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Review Article

The Eye in the Hermansky-Pudlak Syndrome: A Literature Review

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Abstract

Introduction: The Hermansky-Pudlak syndrome is an autosomal recessive disease characterized by oculo cutaneous albinism, a bleeding diathesis and lysosomal accumulation of ceroid lipofuscin.

Objectives: To do a comprehensive literature review of the clinicopathological findings in patients with the Hermasnky-Pudlak syndrome, its diagnosis, management, and treatment.

Methods: A literature review of the Hermansky-Pudlak syndrome was done.

Conclusion: Patients with the various genotypes leading to the Hermansky-Pudlak syndrome have multiple ocular and systemic manifestations with extensive genotypic and phenotypic variability. Co-management between Primary Physicians, Ophthalmologists, and other sub-specialists is of outmost importance. Patients' co-management must be customized individually, taking into account patient's end goal, comorbidities, and bleeding diathesis. Genetic testing and counseling is of outmost importance in patients with the syndrome.

ABBREVIATIONS

HPS: Hermansky-Pudlak Syndrome; OCA: Oculocutaneous Albinism; BCVA: Best Corrected Visual Acuity; OCT: Optical Coherence Tomography

INTRODUCTION

The Hermansky-Pudlak syndrome (HPS) was first described in 1959 [1]. Patients with the syndrome have a triad including: atyrosinase-positive oculocutaneous albinism (OCA); accumulation of a ceroid-like material in body tissues; and bleeding diathesis [1,2]. Other manifestations that have been described in patients with the syndrome include: interstitial pulmonary fibrosis; inflammatory bowel disease, and renal failure [1-7]. The pathogenesis of thesyndrome involves abnormalities in the biogenesis and function of lysosome-related organelles [4].

Although a rare condition worldwide, HPS has a higher prevalence in Puerto Rico, and patients with Puerto Rican descent [8-10]. The HPS is inherited as an autosomal recessive trait. Nine genetically heterogeneous subtypes have been described [10]. The loci, ocular and systemic manifestations found in patients with the syndrome are summarized in Table (1).

HPS type-1 is the most common form of albinism found in Puerto Rico [10]. It is more prevalent in the northwestern region of the Island [10]. On the other hand, the HPS-type 3 mutation was found in the geographically isolated mountainous regions of the Island. The HPS-type 2 is more prevalent in Asia.

Herein, we present a literature review of the most common ocular and systemic manifestations of patients with the HPS, diagnosis, co-management, and treatment.

DISCUSSION

The diagnosis of HPS consists of clinical findings of OCA with a variable degree of bleeding diathesis. The medical community should be aware of the genotypic and phenotypic variability of individuals affected by the HPS as it has important prognostic and treatment implications.

Epidemiology

HPS is inherited as an autosomal recessive pattern affecting approximately 500,000 to 1,000,000 of patients worldwide [10,11]. At least nine subtypes of HPS have been described, each with unique signs and symptoms, and extensive locus heterogeneity [10,11].

The mutation leading to HPS type 1 (HPS-1) is the most common subtype with the highest prevalence seen in the northwestern part of Puerto Rico affecting almost 1 out of 1,800 individuals [11]. However, a patient with the HPS-1 has also been identified in other patient populations including: Japanese;

Table 1: Genetics and clinical manifestations of HPS subtypes [6].

Subtype and Gene	Location	Presentation	Counseling Principles	Management
HPS-1	10q24.2	Hypo pigmented hair and skin with increased incidence of pulmonary fibrosis and granulomatous colitis	80% die 4th- 5th decade due to pulmonary disease	Assess lung function tests and GI complains
HPS-2 AP3B1	5q14.1	Frequent infections due to defects in innate immunity		Distinguish from Chediak-Higashi syndrome
HPS-3	3q24	Milder form with less bleeding diathesis and hypopigmentation. No pulmonary involvement	Colitis is rare	Assess GI complains
HPS-4	22q12.1	Similar to HPS1.	Similar to HPS1	Assess lung function tests
HPS-5	11p15.1	Milder phenotype similar to HSP3 without systemic involvement	Similar to HPS3	
HPS-6	10q24.32	Similar to HSP3 and HPS5	Similar to HSP3 and HPS5	
HPS-7 DTNBP1	6p22.3	OCA with bleeding diathesis with no pulmonary involvement.		
HPS-8 BLOC1S3	19q13.32	Mild phenotype with minimal systemic complications.		
HPS-9 (BLOC1S6 gene)	15q21.1	No systemic abnormalities have been described to date		

Indian; Swiss; African Americans; and other Hispanics [12-16]. Although thought to be under diagnosed, 100 cases have been reported in the United States [17].

Central Puerto Rico has the highest incidence of patients with the mutation leading to the HPS type 3 (HPS-3), followed by Ashkenazi Jews population [8,18]. Other mutations leading to the HPS are extremely rare.

Ocular Findings in patients with the Hermansky-Pudlaksyndrome include

Vision: Patients with the HPS have been shown to have a decreased best-corrected visual acuity (BCVA) in multiple studies [2,6,8,9]. One study [8] reported the BCVA ranges between 20/50 to 20/200 in patients with the HPS. Sixty-eight percent (68%) of these patients were legally blind. Jardón and co-workers suggested that patients with the HPS-1 mutation have a poorer BCVA when compared to patients with the HPS-3, thus demonstrating a variable expression of visual acuity mid the various subtypes of the HPS [9].

Color vision deficiencies, not associated with sex chromosomes, have also been described in patients with the syndrome. Mild red-green deficiency was the most common color deficiency found in patients with the HPS-1 and HPS-3, upon evaluation with the HRR pseudoisochromatic plates [9,19].

Refractive errors: Patients with the HPS have a variety of high refractive errors [8,20]. The most common refractive error found in patients with the HPS is astigmatism, followed by myopia. [8,20]. Some authors [8,21,22] have suggested that astigmatism in this patient population may be explained by horizontal nystagmus and/or as a consequence of persistent eyelid squeezing secondary to photophobia. Further, high astigmatism may become amblyogenic in patients with the syndrome.

Poor visual acuity and refractive errors are usually corrected with spectacles, tint glasses, photochromic lenses, and cosmetic contact lenses [23]. Low vision rehabilitation aids in patients with OCA have been traditionally used with good results [24]. Van Rijn and co-workers reported on the use of iris-fixated phakic intraocular lenses for refractive errors management in patients with OCA [25]. Further studies on the use of this technique on patients with the syndrome are warranted.

Strabismus: Strabismus is a common finding in patients with all types of OCA. Studies have shown a higher incidence of esotropia in patients with the syndrome (type 1 and type 3) [2,3,8]. Jardón and co-workers reported a higher incidence of esotropia in patients with the HPS-1 and exotropia inpatients with the HPS-3 [9].

Gradstein and co-workers reported that 50% to 64% of patients with the syndrome who undergo strabismus surgery may remain with deviation [26]. Izquierdo and co-workers [27] suggested that surgical muscle recession and/or resection amount should be decreased by 0.5 mm on each eye to prevent overcorrection in patients with the syndrome. Davis and co-workers reported improved visual acuity and decreased refractive errors in patients with OCA and HPS who underwent strabismus surgery [28]. The decision of strabismus surgical correction must be evaluated in an individual basis taking into account patient' send goal, comorbidities such as: pulmonary fibrosis, and bleeding diathesis.

Nystagmus: Congenital nystagmus is often the reason for seeking medical evaluation in patients with the HPS. Izquierdo and co-workers reported that 97% of patients with the syndrome (both type 1 and 3 included) have periodic alternating nystagmus [8]. A study by Gradstein [26] concluded that patients with the syndrome and without clinical evidence of nystagmus

have decreased iris Tran's illumination, less macular hypo pigmentation, and better BCVA when compared with patients with clinically evident nystagmus.

Nystagmus found in patients with OCA may have similar characteristics to patients with infantile idiopathic nystagmus [29]. According to Kumar and co-workers, genetic testing may help in the differential diagnosis between OCA related nystagmus and Idiopathic infantile nystagmus. Their study compared nystagmus characteristics between infantile nystagmus with the FRMD7-IIN mutation and patients with albinotic phenotype in order to elucidate the underlying mechanism. In contrast, other studies [30], reported that patients with albinism had more jerk waveforms compared to a higher proportion of pendular waveforms in the FRMD7. These findings suggest different mechanisms between the two groups. Further studies should evaluate the relationship between genotype variability with the type of nystagmus found in patients and thus reach an accurate diagnosis.

Anterior segment: The most characteristic anterior segment finding in patients with the HPS is iris transillumination defects. Iris hypopigmentation and transillumination defects vary among patients with the various HPS subtype [6]. Patients with HPS-1 have iris hypo pigmentation and increased iris transillumination defects than other HPS subtypes. A recent study reported an improvement in iris pigmentation of mouse homozygous to OCA-1B gene mutation with the use of nitisinone, an inhibitor of tyrosine degradation [31]. This promising approach may decrease photophobia in patients with HPS. Further clinical trials on this treatment are warranted.

Other anterior segment findings in patients with HPS may include: posterior embryotoxon; Axenfeld anomaly; and elevated intraocular pressure [8]. Izquierdo and co-workers suggested that patients with the syndrome have cataract formation at an earlier age [8]. Early cataract formation in patients with the HPS may be explained by the use of glucocorticoids in the management of systemic manifestations of the syndrome, and/or ultraviolet phototoxic effect on the lens with patients with the syndrome [8]. Dávila and co-workers [32], reported a statistically significant improvement in both BCVA and astigmatism in patients with HPS-1 who underwent phacoemulsification and intraocular lens implantation.

Using clear corneal incisions [33], pre-placed sutures, intraoperative irrigation with cold normal saline or epinephrine are some techniques have all been reported to help decrease the incidence of intraoperative bleeding in these patients [8].Topical anesthesia with intravenous sedation and general anesthesia are preferred to retrobulbar block to help prevent retrobulbar bleeding in patients with the syndrome [8].

Posterior Segment: Foveal hypoplasia, macular underdevelopment and abnormal retinal pigmentary epithelium have all been described in patients with the HPS [2,8-10,19,20,26,29,34]. Studies have shown that genetic variability plays a role in the degree of macular transparency [9,34].Patients with the HPS-type 1 patients appear to have increased macular transparency when compared to patients with the HPS-type 3 mutation [9,34]. Emanuelli and co-workers [35] have reported that patients with the syndrome show an increased foveal thickness with lower macular volumes when compared to the general population.

Neurophthalmology: Albinism has also been associated with abnormal decussating of the visual pathway. According to Jeffery [36] this abnormal decussating is thought to be due to defects in retinal melanin synthesis. A study comparing foveal hypoplasia in patients with albinism versus patients with aniridia showed that although caused by different mutations, both affect central retina development [36]. However, patients with aniridia did not have an abnormal chiasmal decussation. These findings suggest that foveal hypoplasia is not the definitive cause of abnormal decussation seen in patients with albinism [37].

Extraocular manifestations: Patients with the HPS can develop a wide array of systemic complications. The severity and type of manifestation is influenced by the patient's genotype. The most common systemic manifestations of patients with the syndrome include: bleeding diathesis [1]; restrictive pulmonary fibrosis [4]; granulomatous colitis [5]; and skin malignancies [38,39].

Bleeding diathesis is a major cause of morbidity and mortality in patients with the HPS [40-42]. Bleeding tendencies are attributed to decreased platelet dense bodies and platelets aggregation dysfunction. Bleeding diathesis may complicate surgical management in this patient population. A hematology consultation is recommended in patients with the syndrome prior to surgery. Córdovaand co-workers [43] found poor response with the use of preoperative desmopressin in HPS patients and concluded that platelet transfusion may be useful to prevent surgery-related bleeding.

Pulmonary fibrosis remains the most common cause of mortality in patients with some subtypes of the HPS. As shown in Table 1, pulmonary fibrosis has been associated in patients with the HPS-1 and HPS-4. Almost eighty percent (80%) of patients with HPS-1 die from lung disease during their fourth or fifth decade of life and is it considered its major complication [6]. Pulmonary fibrosis is due to deposition of ceroid-lipofuscin within the lungs instertitium [4].Recent clinical trials using pirfenidone have shown to decrease pulmonary fibrosis progression in selected patients. However, pulmonary transplant remains as the only definitive treatment to date in patients with the syndrome [4]. Co-management with pneumologists may benefit patients with the syndrome, both for follow-up and prior to surgeries under general endotracheal anesthesia.

Granulomatous enterocolitis affects up to 20% of patients with the syndrome. It has a higher prevalence in patients with HPS type 1 [5,6]. The underlying mechanism is thought to be a reaction to the abnormal deposition of ceroid-lipofuscin in colonic mucosa [5]. This type of enterocolitis typically has poor medical response to sulfasalazine and steroids commonly used in other types of enterocolitis [5].

Genetics: Table (1) summarizes the genetic loci associated to the various sub-types of syndrome. Almost 75% of the patient isolate population in northwestern Puerto Rico carry a 16 bp duplication on the HPS1 gene on chromosome 10q23[44]. On the other hand, 45% of affected individuals of non-Puerto Rican

ancestry have other mutations in the same gene (10).Mutations in this gene as well as the HPS-4 are associated with the most severe form of the disease and have been associated with pulmonary fibrosis (6, 45). The gene codes for proteins products associated with lysosome-related organelles complex-3 (BLOC-3) responsible for adequate cellularprotein transportation.

Both HPS1 and HPS3 have been linked to a founder mutation in northwestern and central Puerto Rico, respectively [44]. Other HPS3 mutations have been implicated in subtypes of HPS3-disease in non-Puerto Rican patients. Other types of HPS are rare and present with a less severe form of disease. New molecular findings suggesting genetic heterogeneity increase the molecular platform for screening and diagnosis with important implications in prognosis and treatment. A recent study done in Puerto Rican newborns showed that the increase in HPS-3 carrier allele frequency justifies universal screening for this population [46].

As shown in Table (1), the extent and severity of the ocular and systemic manifestations associated with the syndrome vary considerably between subtypes and.

DIAGNOSIS

Clinical Diagnosis

Clinical findings including: a phenotype of OCA, with a variable degree of bleeding diathesis, may lead health providers to reach a diagnosis [47].

Findings in patients with OCA comprise: a variable degree of hair and skin hypo pigmentation on physical examination; ocular findings as described above; physical examination and radiological findings suggestive of pulmonary fibrosis (in patients with HPS subtypes 1 and 4).

Ancillary testing

Several tests are used to confirm the HPS diagnosis including: hairbulb incubation test to evaluate for tyrosinase positive OCA [44]; Electron Microscopy to show absence of dense granules; prolonged bleeding time with normal platelet count and coagulation factors activity.

Molecular genetic testing

Molecular genetic testing may include the analysis of a single gene, pathogenic variants of common known HPS genes, multi gene panels, and genomic testing. For patients of Puerto Rican descent, first molecular studies should focus on the two founder mutations of HPS1 and HPS3 [44,48]. For other patients, molecular studies should first focus on the pathogenic variants associated with the most common genes [44]. The severity of ocular findings as well as systemic involvement may help to elucidate the course of molecular testing [44]. A recent study used microsatellites for rapid autozygosity mapping [49], while another study done by Nazarian et al., used skin fibroblast cell extract with protein analysis in order to determine protein complex defects [50]. This helped in the molecular diagnosis by narrowing down the possible causative gene mutation [50].

Treatment and management

The type and severity of the disease have strong implications on the treatment and management modalities and are presented in Table (2).

Table 2: Treatment modalities in patients with the Hermansky-Pudlak syndrome.

Manifestation	Treatment
Bleeding Diathesis	Platelet transfusion Desmopressin acetate
Pulmonary Fibrosis	Lung transplant Pirfenidone
Strabismus	Correction Surgery
Cataract	Phacoemulsification and intraocular lens implantation
Refractive Errors	Corrective spectacles Tint glasses Photochromic lenses Cosmetic contact lenses Low vision rehabilitation aids Intraocular lenses

CONCLUSIONS

Patients with the Hermansky-Pudlak syndrome seek ophthalmic evaluation due to their congenital ocular findings leading to sensorial disabilities. Ophthalmologists remain an important health provider in the co-management of patients with the syndrome. Ophthalmologists may contribute by referring patients to other knowledgeable sub-specialists including: hematologists; pneumologists; gastroenterologists; and gynecologists. Further, ophthalmologists may aid primary physicians to reach a diagnosis in patients with the syndrome. Hematology evaluation is recommended prior to ophthalmic surgery. Genetic evaluation and counseling may benefit patients with the syndrome. A multi-specialty team co-management may benefit patients with the Hermansky-Pudlak syndrome.

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