A 25 year old woman presenting with bleeding disorder and nystagmus

M W Saif, J M Hamilton

A 25 year old white woman presented with a history of severe bleeding after tooth extraction for a wisdom tooth. She admitted to a long history of nose bleeds; these had occurred about once every three weeks for many years and had required blood transfusion twice. She had an appendicectomy done at the age of 11 complicated by severe bleeding that required blood transfusion. The patient said that since childhood she had easily bruised and had severe bleeding after minor cuts. She started her menarche at the age of 14 and since then had menorrhagia. She denied experiencing haematemesis, haematochezia, joint pains, shortness of breath, abdominal pain, or any other systemic complaints.

The patient's parents were healthy and she was the only child. Her only medication was oral contraceptives, which she had started about three months previously.

Physical examination revealed a young woman with blond-brown hair, areas of considerable freckling on skin areas being exposed to sun, pale irides, visual acuity 20/100, and horizontal nystagmus which increased with lateral gaze.

Diagnostic data included a leucocyte count of $7.6 \times 10^9/l$; packed cell volume 0.31; platelet count $178 \times 10^9/l$; prothrombin time 12.5 sec; partial thromboplastin time 23.5 sec; normal liver function tests; normal electrolytes including serum creatinine; negative urine analysis

Figure 1 Ultrastructure of platelets indicating storage granules.

for ceroid; bleeding time 13 sec (prolonged); positive tyrosinase skin biopsy; normal pulmonary function tests; absence of dense granules in platelets evidenced by electron microscopy and aggregation defects in response to adrenaline (epinephrine), collagen, and the lowest concentration of ADP found on platelet aggregation studies (fig 1). Platelets responded normally to 2.0×10^{-6} M ADP.

Questions

- (1) What is the diagnosis?
- (2) What are the main features of this syndrome?
- (3) How would you diagnose the bleeding defect in such patient?

National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

M W Saif
J M Hamilton

Correspondence to:
Dr Muhammad Wasif Saif,
Gastrointestinal
Malignancies, UAB Division
of Hematology/Oncology,
Wallace Tumour Institute,
Room 262-A, 1824 6th
Avenue South, Birmingham,
AL 35294-3300, USA
wasif.saif@ccc.uab.edu

Submitted 4 February 2000
Accepted 28 November 2000

Answers

QUESTION 1

Hermansky-Pudlak syndrome.

QUESTION 2

It is composed of a triad of: (1) partial oculocutaneous albinism, (2) a storage pool platelet defect, and (3) tissue accumulations of ceroid pigment.

QUESTION 3

Abnormalities seen in this haemostatic diathesis can be evaluated by noting: (1) bleeding time (usually prolonged), (2) absence of dense granules in platelets seen by electron microscopy, and (3) aggregation defects in response to adrenaline (epinephrine), collagen, and the lowest concentration of ADP.

Discussion

Hermansky-Pudlak syndrome is a rare disease with worldwide distribution but is primarily found in north west Puerto Rico. It is a *recessively inherited autosomal* disease. The common Puerto Rican mutation is a 16 bp duplication in exon 15 of the Hermansky-Pudlak syndrome gene on 10q23, which produces a 79.3 kD protein of unknown history.^{1,2}

It is composed of a triad of partial oculocutaneous albinism, a storage pool platelet defect, and tissue accumulations of ceroid pigment.

(1) PARTIAL ALBINISM

In contrast to those with total albinism, tyrosine is present in the melanosomes of these patients. The albinism causes congenital nystagmus, a visual acuity approximating 20/200, transillumination of the iris, and mild to severe dilution of skin and hair pigmentation.

(2) STORAGE POOL DISEASE

The platelet defect, a *storage pool deficiency*, is associated with a decreased number or absence of platelet dense bodies, which serve as storage sites for ADP, ATP, serotonin, and calcium secreted during the release reaction. The platelets look morphologically normal on Wright stained smears, and electron microscopy reveals the absence or deficiency of dense bodies (see fig 1). Ex vivo studies have tested the ability of dense granule deficient platelets to form thrombi on subendothelium under various conditions of shear. They have shown that the thrombus dimensions were reduced in proportion to the degree of the dense granules deficit, suggesting the role of granules in either potentiating the growth of thrombi on the subendothelium or helping to stabilise the thrombi in the presence of high shear stress.³

These phenomena are often associated with a mild to moderate haemorrhagic diathesis. It has also been found that the volume of blood that oozes out of the bleeding time wounds is increased over normal, particularly during early time points. This finding suggests the role of dense granules in the contraction after a vascular transection. The distinctive platelet aggregation abnormalities consist of the absence of a second wave of aggregation in

response to adrenaline (epinephrine), disaggregation with lower concentrations of ADP, and reduced reactivity to connective tissue or collagen.

(3) CEROID DEPOSITION

The last component of this syndrome is the accumulation of ceroid pigment in *reticuloendothelial cells* and *macrophages* of bone marrow and other tissues like *gastrointestinal tract* (causing colitis) and *lungs* (causing fibrosis).

Laboratory findings

Laboratory findings are shown in table 1.

Platelet aggregometry findings

(A) TYPICAL AGGREGATION RESPONSE CURVES ARE SHOWN IN FIGS 2 AND 3.

The *horizontal axis* is time in minutes (usually 0 to 3–5 minutes) and the *vertical axis* is per cent transmittance.

Response to ADP

At *low* concentration (1 μ M), an initial (primary) response is seen, followed by platelet disaggregation and a return to baseline.

At *optimal* concentration (5 μ M), two aggregation waves are seen: a primary response is followed by a brief plateau, and then a much larger secondary response occurs.

At *higher* concentrations (10 μ M), the stimulus is strong enough to obliterate the primary response, and a single wave of aggregation is seen (fig 2).

Response to adrenaline (epinephrine)

Normal response to adrenaline (epinephrine) (10 μ M) is quite similar to a response to ADP with a subtle, shallow primary wave (fig 3).

Table 1 Laboratory findings in storage pool disease

Laboratory test	Finding
Bleeding time	Prolonged
Platelet count	Normal
PTT	Normal
Fibrinogen	Normal
ADP response	Abnormal
Ristocetin response	Normal

PTT = partial thromboplastin time.

Figure 2 Dose response to ADP.

Agonist	Platelet aggregation response (normal)	Response in storage pool disease
ADP
Adrenaline (epinephrine)
Collagen
Ristocetin
Thrombin
Arachidonic acid

Figure 3 Platelet storage disease defect seen in platelet aggregation studies and normal platelet aggregation studies.

Response to collagen

Collagen (5 µM/ml) produces a single wave of aggregation after a lag phase due to the following reasons: polymerisation of acid soluble collagen to fibrillar form in plasma, adhesion of

platelets to the collagen fibril, platelet release of ADP, and response of other platelets to released ADP (fig 3).

Response to ristocetin

Ristocetin aggregation curve (1.0–1.5 mg/ml) yields a two wave response (fig 3).

Response to arachidonic acid

Arachidonic acid (1.0 mM) typically produces a two wave response (fig 3).

Response to thrombin

Thrombin (0.3 units/ml) also produces a two wave response (fig 3).

(B) AGGREGATION RESPONSE CURVES IN STORAGE POOL DISEASE

Storage pool disease is characterised by deficient platelet aggregation with ADP (low concentrations), adrenaline (epinephrine) (absence of a secondary wave), collagen (absence of collagen induced aggregation), and thrombin. Ristocetin induced aggregation response is normal in such patients (fig 3).

Treatment and prophylaxis

About 75% of patients with storage pool disease demonstrate a shortening of their prolonged bleeding times approximately an hour after DDAVP (desmopressin) infusion, and this improvement in bleeding time results in less bleeding after procedures. This suggests a role for DDAVP in surgical prophylaxis and in pregnant women during delivery. The combination of DDAVP with tranexamic acid or ethamsylate (antifibrinolytic drugs) has proved to be more effecting in controlling haemostasis. No correlation between pre-therapy plasma vWF antigen or activity and response to DDAVP has been found. Similarly, there is no correlation between post-therapy changes in platelet aggregation and efficacy. Haemostasis has shown to improve after cryoprecipitate infusion. Platelet transfusions should be given only in life threatening bleeding due to the associated development of alloantibodies after transfusion. A role for prednisone (20–50 mg for 3–4 days) has been found in a single study, which showed improved haemostasis in patients with inherited platelet defects. Avoidance of aspirin is mandatory.

Final diagnosis

Hermansky-Pudlak syndrome.

- Schinella RA, Greco MA, Garay SM. Hermansky-Pudlak syndrome: a clinicopathologic study. *Hum Pathol* 1985;16:366–76.
- Gahl WA, Brantly M, Kaiser-Kupfer MI. Genetic defects and clinical characteristics of patients with a form of oculocutaneous albinism (HPS). *N Engl J Med* 1998;338:1258–64.
- Witkop CJ, Krumwiede M, Sedano H. Reliability of absent platelet dense bodies as a diagnostic criterion for Hermansky-Pudlak syndrome. *Am J Hematol* 1987;26:305–11.