

Hermansky–Pudlak Syndrome: Dental Management Considerations

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ABSTRACT

Hermansky-Pudlak syndrome (HPS) is an autosomal recessive disorder characterized by oculocutaneous albinism (OCA), platelet dysfunction, and ceroid storage. It is common among the Puerto Rican population and is expected to spread within the United States and other countries. Due to the platelet deficiency, these patients are of major concern to pediatric dentists. The purpose of this article is to explain in detail the characteristic triad of this syndrome and to propose an adequate approach to perform dental treatment, using appropriate protection recommendations for HPS patients. Recommendations for dental treatment are considered. They include the use of: (1) eyeglasses with 99 UV filter to protect them from the unpleasant dental light stimulus; (2) an extra-soft toothbrush and conservative brushing technique; (3) medication with antifibrinolytic agents; and (4) local measures to achieve hemostasis. (*J Dent Child* 2006;73:51-56)

KEYWORDS: HERMANSKY-PUDLAK, PLATELET DYSFUNCTION, BLEEDING TENDENCY, ORAL BLEEDING, OCULOCUTANEOUS ALBINISM, CEROID ACCUMULATION

Generalized hypopigmentation may be present in several albinoid syndromes, such as phenylketonuria (PKU). Oculocutaneous albinism, on the other hand, can be divided into tyrosinase-negative and tyrosinase-positive albinism. Hermansky-Pudlak syndrome (HPS) and Chediak-Higashi disease belong to the tyrosinase-positive group.

HPS is a group of complex disorders, characterized by oculocutaneous albinism, bleeding tendency, and lysosomal ceroid storage, resulting from defects of multiple cytoplasmic organelles (melanosomes, lysosomes, and platelet dense bodies). In 1959, it was originally identified in Czechoslovakia in 2 patients by Drs. F. Hermansky and P. Pudlak.

The first patient was a 33-year-old farmer who developed chronic interstitial pulmonary fibrosis. Since then, it has been identified in people in nearly every country around the world.²⁻⁶

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HPS is rare, but it is common among the Puerto Rican population, where it occurs in an estimated frequency of 1/1,800 persons. It is also frequent in an isolated Swiss Alps village. These 2 populations were instrumental in mapping the gene HPS1 to 10q23.^{8,9} The gene encodes a 700-amino acid polypeptide that contains 2 apparent transmembrane domains but has no evident homology to any other known protein.¹⁰

More recently, several mutations have been identified. HPS-2 is caused by mutation in the gene encoding the beta-3A subunit of the heterotetrameric AP3 complex, which resides in chromosome 5.^{5,11,12} This coat protein complex has been localized to the trans Golgi network, as well as to a peripheral endosomal compartment. Evidence indicates that AP3 plays a role in the stepwise process of vesicular trafficking, which leads to formation of the melanosomal, platelet dense body and lysosomal compartments.^{5,11} Anikster et al used homozygosity mapping on the pooled DNA of 6 families from central Puerto Rico to localize the HPS-3 gene to a 1.6-cM interval on chromosome 3q24. These patients only present ocular albinism, and the melanin component of the skin is normal, thus not presenting the typical phenotype, and may be difficult to identify clinically. Other mutations identified are HPS-4, HPS-5, and HPS-6, as reported by Zhang et al.¹³⁻¹⁵

The so-called process of globalization may contribute to the spreading of the syndrome throughout the world, especially the continental United States. It is presumed that constant migration of carriers and patients presenting this condition in any of its expressions might be expected. Sentinel events like circumcision, dental eruption cyst, teething, natural shedding of teeth, or trauma may sometimes be the first consideration for the diagnosis. On the other hand, fatal bleeding following tooth extraction has been reported in these patients.¹⁶ Thus, it is the responsibility of every dentist to know how to deal with this condition properly in order to render the appropriate dental treatment without submitting these patients to inappropriate risks.

The purpose of this article is to explain in detail the characteristic triad of this syndrome and to propose an adequate approach to perform dental treatment, using appropriate protection recommendations for HPS patients.

OCULOCUTANEOUS ALBINISM (OCA)

This typical phenotypic characteristic is defined as deficient pigment and may present various expressions. Tyrosine is the essential substrate of tyrosinase, required for the formation of melanin within the pigment organelles (melanosomes) of melanocytes. An impairment in this mechanism causes hypopigmentation of the skin and hair and visual problems like blindness, photophobia, strabismus, nystagmus, and others.^{7,17} Generally, the less melanin pigment in the iris and the retina, the less quality of vision. The central vision is affected, causing myopia, while the peripheral vision remains unaffected. There is a translucent iris with reduced retinal pigment and foveal hypoplasia with significant reduction of visual acuity, usually in the range of 20/100 to 20/400.¹⁷

HPS-3 patients do not necessarily present with the typical skin and hair hypopigmentation. The major clinical finding may be the ocular albinism (OA), with the consequent characteristic of nystagmus, photophobia, and blindness.¹⁸ This type presents a challenge to pediatric dentists, since they are usually diagnosed during adolescence and may not be identified clinically.¹⁸

PLATELET DYSFUNCTION

The platelet count appears to be within normal range, but the platelets' function is impaired. Therefore, mucocutaneous bleeding is expected. Nasal, oral, vaginal, and rectal bleeding may be present.¹⁸⁻²⁰

The bleeding diathesis is related to a storage capacity deficiency of the dense bodies in platelets,^{19,20} which can cause these structures to be absent or empty. ADP, serotonin, ATP, and calcium are chemical substances normally stored in these granules. As a result, platelets do not show irreversible secondary aggregation when stimulated. This deficiency produces hemorrhagic episodes in affected individuals, which leads to easy bruising, hemoptysis, epistaxis, gingival bleeding with brushing or dental extraction, and postpartum bleeding.^{16,18} The amount of prolonged bleed-

ing varies in individuals from very mild to life threatening. Bleeding problems may be HPS' most important aspect that concerns the dental profession.

Standard laboratory blood test results are usually within normal limits in HPS patients, as expected in conditions where platelet function is impaired.^{22,23} Prothrombin time (PT), partial thromboplastin time (PTT), and platelet counts are within normal values in most of the cases. Bleeding time is often prolonged, but may be within normal range in mild cases. Examining prepared platelets under electron microscope and identifying the lack of dense bodies are currently the only definitive diagnostic tests for HPS.²¹ So far, multiple HPS models have been identified in mice.¹³⁻¹⁵ Nevertheless, since all of the genetic variants in mice have not yet been identified in humans, diagnosis through molecular analysis is not comprehensive and sentinel events may sometimes be the first consideration for the diagnosis.

CEROID ACCUMULATION

There is storage of ceroid-like material in the lysosomes.²⁴⁻²⁶ A type of dolychol increases in concentration and accumulates primarily in lysosomes as free alcohol and its fatty acid esters. The primary functions of the phosphate esters are to serve as carbohydrates in N-linked glycoprotein biosynthesis.²⁶ Dolychol and its derivatives also function in glycosyl phosphatidyl inositol anchor biosynthesis and have been suggested to have a role in modulating membrane properties. Dolychol biosynthesis branches from the pathway for cholesterol biosynthesis at farnesyl diphosphate, which also serves as a precursor to other essential metabolites such as ubiquinone and prenylated proteins.²¹ The accumulation of this ceroid material may cause dysfunction in some organs like the intestines, lungs, and kidneys. Patients with this syndrome may present pulmonary fibrosis,²⁷ granulomatous enteropathic disease, and renal failure.²⁸

The ceroid accumulation may manifest in different organs. In the mouth, mild fibrotic gingival enlargement may be observed. This manifestation was reported after an oral mucosa biopsy, where histologic and autofluorescence studies revealed findings consistent with a ceroid-like lipofuscin storage.²⁹ There may also be cardiomyopathies, diabetes, inflammatory bowel disease, pulmonary fibrosis, and renal failure.^{12,28,30} The accumulation of ceroid is associated with an inflammatory response in the lungs, which eventually scars the lung tissue—causing it to lose its ability to expand and contract while breathing. The pulmonary fibrosis is the most common cause of death in HPS patients.²⁷

PEDIATRIC DENTAL AND MEDICAL CONSIDERATIONS

It has been proposed that every person with albinism and bleeding tendency should be evaluated by the hematologist and that the diagnosis of HPS should be considered.³⁰

Table 1. Hermansky–Pudlak Syndrome Classic Triad Occulocutaneous Albinism (OCA)

Occulocutaneous albinism (OCA)	Platelet dysfunction	Ceroid accumulation
Deficient pigmentation Many present various expressions Skin and hair hypopigmentation Translucent iris only (OA) Blindness, otophobia, myopia, strabismus, nystagmus, etc	Impaired platelet function Mucocutaneous bleeding Deficiency of storage capacity of dense bodies Prolonged bleeding time PT, PTT, platelet count within normal range	Storage of ceroid-like material in lysosomes Dysfunction of lungs, kidneys, and intestines Inflammatory response in lungs causing pulmonary fibrosis Fibrotic gingival enlargement, cardiomyopathies, and diabetes

Table 2. Treatment Recommendations for Patients With Hermansky–Pudlak Syndrome

Systemic	Local dental measures
Nasal packing for nose bleeding Vaseline gauze and pressure on cuts Prevention on URT (STANDS) Vaccines Skin protection Protective eyeglasses with 99% UV filter Antifibrinolytics for dental appointments as indicated	Strong prevention program; 3-month recall interval Soft dental brush and conservative brushing Local pressure at area of surgery Oxidized regenerated cellulose (Surgicel) Absorbable gelatin sponge (Surgifoam) Topical thrombin Fibrin seal (Tisseal VH)

Though several HPS-causing genes have been identified, it is premature to genetically diagnose all HPS cases. Early diagnosis is an important factor in the prevention of emergency episodes.

Unfortunately, standard blood tests like PT, PTT, and platelet count usually do not identify the platelet defect in HPS.^{20,21} Also, the family history may be negative in many cases. On the other hand, prolonged bleeding time may suggest a platelet disorder or von Willebrand disease. For the correct diagnosis, the platelets must be examined under an electron microscope.²¹ The dense bodies may be found to be decreased, absent, or empty.^{19,20} A high index of suspicion must be kept in patients with the clinical findings previously described.

HPS patients usually need eyeglasses to improve their impaired vision.¹⁷ In the dental environment, the use of the direct light for proper vision while administering dental care should be used with caution because of the photophobia they present.^{5,17,18} The use of protective eyeglasses with a 99% UV filter may be a useful alternative to protect them from the unpleasant light stimulus. These are also used for sunlight protection.

Even though these patients are not mentally retarded, their improper vision may affect the development of visual dependent skills. This should be taken into consideration when deciding on the behavior management approach in the dental environment. Adequate familiarization with the dental environment and equipment are of primary importance. Also, the use of protective stabilization is not recommended and should be avoided, as in other bleeding disorders.²³

Due to the platelet deficiency, the provision of high quality dental care presents a challenge for the pediatric dentist.³¹ To avoid risks, consultation with hematologist is mandatory.^{32,33} With improvements in dental care protocols and surgical procedures, the risk of excessive bleeding as a re-

sult of dental procedures should be minimal, particularly if they are well prepared and treated beforehand.³⁴ Also, a strong prevention program is of primary importance.³⁵ These patients should be recalled every 3 months, and reinforcement in oral hygiene methods should be given.

An extra soft toothbrush is recommended, and a proper, conservative brushing technique should be implemented to avoid gingival bleeding. For dental appointments, medication with antifibrinolytics like aminocaproic acid (80-100 mg/kg) is suggested, starting 1 hour before intervention and for 3 to 4 doses thereafter.³⁶⁻³⁸ The use of desmopressine is not recommended for standard dental care because response to this drug is inconsis-

tent.³⁰ In some cases, platelet transfusion may be needed, especially in cases where invasive procedures are needed. The hematologist's recommendation on the use of this medicament must also be considered.

Alternate methods of achieving hemostasis have been proposed. The use of local hemostatic techniques combined with systemic therapy has been effective in controlling the bleeding problems in oral surgical procedures.³⁶⁻³⁸ In Europe, the use of a mouthwash with 10 ml of 4.8% solution of tranexamic acid for 2 minutes, 4 times a day, has proven to be effective in treating patients needing oral surgical procedures, without the modification of oral anticoagulant therapy.³⁹⁻⁴¹ The inability of children to swish and swallow may be a disadvantage in this technique.

The use of fibrin seal (Tisseal, Baxter Healthcare Corp, Glendale, Calif; Tissucol, Baxter AG, Vienna, Austria) as an agent for topical hemostasis has also been proposed.⁴²⁻⁴⁴ The fibrin seal is composed of 2 separate solutions of fibrinogen and thrombin. When mixed together, these solutions mimic the final stages of the clotting cascade to form a fibrin clot.⁴⁴ These products have been reported to successfully control bleeding in dental extractions and/or dentoalveolar surgery in high hemorrhagic risk patients,^{40,45} including those with hemophilia A and B.⁴²

In the United States, Rousou et al reported success in the use of fibrin sealant as a topical hemostatic agent in patients undergoing either reoperative cardiac surgery or emergency re sternotomy in 1989.⁴⁶ They reported that fibrin sealant had a 93% success rate at controlling bleeding within 5 minutes of application, compared to only a 12% success rate with conventional topical agents ($P<.001$). This product is currently used experimentally in rats.^{47,48} Also, autologous fibrin glue is being used in reconstructive maxillofacial surgery.⁴⁹

As an alternative, the use of local pressure in conjunction with a topical adjuvant is proposed to control bleeding when

dental extractions are performed in patients with mild cases of HPS. The use of oxidized regenerated cellulose (Surgicel, Becton Dickinson, Franklin Lakes, NJ), absorbable gelatin sponge for hemostatic use (Surgifoam, Johnson & Johnson Health Care Systems Inc, NJ), and topical thrombin are suggested.^{38,42} When possible, the fibrin sealant (Tisseal VH, Baxter AG, Vienna Austria) should also be seriously considered to avoid unnecessary systemic premedication in mild cases.^{38,42-45} Further experimentation is needed with these agents. In severe cases, systemic premedication with antifibrinolytic agents may be indicated in conjunction with the topical agents.⁴³ In severe cases, transfusion may also be needed for the substitution of dysfunctional platelets. This alternative should be coordinated with the hematologist in a hospital environment. The proposal of these local measures may significantly help protect the undiagnosed patients from unnecessary risks.^{43,44} The use of aspirin and nonsteroidal anti-inflammatory agents should be avoided in these patients.²² Acetaminophen is the drug of choice when analgesia is indicated.

CONCLUSIONS

Hermansky-Pudlak syndrome, first described in 1959, is a rare genetic condition that primarily affects the Puerto Rican population. It is expected to spread into the continental United States and throughout the world because of the globalization process and constant migration of the Hispanic population. The condition's 3 main characteristics are: (1) oculocutaneous albinism; (2) platelet dysfunction; and (3) ceroid accumulation. Platelet dysfunction is of major concern to the dental profession.

A protocol for dental treatment has been proposed to protect these patients from unnecessary risks. It consists of:

1. systemic medication with an antifibrinolytic agent;
2. the use of:
 - a. local pressure in conjunction with oxidized regenerated cellulose; and
 - b. absorbable gelatin sponge for hemostatic use; and
3. topical thrombin.

Also, experimenting with the use of a fibrin sealant should be seriously considered in these patients, due to its advantages. Nevertheless, platelet transfusion may be needed in some cases.

It is important for the dental profession to be aware of the appropriate standards of care for these patients. Caution should be taken in those cases in which the diagnosis has not been reached, especially in those whose phenotypical characteristics do not present albinism. It is of extremely important that pediatric dentists be aware of the correct dental care approach.

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