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Commentary

Physical therapy management of infants and children with hypophosphatasia

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ABSTRACT

Hypophosphatasia (HPP) is a rare inborn error of metabolism resulting in undermineralization of bone and subsequent skeletal abnormalities. The natural history of HPP is characterized by rickets and osteomalacia, increased propensity for bone fracture, early loss of teeth in childhood, and muscle weakness. There is a wide heterogeneity in disease presentation, and the functional impact of the disease can vary from perinatal death to gait abnormalities. Recent clinical trials of enzyme replacement therapy have begun to offer an opportunity for improvement in survival and function. The role of physical therapy in the treatment of the underlying musculoskeletal dysfunction in HPP is underrecognized. It is important for physical therapists to understand the disease characteristics of the natural history of a rare disease like HPP and how the impairment and activity limitations may change in response to medical interventions. An understanding of when and how to intervene is also important in order to optimally impact body function, lessen structural impairment, and facilitate increased functional independence in mobility and activities of daily living. Individualizing treatment to the child's needs, medical fragility, and setting (home/school/hospital), while educating parents, caregivers, and school staff regarding approved activities and therapy frequency, may improve function and development in children with HPP.

1. Introduction

Hypophosphatasia (HPP) is a rare, inherited, metabolic disorder characterized by undermineralization of bone and caused by low activity of the tissue nonspecific isoenzyme of alkaline phosphatase (TNSALP) [1,2]. Deficiency in the enzymatic activity of TNSALP results in elevated circulating levels of its known substrates, inorganic pyrophosphate (PPi) and pyridoxal-5′-phosphate (PLP) [3]. Elevated extracellular levels of PPi inhibit bone mineralization leading to rickets in infants and children and osteomalacia in adults [3]. The prevalence of severe HPP is estimated at approximately 1 in 300,000, while more moderate forms of HPP occur with a greater frequency estimated to be 1 in 6370 in the European population [4].

Children with HPP fall into 2 broad categories [5]:

1) **Infantile HPP** (onset postnatal to <6 months of age) is characterized by generalized impairment of skeletal matrix leading to rickets and osteomalacia, failure to thrive, global developmental delay, respiratory compromise due to rachitic chest deformity, hypotonia, and nontraumatic fractures. There is a 50% to 100% mortality rate in infants, generally due to respiratory failure [3,6].

2) **Childhood HPP** (onset ≥6 months to <18 years of age) is characterized by reduced mortality compared with the infantile form but is

Abbreviations: ADL, activities of daily living; BOT-2, Bruininks-Oseretsky Test of Motor Proficiency, Second Edition; CHAQ, Childhood Health Assessment Questionnaire; FLACC, Face, Legs, Activity, Cry, Consolability Scale; HPP, hypophosphatasia; N-PASS, Neonatal Pain, Agitation and Sedation Scale; Pi, inorganic phosphate; PLP, pyridoxal-5′-phosphate; PODCI, Pediatric Outcomes Data Collection Instrument; PPi, inorganic pyrophosphate; PRO, patient-reported outcome measure; PT, physical therapy; ROM, range of motion; TNSALP, tissue nonspecific isoenzyme of alkaline phosphatase.

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associated with high morbidity [3,7] and key characteristics of rickets, rachitic deformities, poorly healing or recurrent fractures, short stature, musculoskeletal pain, muscle weakness, motor developmental delays, valgus knee deformities [8], weak lower extremity hip and knee musculature, abnormal waddling gait or increased "trunk sway," and premature loss of teeth.

Other categories of HPP include perinatal HPP and adult HPP, which will not be discussed in this commentary. However, it is important to recognize that HPP represents a disease continuum so that there are presentations and features of the disease which will be better recognized with long-term follow-up.

Recently, asfotase alfa, a human recombinant, bone-targeted, TNSALP enzyme replacement therapy, has been approved in Canada, Japan, Europe, Australia, and the United States as a treatment for HPP. Asfotase alfa [9] has been shown to significantly heal rickets as assessed radiologically, with improved functional milestones, pulmonary function, strength, speed, agility, and independence in activities of daily living (ADL), along with reduced pain and improved survival in infants and children with perinatal or infantile HPP [10–12]. The goal of this report is to highlight the role of physical therapy (PT) in the management of the musculoskeletal aspects of infants and children with HPP.

2. Clinical aspects of infantile and childhood HPP

The main clinical feature of HPP in infants and children is persistent bone fragility. This can result in numerous sequelae, including multiple fractures and progressive skeletal deformity. Joint laxity, cardiorespiratory difficulties, and muscle hypotonia or static myopathy may also be present. Whyte et al. reviewed the medical histories of pediatric patients with HPP and reported skeletal abnormalities including genu valgus (knock knees) (77%), rachitic chest (46%), bowing of leg(s) (39%), craniosynostosis (31%), and bone pain that often limited activities (46%) and/or required analgesics (39%) [13]. Atypical gait patterns were found in all patients [13]. Recent evidence supports that persistent gait impairment is a significant feature of HPP in children [14]. Video gait analysis of participants in a natural history study documented that all patients had a trunk sway or compensatory patterns to increase stability, 5/6 had a high stepping gait pattern, 4/6 had a reduced step size and decreased step continuity, and 3/6 had a widened base of support [14]. Gait impairments are commonly associated with deficits in hip abductor and extensor muscle and a positive Trendelenburg sign, indicative of muscle weakness. Reduced growth, failure to thrive, and delayed development (greatest delays noted in gross motor skills) result in reduced quality of life due to inability to effectively perform daily activities. Among children aged 6–12 years at baseline in a recent asfotase alfa interventional study, the medical history for 11/13 patients (85%) included significantly delayed walking (≥15 months) [13]. The baseline Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2 [15]) Strength and Agility composite score was >2 standard deviations (SD) below the mean score for healthy age-matched peers. Delayed development and decreased independence in ADL can affect infants and children differently in the home, school, and community environments suggesting that the local environment needs to be taken into account when coordinating PT needs for a child with HPP.

3. Role of PT in managing HPP

While diagnosis of HPP in infants and children is most frequently made by pediatricians, neonatologists, or endocrinologists, physical therapists often are called upon to aid in assessment and treatment programs. As there are currently no published guidelines for PT in infants or children with HPP, an Advisory Board, sponsored by Alexion Pharmaceuticals Inc., was convened from March 13–14, 2015, specifically to address this issue. The outcome of this Advisory Board as presented in this commentary represents the views of physical therapists and physicians who have been working with children and adults with HPP in clinical care and research from institutions in the USA, Canada, and Spain. The meeting goals were to present a variety of case studies and intervention strategies and to develop consensus from key opinion leaders on the most appropriate PT assessment, interventions, and equipment selection for treatment of children and infants with HPP. PT can be useful in the management of the following manifestations of HPP:

1) Respiratory complications, with resultant effects on endurance and limitations in activity
2) Muscle weakness and bone fragility that can interfere with function and lead to gross and fine motor delays and bone alignment abnormalities. Reduced ability to engage and manipulate age-appropriate toys can also result in cognitive delays
3) In infantile-onset and more severe cases of HPP, an inability to sit, stand, and walk may limit access to/engagement with the environment without intervention and adaptive equipment
4) Decreased independence in ADL
5) Decreased ability to participate in age-appropriate recreational activities and to keep up with their peers at home and school environments
6) The need for postoperative management from surgical interventions or recovery from fracture

The primary goals of PT should be to maximize functional mobility and independence in ADL, to optimize strength and endurance, to promote optimal skeletal alignment and joint range of motion (ROM) in order to reduce the risk of long-term sequelae, to provide caregiver and patient education on reduction of fracture risk and management of the musculoskeletal system, and to provide recommendations for use of adaptive equipment and orthotics.

PT interventions may be completed in conjunction with a multidisciplinary healthcare team involving other therapists as appropriate, including occupational, speech, respiratory therapists, primary care physicians, radiologists, and nutritionists, as well as specialists in orthopedics, endocrinology, genetics, psychology, and social work. The extent of team involvement will vary depending on the environment of assessment (hospital, clinic, or school) and on the child's needs. A baseline PT assessment should identify the specific pathophysiological limitations imposed by the disease and establish potential risks. Such an assessment will identify the individualized degree of medical fragility, determine which physical systems will require remediation, and recognize abilities/strengths. Use of standardized developmental assessments, such as the Bayley Scales of Infant Development [16], Peabody Development Motor Scales [17], and BOT-2 [15], will help to discriminate the level of delay relative to a normative sample and serve as an objective measurement of change in response to therapy intervention. In addition to standardized functional measures, assessment should include measurement of specific impairments in body function and structure, activity limitations, and participation restrictions. A thorough musculoskeletal assessment and consultation with other team members is required. In older children, manual muscle testing or handheld dynamometry can be used to measure strength. Frequency of service delivery is dependent on the individual needs, the child and family goals for intervention, and the model of delivery in a specific environment (i.e., preschool vs hospital vs outpatient), with advocacy potentially needed to coordinate with payor service guidelines.

3.1. Key points to consider

- Assessment should be comprehensive
- Help manage respiratory and motor function
- Strive to improve ADL and functional mobility
- Provide patient and caregiver education to reduce fracture risk