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Burden of disease in adult patients with hypophosphatasia: Results from two patient-reported surveys

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ABSTRACT

Background. Hypophosphatasia (HPP) is a rare metabolic bone disease caused by loss-of-function mutation(s) in the tissue-nonspecific alkaline (TNSALP) phosphatase gene, which manifests as rickets and/or osteomalacia with systemic complications and affects patients of all ages. The burden of disease is poorly characterized in adult patients.

Aims. We assessed patient-reported burden of disease using two surveys reasonably specific for HPP symptomatology, the Hypophosphatasia Impact Patient Survey (HIPS) and the Hypophosphatasia Outcomes Study Telephone interview (HOST).

Methods. Patients with HPP were invited to participate via patient advocacy groups or their medical provider. Survey questions captured demography, HPP-related medical history, mobility, and health-related quality of life (using Short Form 12 [version 2] Health Survey [SF-12v2]) via internet report (HIPS) or telephone interview (HOST).

Results. One hundred twenty-five adults responded (mean [standard deviation, SD] age: 45 [14.3] years). Eighty-four patients (67%) reported pediatric-onset of their symptoms. Common clinical features in the study population included pain (95% of patients), fractures (86% of patients) muscle weakness (62%) and unusual gait (52%). Use of assistive devices for mobility (60%) was also prevalent. Twenty-six percent of patients reported more than 10 fractures. Seventy-four percent of patients had undergone orthopedic/dental surgical procedures. The health profile of patients responding on the SF-12 showed a broad and substantial impact of HPP on health-related quality of life, with domains related to physical ability showing the greatest decrement compared to normative data.

Conclusions. In aggregate, these data indicate that HPP can confer a high burden of illness in adulthood.

Abbreviations: CPAP, continuous positive airway pressure; HIPS, Hypophosphatasia Impact Patient Survey; HOST, Hypophosphatasia Outcomes Study Telephone Interview; HPP, hypophosphatasia; TNSALP, tissue-nonspecific alkaline phosphatase; PLP, pyridoxal-5′-phosphate; PPi, inorganic pyrophosphate; QoL, quality of life; SF-12v2, 12-item Short Form Health Survey Questionnaire version 2; SF-36, 36-item Short Form Health Survey Questionnaire.

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1. Introduction

Hypophosphatasia (HPP) is a rare metabolic bone disease caused by loss-of-function mutation(s) in the tissue-nonspecific alkaline phosphatase (TNSALP) gene (*ALPL*) [1,2]. Approximately 300 pathogenic mutations have been identified [3], resulting in variable levels of TNSALP activity and a spectrum of clinical phenotypes. Historically, HPP has been defined on the basis of age at onset of symptoms (perinatal, infantile, childhood [6 months to 18 years of age], and adult onset), with disease severity inversely related to age at symptom onset. Although severity in terms of mortality risk is highest in infants, it is now recognized that the clinical presentation of HPP can be variable, with severe complications occurring at any age, and that overlap in symptoms is observed across these subtypes. Odontohypophosphatasia, in which a patient of any age manifests only dental symptoms (premature tooth loss and overall poor dentition), has also been described [1]. However, dental symptoms are frequent across all forms of HPP and may present as the first indication of disease [1,4].

TNSALP is a cell-surface ectoenzyme that plays a key role in skeletal mineralization through the hydrolysis of inorganic pyrophosphate (PPi), a potent inhibitor of skeletal mineralization [5]. In HPP, accumulation of PPi due to deficient TNSALP activity results in skeletal hypomineralization, leading to osteomalacia at all ages and HPP-related rickets in infants and children [1]. Mortality is high (50%–100%) within first two years of life in patients with perinatal- and infantile-onset HPP [1,6,7], primarily due to respiratory compromise most likely resulting from the presence of a rachitic chest [8–11]. Pyridoxine-responsive seizures may occur in infants due to central nervous system deficiency of pyridoxal-5′-phosphate (PLP, the active form of vitamin B6 and cofactor for multiple neuronal pathways), which requires dephosphorylation by TNSALP to cross the cell membrane. Pyridoxine-responsive seizures are considered a poor prognostic sign [6,7].

Children who survive infancy, as well as those who first present with symptoms at age 6 months or later, may develop craniosynostosis, often with a consequent increase in intracranial pressure and neurological complications, requiring surgical intervention. Skeletal deformities (including rickets, kyphosis or scoliosis, and bowing of legs), fractures (some of which may require fixation), chronic bone, muscle and/or joint pain, proximal muscle weakness, gait abnormalities, short stature, hypercalcemia and/or hypercalciuria, nephrocalcinosis, and delayed or missed gross motor milestones may also occur [1,2,11]. Early tooth loss is common and may represent the first sign of HPP in patients presenting after 6 months of age [1,2].

Morbidity of HPP in adults largely has been reported via case reports, kindred studies, and single-center retrospective chart reviews [12–17] that collectively report osteomalacia, fractures (nontraumatic, recurrent, non-healing) or pseudofractures, muscle weakness and pain, ectopic calcification in the joints causing swelling and pain, and bone pain as prominent features of HPP in adults, regardless of age at onset [11]. Some case reports describe progressive decline in physical function and mobility in adults [14,18,19], indicating a risk for accumulation or worsening of symptoms over time. The generalizability of these studies to the broader adult patient experience is not known. The goal of the present study was to understand and characterize the burden of disease in adult patients with HPP from the patient perspective.

2. Materials and Methods

2.1. Survey Instruments

Two survey instruments were developed by the study sponsor (Alexion Pharmaceuticals, Inc.) to evaluate the patient-reported symptomology and burden of disease of HPP (provided in Appendix). Questions were designed to capture HPP-related events of interest through yes/no, “check all that apply”, and multiple choice answers. Free text fields provided additional information for some categories. No psychometric assessments were performed for these instruments.

2.1.1. *Hypophosphatasia Impact Patient Survey (HIPS)*

The HIPS consists of approximately 40 questions on demography, medical history, and functional abilities. A portion of the HIPS comprised the 12-item Short Form Health Survey Questionnaire version 2 (SF-12v2) [20]. The SF-12v2 is a modified and validated version of the 36-item Short Form Health Survey Questionnaire (SF-36) that assesses health-related quality of life (QoL) through Physical and Mental Health Component summary scores and 8 health-related domains. No modifications were made to the SF-12v2 questions, and the tool was included in its entirety as part of the HIPS (questions 1–7, Appendix). Medical history of developmental, bone, joint, pulmonary, oral, muscular, and renal complaints was assessed via “check all that apply” questions listing symptoms associated with HPP. Surgical history, home modifications, and use of outpatient health services, paid assistance, and mobility aids were also all assessed through “check all that apply” questions. Fracture history and current respiratory requirements were assessed through yes/no questions, followed by free text fields and multiple choice questions querying location and healing status.

2.1.2. *Hypophosphatasia Outcomes Study Telephone Interview (HOST)*

The HOST consisted of approximately 37 questions covering demography, medical history, and physical function. First and current HPP symptoms were collected via free text responses. Medical history of HPP-related symptoms was queried via yes/no responses to a list of symptoms covering developmental, bone, joint, pulmonary, oral, muscular, and pain complaints. Change in disease state was assessed through multiple choice options asking whether each symptom was better, worse, or unchanged compared to 5 years ago. Location of fractures and pain complaints were collected via free text responses. Functional ability was measured through “check all that apply” questions listing activities necessary for daily living and use of mobility aids as well as yes/no questions related to difficulties with work or school, sleeping, and eating.

2.2. Participants and Survey Administration

All patients or their caregivers provided informed consent prior to participation. The HIPS was conducted between September 9, 2009 and June 15, 2011 and administered via