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Bleeding Assessment in female patients with the Hermansky-Pudlak syndrome - A Case Series

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Keywords

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Introduction

The Hermansky–Pudlak syndrome (HPS) is a genetically heterogeneous group of autosomal recessive disorders characterized by: oculocutaneous albinism (OCA); bleeding diathesis; and other systemic complications including: chronic granulomatous colitis, and pulmonary fibrosis[1].

Despite HPS being a rare genetic disease worldwide, it is the most common single-gene disorder in the island of Puerto Rico (PR), particularly in the northwestern region, where it

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Author Contribution:

1- Joel Rivera-Concepción, MD JD- Conceived of the presented idea. Participated in patient evaluation and questionnaire administration. Took the lead in writing the manuscript

2- Jorge Acevedo-Canabal, MD- Verified the analytical methods. Supervised the findings of this work. Participated in patient evaluation and questionnaire administration.

3- Antonio Burés- Participated in patient evaluation and questionnaire administration. Provided critical feedback and helped shape the research, analysis and manuscript.

4- Gustavo Vargas- Participated in patient evaluation and questionnaire administration. Provided critical feedback and helped shape the research, analysis and manuscript.

5- Carmen Cadilla, PhD- Provided the genetic confirmation of the HPS patients

6- Natalio J. Izquierdo, MD- Supervised the findings of this work. Conceived of the presented idea.

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occurs with a frequency of 1:1,800 and where carrier frequency is estimated to be 1 out of 21 citizens[2]. HPS thus represents a significant public health issue in PR.[1,3]

Several HPS types with distinct genetic origins have been described. In PR, most patients have either the HPS genetic type 1 or type 3 variants.[4] It has been described that HPS type 1 exhibit severe forms of oculocutaneous albinism, bleeding diathesis and lethal pulmonary fibrosis. HPS type 3 are generally described with milder clinical symptoms than those with HPS type 1.[5]

In patients with HPS, platelets lack inherently electron opaque dense bodies. These are storage sites for substances that assist in blood clotting. This may explain the bleeding diathesis in patients with this syndrome. Previous studies have reported multiple skin bruises and increased bleeding times in patients with HPS.[6,7]

Some female patients with the syndrome have complained of menometrorrhagia during their monthly cycles[2], and a significant number them need gynecologic surgical interventions as treatment for abnormally abundant menstrual bleeding events. In addition, the use of prophylactic blood transfusion and desmopressin (DDVAP) before delivery has been reported in female patients with the syndrome.[8,9]

Previous case reports and review of literature have suggested the use of platelet transfusions, blood transfusions, DDAVP, avoiding nonsteroidal inflammatory medications and/or avoiding spinal or epidural anesthesia to control bleeding risk and events in patients with severe platelet function disorders.[7,10,11]

Developing definitive guidelines for bleeding management for this population remains a challenge due to the scarcity of HPS patients worldwide.

To the best of our knowledge no prior studies have been conducted to assess the hematologic and gynecologic bleeding events in the HPS population. For this reason, we attempt to identify these events in HPS types 1 and 3 through a comprehensive and validated questionnaire (ISTH-BAT).

Methods and Subjects

This case series report involves female adult patients who were diagnosed with Hermansky Pudlak using genetic analysis. They were selected from medical records of a private ophthalmology clinic in San Juan, PR. Inclusion criteria were: females with HPS by genetic analysis and age more than 21 years old. Exclusion criteria were: patients unable to provide informed consent, history of other bleeding disorders, history of chronic use of antiplatelet or anticoagulants medication, hepatic disease (defined as ALT > 4 x the upper limit of normal), renal disease (defined as a serum creatinine >2 x the upper limit of normal), thrombocytopenia (platelets < 100 per microliter of blood).

Genetic Studies

Genetic analysis was used to analyze the patient's mutations leading to the clinical findings associated to the syndrome. Peripheral blood samples were drawn for DNA analysis. For the

HPS1 gene, DNA analysis for the founder 16 base pair (bp) duplication in exon 15 of the *HPS1* gene was done by PCR amplification of the *HPS1* gene exon 15, using the primer sets described by Oh et al.[12] The expected sizes of the PCR products are 269 bp for the normal allele and 285 bp for the HPS-1 PR allele. The PCR products were run on a 3.5% agarose gels together with positive and negative control DNAs from known alleles for this region. To test for the *HPS3* gene 3904-BP DEL mutation, PCR analysis was carried out using the primer sets described for detecting this founder mutation[13] and amplification products evaluated on 1.6% agarose gels. The expected products were a 397 bp band for the normal allele; a 650 bp band for the 3904-BP DEL allele.[13]

ISTH-BAT administration

A questionnaire was administered in a private medical office within a private environment by one of the co-investigators. In cases were additional information was required, a telephone call to the patient was done. An Informed consent and space for questions was provided before beginning each questionnaire. Our results were analyzed using the internationally validated ISTH-BAT. We used the standardized questionnaire for inherited bleeding disorders translated to the Spanish language (used in a previous multinational study)[14].

The variables analyzed with the ISTH-BAT included: socio-demographic data, history of: obstetrical bleeding, gynecological bleeding, surgical procedure bleeding, musculo-skeletal bleeding, gastrointestinal bleeding, renal bleeding, mucosal bleeding and cerebral bleeding.

Descriptive statistics were used.

Results

Twelve female patients with the syndrome were enrolled in the study, ten HPS-1 and two HPS-3. None of the interviewed patients were excluded from the study. The mean Bleeding Score (BS) for HPS −1 was 11.4 (Std. Dev.= 5.6), while for HPS-3 it was 8 (Std. Dev.=1.4). Both HPS-1 and HPS-3 showed mean BS score above the established normal score for women (>6). Shown in Table 1.

The mean age for HPS-1 was 45.9 years (Std. Dev.=12.7). The most common bleeding events occurred during menorrhagia (2.7), post-surgery (1.7), oral cavity (1.5) and post-dental procedures (1.4). The events that required medication as prophylaxis were dental extractions (6/10), menorrhagia (2/10) and surgical interventions (3/10). Medications used for bleeding prophylaxis were hormonal therapy, aminocaproic acid, desmopressin and platelet transfusion. Bleeding events requiring medical intervention were: menorrhagia (6/10), surgical intervention (3/10), dental extraction (5/10), post partum hemorrhage (3/10), oral cavity (1/10) and gastrointestinal bleeding (1/10). Medications used to control these bleeding events were: desmopressin, hormonal therapy, platelet transfusion, amino-caproic acid, hysterectomy, suture, packing and fresh frozen plasma.(Table 2). No account of which medications worked better was reported.

The age of the two HPS-3 patients were 25 and 27 years. The most common bleeding events occurred during post-dental procedures (2.0), oral cavity (2.0), and spontaneous cutaneous events (1.5). The events that required medications as prophylaxis were dental extractions (1/2) and post-event bleeding control were oral cavity (1/2). The Medication used for both prophylaxis and post event bleeding control was aminocaproic acid. (Table 2)

A relationship between HPS-1 patients with history of pulmonary fibrosis (PF) and their mean bleeding score was noted. Patients with a history of pulmonary fibrosis had a higher mean bleeding score than those who had no history of PF (See Table 3).

Discussion

This study was designed to understand the bleeding complications of female patients with HPS type 1 and 3. An international validated questionnaire was used, since literature shows that bleeding assessment tools prove to be an important tool in the evaluation of patients with inherited bleeding disorders. Currently, no clinical practice guidelines or algorithms for management of bleeding events are available for patients with HPS.

Our study confirms that HPS female patients experienced significant abnormal bleeding events, mostly during menstrual period and dental procedures. Interestingly, no reported bleeding events required hospitalizations or significant medical interventions.

Results showed that in some cases multiple actions used to control or prevent bleeding such as: suturing, packing, anti-fibrinolytics, desmopressin, fresh frozen plasma, platelet infusion and/or blood transfusions were used. As shown in Table 2, medications to control bleeding events were inconsistent and varied independently among healthcare professionals.

Our study demonstrates that females with type 1 and 3 HPS had a mean bleeding score above the ISTH-BAT cutoff (≥6 for adult females).[15]

Unfortunately, HPS patients with chronic administration of platelet infusions maybe at risk of developing alloimmunization, which may complicate the process of future major surgery. Thus, adequate bleeding control strategies unique to HPS are warranted.

Conclusions

This is the first study evaluating bleeding events in female patients with HPS, using the international recognized ISTH-BAT. Results could be compared to other inherited bleeding disorders using the same questionnaire and similar administration techniques. The analysis of the gathered data places the HPS in the spectrum of genetic bleeding disorders.

Limitations of this study include: the small amount of patients that meet the inclusion criteria, recall bias of bleeding events, selection bias due to single center sample and different age groups.

Further studies are needed to assess the bleeding risk of all known HPS genotypes.

Results suggest that patients with the HPS should be co-managed by a multidisciplinary medical team approach. The ultimate goal should be to develop preventive and therapeutic bleeding control strategies for the HPS population.

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Essentials

- The Hermansky–Pudlak syndrome (HPS) is a rare disorder characterized by oculocutaneous albinism, bleeding diathesis, chronic granulomatous colitis and/or pulmonary fibrosis.
- Puerto Rican females and adult participants with HPS based on genetic linkage were enrolled and the International Society on Thrombosis and Hemostasis Bleeding Assessment Tool (ISTH-BAT) was administered.
- Participants with HPS-1 and HPS-3 reported abnormal bleeding events.
- Bleeding medications were inconsistently used and varied independently from healthcare professionals.

Table 1.

ISTH-BAT BS and women with bleeding disorders

Mean	**HPS type 1 (n=10)**	**HPS type 3 (n=2)**
Age (years)	45.9	26
Total ISTH-BAT BS	11.4	8.0
Epistaxis *	0.4	0.5
Cutaneous	0.7	1.5
Minor Wounds	0.8	0.5
Haematuria	0.0	0.0
GI Bleeding	0.6	0.0
Oral Cavity	1.5	2.0
Postdental	1.4	2.0
Surgical	1.7	1.0
Menorrhagia	2.7	0.5
Postpartum	0.9	0.0
Muscle Haematomas	0.1	0.0
Haemarthrosis	0.3	0.0
CNS bleeding	0	0.0
Other	0.3	0.0
Received prophylaxis medications	Yes (8/10)	Yes (1/2)
Required post-event medical intervention	Yes (9/10)	Yes (1/2)

* Values indicate the average symptoms score from a 0 to 4 scale used in the ISTH-BAT.

Table 2:

History of bleeding complications and management

Patient	Age	Total ISTH-BAT BS	HPS GENOTYPE	Pulmonary Fibrosis	Events treated with Prophylaxis	Medication used as prophylaxis	Bleeding events that required intervention	Medication used to controlled bleeding event
1	33	12	1	no	1-Dental 2- Surgical Intervention	1-Aminocaproic acid 2- Desmopressin	A-Menorrhagia B-Surgical Intervention	A-Desmopressin and hormonal therapy B- Desmopressin and Factor concentrate
2	44	8	1	yes	1-Menorrhagia 2-Surgical Intervention 3-Dental	1- Aminocaproic acid 2-Platelet transfusion 3-Platelet transfusion	A-Dental B- Menorrhagia	A-Platelet transfusion B-Platelet transfusion, hormonal therapy and aminocaproic acid
3	22	6	1	no	1-Dental	1-Aminocaproic acid	A-Dental	A-Aminocaproic acid
4	50	7	1	no	1-menorrhagia	1-Homonal therapy	none	none
5	67	15	1	no	1- Dental	1-Desmopressin	A-Dental B-menorrhagia C-post partum hemorrhage	A-Suture B-Hysterectomy C-Platelet transfusion and blood transfusion
6	56	7	1	no	none	none	A-Post-partum hemorrhage	A- Iron supplement
7	51	10	1	no	none	none	A-Surgical	A- Desmopressin
8	51	14	1	yes	1-Dental	1-Aminocaproic acid	A-Oral cavity B-Dental C-Menorrhagia	A-Haemostatis with suture and aminocaproic acid B-Aminocaproic acid C-Hormonal Therapy
9	36	10	1	no	1-Dental	1- Aminocaproic acid and desmopressin	A-Oral cavity B-Menorrhagia	A-Aminocaproic acid and desmopressin B-Desmopressin
10	49	25	1	yes	1- Surgery	1-Desmopressin	A-Gastrointestinal B- Dental C-Surgery D- Menorrhagia E- Postpartum	A-Desmopressin, Platelet transfusion, Fresh Frozen Plasma B-packing C- Desmopressin and blood transfusion D-Hormonal therapy, Iron supplement and endometrial ablation. E- Fresh Frozen Plasma and Iron supplement
11	27	7	3	no	1-Dental	1-- Aminocaproic acid	A-Oral Cavity B-Dental	A-Aminocaproic acid B-Aminocaproic acid
12	25	9	3	no	none	none	none	none

[*] All participants in the groups were female with HPS.

[^] Number and letters indicate events and medications used for that particular event.

Table 3.

Relationship between HPS-1, pulmonary fibrosis and bleeding score

HPS-1 (n=10)	**Bleeding Score (mean score)**
Pulmonary Fibrosis (n=3)	15.6 (Std. Dev.= 8.6)
No Pulmonary Fibrosis (n=7)	8.5 (Std. Dev.= 3.2)