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Review article

Enzyme-replacement therapy in perinatal hypophosphatasia: Case report and review of the literature

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ABSTRACT

Hypophosphatasia (HPP) is a rare disease resulting from alterations of the *ALPL* gene encoding tissue-nonspecific alkaline phosphatase (TNSALP). Perinatal HPP is mainly characterized by bone hypomineralization and severe respiratory insufficiency. We describe a full-term boy diagnosed with perinatal HPP after birth, showing dramatic improvement after treatment with Asfotase Alfa, an enzyme-replacement therapy (ERT) prescribed in HPP cases. He initially presented with respiratory insufficiency due to bone hypomineralization, and severe pulmonary hypoplasia that required tracheostomy and invasive ventilation for 8 months. He was taken off ventilation at 41 weeks of age. He also presented complications including hypercalcemia, craniosynostosis, nephrocalcinosis, hypotonia, and a severe feeding disorder. He is still alive at 30 months of age, and his respiratory status and tonus is steadily improving. This case reflects the progression of HPP patients with specific therapy added to symptomatic management. Some aspects of the disease are now well known, such as nephrocalcinosis and craniosynostosis, related to the natural course of the disease, which persisted despite the ERT. The long-term prognosis and outcome for this newborn child remain unknown.

1. Introduction

Hypophosphatasia (HPP) is a rare metabolic bone disease due to loss-of-function mutations in the tissue-nonspecific alkaline phosphatase gene (*TNSALP*). The disease inheritance differs between severe forms, transmitted as an autosomal recessive trait, while both autosomal recessive and autosomal dominant transmissions have been shown in clinically moderate and milder forms [1]. There are more than 300 mutations identified to date, and most are missense mutations [2]. The prevalence of severe HPP has been recently estimated at 1/300,000 in France, 1/500,000 in Europe [3], and more frequently in Canada with an estimated prevalence at of 1/100,000 [2]. HPP has been divided into six clinical subtypes with highly variable symptoms, depending on the age of onset [2]. Perinatal HPP is the most severe form and is classically almost always lethal soon after birth. The cause of death in this form of HPP is often associated with pulmonary complications. Other clinical features include intrauterine growth retardation, extensive bone mineralization defect, severe hypercalcemia and hyperphosphatemia, seizures, early-onset craniosynostosis, and nephrocalcinosis. Recently developed, the enzyme-replacement therapy (ERT) Asfotase Alfa was designed to reverse the skeletal hypomineralization and to correct the other ensuing manifestations of the severe condition [4]. The dramatic benefit of this new therapy has been demonstrated in perinatal and infantile forms, leading to significant improvements of the life prognosis (95% survival at 1 year with treatment versus 42% without), with pulmonary and radiological parameter improvements [5].

Here, we describe a case of perinatal HPP, treated with Asfotase alfa, with a specifically detailed respiratory status history. We also performed a systematic review of the early literature (Table 1) on perinatal cases, although few have been detailed with this new

Abbreviations: CPAP, Continuous positive airway pressure; ERT, Enzyme-replacement therapy; HPP, Hypophosphatasia; TNSAL, tissue-nonspecific alkaline phosphatase gene.

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Table 1
A systematic review of the literature on overall survival, respiratory improvement, craniosynostosis, and nephrocalcinosis in perinatal hypophosphatasia, with or without treatment by Asfotase alfa (ERT, enzyme-replacement therapy).

Articles	ReferenceAuthor	Global Survival	Respiratory improvement	Craniosynostosis	Nephrocalcinosis	ERT
1/Lethal hypophosphatasia successfully treated with enzyme replacement from day 1 after birth [8]	Y. Okazaki *European Journal of Pediatrics 2015*	The patient survived at least until 18 months (end of study)	Intubation at birth Tracheostomy at 59 days Weaned of ventilation at 7 months of age, but he still had tracheostomy and oxygen at 18 months of age	No craniosynostosis was found, although this is a major complication	x	Yes
2/Enzyme-replacement therapy in life-threatening hypophosphatasia [4]	M.P. Whyte *The New England Journal of Medicine*	x	5 patients with perinatal HPP: baseline 1/11 breathed alone; at 48 days: 6/9 had no ventilation; 1/9 had oxygen on canula; 1/9 had mechanical ventilation at night, and 1/9 had full ventilation	One case was considered possibly related to treatment. No evidence of ectopic calcification from the treatment was observed	3/5 severe HPP cases had nephrocalcinosis, 1 of whom had nephrolithiasis. No progress after 6 months	Yes
3/Asfotase alpha treatment improves survival for perinatal and infantile hypophosphatasia [5]	M.P. Whyte *Endocrinology Metabolism 2016*	Survival without treatment versus under treatment: 1 year: 42% vs. 95% 3.5 years: 27% vs. 86% 5 years: 27% vs. 82%	14/37 Required ventilation at birth: 7/10 weaned, 3/14 died 23/37 Required no ventilation at birth: 7/23 required secondary ventilation, among whom 5/7 weaned and 2/7 died	x	x	Yes
4/Hypophosphatasia [10]	K. Kozlowski *Pediatric Radiology 1976*	x	x	13/18 Had craniosynostosis, 3 of whom had cognitive delay	One case of nephrocalcinosis on radiology was discovered on autopsy	No
5/Clinical and genetic aspects of hypophosphatasia in Japanese patients [9]	T. Taketani *Archives of Disease in Childhood 2014*	The average age at death was 4 months (0–68 months); 4 patients survived more than 3 years	100% (21/21) Respiratory failure 19/21 Had a narrow thorax	2/21 had craniosynostosis in lethal perinatal forms, but this is not poor prognosis 5/21 Had mental retardation	In 3/21 calcification in kidney was only found in lethal forms	No
6/Clinical characteristics of perinatal lethal hypophosphatasia [12]	A. Nakamura-Utsunomiya *Clinical Pediatric Endocrinology 2010*	All 6 patients died: 2/6 died at birth 3/6 died during the 1st year 1/6 died at 27 months	They died due to respiratory insufficiency 2/6 Did not establish spontaneous breathing Patient 3: tracheostomy et day 62 Patient 4: beginning of ventilation at 25 days of age Patient 5: intubation at birth, tracheostomy at day 62 and death at 12 months of age Patient 6: ventilation started at 121 days, tracheostomy at 131 days, death at 27 months of age (pulmonary hemorrhage)	One patient had narrow cerebral ventricle and a brain fissure caused by the craniostenosis He had hypertensive intracranial and hypsarhythmia at 27 months	x	No
7/Respiratory mechanics in an infant with perinatal lethal hypophosphatasia treated with human recombinant enzyme replacement therapy [6]	E. Rodriguez *Pediatric Pulmonology 2012*	The patient died at 34 weeks of pulmonary infection	Tracheostomy at 7.5 weeks Decreased oxygen and pressure at 10 weeks Returned home with ventilation without oxygen at 32 weeks	x	x	Yes
8/Perinatal HPP presenting as neonatal epileptic encephalopathy with abnormal neurotransmitter metabolism secondary to reduced co-factor pyridoxal-5′-phosphate availability [14]	S. Balasubramaniam *Journal of Inherited Metabolic Disease 2010*	There were 2 patients: one died at 5 weeks and one at 7 days	They had mechanical ventilation at birth both died of respiratory distress	x	x	No

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