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Management of Tracheobronchomalacia During Asfotase Alfa Treatment in Infants With Perinatal-Onset Hypophosphatasia: A Case Series

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INTRODUCTION

- Hypophosphatasia (HPP), a rare and inherited metabolic disease resulting in hypomineralisation of bone, is caused by loss-of-function mutations in the *ALPL* gene, which encodes tissue-nonspecific alkaline phosphatase (TNSALP)[1,2]
  - Perinatal HPP is characterized by respiratory failure secondary to poor skeletal mineralisation, rachitic chest, and pulmonary hypoplasia[1]
- Tracheobronchomalacia (TBM) may contribute to respiratory failure in infants with HPP. TBM is characterised by weakness of the tracheal and bronchial walls caused by hypotonia of myoelastic elements and softening of the supporting cartilage. The primary form of TBM is congenital[3]
  - Collapse of the airways occurs because of increased intrathoracic pressure (i.e., during forced expiration, coughing, or the Valsalva manoeuvre [as occurs during bowel movement])[4]
  - Severe TBM results in imminent risk of death from respiratory failure, complicated pulmonary infections, and life-threatening cardiopulmonary arrests; infants with TBM require intensive respiratory support[5]
- Asfotase alfa, the first TNSALP enzyme replacement therapy for HPP, has been approved in multiple countries, including Australia, Canada, Europe, Japan, and the United States[6,7]
  - Asfotase alfa improved skeletal mineralisation and respiratory function in patients with perinatal and infantile HPP[8]
  - Infants presenting with HPP at age <6 months who were treated with asfotase alfa had a survival rate of 95% at 1 year; in contrast, only 42% of historical controls who were untreated survived to age 1 year[8]
- We present the cases of 4 patients with HPP and TBM, which contributed to severe respiratory compromise

OBJECTIVE

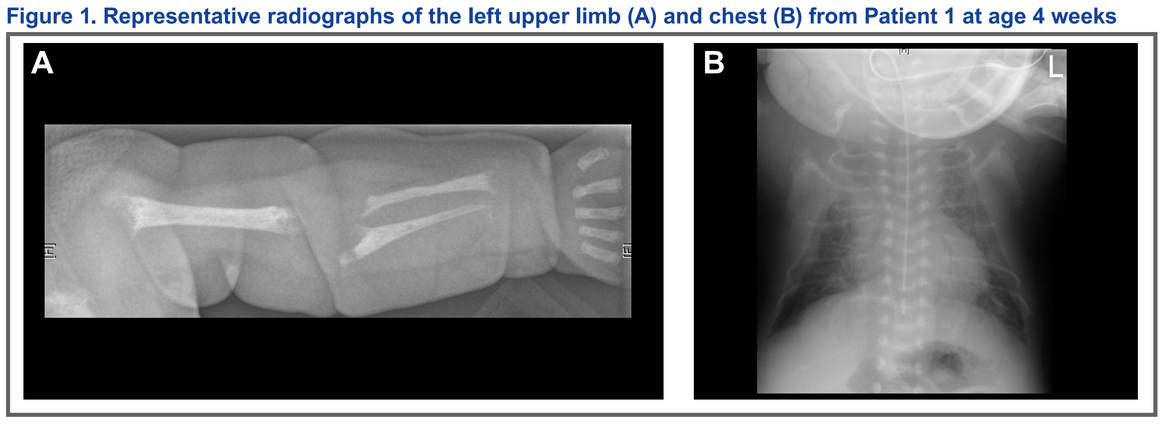
- To characterise TBM in infants with HPP treated with asfotase alfa

METHODS

Patients

- HPP diagnosis was confirmed in 4 patients by physical examination, skeletal survey (**Figure 1**), and serum biochemistry analysis (i.e., ALP, pyridoxal phosphate, and/or phosphoethanolamine levels) supplemented by genetic testing
- TBM was identified by direct laryngotracheobronchoscopy or flexible bronchoscopy

Figure 1. Representative radiographs of the left upper limb (A) and chest (B) from Patient 1 at age 4 weeks



Respiratory Status

- Respiratory support requirements were documented and defined as:
  - Mechanical ventilation via intubation or tracheostomy
  - Ventilation by continuous positive airway pressure (CPAP) or bilevel positive pressure support (bilevel PS)

Asfotase Alfa Administration

- Asfotase alfa was administered as a subcutaneous injection at an initial dose of 2 mg/kg 3 times per week (with dose adjustment as clinically indicated)

RESULTS

Patients and Demographics

- 4 infants with HPP (2 female, 2 male) were identified as having TBM (**Table 1**)
  - Patients 1–3 received asfotase alfa in Study ENB-010-10, an ongoing Phase 2, open-label, global, multicentre study (ClinicalTrials.gov: NCT01176266; EudraCT:2010-019850-42)
  - Patient 4 was provided asfotase alfa through a compassionate use programme
- All patients experienced respiratory distress at birth and required respiratory support

Genetic Analyses

- *ALPL* gene mutations were found in all 4 patients (**Table 1**); Patients 2 and 3 have compound heterozygous gene mutations, and Patients 1 and 4 have homozygous mutations
  - All mutations except the c.876_872delAGGGGACinsT mutation in Patient 3 have been previously reported[9]

Table 1. Baseline clinical characteristics at birth

Characteristics	ENB-010-10			Compassionate Use
	Patient 1	Patient 2	Patient 3	Patient 4
Gender	Male	Male	Female	Female
Ethnicity	Caucasian	Caucasian	Caucasian	Asian-Pakistani
Birth information				
Gestational age	Term	37 wk, 5 d	35 wk, 4 d	34 wk
Weight, kg	2.89	3.46	3.06	1.69
ALPL genetic mutation	Homozygous: NM_000478.4:c.147 G>A, p.G491R secondary to uniparental disomy[10]	Compound heterozygous: c.668 G>A and c.1171 C>T	Compound heterozygous: c.876_872delAGGGGACinsT and c.650 T>C (p.V217A)	Homozygous: c.1336 G>A (p.A466T)
Respiratory support post-birth	CPAP ventilation at birth; intubation and ventilation starting at 4 wk	Intubation and ventilation	Intubation and ventilation	Intubation and ventilation; surfactant

CPAP=continuous positive airway pressure

Treatment and Patient Outcomes (Table 2)

- All patients required ventilation at birth and subsequent tracheostomy for long-term ventilation with positive-end expiratory pressure (PEEP; up to 12 cm H_2O)
- All patients received ongoing treatment with asfotase alfa 6–15 mg/kg/wk starting at 4–7 weeks
- TBM was confirmed within 6 months of birth for all 4 patients and was suspected in 1 patient from the ENB-010-10 study as early as age 8 weeks
- All 4 patients had frequent episodes of profound desaturations and bradycardia; Patients 2, 3, and 4 experienced cardio-respiratory arrests

Current Status (*Table 2*)

- TBM completely resolved in Patients 1 and 4, and all ventilator support has been discontinued
- TBM improved in Patient 2; the need for ventilator support persists, although the patient is weaning from PEEP and has brief ventilator-free periods during the day
- Patient 3 was discharged to home at age 15 months, but flexible bronchoscopy revealed significant TBM; tracheostomy with ventilator support remains in place at age 23 months

Table 2. Overview of case studies: treatment and patient outcomes

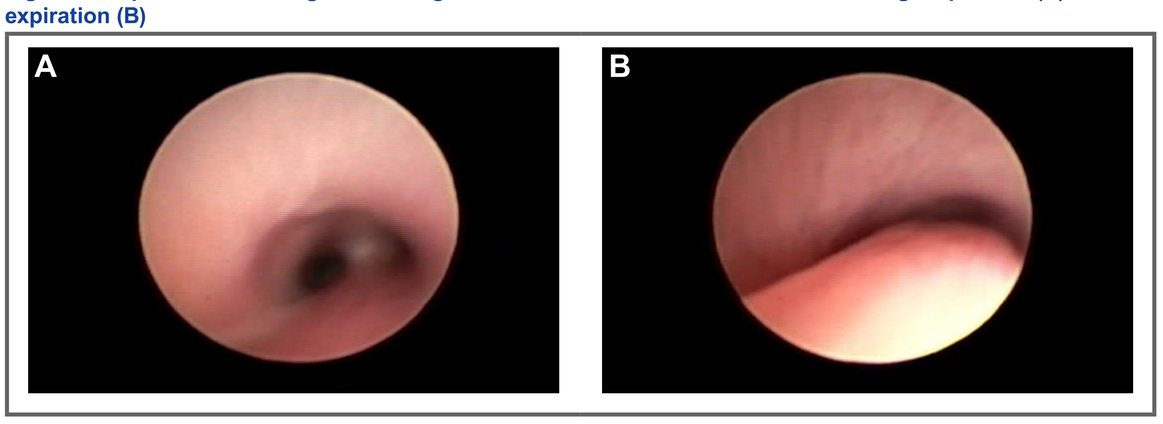
Characteristics	ENB-010-10			Compassionate Use
	Patient 1	Patient 2	Patient 3	Patient 4
Asfotase alfa dosage	• 1 mo: 6 mg/kg/wk • 3 mo: 9 mg/kg/wk • Current: 2.5 mg/kg/wk	• 5 wk: 6 mg/kg/wk • 6 mo: 7.8 mg/kg/wk • 9 mo: 7.5 mg/kg/wk • Current: 9 mg/kg/wk	• 7.5 wk: 6 mg/kg/wk • Current: 12 mg/kg/wk	• 1 mo: 6 mg/kg/wk • 3.5 mo (post–cardiac arrest): 15 mg/kg/wk • Current: 2.5 mg/kg/wk
Surgical treatments	• 1 mo 8 d: Tracheostomy	• 6 wk: Tracheostomy • 4 mo: Gastrostomy	• 7 wk: Tracheostomy • 3 mo: Gastrostomy	• 1 mo 15 d: Tracheostomy • 1 y: Gastrostomy
Age at TBM diagnosis	2 mo	5 mo	5 mo (suspected at 8 wk)	5 mo
Additional findings	• 1 mo: CPAP: PEEP 5 cm H_2O • 1 mo 2 d: Change from CPAP to bilevel PS and central venous line insertion: PIP 18 cm H_2O, PEEP 8 cm H_2O • 1 mo 5 d: Bilevel PS: PIP 22 cm H_2O, PEEP 10 cm H_2O • 2 mo: Severe TBM identified; bilevel PS: PIP 20 cm H_2O, PEEP 12 cm H_2O • 9 mo: Flexible DLTB revealed normal patency of larynx, trachea, and left main bronchus; residual left bronchomalacia required bilevel PS: PIP 18 cm H_2O, PEEP 6 cm H_2O • 12 mo: Repeat DLTB revealed resolution of TBM, with mild left bronchomalacia; weaned to CPAP: PEEP 5 cm H_2O	• 3 mo: Respiratory arrest requiring bag and mask positive pressure ventilation; bilevel PS: PIP 26 cm H_2O, PEEP 10 cm H_2O • 4 and 6 mo: Cardio-respiratory arrest (4 mo: bilevel PS: PIP 27 cm H_2O, PEEP 10 cm H_2O) • 5 mo: MLB revealed Grade 3 stenosis of subglottis; flexible bronchoscopy revealed narrowed subglottic space and severe cervical tracheomalacia; bilevel PS: PIP 28 cm H_2O, PEEP 12 cm H_2O • 10 mo: TBM improved with mild dynamic collapse during restful breathing; bilevel PS: PIP 29 cm H_2O, PEEP 11 cm H_2O • 12 mo: Significant improvement to mild TBM; bilevel PS: PIP 26 cm H_2O, PEEP 10 cm H_2O • 13 mo: Discharged to home; bilevel PS: PIP 27 cm H_2O, PEEP 10 cm H_2O	• 7 wk: Bilevel PS: PIP 26 cm H_2O, PEEP 6 cm H_2O • 8 wk: TBM suspected; bilevel PS: PIP 24 cm H_2O, PEEP 10 cm H_2O • 2 mo: Cardio-respiratory arrest necessitating chest compressions with recovery; bilevel PS: PIP 28 cm H_2O, PEEP 6 cm H_2O • 3 mo: Cardio-respiratory episodes requiring major intervention began; bilevel PS: PIP 30 cm H_2O, PEEP 8 cm H_2O • 6 mo: Moderate/severe TBM confirmed (complete loss of airway lumen with coughing/ heavy breathing); bilevel PS: PIP 30 cm H_2O, PEEP 12 cm H_2O • 12 mo: Improvement to moderate TBM; bilevel PS: PIP 23 cm H_2O, PEEP 9 cm H_2O • 15 mo: Discharged to home; bilevel PS: PIP 26 cm H_2O, PEEP 12 cm H_2O	• 1 mo: Bilevel PS: PIP 30 cm H_2O, PEEP 6 cm H_2O • 3 mo 10 d: Cardio-respiratory arrest • 3 mo 14 d: Asfotase alfa dose increased to 15 mg/kg/wk; improvement seen within 2 wk and patient placed back into conventional ventilation • 5 mo: Significant TBM identified; bilevel PS: PIP 20–22 cm H_2O, PEEP 12 cm H_2O • 8 mo: Significant improvement in respiratory function; bilevel PS: PIP 16–18 cm H_2O, PEEP 9 cm H_2O • 11 mo: Complete resolution of TBM; bilevel PS: PIP 10 cm H_2O, PEEP 5 cm H_2O • 12–22 mo: CPAP (with time off ventilation): PEEP 4–5 cm H_2O • 23 mo: Discharged to home; CPAP 1 night/wk: PEEP 5 cm H_2O
Current status	• 15 mo: **Complete clinical resolution** and **self-ventilating in room air**	• 17 mo: **Normal appearing lower airways**, but profound TBM when coughing or bearing down; bilevel PS: PIP 24 cm H_2O, PEEP 10 cm H_2O • 27 mo: **Remains on ventilator**; respiratory issues (viral infections) requiring hospital readmission; bilevel PS: PIP 22 cm H_2O, PEEP 8 cm H_2O	• 18 mo: **Significant TBM identified** (severity difficult to assess owing to well-positioned custom tracheostomy tube in distal trachea); bilevel PS: PIP 26 cm H_2O, PEEP 12 cm H_2O • 23 mo: **Tracheostomy in situ with ventilator support**; bilevel PS: PIP 25 cm H_2O, PEEP 12 cm H_2O	• 2 y: **All ventilator support removed**

Note: Numbers given for timing of tests, treatments, and status are patient ages.
Bilevel PS=bilevel positive pressure support; CPAP=continuous positive airway pressure; DLTB=direct laryngotracheobronchoscopy; MLB=microlaryngobronchoscopy; PEEP=positive-end expiratory pressure; PIP=peak inspiratory pressure; TBM=tracheobronchomalacia.

Diagnosing TBM in Patients With HPP

- Clinical suspicion of TBM in these 4 patients was raised after episodes of profound desaturations and bradycardia (especially on handling) and subsequent transient/episodic increases in ventilator requirements
- Diagnosis was confirmed by direct laryngotracheobronchoscopy or flexible bronchoscopy. Whenever possible, evaluations were performed under light anaesthesia in unsedated infants during spontaneous breathing to reflect near-normal airway dynamics; however, some airway collapse could be evaluated in patients whose respiratory efforts were supported by mechanical ventilation[11]
- Images from Patient 2 at age 5 months show the right mainstem bronchus during inspiration (**Figure 2A**) and expiration (**Figure 2B**). Whereas normal anatomy and airway patency are evident during inspiration, near-complete collapse of the right mainstem bronchus is shown during expiration

Figure 2. Representative images of the right mainstem bronchus from Patient 2 during inspiration (A) and expiration (B)



SUMMARY

- Infants with HPP with associated TBM require prolonged respiratory support with high PEEP in an intensive care unit setting and ongoing CPAP to prevent collapse of airways
- It is difficult to determine whether the improvements in TBM can be attributed to treatment with asfotase alfa or to gradual improvements in airway lumen and cartilage rigidity that may occur naturally with age[3]
  - Nevertheless, TBM completely resolved in 2 patients and partially resolved in 1 patient, all of whom were treated with asfotase alfa
- Now that asfotase alfa is approved for the treatment of HPP in many countries, we have the opportunity to expand our knowledge about how this treatment may affect infants with HPP and TBM

CONCLUSIONS

- Infants diagnosed with HPP during the perinatal period should be screened for TBM using direct laryngotracheobronchoscopy or flexible bronchoscopy, particularly if they require intermittent positive pressure ventilation
- Three of the 4 infants with TBM who were treated with asfotase alfa for HPP experienced either a partial or complete resolution of TBM within 2 years of birth
- Asfotase alfa improves respiratory function by promoting skeletal mineralisation and may have a role in directly improving TBM or indirectly by improving survival and thereby allowing airways to mature

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DISCLOSURES

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Bone & Mineral Metabolism

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