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Hermansky-Pudlak Syndrome: Health Care Throughout Life

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KEY WORDS
Hermansky-Pudlak, albinism, platelet storage pool deficiency, standard of care

ABBREVIATIONS
AAP—American Academy of Pediatrics
BLOC—biogenesis of lysosome-related organelle complexes
CHS—Chediak-Higashi syndrome
COX—cyclooxygenase
HPS—Hermansky-Pudlak syndrome
HRCT—high-resolution computed tomography
IBD—inflammatory bowel disease
IEP—Individual Education Plan
ILD—interstitial lung disease
NSAIDs—nonsteroidal anti-inflammatory drugs
OCA—oculocutaneous albinism
PF—pulmonary fibrosis
PFT—pulmonary function test

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abstract

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disease that displays genetic heterogeneity; there are 9 known subtypes. HPS is characterized by oculocutaneous albinism, a platelet storage pool deficiency and resultant bleeding diathesis, and lysosomal accumulation of ceroid lipofuscin. Patients with HPS, specifically those with the genotypes HPS-1, HPS-2, or HPS-4, are predisposed to interstitial lung disease. In addition, some patients with HPS develop granulomatous colitis. Optimal health care requires a thorough knowledge of the unique health risks and functional limitations associated with this syndrome. *Pediatrics* 2013;132:153–160

Hermansky-Pudlak syndrome (HPS), a rare autosomal recessive disease, was first described in 1959. In the ensuing decades, much has been learned about the genetic basis, cellular mechanisms, and phenotypic presentation of this disease. There are 9 genetic loci associated with HPS in humans; mutations in HPS-associated genes result in defects in intracellular protein trafficking and in the biogenesis of lysosomes and lysosome-related organelles (eg, platelet-dense granules and melanosomes).

The largest groups of patients with HPS originate from the northwestern region Puerto Rico, where its frequency is estimated to be 1:1800,[1] and central Puerto Rico. Patients with HPS of non–Puerto Rican descent have been identified in many other parts of the world, including the Indian subcontinent,[2] Japan,[3] the United Kingdom,[4] and Western Europe.[3] The overall frequency in the human population is not known. To date, no publication has described the standard of medical care for patients with HPS, who face a myriad of health issues throughout life.

ETIOLOGY AND DIAGNOSIS

All 9 distinct HPS mutations result in oculocutaneous albinism (OCA) and a platelet storage pool deficiency.[5,6] Of these, HPS-1, with its Puerto Rican founder mutation, a 16-bp duplication in exon 15 of the *HPS1* gene on chromosome 10, is the most common.

A focus of investigation has been the ubiquitous intracellular protein complex adaptor protein-3 and the biogenesis of lysosome-related organelle complexes-1, 2, and 3 (BLOC-1, BLOC-2, and BLOC-3), whose subunits include products of genes defective in various HPS subtypes. The genetic mutations associated with HPS-1 and HPS-4, for example, have been linked to defects in the formation of BLOC-3, whereas the HPS-2 mutation results in defective adaptor protein-3.[7]

The differential diagnosis for HPS includes Chediak-Higashi syndrome (CHS), with its salient phenotypic features of OCA, neutropenia, natural killer cell dysfunction, and frequent bacterial infections. The diagnosis of CHS requires the presence of giant granules in neutrophils and other leukocytes; Griscelli syndrome is phenotypically similar to CHS, but without the presence of giant granules.

To meet criteria for diagnosis, all patients with HPS must have (1) tyrosinase-positive OCA and (2) a specific platelet storage pool deficiency (ie, absence of δ granules). The hallmarks of OCA are diffuse hypopigmentation of the skin, hair, iris, and retina. OCA is, for all practical purposes, a clinical diagnosis and can first be suspected in the newborn nursery where there can be evidence of diminution of skin pigmentation such that it appears pink or chalky white. The hair varies from silvery-white to light brown and the eyes are light blue, light green, or hazel. Additional eye findings are positive iris transillumination and findings consistent with retinal hypopigmentation.

However, it is possible to encounter patients with HPS with less severe hypopigmentation and brown hair and eyes, particularly with the HPS-3, HPS-5, or HPS-6 subtypes (Fig 1). Iris transillumination is a simple bedside test that uses the direct ophthalmoscope; when light is shone into the pupil, the examiner notes light emanating through the iris.[8] Retinal hypopigmentation can also be visualized with the direct ophthalmoscope; the examiner identifies areas of the retina that appear yellow or orange instead of the usual red.[8] Additional findings include evidence of decreased visual acuity as the child develops; on formal testing, patients with HPS often have visual acuity $\leq$20/200. (Note this meets the legal definition of blindness, thereby qualifying many patients with HPS for disability benefits through the Social Security Administration.) Horizontal nystagmus is often present from birth and is sometimes the most distressing physical sign of HPS for parents.

In conjunction with OCA, patients with HPS must have evidence of the platelet storage pool defect and resultant bleeding diathesis. This might be first evident in newborn boys at the time of circumcision, with prolonged bleeding after the procedure. Later, when patients become ambulatory, there is frequently evidence of excessive bruising of the lower extremities from minimal trauma after inadvertently banging into chairs, table legs, and other stationary objects as the toddler experiments with walking. This excessive bruising has been mistaken for evidence of child abuse.[9]

It is recommended that any patient with OCA who reports Puerto Rican ancestry and/or an abnormal bleeding history be formally evaluated for HPS.

When present and functioning normally, platelet-dense granules play a critical role in the secondary phase of platelet aggregation, which involves recruitment of other platelets to form a clot on release of the chemical contents of δ (and α) granules. In the absence of dense granules, physiologically effective clot formation at the site of an injury takes longer than in unaffected individuals. The actual time to clot formation is highly variable.

Historically, platelet aggregation defects were evaluated by using the bleeding time test. This test has been shown to be

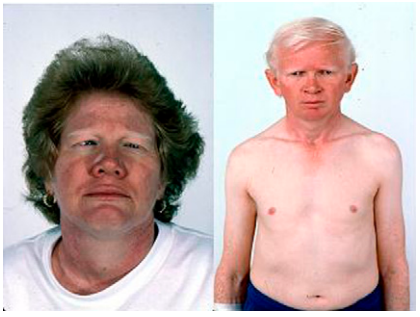

FIGURE 1
Phenotypic heterogeneity of the HPS-1 genotype. Note differences in degree of hair and skin pigmentation.

unreliable and is not recommended.[10] Today, the aggregation defect can be assessed in 2 ways, neither of which is currently available in commercial laboratories. First, platelet aggregation can be timed and compared with normal values using platelet stimulants, such as adenosine diphosphate or epinephrine and a platelet aggregometer.[11] A second, more diagnostically sensitive, approach uses fresh platelet-rich plasma, prepared from the patient's blood, and electron microscopy as first described by Witkop et al,[12] where complete absence of δ granules is consistent with HPS (Figs 2 and 3). Electron microscopy is the preferred method of diagnosis.

Ceroid lipofuscin, an autofluorescent pigment, has been identified in lysosome-related organelles of multiple organs (eg, the kidney) and the reticuloendothelial system of patients with HPS. Although it has been hypothesized as a putative trigger of inflammation in HPS-associated inflammatory bowel disease (HPS-IBD) and HPS-associated interstitial lung disease (HPS-ILD), this has not been confirmed.

MOLECULAR SUBTYPING

Besides OCA and the platelet defect, other important and potentially life-threatening manifestations of HPS are associated with specific genetic subtypes of the disease. Therefore, it is important for the physician to be aware of the phenotypic distinctions among the main HPS subtypes and, when such testing is feasible, to pursue mutation analysis for the patient. Table 1 illustrates the phenotypic distinctions among the 9 HPS subtypes. An excellent comprehensive review of these molecular subtypes can be found in *GeneReviews*.[13]

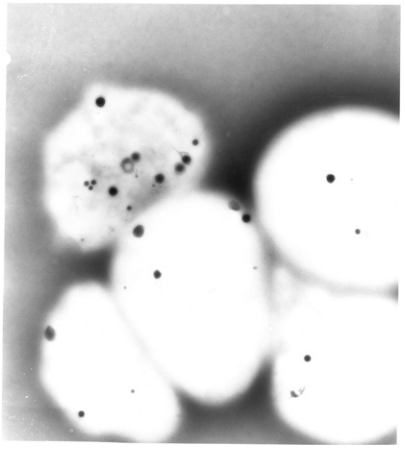

FIGURE 2
Normal platelets revealing presence of δ granules.

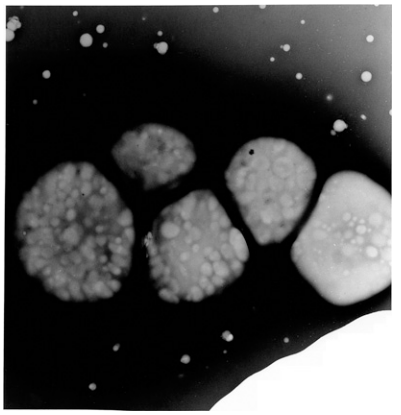

FIGURE 3
Example of HPS platelets revealing total absence of δ granules.

In the United States, testing for the HPS-1 and HPS-3 Puerto Rican and Ashkenazi Jewish founder mutations is currently available through the commercial laboratory, GeneDx (Gaithersburg, MD, www.genedx.com). Before completing molecular subtyping, it is important that the physician or a trained genetic counselor discuss with the patient the implications of such testing. Although the overall frequency of HPS is not known, the Hermansky-Pudlak Syndrome Network, which serves as a clearinghouse for the general public and health care professionals, as of March 2013, reported >1000 unique individuals with HPS in its patient registry.

PREVENTIVE CARE AND HEALTH MAINTENANCE

Immunizations

In the absence of individual patient-specific contraindications (for instance, long-term treatment with an immunosuppressive agent), the American Academy of Pediatrics (AAP) pediatric vaccine schedule is recommended for all infants and children with HPS. Vaccines may be administered without any special precautions; however, because of the platelet aggregation defect, parents should be counseled to be alert for signs of intramuscular bleeding (ecchymoses, pain, paresthesias, numbness) at the injection site and the distal extremity. There may be utility in applying an ice pack to the injection site for 10 to 15 minutes postinjection to decrease the likelihood of this complication, but this has not been studied.

The influenza vaccine is recommended annually and throughout life for all patients with HPS, in the absence of contraindications.

In addition to the 13-valent pneumococcal conjugate vaccine, provided as part of the AAP-recommended primary vaccination series, patients with HPS should receive the 23-valent pneumococcal polysaccharide vaccine in adulthood. A booster dose of polysaccharide vaccine 5 years later can be considered for specific patients.[14]

Developmental Assessment

Children with HPS should receive regular assessments of all normal milestones as recommended by the AAP, including head circumference, height, weight, and BMI; language acquisition and expression; fine and gross motor development; intellectual development, reasoning, problem solving, and school performance; and social adaptation. Significant delay in any of these areas requires further evaluation.

Because of the expected defect in visual acuity, children with HPS are likely to experience significant challenges related to reading and visual information processing. The pediatrician should expect that the patient will require a learning environment that includes

TABLE 1 Phenotypic Characteristics of HPS Molecular Subtypes 1–9

HPS Subtype	OCA	Platelet Defect	PF	Granulomatous Colitis	Neutropenia
HPS-1	√	√	√ (Nearly all affected individuals)	√ (~30% of affected individuals)	—
HPS-2	√	√	√	?	√
HPS-3	√	√	—	?	—
HPS-4	√	√	√ (frequency unknown)	√ (frequency unknown)	—
HPS-5	√	√	—	?	—
HPS-6	√	√	—	√ (frequency unknown)	—
HPS-7	√	√	?	?	—
HPS-8	√	√	?	?	—
HPS-9	√	√	?	?	—

√, presence of phenotypic feature; —, absence of feature; ?, it is not currently known.
Adapted from Wei ML. Hermansky-Pudlak syndrome: a disease of protein trafficking and organelle function. Pigment Cell Res. 2006;19(1):19–42.

assistive technology appropriate to the visual disability; this should be discussed with parents of the preschool child. More information about visual aids can be found at the National Organization for Albinism and Hypopigmentation Web site (www.albinism.org).

Early intervention programs can be helpful to the family in assessing their child's needs, and the pediatrician can play a critical role in connecting families with their local early intervention programs center. As mandated by the Americans with Disabilities Act, an Individual Education Plan (IEP) should be developed for each school-aged child with HPS by the administration of their public school district. The IEP should be reevaluated on an annual basis, or more frequently if indicated, to confirm that it continues to conform to the disability-related educational needs of the student with HPS.

On reaching college age, children with HPS often experience transitional issues regarding the ability to access disability-related accommodations in the higher-education setting. In particular, per the Americans with Disabilities Act, the student with HPS needs to become a more active participant in applying for and receiving appropriate accommodations, in contrast to primary and secondary school, in which mandates govern these issues. For instance, universities are not required by legal statute to develop IEPs for each disabled student. The physician can play a critical role in assisting a patient with HPS by providing up-to-date health-related documentation to the university disabilities office.

Likewise, when an individual with HPS enters the workforce, the physician can play an important role by encouraging the patient to advocate for disability-related accommodations, including specialized computer software for the visually disabled, additional time to complete assignments, and facility access.

Skin and Eye Protection

Patients with HPS have congenital hypopigmentation of the hair, skin, iris, retina, and choroid, with variable degrees of severity.[15] Patients with diffuse hypopigmentation of the skin are at increased risk for sunburn, photo-aging of the skin, solar keratoses, and each of the 3 major forms of cutaneous malignancy: squamous cell carcinoma, basal cell carcinoma, and melanoma.[15] (An indication of this is that although nonmelanomatous skin cancers are rare in people with brown or black skin, they are common among patients with albinism originating from the same ethnic and regional communities.[16])

Childhood is a high-risk time for UV-associated skin damage,[17] compounded in patients with HPS by the relative absence of the protective benefits of melanin. As such, beginning in infancy, parents and caregivers of patients with HPS require counseling regarding strict adherence to prophylactic measures. These include avoiding being under direct sunlight in the peak hours of the day; the use of wide-brimmed hats and other protective clothing; and the use of UV-A and UV-B protecting ointment on all exposed skin areas, with a minimum sun protection factor of 30, throughout the year. Attention should be given to whether sunscreen is waterproof or resistant, depending on planned activities, because both perspiring and swimming can impair effectiveness. It is important to counsel parents that sunscreen, no matter the sun protection factor, does not completely eliminate the risk of photo-damage at the molecular level, including DNA damage. This risk is the clearest argument for sun avoidance during peak hours, generally considered to be 10 AM to 3 PM,[18] which can prove very challenging in school-aged children wanting to participate in outdoor recess and organized sports.

Eye protection also involves sun avoidance during the peak hours, wide-brimmed hats, and the use of darkly tinted UV-protecting sunglasses.

Secondary Prevention and Early Disease Detection

In addition to addressing issues related to their genetic disorder, patients with HPS require all the usual evaluations regarding prevention and early disease detection as recommended by the AAP, the US Preventive Services Task Force,

and other like authoritative organizations. Examples of these include documenting family history of disease prevalence, hypertension screening, diabetes screening, dyslipidemia screening, and cervical and breast cancer screening.

Although not fully documented in the literature, vitamin D deficiency secondary to decreased exposure to sunlight, with consequent increased risk for osteopenia and osteoporosis, is a concern for the patient with HPS. Because of the HPS-associated OCA, sun avoidance is common, either because of physician recommendation or because the patient wishes to avoid eye discomfort and sunburn.

BLEEDING DIATHESIS

As noted, the HPS platelet storage pool deficiency often manifests clinically in infancy and early childhood, and persists throughout life. Simple lacerations and abrasions can result in prolonged bleeding, up to many hours.

Menarche is another important time when the qualitative platelet defect may become manifest. It is important to ask patients and their caregivers to quantify both the duration and quantity of menstrual flow.

There is no simple, inexpensive, commercially available laboratory test to diagnose the platelet storage pool deficiency. Commercially available tests, such as platelet counts and bleeding times, are of little clinical value[10] and are not recommended. In some academic medical centers, it is possible to arrange to have platelet aggregation studies completed; however, the finding of abnormal aggregation is not pathognomonic for HPS, nor is the finding of normal aggregation proof of its absence. Physicians can pursue formal electron microscopic testing for the presence of platelet-dense granules by contacting the HPS Network (www.hpsnetwork.org).

When possible, it is beneficial for the primary care physician to seek the consultative assistance of a hematologist.

Treatment requires a thoughtful and systematic approach related to the site and the severity of bleeding:

- **Cutaneous.** Episodes of bleeding in patients with HPS associated with simple trauma to the skin can almost always be managed with application of pressure, using gauze moistened with either water or a petroleum-based jelly. Conform and self-adhesive stretch bandages (such as Medi-Rip [Hartmann-Conco, Rock Hill, SC] and Ace [3M, Maplewood, MN]) can be used as an alternative to applying manual pressure.

More extensive injuries to the skin and underlying tissues are most appropriately managed in an emergency department, with the consultation of a hematologist as appropriate. Careful suturing and occasionally platelet transfusion can play an important role in establishing hemostasis.

- **Dental.** Bleeding can occur with dental extractions, as well as dental cleanings that include vigorous manipulation of the gums. Again, local pressure is often the only necessary treatment. However, pretreatment with intranasal desmopressin (at the hemostatic dose, 150 μg/0.1 mL [1 spray], as available in the product, Stimate [CSL Behring, King of Prussia, PA]), can be beneficial.

There are a number of other potential therapeutic options, including suturing and topical application of a recombinant thrombin product.

- **Gynecologic and obstetric.** Menstrual bleeding for many women with HPS, without appropriate treatment, can be very disruptive, requiring them to miss school or work during the heaviest bleeding days of the month. Many women are not aware that menstrual bleeding can be addressed with medications, assuming that no pathology is present and the only issue is volume. There are 3 effective treatment options: oral contraceptives, progesterone-impregnated intrauterine devices, and aminocaproic acid. Dosing for aminocaproic acid is based on the site and severity of bleeding; generally, between 6 and 30 g are required per 24 hours.

Pregnancy should be categorized and managed as high risk because of the platelet storage pool deficiency and bleeding diathesis; the expert input of a hematologist is beneficial.[19]

- **Surgical.** Surgical procedures, whenever possible, should be planned well in advance, in consultation with a hematologist, as the risk of hemorrhagic bleeding associated with invasive procedures is high. General recommendations include the use of preoperative intravenous desmopressin, in a setting where the patient's vitals are monitored continuously, and having platelets "on hold" for the procedure in the event of hemorrhagic bleeding. As a general principle, and when practical, most procedures should be completed in-hospital with 24 hours of postoperative hematologic monitoring.

PAIN MANAGEMENT

Given the presence of the congenital platelet defect, it is important to be judicious in the treatment of pain, as many commonly prescribed and over-the-counter agents can affect platelet life span and function. A brief discussion of these classes of agents follows.

- **Salicylates.** Although aspirin is an effective agent for mild to moderate pain, in the United States it is

principally used as a platelet inhibitor in patients with known or suspected vascular diseases. A single dose of aspirin irreversibly inhibits its platelet function for the 8- to 10-day life span of a platelet.[20] As such, aspirin is not recommended for patients with HPS for pain relief and should be used judiciously under the close supervision of a knowledgeable physician for other medical indications, such as cardiovascular disease.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs).** Nonselective NSAIDs inhibit both cyclooxygenase-1 (COX-1) and COX-2 and, in single full doses, are generally found to be more effective analgesics than aspirin or acetaminophen. They also cause reversible inhibition of platelet aggregation that persist until the platelets are metabolized to near-elimination from the body. Therefore, nonselective NSAIDs are not recommended for patients with HPS.
- **Selective COX-2 NSAIDs.** Currently, the only selective NSAID available in the United States is celecoxib, which has been found to be more effective as an analgesic than placebo but less effective than full-dose ibuprofen or naproxen.[20] Celecoxib has not been shown to inhibit platelet aggregation or increase bleeding time and, therefore, is generally felt to be a safe and useful agent for patients with HPS. (Note that the US Food and Drug Administration advises caution in patients who have comorbid risk of thrombotic events, such as myocardial infarction and stroke.)
- **Acetaminophen.** Acetaminophen, at full doses, is less effective than the nonselective NSAIDs and has never been studied head-to-head against the selective COX-2 antagonist, celecoxib. Unlike aspirin and the nonselective NSAIDs, acetaminophen does not interfere with platelet function and, therefore, is recommended for patients with HPS, in the absence of contraindications.[20]
- **Opioids.** There are many opioid agents of varying efficacy used in the treatment of pain in the United States. There are no HPS-specific contraindications to the use of opioids or the opioid-related agent, tramadol, and in the absence of contraindications, they are recommended in the appropriate clinical settings.

ILD

As depicted in Table 1, patients with HPS-1, HPS-2, and HPS-4 are at risk for the development of a specific form of ILD, HPS-associated pulmonary fibrosis (HPS-PF).[21–23] There are many known causes of ILD[24]; HPS-PF is an example of a hereditary etiology in which discrete genetic mutations result in progressive fibrosis of the lung parenchyma and ultimate respiratory failure.

Based on published reports, patients generally first manifest symptoms of HPS-PF in middle age; however, anecdotal experience includes rare patients with HPS-1 beginning to develop ILD in late adolescence. The characteristic symptoms of HPS-PF are nonproductive cough and exertional dyspnea. Physical examination can reveal "dry" rales initially in the lower lung fields. With progression of disease, patients develop exercise-associated hypoxia, followed by hypoxia at rest, and diffuse rales.

Because the physical examination findings are characteristic, it is useful to document a lung examination at the first office visit, thereby establishing a baseline, and then with each subsequent visit. Pulse oximetry should be completed regularly beginning in adolescence and can include in the appropriate setting, in-office exercise-oxygen saturation monitoring; for instance, the 6-Minute Walk Test.

Diagnosis of HPS-PF is confirmed with high-resolution computed tomography (HRCT) scan of the lungs, using 1-mm cuts to allow close inspection of the interstitium. Characteristic changes include ground-glass opacities, reticulation of the interstitial spaces, scarring, and, with advanced disease, loss of lung volume and bronchiectatic changes. Pulmonary function tests (PFTs) show loss of lung volume consistent with a restrictive disease pattern (decreased total lung capacity and vital capacity and decreased diffusion of carbon monoxide). Interpretation of these results is most accurately completed with the assistance of radiology and pulmonology specialists. In general, in the presence of characteristic findings on HRCT and PFTs, and because of the risk of bleeding, diagnostic lung biopsy is not recommended.

Because symptoms can develop in late adolescence, it is useful to obtain a baseline HRCT at this time. Subsequent HRCT studies are indicated largely based on symptomology and should be reviewed by a radiologist familiar with classic early abnormalities of ILD. Annual PFTs (spirometry, lung volumes, and diffusion capacity) should commence in late adolescence as well, and be performed annually. Bronchoscopy has utility limited to the research community as of this writing. For instance, bronchoalveolar lavage fluid analysis has revealed a nonspecific lymphocytosis in related lung disorders.[24,25]

Counseling of individual patients should include the recommendation to avoid the use of all tobacco products.

Effective treatment of PF remains elusive but continues to be an area of active investigation. Recently, promising results have been published in several randomized, double-blinded, placebo-controlled studies regarding the transforming growth factor-β inhibitor, pirfenidone, for treatment of patients

with a related lung disorder, idiopathic PF, with subsequent approval for its use in Japan and Europe.[26–28]

After the diagnosis of HPS-PF, physician evaluations should include questions regarding the patient's functional status, focusing on exercise tolerance and the ability to perform normal daily activities. Early evaluation by a lung transplantation program is advised. In addition, where available, referral to a pulmonary rehabilitation program for patients with moderate to severe disease can be beneficial.

Life expectancy for patients with HPS is directly related to genetic subtype. With respect to HPS-1, 100% of patients will develop HPS-PF, usually in the third to fourth decades, succumbing within 3 to 10 years of diagnosis, in the absence of lung transplantation.

IBD

Patients with the HPS-1, -4, and -6 genotypes have developed HPS-IBD. Symptoms of HPS-IBD include crampy abdominal pain, fever, weight loss, malabsorption, and frequent watery and bloody diarrhea. Symptoms can first occur at any age, including early childhood, but are believed to be most common in adolescence and early adulthood. Pathologically, HPS-IBD has many of the same features as the more common Crohn's colitis: irregular involvement of the large bowel with regions of normal mucosal architecture, superficial crypt abscesses, and a prominent inflammatory cell infiltration in involved areas. Although the large bowel is the most common site of inflammation, patients may develop diseased regions throughout the length of the gastrointestinal tract.

Early involvement of a gastroenterologist in the care of patients with symptoms and signs suggestive of HPS-IBD is advised.

Treatment includes all of the therapies typically used in the management of Crohn's colitis. However, the use of compounds with 5-aminosalicylic acid is an area of controversy because of the HPS platelet storage pool defect.

Surgical interventions for HPS-IBD are best reserved for patients with disease clearly refractory to medical treatment. When surgery becomes necessary, a goal should be to preserve as much colon as possible.

MENTAL HEALTH ISSUES

It is well documented that patients living with chronic disabling health conditions are at increased risk for clinical depression, anxiety disorders, and substance abuse disorders.[29,30] HPS caregivers recognize the chronicity and severity of many of the health issues associated with the disease, the risk of developing HPS-PF for patients with HPS-1, HPS-2, and HPS-4; the abbreviated life span in these same populations; and the challenges associated with living with diminished visual acuity and bleeding symptoms. Therefore, patients with HPS are very likely at increased risk for mental health issues, although this has not been independently documented. The physician caring for the patient with HPS should survey for signs and symptoms attributable to mental health issues.

ADVANCE DIRECTIVES AND ASSOCIATED ISSUES

As with any patient, at the appropriate time in the clinical relationship between the physician and the patient with HPS, it is important to address issues related to end-of-life care. It is reasonable for the physician to assume that the patient with HPS, through Web-based resources, including social media directed to the HPS community, is aware of the potential for developing life-threatening complications of HPS, including PF. Therefore, the typical patient with HPS is likely to welcome a frank yet supportive conversation about end-of-life issues, including the completion of a Health Care Proxy, Living Will, and the like.

CONCLUSIONS

HPS is a rare congenital disorder associated with biallelic mutations in 1 of 9 distinct genes. The classic clinical dyad of HPS is OCA and a platelet storage pool defect. Other manifestations include HPS-IBD and HPS-associated ILD.

The physician caring for the patient with HPS has the dual challenges of providing excellent health maintenance and guidance, as for any patient, plus addressing the specific phenotypic manifestations of the HPS mutations.

Resources available to the physician caring for the patient with HPS include a growing body of literature, both basic and clinical, and the HPS Network, which functions as a clearinghouse for patients, families, and physicians involved with the HPS community.

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