaketani@med.shimane-u.ac.jp

C. Fonta and L. Négyessy (eds.), *Neuronal Tissue-Nonspecific Alkaline Phosphatase (TNAP)*, Subcellular Biochemistry 76,
DOI 10.1007/978-94-017-7197-9_14

14.1 Introduction

Hypophosphatasia (HPP) is a metabolic bone disorder caused by mutations in the liver/bone/kidney alkaline phosphatase (*ALPL*) gene, which encodes tissue-nonspecific alkaline phosphatase (TNAP) (Whyte 2001, 2010; Mornet 2008). This disorder is characterized by defective bone and tooth mineralization, and reduced serum AP activity (Whyte 2001, 2010; Mornet 2008). According to several reports from Western populations, HPP patients exhibit both autosomal dominant (AD) inheritance and autosomal recessive (AR), while almost all HPP patients in the Japanese population are AR (Mornet et al. 2011; Michigami et al. 2005; Ozono and Michigami 2011; Watanabe et al. 2011). Patients with AR inheritance have a severe or mild clinical phenotype, whereas those with AD have a mild phenotype (Whyte 2001, 2010; Mornet 2008; Mornet et al. 2011; Michigami et al. 2005; Wenkert et al. 2011). The clinical severity of HPP often depends on the age of onset (Whyte 2001, 2010; Mornet 2008) (see also Chap. 1). The six clinical types of HPP are: (1) perinatal lethal which is apparent at birth; (2) infantile from 1–6 months; (3) childhood type from the age of 6 months–18 years; (4) odonto type, which is characterized by the premature loss of deciduous teeth by 5 years without apparent bone symptoms; and (5) adult. Interestingly, some patients with prenatal onset, namely the prenatal benign type have ameliorated spontaneous skeletal defects and survive (Ozono et al. 1996; Brun-Heath et al. 2008; Wenkert et al. 2011). The perinatal lethal type usually has poor prognosis because of a profound reduction of bone mineralization; half of patients with the infantile type and all patients with the childhood type survive but experience premature loss of deciduous teeth as well as delayed walking and waddling, which reflect the degree of the skeletal disease (Whyte 2001, 2010; Mornet 2008). Low AP activity contributes to elevated levels of AP substrates, i.e., pyridoxal 5′ phosphate (PLP), phosphoethanolamine (PEA), and inorganic pyrophosphate (Whyte 2001). More than 260 types of *ALPL* mutations have been identified in HPP patients, and 80 % of these are missense mutations according to the *ALPL* mutations database (http://www.sesep.uvsq.fr/03_hypo_mutations.php#mutations). The phenotypes of HPP patients are also closely related to the residual enzyme activity effects of *ALPL* mutations (Zurutuza et al. 1999; Mornet 2000). No curative therapy has been established for HPP. Currently, bone-targeted enzyme-replacement therapy, and cell transplantation from bone marrow and other bone sources are under development (Nishioka et al. 2006; Whyte et al. 2003, 2012; Cahill et al. 2007; Tadokoro et al. 2009 (see Chap. 15).

In addition to bone and tooth symptoms, patients with HPP present with neurological symptoms including seizure, encephalopathy, intracranial hypertension, mental retardation, deafness, and growth hormone deficiency (GHD). This chapter describes these neurological symptoms of HPP in detail.

14.2 Seizure

We summarized several cases of seizures with HPP that have been fully reported (Balasubramaniam et al. 2010; Baumgartner-Sigl et al. 2007; Bethenod et al. 1967; Belachew et al. 2013; Demirbilek et al. 2012; Hofmann et al. 2013; Litmanovitz et al. 2002; Nunes et al. 2002; Sia et al. 1975; Smilari et al. 2005; Yamamoto et al. 2004). Seizures of HPP usually occur from days after birth. Only severe types including perinatal lethal and infantile type have seizures while perinatal benign, childhood, adult and odonto types have not. Therefore, bone symptoms including hypomineralization and shortening or deformity of the extremities and respiratory failure precede appearance of seizures. But, two cases reported by Baumgartner-Sigl et al. (2007) and Belachew et al. (2013) developed refractoryseizures before any sign or symptom of HPP, suggesting that intractable seizures in neonates need to suspect HPP. Tonic or/and clonic seizures, myoclonic convulsion and spasm often occur. Complete blood count and blood biochemical examination such as serum electrolytes, glucose, or ammonia are normal except for low titer of AP. Laboratory findings of bacterial and viral infection in blood, urine, and cerebrospinal fluid (CSF) are negative. Electroencephalogram (EEG) ordinarily reveals mono- or multi-focal epileptic discharge. Hypsarrhythmia, a burst-suppression pattern in EEG, sometimes developed, resulting in West syndrome (Balasubramaniam et al. 2010; Baumgartner-Sigl et al. 2007; Yamamoto et al. 2004). Brain computed tomography and magnetic resonance imaging (MRI) do not indicate abnormalities. Hofmann et al. (2013) first reported that cranial MRI demonstrated progressive cystic and destructive encephalopathy in an infant without hypoxic–ischemic episode. Seizures are refractory to standard anticonvulsants such as diazepam, phenobarbital, phenytoin, clonzepam, or valproic acid. But, pyridoxine (PN, vitamin B6) is the only effective anticonvulsant drug, showing that HPP-related seizures are pyridoxine-responsive seizures (PRS). Initial dosage of PN is 100 mg/day or 30–60 mg/kg/day, and maintenance dosage is 50 mg/day or 5–10 mg/kg/day. The duration of PN administration cannot be clarified because except a single case (Belachew et al. 2013) all studied HPP patients with neonatal seizures died within the age of 18 months, demonstrating that PRS of HPP is an indicator of lethal prognosis compared to ordinary PRS which do not recur after the withdrawal of PN (Basura et al. 2009). In the single case survived as reported by Belachew et al. (2013) the PN supplementation could be stopped without seizure recurrence once enzyme replacement therapy, asfotase alfa (Alexion Pharmaceuticals), a bone-targeted recombinant TNAP, has been started. This enzyme therapy has been reported to improve survival and clinical outcome in HPP (Whyte et al. 2012). Further details on this therapy and long-term neurological outcomes will be reported (see Chap. 15).

PN-dependent seizure was found in a deficiency of a-aminoadipic semialdehyde dehydrogenase (antiquitin), which is encoded by the *ALDH7A1* gene, folinic acid-responsive seizures, which are also caused by antiquitin deficiency, familial hyperphosphatasia (PIGV deficiency) and nutritional vitamin B deficiency (Gospe 2010; Plecko and Stöckler 2010). As for PLP-dependent seizure, there is a

deficiency of pridox(am)ine 5′-phosphate oxidase which is encoded by the *PNPO* gene (Gospe 2010; Plecko and Stöckler 2010). It is necessary to confirm the diagnosis of PRS because management of each of these diseases differs.

The pathogenesis of PRS in HPP is not understood. Hypotheses have included cranial deformities, intracerebral hemorrhage, and hypoxia (Whyte et al. 1988), but many of HPP patients without these complications have PRS. Interestingly, neonatal seizure in HPP has a unique metabolic basis due to either accumulation of substrates or diminished products of TNAP-mediated hydrolysis (Whyte 2001). However, PEA excess in HPP does not appear to explain the occurrence of PRS. Instead, PLP accumulation reveals the important role that TNAP in vitamin B6 metabolism: as a plasma membrane-bound ectoenzyme that dephosphorylates PLP to pyridoxal (PL) (Whyte et al. 1988). PL is the form of vitamin B6 that crosses cell plasma membranes to be phosphorylated intracellularly to PLP (Whyte et al. 1988). PLP is the active metabolite of vitamin B6 and is an essential coenzyme for synthesis of various neurotransmitters and biogenic amines. It acts as a co-factor for more than 100 apoenzymes (see Chap. 11). The corresponding holoenzymes catalyse diverse reactions such as transamination, decarboxylation, racemisation, degradation and replacement. In the brain, PLP-dependent enzymes [aromatic amino acid decarboxylase (AADC), branched-chain amino acid 2-oxoglutarate aminotransferase, gamma-aminobutyric acid (GABA) transaminase, glutamate decarboxylase (GAD), glycine cleavage enzyme, kynureninase, kynurenine aminotransferase and L-serine racemase are involved in the metabolism of dopamine, serotonin, glutamate, glycine, GABA, D-serine and taurine (Surtees et al. 2006) (Fig. 14.1). Although low TNAP activity in HPP causes high circulating (extracellular) levels of PLP, plasma PL levels are typically normal (Baumgartner-Sigl

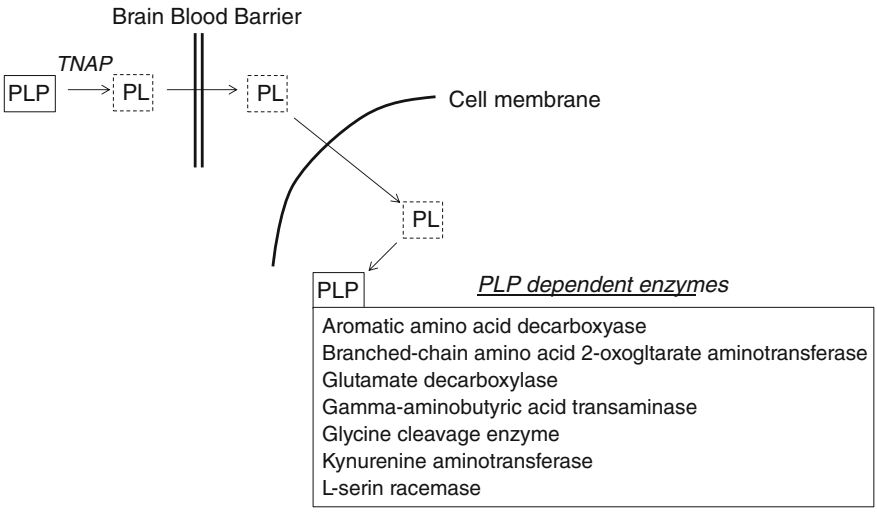

Fig. 14.1 Role of TNAP in vitamin B6 metabolism for brain. *PL* pyridoxal, *PLP* pyridoxal 5′ phosphate

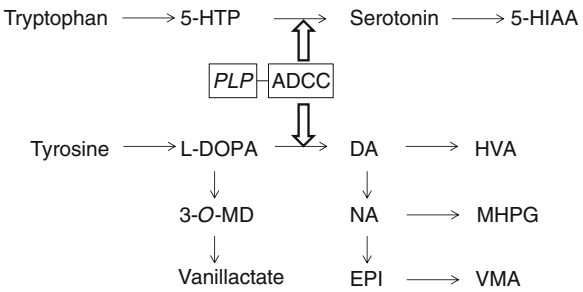

Fig. 14.2 Biochemical pathway related to AADC (modified from Balasubramaniam et al. 2010). *AADC* Aromatic L-amino acid decarboxylase; *5-HTP* hydroxytryptophan, *3-O-MD* 3-*O*-methyldopa, *DA* dopamine, *LDOPA* L-dopamine, *NA* noradrenaline, *EPI* epinephrine, *5-HIAA* 5-hydroxyindole acetic acid, *HVA* homovanillic acid, *MHPG* 3-methoxy-4 hydroxyphenylglycol, *VMA* vanillylmandelic acid, *PL* pyridoxal, *PLP* pyridoxal 5′ phosphate

et al. 2007) (see also Chap. 1). Occasionally, plasma PL levels are low especially in severe HPP cases (Whyte et al. 1988). Low extracellular levels of PL, and resulting low brain PLP levels, may lead to decreased activity of PLP-dependent enzymes (Baumgartner-Sigl et al. 2007). Analysis of biogenic amines in CSF of HPP patients revealed an elevated 3-ortho-methyldopa and 5-hydrotryptophan levels and decreased 5-hydroxyindole acetic acid (Balasubramaniam et al. 2010; Baumgartner-Sigl et al. 2007). Urinary levels of vanillactate were elevated (Balasubramaniam et al. 2010). These metabolites indicate functional deficiency of AADC (Fig. 14.2). Only a few primary AADC deficiency patients were reported with epileptic seizures (Balasubramaniam et al. 2010). Moreover, PL/PLP deficiency in brain cells (despite normal PLP levels in CSF) reduces GABA synthesis because of low GAD activity (Baumgartner-Sigl et al. 2007). PLP is a co-enzyme for GAD, which plays a crucial role in the synthesis of GABA (Baxter 2003). GABA is an inhibitory neurotransmitter and when reduced, the unopposed excitatory neurotransmitters lead to seizure activity (Belachew et al. 2013) (Fig. 14.3). Strong support for this hypothesis comes from null homozygous mouse models null for TNAP gene. These mice have low circulating PL as well as high PLP levels and neonatal seizures that are partially controlled by oral PN/PL (Waymire et al. 1995; Narisawa et al. 2001). In these mice, low PL and PLP levels in brain tissue (before PN treatment) compromised GAD activity and impaired GABA synthesis. Therefore, inadequate levels of PLP in the neurons might lead to PRS.

14.3 Encephalopathy

PRS often presents with epileptic encephalitis (Gospe 2010). Only one HPP patient progresses to encephalopathy (Hofmann et al. 2013). On the patient's seventh day of life, seizures started and rapidly progressed in the following weeks.

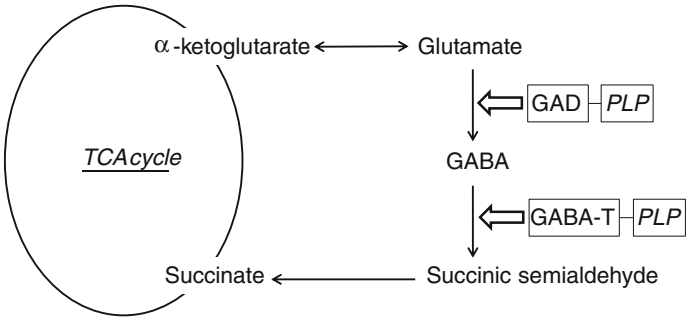

Fig. 14.3 GABA and glutamate metabolic pathway, *GABA* gamma-aminobutyric acid, *GAD* glutamic acid decarboxylase, *GABA-T* GABA transaminase, *PLP* pyridoxal 5′ phosphate, *TCA* tricarboxylic acid

Standard EEG during seizures showed severe generalized hypersynchronous activity but was normal during intermission. Unfortunately, the patient did not show a sustained response to repeated high doses of vitamin B6/pyridoxine, phenobarbital or levetiracetam. The patient continued to have seizures until he was 6 weeks of age when he was deeply sedated. Discontinuation of the sedative medication did not lead to consciousness. EEG-follow up showed discontinuous activity with higher amplitudes than before sedation and hypersynchronous activity was unmasked again. No spontaneous breathing was found and after stimulation the patient opened his eyes without any fixation or spontaneous movements. Particularly synchronous mass movements and exhaustible cloni were obvious and the patient showed a severe muscular hypotonia. Brain MRI revealed a progressive cystic degradation of the cortex and peripheral white matter with nearly complete destruction of the cerebrum. The patients died at the age of 10 weeks.

The patient had PL resistant seizure and obvious brain damage. These findings indicate that the MRI damage pattern of this patient seemed to be due to a hypoxic–ischemic event occurring in conjunction with seizures and was possibly aggravated by the underlying metabolic disease. Considering that there is no clear hypoxic–ischemic episode in this patient's history, the TNAP deficiency is considered to be at least partially involved in this damage pattern leading to neuronal cell death via imbalances or disturbances in phosphate, vitamin B6 or adenosine triphosphate (ATP) metabolism. No similar images have been reported in patients with HPP. TNAP is present in the synapses of the cerebral cortex (Fonta et al. 2004) that are involved in neurotransmitter synthesis, synaptic stabilization, and myelin pattern formation (Fonta et al. 2004, 2005; Négyessy et al. 2011; Hanics et al. 2012). A study in TNAP-KO mice also showed that lack of TNAP compromises myelination and synaptogenesis in the cerebral cortex (Hanics et al. 2012). The Brain Blood Barrier (BBB) is formed by brain capillary endothelial cells (with other cells) which are alkaline phosphatase positive in many animals but lose their marker enzyme in culture (Deracinois et al. 2012) (see Chap. 7). TNAP function in human endothelial cells is not clearly identified. TNAP, however, is known to be involved

in the transport of pyridoxine across the BBB subsequently used in neurotransmitter metabolism (Hofmann et al. 2013). TNAP is expressed during early stages of brain vessel development coincident with the appearance of functional BBB. In addition, TNAP seems to be involved in purinergic signaling by producing adenosine through dephosphorylation of ATP. TNAP is localized in growth cones next to ATP-receptors (P2X7) and it seems to be essential for axonal growth of hippocampal neurons by regulating both ligand availability and protein expression of P2X7 receptor (Díez-Zaera et al. 2011). These data suggest that TNAP may play a role in central nervous system (CNS) development and activity-dependent cortical functions (see Chaps. 4, 5 and 18).

14.4 Intracranial Hypertension

The premature closure of sutures is held responsible for intracranial hypertension in patients with HPP (Whyte 2001, 2010; Mornet 2008). Craniosynostosis is a well-known feature of the infantile and childhood HPP (Whyte 2001, 2010; Mornet 2008) while it misses in the adult and odonto-HPP types, thereby suggesting a direct relationship with the degree of enzymatic deficiency (Collmann et al. 2009). Collmann et al. (2009) reported a series of 7 children among 20 cases of infantile and childhood HPP who had craniosynostosis and discussed the functional problems arising from HPP. However, biochemical analysis in these 7 cases did not reveal any overt differences from the 13 other childhood HPP individuals not affected by craniosynostosis. No particular genetic mutational pattern was found in the synostotic individuals. In addition, the age range and the distribution of subtypes did not differ between these two subgroups. Intracranial hypertension developed after the age of 1 year. Neurosurgical intervention was necessary in 4 cases. Secondary ectopia of the cerebellar tonsils were detected in five of the 7 patients and caused hydrosyringomyelia in one of them.

Skull pathology in HPP has been reported as hypomineralization, which, in the most severe perinatal form, results in a “caput membranaceum”. In the less severe infantile form, widely diastatic sutures or at least multiple Wormian bones have been reported (Macpherson et al. 1972; Kaplan et al. 1991). They seem to precede sutural obliteration and should, therefore, be considered as functionally closed sutures (Collmann et al. 2009). In fact, MacPherson et al. (1972) found uncalcified osteoid as substrate mimicking this sutural gap. According to Collmann et al. (2009), premature fusion in HPP appears to start with the sagittal or coronal suture. However, synostosis may progressively involve all main cranial sutures during childhood. In these cases, intracranial hypertension putting the optic nerve at risk should be anticipated. Of importance, the lambdoid suture tends to close early, thereby possibly preventing normal expansion of the posterior fossa. This may explain the herniation of the cerebellar tonsils as a secondary phenomenon. Of note, none of patients with intracranial hypertension developed epileptic seizures (Collmann et al. 2009).

Since cranial sutures are frequently involved in infantile and childhood HPP, a multidisciplinary approach for the clinical care is necessary, including long-term neurosurgical surveillance (Collmann et al. 2009). It often progressively involves all cranial sutures and poses significant functional risks to the optic nerves, as well as the spinal cord. The evaluation of HPP in childhood should include plain radiographs and, in case of premature sutural fusion, MR imaging and repeated ophthalmoscopic assessment (Collmann et al. 2009). With regard to the progressive nature of craniosynostosis, careful surveillance is recommended throughout childhood until adolescence and, in the presence of Chiari I malformation or hydrosyringomyelia, probably throughout life (Collmann et al. 2009).

14.5 Neurological Symptoms of Japanese HPP Patients

There are very few group- or country-specific reports on the clinical and genetic features of HPP in pediatric patients. However, the common *ALPL* mutations observed in Japanese patients, i.e., homozygous mutation of c.1559delT and compound heterozygous mutation of c.T979C (p.F327L) have been shown to be associated with relatively lethal and mild types of HPP, respectively (Michigami et al. 2005; Ozono and Michigami 2011; Watanabe et al. 2011). Therefore, we retrospectively examined the clinical and genetic aspects of HPP in total 56 Japanese children including 52 reported by Taketani et al. (2014) Mutations of the *ALPL* gene were analyzed in 35 patients. The frequencies of patients with perinatal lethal, prenatal benign, infantile, childhood, and odonto type HPP were 23, 16, 5, 9, and 3, respectively. There was neither adult type nor mild HPP with AD inheritance. Clinical characteristics by genotype are show in Table 14.1.

About neurological symptoms, seizure was found in 14 patients (11 perinatal lethal, 1 infantile and 2 childhood types). Seizure in perinatal lethal and infantile types was PRS. They occurred in patients within 1 month after birth. Two cases developed seizure before detection of bone symptoms. Computed Tomography and MRI image did not have abnormal findings. Eight patients of them died within the age of 5 years. Two patients with seizure in childhood type were diagnosed as febrile convulsion and epilepsy in each. These two cases did not exhibit seizure in neonatal period. Encephalopathy was found in two patients with perinatal lethal type. Seizure and disturbance of consciousness occurred in both without hypoxic and ischemic episodes. Brain MRI revealed diffuse cerebral edema. All patients had severe sequelae including mental and developmental retardation, incapacitate status and respiratory failure with artificial ventilation. Mental retardation was detected in 11 patients (5 perinatal lethal, 2 prenatal benign, 1 infantile and 3 childhood types). Assessment of mental retardation was performed by: developmental quotient scores, the Enjoji scale of infant analytical development, or intelligence quotient. Four patients among 11 patients with mental retardation (3 perinatal lethal and 1 infantile types) had hypoxic events, the 7 others did not. This suggested that the TNAP deficiency might be partially involved in mental retardation. Deafness

Table 14.1 Clinical characteristics of Japanese patients with hypophosphatasia

	Perinatal lethal (23)	Prenatal benign (16)	Infantile (5)	Childhood (9)
Clinical findings				
Shortening or deformity of the extremities	17	14	0	4
Bone fracture	3	4	1	0
Respiratory failure	23	0	1	0
Seizure	11	0	1	2
Encephalopathy	2	0	0	0
Enlargement of the anterior fontanelle	5	2	4	0
Renal calcification	3	0	0	0
Short stature	5	8	2	6
Failure to thrive	11	4	5	1
Premature loss of deciduous teeth	5	4	0	3
Mental retardation	5	2	1	3
Premature synostosis of the skull	2	0	2	0
Deafness	5	0	0	0
Radiographic findings				
Hypomineralization	22	5	5	0
Loss of bone	7	2	0	0
Deformity of long bones	13	13	0	4
Flared metaphyses	14	8	5	1
Hypolucent mid-metaphyses	5	5	1	0
Osteochondral spurs	0	0	0	0
Narrow thorax	22	1	4	0
Biochemical tests				
AP (IU/L)	19.4	77.3	98	145
Urine PEA (μmol/mg Cr)	7,401	2,119	1,605	873

Numbers indicate the number of patients for each clinical and radiographic criterion. The plasma AP and urine phosphoethanolamine (PEA) values are averages from 56 and 27 patients respectively. In Japan, the normal blood AP range is as follows: median 490 IU/L (range = 59–921) from birth to 1 month; median 617 IU/L (199–1035) during 2–5 months; median 471 IU/L (180–762) from 6 months to 1 year. The lower cut off level during years 1–7 was 170 IU/L. The normal urine PEA range is 31–110 μmol/mg. *Cr* Creatinine. This table was modified from Taketani et al. (2014)

developed in 5 perinatal lethal patients. The auditory tests were normal at birth, suggesting that deafness was acquired after birth and was not congenital. The kind of hearing loss was both conductive and sensorineural pattern by the auditory tests. The degree of deafness varies and two patients with severe deafness needed to wear a hearing device. It is possible that the acquisition of deafness may be exacerbated by hypomineralization of the ear ossicles. However, auditory brainstem response

audiometry showed that the brainstem or cerebral cortex was damaged. Approximately half of the patients with a short stature had GHD, rather than mineralization dysfunctions or bone deformities. Short stature was defined as −2 SD of height. The diagnostic criteria of GHD were as follows: (1) height less than −2.5 SD, (2) insulin-like growth factor-1 less than 200 ng/mL, and (3) GH release deficiency in GH secretion test with insulin, arginine, or L-DOPA. GHD in all patients was GH release deficiency in GH secretion test with insulin, arginine, or L-DOPA, demonstrated that GH-secretion by the pituitary gland was decreased. GHD developed in all but perinatal lethal type. Bone symptoms such as shortening or deformity of the extremities occasionally delayed the diagnosis of GHD. Interestingly, there was one patient who was diagnosed with HPP because of the differential diagnosis of short stature, suggesting that we need to consider HPP when further examination of short stature is performed.

ALPL mutations were identified in 35 patients: 14 perinatal lethal, 9 prenatal benign, 5 infantile, 5 childhood, and 2 odonto types (Table 14.2). The remaining 21 patients did not receive genetic testing. Two mutant alleles were identified in 35 patients and no heterozygous mutations were found, suggesting that most Japanese HPP cases are the result of AR inheritance. Mutations in c.1559delT (34 alleles) and p.F327L (12 alleles) were the frequent mutations. The most frequent

Table 14.2 Genetic analysis of the *ALPL* gene in HPP Japanese patients

Clinical types	Genotype	Number of patients
Perinatal lethal type	c.1559delT/c.1559delT	8
	c.1559delT/p.N190del	1
	c.1559delT/p.H324R	1
	c.1559delT/p.G426S	1
	c.1559delT/p.R450C	1
	c.1559delT/p.F327del	1
	p.R223Q/p.R272C	1
Prenatal benign type	c.1559delT/p.F327L	4
	p.F327L/p.R428X	1
	p.F327L/p.G456R	1
	p.F327del/p.R184 W	1
	p.A40 V/p.E191G	2
Infantile type	c.1559delT/p.L299P	2
	c.1559delT/p.F327L	1
	c.1559delT/p.Y436C	1
	p.K224E/p.G426C	1
Childhood type	c.1559delT/pF327L	3
	p.F327L/p.G339R	1
	p.F327L/p.A111T	1
Odonto type	c.1559delT/p.R136H	2

Modified from Taketani et al. (2014)

Japanese HPP genotype was a homozygous mutation (c.1559delT/c.1559delT) and the compound heterozygous mutation of c.1559delT/p.F327L which was observed in 8 patients of each. Interestingly, patients with p.F327L were all HPP types except for the perinatal lethal type. In the Japanese population, the prevalence of the 1559delT homozygous mutation in the *ALPL* gene, which is a common mutation that causes the perinatal lethal form, was estimated to be not less than 1/900,000 (Watanabe et al. 2011). Michigami et al. (2005) reported that c.1559delT represent 40.9 % of severe alleles. This mutation was not found in other countries, suggesting that c.1559delT may be a founder mutation in the Japanese population.

Compared with previous reports of HPP clinical characteristics in Western populations (Whyte 2001, 2010; Mornet 2008), the frequency of mental retardation, deafness, and short stature were more frequent in Japanese HPP patients, while seizure and encephalopathy was approximately the same. Difference in the frequency and the degree of each neurological feature remains unknown, but this difference might depend on the severity of the TNAP activity as well as the differences in the genetic backgrounds of patients. Especially, about the most frequent mutation, c.1559delT, this mutant lost TNAP activity and was localized at the juxtanuclear position, but not on the cell surface (Michigami et al. 2005; Komaru et al. 2005). As referred above, TNAP is likely to have a valuable role in CNS development and functions (Fonta et al. 2004, 2005; Négyessy et al. 2011; Hanics et al. 2012; Díez-Zaera et al. 2011). But patients with the same genotype did not necessarily have the same neurological symptoms. This suggests that cerebral impairment, including seizure, encephalopathy, mental retardation, deafness, and GHD might be the consequence not only of genetic alterations but also of epigenetic changes, ethnic factors, environmental factors and nutritious element.

Conflict of Interest The author declares no conflict of interest.

References

Balasubramaniam S, Bowling F, Carpenter K, Earl J, Chaitow J, Pitt J, Mornet E, Sillence D, Ellaway C (2010) Prenatal hypophosphatasia presenting as neonatal epileptic encephalopathy with abnormal neurotransmitter metabolism secondary to reduced co-factor pyridoxal-5′-phosphate availability. J Inherit Metab Dis 33(Suppl 3):25–33

Basura GJ, Hagland SP, Wiltse AM, Gospe SM Jr (2009) Clinical features and the management of pyridoxine-dependent and pyridoxine-responsive seizures: review of 63 North American cases submitted to a patient registry. Eur J Pediatr 168(6):697–704

Baumgartner-Sigl S, Haberlandt E, Mumm S, Scholl-Bürgi S, Sergi C, Ryan L, Ericson KL, Whyte MP, Högler W (2007) Pyridoxine-responsive seizures as the first symptom of infantile hypophosphatasia caused by two novel missense mutations (c.677T > C, p. M226T; c.1112C > T, p.T371I) of the tissue-nonspecific alkaline phosphatase gene. Bone 40(6):1655–1661

Baxter P (2003) Pyridoxine-dependent seizures: a clinical and biochemical conundrum. Biochim Biophys Acta 1647(1–2):36–41

Bethenod M, Cotte MF, Collombel C, Frederich A, Cotte J. (1967) Neonatal discovery of hypophosphatasia. Bone improvement, fatal convulsant encephalopathy. Ann Pediatr (Paris) 14(12):835–841

Belachew D, Kazmerski T, Libman I, Goldstein AC, Stevens ST, Deward S, VockleyJ Sperling MA, Balest AL (2013) Infantile hypophosphatasia secondary to a novel compound heterozygous mutation presenting with pyridoxine-responsive seizures. JIMD Rep 11:17–24

Brun-Heath I, Chabrol E, Fox M, Drexler K, Petit C, Taillandier A, De azancourt P, Serre JL, Mornet E (2008) A case of lethal hypophosphatasia providing new insights into the perinatal benign form of hypophosphatasia and expression of the ALPL gene. Clin Genet 73(3):245–250

Cahill RA, Wenkert D, Perlman SA, Steele A, Coburn SP, McAlister WH, Mumm S, Whyte MP (2007) Infantile hypophosphatasia: transplantation therapy trial using bone fragments and cultured osteoblasts. J Clin Endocrinol Metab 92(8):2923–2930

Collmann H, Mornet E, Gattenlöhner S, Beck C, Girschick H (2009) Neurosurgical aspects of childhood hypophosphatasia. Childs Nerv Syst 25(2):217–223

Demirbilek H, Alanay Y, Alikaşifoğlu A, Topçu M, Mornet E, Gönç N, Özön A, Kandemir N (2012) Hypophosphatasia presenting with pyridoxine-responsive seizures, hypercalcemia, and pseudotumor cerebri: case report. J Clin Res Pediatr Endocrinol 4(1):34–38

Deracinois B, Duban-Deweer S, Pottiez G, Cecchelli R, Karamanos Y, Flahaut C (2012) TNAP and EHD1 are over-expressed in bovine brain capillary endothelial cells after the re-induction of blood-brain barrier properties. PLoS One 7(10):e48428

Díez-Zaera M, Díaz-Hernández JI, Hernández-Álvarez E, Zimmermann H, Díaz-Hernández M, Miras-Portugal MT (2011) Tissue-nonspecific alkaline phosphatase promotes axonal growth of hippocampal neurons. Mol Biol Cell 22(7):1014–1024

Fonta C, Négyessy L, Renaud L, Barone P (2004) Areal and subcellular localization of the ubiquitous alkaline phosphatase in the primate cerebral cortex: evidence for a role in neurotransmission. Cereb Cortex 14(6):595–609

Fonta C, Negyessy L, Renaud L, Barone P (2005) Postnatal development of alkaline phosphatase activity correlates with the maturation of neurotransmission in the cerebral cortex. J Comp Neurol 486(2):179–196

Gospe SM Jr (2010) Neonatal vitamin-responsive epileptic encephalopathies. Chang Gung Med J 33(1):1–12

Hanics J, Barna J, Xiao J, Millán JL, Fonta C, Négyessy L (2012) Ablation of TNAP function compromises myelination and synaptogenesis in the mouse brain. Cell Tissue Res 349(2):459–471

Hofmann C, Liese J, Schwarz T, Kunzmann S, Wirbelauer J, Nowak J, Hamann J, Girschick H, Graser S, Dietz K, Zeck S, Jakob F, Mentrup B (2013) Compound heterozygosity of two functional null mutations in the ALPL gene associated with deleterious neurological outcome in an infant with hypophosphatasia. Bone 55(1):150–157

Kaplan SB, Kemp SS, Oh KS (1991) Radiographic manifestations of congenital anomalies of the skull. Radiol Clin North Am 29(2):195–218

Komaru K, Ishida Y, Amaya Y, Goseki-Sone M, Orimo H, Oda K (2005) Novel aggregate formation of a frame-shift mutant protein of tissue-nonspecific alkaline phosphatase is ascribed to three cysteine residues in the C-terminal extension. Retarded secretion and proteasomal degradation. FEBS J 272(7):1704–1717

Litmanovitz Reish O, Dolfin T, Arnon S, Regev R, Grinshpan G, Yamazaki M, Ozono K (2002) Glu274Lys/Gly309Arg mutation of the tissue-nonspecific alkaline phosphatase gene in neonatal hypophosphatasia associated with convulsions. J Inherit Metab Dis 25(1):35–40

Macpherson RI, Kroeker M, Houston CS (1972) Hypophosphatasia. J Can Assoc Radiol 23(1):16–26

Michigami T, Uchihashi T, Suzuki A, Tachikawa K, Nakajima S, Ozono K (2005) Common mutations F310L and T1559del in the tissue-nonspecific alkaline phosphatase gene are related to distinct phenotypes in Japanese patients with hypophosphatasia. Eur J Pediatr 164(5):277–282

Mornet E (2000) Hypophosphatasia: the mutations in the tissue-nonspecific alkaline phosphatase gene. Hum Mutat 15(4):309–315

Mornet E (2008) Hypophosphatasia. Best Pract Res Clin Rheumatol 22(1):113–127

Mornet E, Yvard A, Taillandier A, Fauvert D, Simon-Bouy B (2011) A molecular-based estimation of the prevalence of hypophosphatasia in the European population. Ann Hum Genet 75(3):439–445

Narisawa S, Wennberg C, Millán JL (2001) Abnormal vitamin B6 metabolism in alkaline phosphatase knock-out mice causes multiple abnormalities, but not the impaired bone. J Pathol 193(1):125–133

Nishioka T, Tomatsu S, Gutierrez MA, Miyamoto K, Trandafirescu GG, Lopez PL, Grubb JH, Kanai R, Kobayashi H, Yamaguchi S, Gottesman GS, Cahill R, Noguchi A, Sly WS (2006) Enhancement of drug delivery to bone: characterization of human tissue-nonspecific alkaline phosphatase tagged with an acidic oligopeptide. Mol Genet Metab 88(3):244–255

Négyessy L, Xiao J, Kántor O, Kovács GG, Palkovits M, Dóczi TP, Renaud L, Baksa G, Glasz T, Ashaber M, Barone P, Fonta C (2011) Layer-specific activity of tissue non-specific alkaline phosphatase in the human neocortex. Neuroscience 172:406–418

Nunes ML, Mugnol F, Bica I, Fiori RM (2002) Pyridoxine-dependent seizures associated with hypophosphatasia in a newborn. J Child Neurol 17(3):222–224

Ozono K, Yamagata M, Michigami T, Nakajima S, Sakai N, Cai G, Satomura K, Yasui N, Okada S, Nakayama M (1996) Identification of novel missense mutations (Phe310Leu and Gly439Arg) in a neonatal case of hypophosphatasia. J Clin Endocrinol Metab 81(12):4458–4461

Ozono K, Michigami T (2011) Hypophosphatasia now draws more attention of both clinicians and researchers: A Commentary on prevelance of c. 1559delT in ALPL, a common mutation resulting in the perinatal (lethal) form of hypophosphatasias in Japanese and effects of the mutation on heterozygous carriers. J Hum Genet 56(3):174–176

Plecko B, Stöckler S (2010) Vitamin B6 dependent seizures. Can J Neurol Sci 36(Suppl 2):S73–S77

Sia C, Wapnir R, Sokal M, Harper RG, Intizar S, Lifshitz F (1975) Effects of pyridoxine on neonatal hypophosphatasia. Pediatr Res 9:355

Smilari P, Romeo DM, Palazzo P, Meli C, Sorge G (2005) Neonatal hypophosphatasia and seizures. A case report. Minerva Pediatr 57(5):319–323

Surtees R, Mills P, Clayton P (2006) Inborn errors affecting vitamin B6 metabolism. Future Neurol 1:615–620

Tadokoro M, Kanai R, Taketani T, Uchio Y, Yamaguchi S, Ohgushi H (2009) New bone formation by allogeneic mesenchymal stem cell transplantation in a patient with perinatal hypophosphatasia. J Pediatr 154(6):924–930

Taketani T, Onigata K, Kobayashi H, Mushimoto Y, Fukuda S, Yamagichi S (2014) Clinical and genetic aspects of Hypophosphatasia in Japanese patients. Arch Dis Child 99(3):211–215

Watanabe A, Karasugi T, Sawai H, Naing BT, Ikegawa S, Orimo H, Shimada T (2011) Prevalence of c.1559delT in ALPL, a common mutation resulting in the perinatal (lethal) form of hypophosphatasia in Japanese and effects of the mutation on heterozygous carriers. J Hum Genet 56(2):166–168

Waymire KG, Mahuren JD, Jaje JM, Guilarte TR, Coburn SP, MacGregor GR (1995) Mice lacking tissue non-specific alkaline phosphatase die from seizures due to defective metabolism of vitamin B-6. Nat Genet 11(1):45–51

Wenkert D, McAlister WH, Coburn SP, Zerega JA, Ryan LM, Ericson KL, Hersh JH, Mumm S, Whyte MP (2011) Hypophosphatasia: nonlethal disease despite skeletal presentation in utero (17 new cases and literature review). J Bone Miner Res 26(10):2389–2398

Whyte MP, Mahuren JD, Fedde KN, Cole FS, McCabe ER, Coburn SP (1988) Perinatal hypophosphatasia: tissue levels of vitamin B6 are unremarkable despite markedly increased circulating concentrations of pyridoxal-5′-phosphate. Evidence for an ectoenzyme role for tissue-nonspecific alkaline phosphatase. J Clin Invest 81(4):1234–1239

Whyte M (2001) Hypophosphatasia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B (eds) The metabolic and molecular bases of disease, 8th edn. McGraw-Hill Book Company, New York, pp 5313–5329

Whyte MP, Kurtzberg J, McAlister WH, Mumm S, Podgornik MN, Coburn SP, Ryan LM, Miller CR, Gottesman GS, Smith AK, Douville J, Waters-Pick B, Armstrong RD, Martin PL (2003) Marrow cell transplantation for infantile hypophosphatasia. J Bone Miner Res 18 (4):624–636

Whyte MP (2010) Physiological role of alkaline phosphatase explored in hypophosphatasia. Ann N Y Acad Sci 1192:190–200

Whyte MP, Greenberg CR, Salman NJ, Bober MB, McAlister WH, Wenkert D, Van Sickle BJ, Simmons JH, Edgar TS, Bauer ML, Hamdan MA, Bishop N, Lutz RE, McGinn M, Craig S, Moore JN, Taylor JW, Cleveland RH, Cranley WR, Lim R, Thacher TD, Mayhew JE, Downs M, Millán JL, Skrinar AM, Crine P, Landy H (2012) Enzyme-replacement therapy in life-threatening hypophosphatasia. N Engl J Med 366(10):904–913

Yamamoto H, Sasamoto Y, Miyamoto Y, Murakami H, Kamiyama N (2004) A successful treatment with pyridoxal phosphate for West syndrome in hypophosphatasia. Pediatr Neurol 30 (3):216–218

Zurutuza L, Muller F, Gibrat JF, Taillandier A, Simon-Bouy B, Serre JL, Mornet E (1999) Correlations of genotype and phenotype in hypophosphatasia. Hum Mol Genet 8(6):1039–1046