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Case Report

Hermansky-Pudlak Syndrome: Report of a Case and Review of the Literature

Matthew T. Hurford and Christopher Sebastiano

Department of Pathology and Laboratory Medicine, Temple University Hospital, Philadelphia, PA

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Abstract: Hermansky-Pudlak syndrome is a rare autosomal recessive disorder characterized by excessive bleeding post surgery. Here we reported such a case and reviewed the clinicopathological features and our current understanding of this rare congenital disorder.
Key Words: Hermansky-Pudlak syndrome, bleeding disorder, platelet

Introduction

Hermansky-Pudlak syndrome (HPS) was first documented in 1959 by two Czechoslovakian physicians, who described two albino adults in their fourth decades with severe bleeding and prolonged bleeding time [1]. Worldwide it is extremely rare, but in Puerto Rico it is found in five of every six albinos [2]. Approximately 1 in 1,800 persons in Northwestern Puerto Rico are affected making it the most common single-gene disorder amongst that population [2]. It is an autosomal recessive disorder characterized by prolonged bleeding with oculocutaneous albinism, a storage pool deficiency of platelets and lysosomal accumulation of ceroid lipofuscin. In this report, we described a case of HPS and reviewed the current literature.

Patient History

The patient is a 33 year old Puerto Rican male who presented at the age of 13 with severe bleeding associated with a tonsillectomy. He has a history of easy bruising, increased bleeding with minor cuts and increased persistent episodes of epistaxis. Over the years, he has undergone several surgical procedures including hernia repair, and tooth extractions, without significant bleeding associated with prophylactic platelet transfusions. He recently had severe bleeding associated with open lung biopsy for increased shortness of breath diagnosed as pulmonary fibrosis. The bleeding resolved with multiple transfusions of platelets and packed red blood cells. Physical examination demonstrated oculocutaneous albinism and nystagmus. There is no family history of albinism or easily bruising in the family. There is no clinical history of diabetes, cardiac disorder, gastrointestinal disorder or renal insufficiency.

Laboratory Data

The platelet count was normal (285 x $10^3/\mu L$). The bleeding time was prolonged (>15 minutes; normal 2-9 minutes). The APTT was mildly prolonged, 38.7s (normal, 25.2-36.0). The APPT mixing study corrected immediately at 34 seconds but prolonged to 36.7 seconds at 2 hours. The coagulation factors VIII, IX, XI and XII, vWF antigen and ristocetin cofactor were all normal. Serum anticardiolipin levels were increased for IgA (17.8 APL; normal < 13). IgG and IgM levels were normal. The TTI and DVVRT test were normal. The platelet function studies demonstrated a primary wave of aggregation without secretion to multiple doses of multiple agonists including ADP (2.5, 5.0 & 7.5 μM), epinephrine (2.5, 5.0, 7.5, 10.0 μM), arachdonic acid (50.0 μg/mL) and collagen (1.0 & 5.0 μg/ml) (see **Figure 1**). There was no secretion with 1 and 2 units/mL of thrombin. The response to two doses of ristocetin (0.5 & 1.2 μg/mL) was normal.

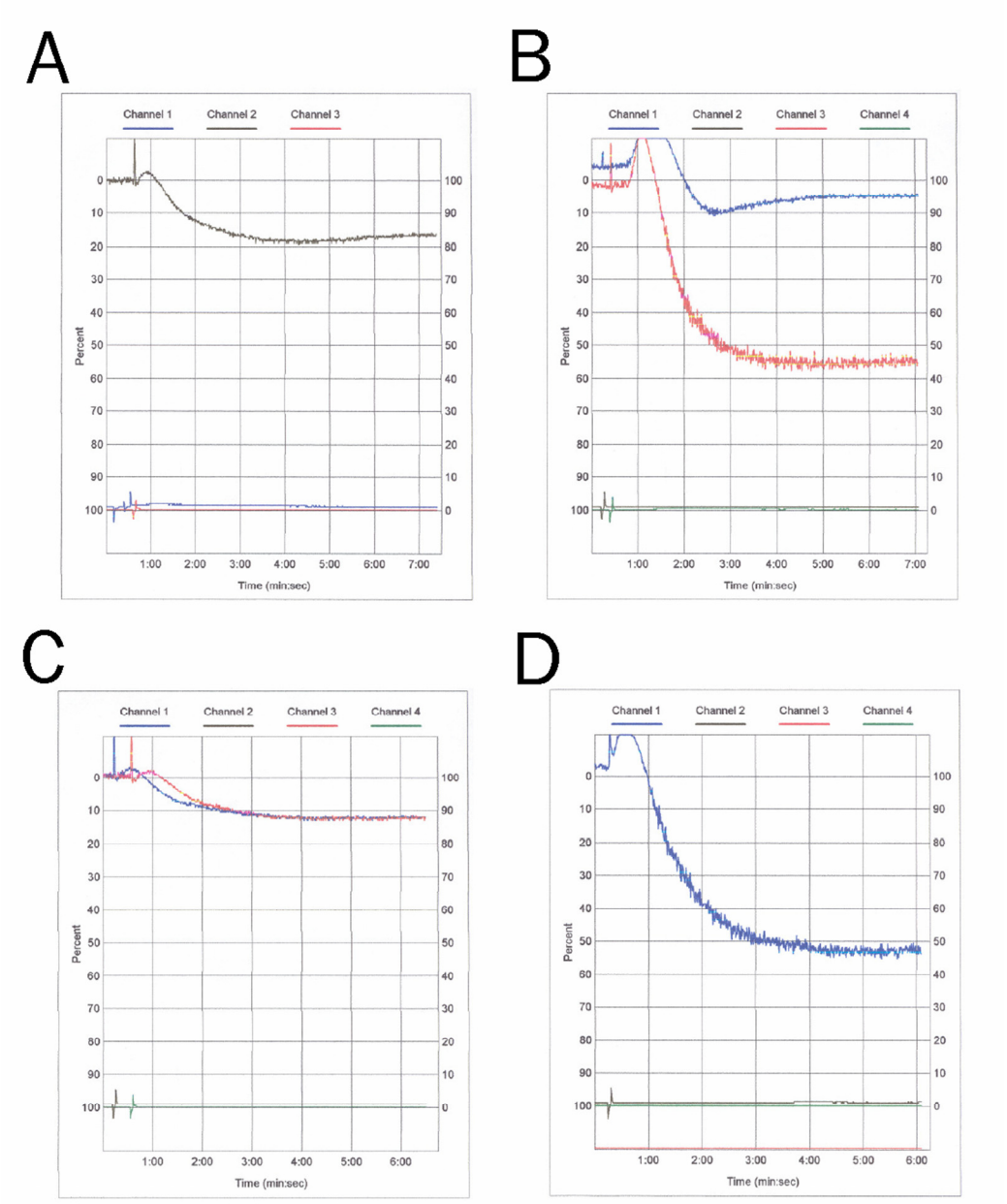

Figure 1 Tracings of platelet aggregation and ATP secretion in response to various platelet stimulatory agents. **A**. black, 2.5 μM ADP for aggregation; blue, 1 unit thrombin for ATP secretion; red, 2.5 μM ADP for ATP secretion. **B**. black, 1.0 μg/mL collagen for ATP secretion; blue, 1.0 μg/mL collagen for aggregation; red, 5.0 μg/mL collagen for aggregation, and aqua, 5.0 μg/mL collagen for secretion. **C**. black, 2.5 μM epinephrine for ATP secretion; red, 5.0 μM epinephrine for aggregation; blue, 2.5 μM epinephrine for aggregation and aqua, 5.0 μM epinephrine for ATP secretion. **D**. black, 50 μg arachdonic acid for ATP secretion; blue, 50 μg arachdonic acid for aggregation.

Clinical Features

Patients with HPS usually present in early childhood with easy bruisability of soft tissues, epistaxis and prolonged bleeding after dental extraction, surgery, or childbirth [3]. Women may present with medically significant menstrual bleeding. Oculocutaneous albinism is a defining aspect of the disorder but varies widely in the degree of hypopigmentation as well as correlation between retinal pigmentation and hair/skin pigmentation [3,

4]. As with other forms of albinism, patients typically have reduced visual acuity, often at or below the level of legal blindness, and usually exhibit horizontal nystagmus, sometimes with a rotatory component [4]. Complications of HPS may include reduced renal function, granulomatous colitis, pulmonary fibrosis and less likely neutropenia.

Genetics

The syndrome comprises eight known autosomal recessive disorders (HPS-1 to HPS-8) [5]. HPS-1 is the most common subtype. It is also the most common subtype found in most Puerto Rican patients [6]. The majority of the Puerto Rican patients demonstrate a homozygous 16 bp duplication in the HPS1 gene located on chromosome10q23 [4, 6]. This mutation is believed to be the result of a founder effect [4, 6]. This genotype represents the most severe of the known mutations and accounts for a high risk of pulmonary disease, hemorrhage, and granulomatous colitis, all of which may result in death [2]. Of the other subtypes, only HPS-4 approaches HPS-1 in severity [5]. The remaining subtypes are rare, and appear to be milder forms, with little risk of restrictive lung disease [5].

Pathology

HPS is a subtype of platelet storage pool deficiency (SPD), specifically δ-SPD. Platelet SPD is characterized by abnormally low contents of either platelet α granules, δ (dense) granules, or both. The dense granules store ADP, ATP, calcium and serotonin which trigger the secondary aggregation response of platelets. This disorder is associated with a bleeding diathesis and a prolonged bleeding time. The platelet function tests, generally demonstrate a normal primary aggregation in response to ADP and epinephrine [8]. The secondary response, however, is diminished or entirely absent due to the lack of δ (dense) granule content secretion required for aggregation of surrounding platelets [8]. Electron microscopy is necessary to observe deficient granule contents and to exclude secretion defects, which produces a similar pattern in platelet function assays [8]. However, an observed absence of dense body contents and abnormal platelet function tests in conjunction with the clinical presentation are sufficient to confirm the diagnosis of HPS [3]. δ-SPD is sometimes associated with Chediak-Higashi syndrome or Wiskott-Aldrich syndrome as well as HPS, but these diseases are clinically distinct from each other.

The signs and symptoms of HPS are related to various defects in protein trafficking resulting in dysfunction of lysosome-related organelles, which include melanosomes, platelet dense granules, and lamellar bodies of type II alveolar cells [5, 7]. The dysfunction of melanosomes accounts for the oculo-cutaneous albinism and visual impairments found in all HPS patients. The dysfunction of platelet dense granules accounts for the bleeding disorder which is usually the presenting complaint, and is perhaps the most well understood pathologically.

The pathogenesis of the pulmonary fibrosis which represents one of the greatest risks to HPS patients is less well understood. The underlying cause appears to be accumulation of ceroid lipofuscin which occurs systemically in HPS patients [3, 9]. It has been suggested that continual deposition of ceroid disrupts type II alveolar cells and leads to chronic inflammation and progressive fibrosis [9]. Ceroid deposition may also be responsible for the reduced kidney function and granulomatous colitis found in some patients, as these are amongst the sites where it is highest [3]. The dysfunction of lamellar bodies of type II alveolar cells is probably also a contributing factor. Histologically, these have been found to be degenerated and swollen by accumulation of surfactant in the lung tissue of HPS patients that died of pulmonary fibrosis (histologically identified as usual interstitial pneumonia), suggesting that this is either a triggering or at least contributing factor for its development [10].

Therapy and Prognosis

There is no known cure for HPS. The bleeding diathesis is a major concern during surgery, dental extraction, or childbirth and may be treated with transfusion of platelets or whole blood [4, 11] Desmopressin (DDAVP or 1-desamino-8D-arginine vasopressin,) may also be used prophylactically [12, 13]. Recombinant activated factor VII (VIIa) has also been reported in successfully shortening the bleeding time. Avoidance of aspirin products is essential. The visual acuity defects

that occur in tandem with the oculocutaneous albinism cannot be corrected, and the hypopigmentation itself leaves individuals susceptible to solar damage and skin malignancies [3]. Sunscreen and avoidance of sunlight are important measures for decreasing this risk.

Pulmonary fibrosis is the most serious complication. Pulmonary fibrosis usually presents in the fourth or fifth decade and it accounts for 50% of the morbidity [9]. Patients with HPS-1 or HPS-4 have the highest incidence of pulmonary fibrosis [5]. The only known treatment for pulmonary fibrosis is lung transplantation. To date only one successful bilateral lung transplant has been performed on a patient with HPS after platelet transfusion [14]. Pirfenidone, an antifibrotic agent, has been shown to slow the progression of fibrosis but only in patients who have significant residual lung function [15]. Steroid therapy is not an effective treatment [9].

In summary, HPS is a rare congenital bleeding disorder. Patients usually present with easy bruising and bleeding from epistaxis, dental extractions and obstetric or gynecological bleeding. Patients have an increased bleeding time and a normal platelet count with abnormal platelet function assays. Genetically, HPS comprises at least eight distinct and heterogeneous autosomal recessive genetic disorders (HPS-1 to HPS-8). HPS-1 is the most common subtype and the most common genetic disease amongst Puerto Ricans. It is also the most severe subtype and accounts for a high risk of pulmonary fibrosis, hemorrhage, and granulomatous colitis. Bleeding is managed by platelet transfusions. The most serious and life-threatening complication is pulmonary fibrosis, which generally presents in the fourth or fifth decade of life. Lung transplantation is the only current treatment for pulmonary disease.

Please address all correspondences to Mathew T. Hurford, M.D., Department of Pathology and Laboratory Medicine, Temple University Hospital, 3401 North Broad Street Philadelphia, PA 19140. Tel: 215-707-7740; Fax: 215-707-2053; Email: matthewh@temple.edu

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