Hermansky–Pudlak Syndrome

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Abstract

Hermansky–Pudlak syndrome (HPS) is a multisystemic autosomal recessive disorder characterized by oculocutaneous albinism, bleeding diathesis, and lethal pulmonary fibrosis (PF) in some HPS subtypes. During middle adulthood, ground-glass opacities, reticulation, and traction bronchiectasis develop with progression of PF. HPS is an orphan disease occurring in 1 in 500,000 to 1,000,000 individuals worldwide, though the prevalence is 1 in 1,800 in individuals with Puerto Rican heritage. Recessive mutations or disruptions in *HPS* genes alter the function of HPS proteins which are components of biogenesis of lysosome-related organelle complexes and are critical for intracellular protein trafficking. Diagnosis and management of HPS-related comorbidities represent a challenge to physicians, and a multidisciplinary clinical approach is necessary for early detection, health management, and surveillance of PF in patients with HPS types 1, 2, and 4. Treatment options for individuals with HPS-PF include pirfenidone and lung transplantation. In this article, we describe the epidemiology, genetics, clinical manifestations, and management of HPS.

Keywords

- Hermansky–Pudlak syndrome
- pulmonary fibrosis
- oculocutaneous albinism
- interstitial lung disease
- bleeding diathesis
- rare disease

Hermansky–Pudlak syndrome (HPS) is a rare disease inherited in an autosomal recessive pattern.[1] In 1959, two Czechoslovakian physicians (Dr. F. Hermansky and Dr. P. Pudlak) described hypopigmentation in two adults patients who presented with severe hemorrhagic diathesis,[2] naming the entity as HPS. To date, 10 HPS genetic subtypes (1–10) have been described in the medical literature.[3] Mutations in *HPS* genes disrupt intracellular protein trafficking complexes called the biogenesis of lysosome-related organelles complexes (BLOCs),[4] resulting in impaired intracellular protein trafficking.[5] Clinical features of HPS include oculocutaneous hypopigmentation and bleeding diathesis due to platelet storage pool deficiency. In HPS-1 and HPS-4, pulmonary fibrosis (PF) is highly penetrant and is the leading cause of premature death in this population during adulthood.[6] Interstitial lung disease (ILD) has also been reported in individuals with HPS-2 starting in childhood.[7]

In this article, we address the epidemiology, pulmonary and extrapulmonary manifestations, and suggested algorithms for diagnosis and medical management of HPS. We also highlight recent progress in understanding underlying disease mechanisms and strategies to accelerate progress.

Epidemiology

HPS has been identified in different ethnicities worldwide, including Caucasians, Europeans, Asians, Puerto Ricans, and non-Puerto Rican Hispanics.[8–13] Previous studies suggest that the worldwide prevalence of HPS is 1 in 500,000 to 1,000,000 in non-Puerto Rican individuals. To date, the true frequency of HPS remains unknown. The HPS Network, Inc., a nonprofit organization established in 1992 and incorporated in 1995, has enrolled ~1,200 individuals around the world (oral communication, November 2019).

Due to a founder effect, Puerto Rico has the highest prevalence of HPS-1,[14] accounting for 50% of all cases worldwide.[15] Further, HPS-1 is the most common single genetic disorder in Puerto Rico. One in 1,800 Puerto Ricans has HPS-1, with a carrier rate of 1 in 21 from those individuals living at the northwest of the island[16,17] (►**Fig. 1**). It is estimated that

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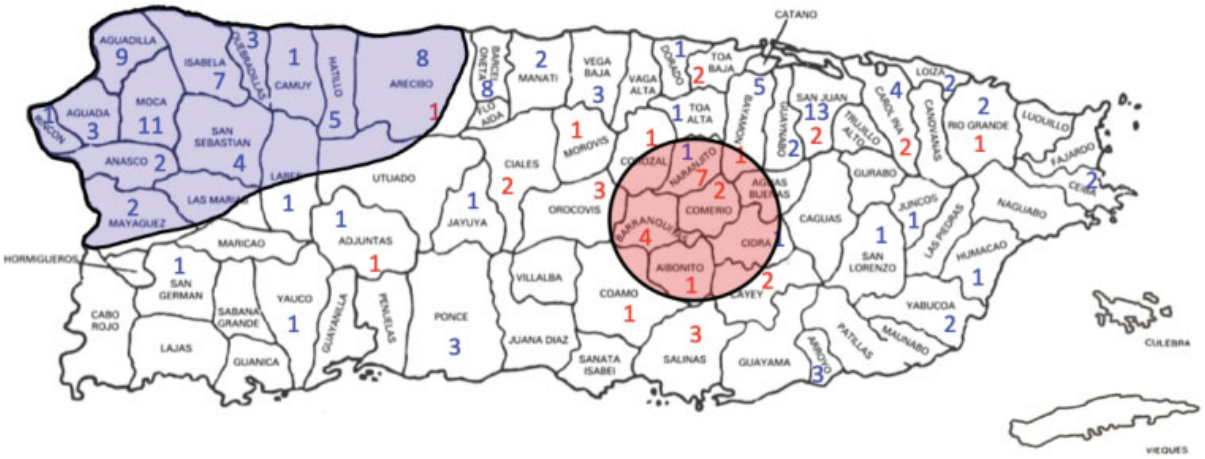

Fig. 1 2018 Geographic distribution of HPS in Puerto Rico. Patient geographic location was verified by direct patient communication including: home visits, phone calls, e-mails, and postal letters. Outline remarks zones of increase prevalence for HPS-1 and HPS-3 on the island. HPS-1 ($n = 119$) and HPS-3 ($n = 37$) are most commonly located in the northwest and central region, respectively. HPS, Hermansky–Pudlak syndrome. The authors thank Beatriz Cáceres, MD, Yashira Ortega, and Enid Rivera, MD, from the University of Puerto Rico for assistance with this figure.

eight children are born with HPS every year in Puerto Rico.[6] Genetic analysis of the HPS Puerto Rican population exposed a founder mutation affecting a 16-base-pair duplication in exon 15 of *HPS1* gene,[18] thus explaining the high incidence of HPS in Puerto Ricans. In addition, HPS-3 is prevalent in the central region of the island secondary to an additional distinct founder mutation.[19] Recent studies, suggest that 1 in 4,000 individuals in Puerto Rico are affected with HPS-3 with carrier rate of 1 in 32.[20] Other regions reporting HPS cases include: Western Europe, India, Japan, China, United Kingdom, Middle East, and Mexico.[21–24] HPS patients with Ashkenazi Jewish background also have been described.[25]

Genetic Mechanisms

Ten different HPS subtypes have been molecularly characterized[1] (►**Table 1**). While the clinical manifestations of each subtype have considerable overlap, there are important differing characteristics and specific HPS-associated comorbidities. Therefore, each HPS patient should be genotyped and classified by specific HPS subtypes due to the prognostic and treatment implications.[26,27] HPS is an autosomal recessive disorder, and females and males are equally affected.[1] Biallelic pathogenic variants in *AP3B1*, *AP3D1*, *BLOC1S3*, *BLOC1S6*, *DTNBP1*, *HPS1*, *HPS3*, *HPS4*, *HPS5*, or *HPS6* confirm the diagnosis in a clinically suspected HPS patient.[1] Several mutations in each subtype have been described as well founder mutations localized in specific regions. For example, a 16-bp homozygous duplication in exon 15 was described as an *HPS1* founder mutation in Puerto Rico.[28] Another Puerto Rican founder mutation that affects a susceptibility genetic region in chromosome 3q24 is responsible for the second *HPS3* founder mutation on the island.[19,20]

Manifestations

HPS is caused by genetic alterations in genes that encode for HPS-related proteins, which are critical in the biogenesis and trafficking of intracellular BLOCs.[4,29] The function of BLOCs has been fairly well elucidated in some cell types, though the

Table 1 HPS genetic subtypes

Human subtype	Affected gene	Affected protein	Chromosome locus	MIM number
HPS-1	*HPS1*	BLOC-3	10q24.2	203300
HPS-2	*AP3B1*	AP-3	5q14.1	608233
HPS-3	*HPS3*	BLOC-2	3q24	614072
HPS-4	*HPS4*	BLOC-3	22q12.1	614073
HPS-5	*HPS5*	BLOC-2	11p15.1	614074
HPS-6	*HPS6*	BLOC-2	10q24.32	614075
HPS-7	*DTNBP1*	BLOC-1	6p22.3	614076
HPS-8	*BLOC1S3*	BLOC-1	19q13.32	614077
HPS-9	*BLOC1S6*	BLOC-1	15q21.1	614171
HPS-10	*AP3D1*	AP-3	19p13.3	617050

Abbreviations: BLOC, biogenesis of lysosome-related organelles complex; HPS, Hermansky–Pudlak syndrome; MIM, Mendelian inheritance in man.
Source: Adapted from Vicary et al.[6]

Table 2 Reported clinical features of HPS classified by genetic subtype

Clinical features in HPS	HPS genetic subtype									
	1	2	3	4	5	6	7	8	9	10
Bleeding diathesis	X	X	X	X	X	X	X	#	X	X
Nystagmus	X	X	X	X	X	X	X	X	X	X
Poor visual acuity	X	X	X	X	X	X	X	X	X	X
Ocular albinism	X	X	X	X	X	X	X	X	X	X
Pulmonary fibrosis/interstitial lung disease	X	X		X						[a]
Skin hypopigmentation	X	#	#	#	#	#	#	#	#	#
Recurrent infections		X								X
Seizures		X								X
Granulomatous colitis	X		#	X		X				

Abbreviations: HPS, Hermansky–Pudlak syndrome; X, presence of clinical feature; #, feature is present to a variable degree.
[a]The single HPS-10 case reports suggest pulmonary involvement, although more cases are needed to confirm this finding.
Source: Adapted and updated from Seward and Gahl.[44]

precise mechanism(s) of how each genetic alteration affects the phenotypic manifestations of HPS is complex and incompletely understood. In this section, we discuss the manifestations of HPS (►**Tables 2** and **3**).

Dermatology

Considerable variation in pigmentation between HPS subtypes may be present.[3,30] The degree of hypopigmentation in this population ranges between white and light-brown skin and hair color. Complications of albinism are accentuated by sun exposure and are frequently observed in HPS patients.[31] These dermatologic manifestations may include: actinic keratosis and skin thickening melanocytic nevi with dysplastic features, acanthosis nigricans-like lesion in the intertriginous areas, and abnormally long eyelashes. Previous studies reported that 80% of patients with HPS exhibited some degree of solar damage including multiple freckles and stellate lentigines.[31] Sporadically, the development of basal cell and squamous cell carcinoma has been described among individuals with HPS.[32,33] In HPS-1, altered transport of tyrosinase-related protein 1 results in oculocutaneous albinism.[34] In HPS-2 and HPS-10, the adaptor protein 3 (AP-3) complex is altered and pigment dilution occurs. Defects in BLOC2 complex affect the amount of hypopigmentation in HPS-3, HPS-5, and HPS-6.

Table 3 Age-dependent manifestations of HPS-1

Clinical features in HPS-1	Children	Adults
Bleeding problems	X	X
Nystagmus	X	X
Poor visual acuity	X	X
Ocular albinism	X	X
Skin hypopigmentation	X	X
Granulomatous colitis	Variable	X
Pulmonary fibrosis	[a]Very rare reports	X, >30 y
Recurrent pulmonary infections	–	–
Seizures	–	–

Abbreviations: HPS, Hermansky–Pudlak syndrome; X, presence of clinical feature.
[a]Pulmonary fibrosis is mainly an adult clinical feature, although there are reports of HPS-PF during adolescence.

Hematology

Defects in the lysosomes-related organelles system may impair the formation of platelet dense bodies, resulting in platelet dysfunction and bleeding diathesis.[35,36] The onset of bleeding is usually observed when children become ambulatory, though the severity and nature of bleeding complications may vary in severity among HPS subtypes.[37] Some patients may experience minimal or no bleeding problems, while others exhibit easy hematoma development with minimal trauma, intermittent epistaxis, gingival bleeding, prolonged menstrual periods, and dental or surgical complications during procedures.[38–41]

While the absolute numbers of platelets are normal, platelet aggregation is compromised due to a reduced number or absence of platelets dense bodies or α-granules.[42] Prolongation in the bleeding time was used in the past to study defects in platelets aggregation in this population.[43] However, due to the unreliable measurements, the use of bleeding time is no longer recommended.[44] Notably, other coagulation profile parameters including prothrombin time and partial thromboplastin time are typically normal in HPS.[37]

Pulmonary

Pulmonary fibrosis is the leading cause of mortality in HPS. To date, HPS-1, HPS-2, and HPS-4 are subtypes in which PF has been reported. HPS-PF is typically diagnosed in the third to fourth decades of life,[6] though some cases may present earlier.[7,45] Available data indicate that 100% of HPS-1 patients eventually develop PF.[44] Symptoms may include

nonproductive cough, dyspnea with activity or rest, shortness of breath, and hypoxemia that lead to the use of chronic supplemental oxygen as the disease progress. Radiologic findings include the presence of subpleural and central infiltrates, ground-glass diffuse opacities, reticulation, and subpleural honeycombing. Traction bronchiectasis may be present in severe cases. The presentation of HPS-PF starts gradually and become progressive overtime with a steady decline in pulmonary function, specifically force vital capacity (FVC). A decline in FVC of 500 mL per year has been reported.[46] The mortality associated with HPS-PF commonly occurs around age 40 and 50 years secondary to respiratory failure.[6]

Most individuals with HPS are never smokers. Proposed additional contributing factors in idiopathic pulmonary fibrosis (IPF) such as viral infections and chronic aspiration have not been studied in HPS.[47] Previous studies suggest that the pathogenesis of PF in HPS is related to a defect that alters alveolar epithelial cell function,[48] with fibrotic signals subsequently transduced to macrophages and fibroblasts to promote the accumulation of extracellular matrix and fibrotic remodeling.[49–51]

Gastroenterology

Patient with HPS subtypes 1, 4, and 6 have been reported to develop a specific type of inflammation of the gastrointestinal (GI) tract called HPS-associated colitis.[52–54] Because of the similar phenotypes of patients with HPS-3 and HPS-6, which both disrupt BLOC2, patients with HPS-3 would also be predicted to be at risk for colitis. Symptoms, including abdominal pain, weight loss, intermittent fevers, and malabsorption with watery and/or bloody diarrhea, vary in severity and may manifest in early childhood.[55] The clinical and histological characteristics of HPS-associated colitis resemble other types of inflammatory bowel disease (IBD) such as Crohn's disease[53] but can occur throughout the GI tract. In one study of 122 subjects with HPS, the prevalence of colitis was 7% and an additional 33% were subsequently diagnosed with HPS-associated colitis during the study,[54] suggesting that colitis is underrecognized or underreported in this population. The specific pathogenesis of HPS-associated colitis is not well understood. Postulated pathways of inflammation include the idea of direct tissue damage as the result of release of lysosomal hydrolases from intestinal ceroid-laden macrophages in the intestinal tract.[56] Mortality has been attributed to HPS-associated colitis in some cases.[57]

Immunology

The HPS-2 subtype is associated with an immunodeficiency presenting with recurrent infections, neutropenia, and impaired cytotoxic immune activity.[58] HPS-2 occurs due to recessive mutations in the AP-3, which is an important cytoplasmic trafficking complex, which is ubiquitously expressed in a variety of cell types.[59] AP-3 deficiency also impacts function of immune cells including T cell lymphocytes and natural killer cells.[60,61] In HPS-2, mutations in *AP3B1* result in loss of expression of the β3A subunit of the AP-3 complex, thereby leading to instability of the complex with degradation of other AP-3 complex components.[62,63] In addition, immunodeficiency has been described in HPS-10, which is caused by mutations in *AP3D1*, another component of the AP-3 complex whose disruption also affects the stability of the entire AP-3 complex.[64] Early-onset seizures, global developmental delay, and neutropenia-associated pulmonary infections are part of the clinical phenotype reported in a young patient with HPS-10.[65] Recurrent pulmonary infection and early ILD have been reported in six children with HPS-2.[7]

Nephrology

To date, no specific renal disorder has been associated with HPS, though some abnormalities in renal function have been reported. Ceroid lipofuscin accumulation has been described in renal biopsies from HPS-1 patients.[66] Renal insufficiency and chronic kidney disease secondary to focal segmental glomerulosclerosis has been described in one child with HPS.[67] In a study that evaluated 49 Puerto Rican and non-Puerto Rican HPS patients, no differences in mean serum creatinine concentrations were observed between homozygous and carrier patients of the *HPS1* 16-bp duplication mutation. However, the creatinine clearance was decreased by 33% in HPS patients with a 16-bp duplication.[68] Recently, a study demonstrated high renal expression of HPS protein in HPS-1 and HPS-3 to HPS-5. Knockdown of *HPS* genes in a zebrafish model impaired glomerular filtration and renal function.[69]

Ophthalmology

Patients with HPS are legally blind, though the presence and severity of ocular symptoms and vision impairment is variable among different HPS subtypes. Ocular findings include congenital horizontal nystagmus, photophobia, decreased visual acuity from 20/25 to 20/320, and iris translucency.[70] In addition to the lack of retinal and iris pigmentation,[71] foveal hypoplasia was universal in patients with HPS.[72] In a study conducted among 55 HPS patients from Puerto Rican heritage, additional findings included strabismus, posterior embryotoxon, and Axenfeld anomaly.[70] Relatively good visual prognosis has been associated with the lack of clinically apparent nystagmus in the pediatric age group.[73]

Diagnostic Approach

Medical History

A high level of suspicion is needed for the diagnosis of HPS. While there are many causes of albinism,[74] hypopigmentation in a newborn with Puerto Rican ancestry should prompt testing for HPS. Family history of hypopigmentation, coagulation problems, and PF may also warrant evaluation for possible HPS. During childhood, patients may present with recurrent epistaxis, prolonged bleeding after a minor surgery, tooth extraction, or circumcision. Visual symptoms of photosensitivity, nystagmus, and poor visual acuity are present early but are not specific to HPS. The presence of abdominal pain and chronic diarrhea may reflect early manifestations of HPS colitis. Respiratory symptoms warrant a broad general pulmonary evaluation, as HPS-PF does not typically manifest in young children, except potentially for children with HPS-2.

During adulthood, exercise intolerance and shortness of breath with minor activities may indicate PF.[44] An algorithmic approach that can guide clinicians in establishing a confirmed diagnosis of HPS in suspected patients has been described.[94]

Physical Examination

A complete physical examination should be performed in patients with HPS, with particular focus on respiratory and skin examinations. Vision screening should be completed with the expertise of an ophthalmologist familiar with HPS vision problems.[73] Retinal evaluation should be completed to explore for retinal hypopigmentation. Cardiorespiratory evaluation includes documentation of adequate saturation, breathing pattern, and the presence of any abnormal pulmonary sounds. Observing for signs of skin bruising, gingival, or nasal bleeding is part of the physical examination. Comprehensive skin evaluation for suspicious neoplastic lesions in sun- and non-sun-exposed areas should be documented.[44]

Laboratory and Diagnostic Tests

Platelet Transmission Electron Microscopy

The near or complete absence of α dense granules in a platelet transmission electron microscopy (PTEM) examination is considered the mainstay for diagnosis of HPS.[75] Availability of this test is limited to specific specialized referral laboratories.

Ophthalmologic Examination

The slit lamp examination is part of the comprehensive ophthalmologic evaluation in patients with HPS.[76] This test provides a three-dimensional view of the eye components to document the present of abnormalities. Additional findings during an ophthalmologic visit may include iris transillumination, fundus hypopigmentation, presence of nystagmus, and decreased visual acuity. Early referral to ophthalmology to correct refractive errors and intervention programs is highly encouraged.[44]

Pulmonary Assessments

Pulmonary Function Test

Pulmonary function tests (PFTs), including spirometry, evaluation of lung volumes, and diffusing capacity for carbon monoxide, are recommended for patients with HPS-1, HPS-2, and HPS-4 starting in adolescence or earlier if respiratory symptoms are present. A restrictive airflow pattern is typically noted in adults with PF.[77] Due to the progressive PF in some HPS subtypes, FVC% serial monitoring is recommended.[6] A decline in FVC% can start at the age of 20 to 25 years, but in some cases can be present earlier.[45,46] When a progressive decline in pulmonary function is noted with a FVC% less than 60%, referral to a lung transplant center is encouraged to facilitate adequate time for consultation.[46]

Chest radiograph (CXR) may be the initial screening tool for identification of ILD in patient with HPS. Findings on CXR may include, interstitial infiltrates, fibrosis, and sometimes areas of consolidation, though high-resolution computed tomography (HRCT) of the chest is required in most cases.[44] Findings of PF on HRCT are similar to those reported in other etiologies of PF, including peribronchial cuffing, traction bronchiectasis, honeycombing, pleural and interlobular septal thickening, parenchymal cyst, and ground-glass infiltrates[78] (►**Fig. 2**). HRCT findings have been correlated with symptoms and progression of PF in HPS.[78] Lung biopsy is generally not indicated in HPS due to increased risk of bleeding and the clinical context of HPS to support the etiologic nature of the lung disease.

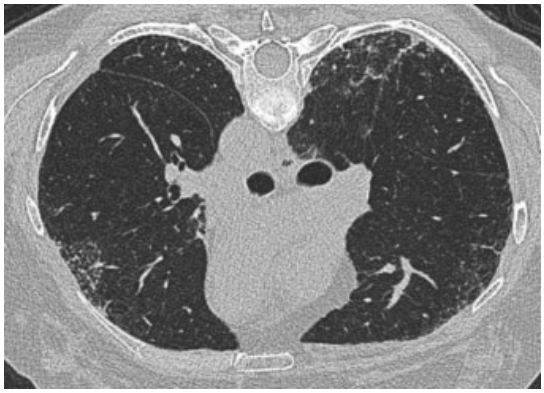

Fig. 2 Representative chest CT findings from an individual with HPS-1. HPS, Hermansky–Pudlak syndrome.

Health Management and Surveillance in HPS

HPS-Pulmonary Fibrosis

Current recommendations are for baseline pulmonary assessments including PFTs and HRCT in asymptomatic individuals with HPS-1 and HPS-4 between ages 18 to 21 years.[44] The ideal follow-up interval is not established, but it is recognized that serial screening is necessary to detect early changes of pulmonary decline. To minimize radiation exposure, annual PFTs are considered with greater spacing of chest imaging to at least 3- to 5-year intervals unless symptoms or PFT decline occurs.

Two clinical trials evaluating the role of pirfenidone in HPS have been conducted by the National Institute of Health,[46,79] with the first starting enrollment in 1997. In the first trial, 21 patients were randomized to pirfenidone (800 mg three times a day) versus placebo. The results were inconclusive, though post hoc secondary analysis suggested that pirfenidone appeared to slow the progression of PF in patients with initial FVC >50%. Food and Drug Administration (FDA) approval was not provided based on these data in a small number of patients with moderate to severe PF.[46] A second trial was conducted restricted to 35 patients with mild to moderate lung disease, with 2:1 randomization to pirfenidone versus placebo. However, in the setting of slow decline in lung function in the placebo group, the trial was stopped in consideration of statistically futility to demonstrate a difference between pirfenidone and placebo group.[79] A recent analysis of open-label pirfenidone suggested prolonged survival for three individuals with HPS-PF as compared with the

untreated comparison group.[80] While nintedanib is also FDA approved for IPF, this drug is considered contraindicated in HPS due to increased risk of bleeding.

Lung Transplantation

Evaluation for lung transplantation should be discussed for patients with HPS-1, HPS-2, and HPS-4 subtypes as soon as there is evidence of PF progression.[44] Evaluation of the barriers to transplantation should be explored with a team with expertise in the field.[81] Enrollment in pulmonary rehabilitation centers is recommended while waiting on a transplant list and during the complete process.[82] Immunizations including influenza vaccine and pneumococcal vaccination should be administered per standard guidelines.[6,44] Medical compliance, family support, and economical aspects should be reviewed and discussed as part of the process for lung transplant consideration. Bleeding complications have been successfully managed and are not a contraindication to lung transplantation in HPS.[83] Other posttransplant complications including infection and development of bronchiolitis obliterans are similar in HPS to those transplanted for other indiciations.[84] A recent report by El-Chemaly et al emphasized that bilateral lung transplantation is a feasible option for patients with HPS.[85]

Dermatology and Ophthalmology

During infancy, evaluation with a dermatologist will provide education about patient skin care, avoidance of ultraviolet (UV) exposure and the use of sunscreen protection throughout the year.[44] Daily use of waterproof sunscreen with a protection factor above 30 should be encouraged beginning in infancy. The use of protective clothing, tinted UV sunglasses, hats, and avoidance of direct sun exposure during peak sun hours (10 AM–3 PM) are strongly suggested.[44] Annual complete ophthalmologic examination is also recommended.

Bleeding Diathesis

Patients with HPS can develop profuse bleeding after minimal trauma or with monthly menstrual periods.[38] Consultation with a hematologist with experience in HPS is recommended. Due to the irreversible inhibition of cyclooxygenase and reduction in platelet aggregation, salicylates and nonsteroidal anti-inflammatory drugs are not recommended in HPS for pain management. Acetaminophen is recommended for pain control if not contraindicated for other reasons. Few HPS cases have reported the use of fibrinolysis inhibitors such as tranexamic acid in the setting of acute bleeding, surgery, or intrapartum hemorrhage with success.[86,87] Desmopressin (DDAVP) and aminocaproic acid have been used both prior to procedures and to treat HPS-related bleeding.[88,89]

Dental Care

Complications during dental procedures due to bleeding are common in all ages. Specific considerations should be taken for HPS patients to minimize complications during dental procedures. The use of UV eyeglasses protects patient vision from light stimulus during dental evaluation. The use of a soft toothbrush and conservative brushing dental technique can minimize dental gum trauma and prevent bleeding.[90] The use of antifibrinolytic agents and DDAVP during dental procedures has been used to achieve adequate hemostasis in HPS patients.[40]

Inflammatory Bowel Disease

Granulomatous colitis symptoms that warrant further evaluation by a gastroenterologist and possible colonoscopy may include abdominal cramps, increased stool mucus, and rectal bleeding. Systemic corticosteroids, immunomodulators, and other therapies used in Crohn's disease have been described as part of the treatment for HPS-IBD,[91] though there have been no controlled trials focused to HPS. Complicated HPS-IBD has been successfully treated with infliximab.[92,93] The concurrent platelet dysfunction in HPS patients places the use of aminosalicylates as a topic of controversy in the medical community.[94] Other cases may need surgical interventions, if refractory to standard medical therapy.[44]

Prognosis

For individuals with HPS-1 and HPS-4, in the absence of lung transplantation, life expectancy is around 10 years postdevelopment of restrictive lung disease.[94] Postlung transplant survival rates in HPS may approach 50% in 5 years similar to outcomes for other posttransplant patients with non-HPS disorders. HPS-2 has been associated with pulmonary manifestations in children, but the natural history and prognosis are not established.[7,95] The clinical course of HPS-3, HPS-5, and HPS-6, which have not been reported to develop PF, is mild. Prognosis of HPS-7, HPS-8, and HPS-10 has not been well described as few individuals with these subtypes have been identified to date.

Summary and Future Directions

HPS is an autosomal recessive syndrome with 10 genetic subtypes described to date. The phenotype of HPS includes the presence of oculocutaneous albinism, bleeding, colitis, and PF in subtypes HPS-1, HPS-2, and HPS-4. Management of HPS-related comorbidities should involve a team with HPS experts in the field using a multidisciplinary treatment approach. Early recognition of HPS manifestations and complications is needed to facilitate timely diagnosis and prompt management. Referral for lung transplantation should be considered in HPS patients with pulmonary symptoms or progressive decline in pulmonary function. Increased awareness and clinical trials for orphan lung disorders such as HPS are needed. Understanding the mechanisms underlying HPS-PF may facilitate development of new therapeutic agents specific for HPS. Therapies established for treatment of other forms of fibrotic lung disease also hold promise for HPS.

Conflict of Interest
None declared.

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