Anesthetic implications of the grey platelet syndrome

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Purpose: To describe the obstetrical anesthetic care provided to two sisters with a rare qualitative platelet disorder, the grey platelet syndrome (GPS).

Clinical features: Both patients manifested thrombocytopenia prior to delivery without previous history of a bleeding diathesis or other abnormal laboratory tests of coagulation function. The first required emergency Cesarean section due to fetal bradycardia. Due to the thrombocytopenia and the emergency nature of the procedure, general anesthesia was used. During the C-section, 1.5-2 litres of old blood was noted in the abdominal cavity which was attributed to an old splenic capsular tear of unknown etiology. Work-up for the thrombocytopenia revealed large platelets on the peripheral smear with abnormal aggregation on platelet function studies. Electron microscopy of the platelets revealed absent alpha granules, diagnostic of GPS. The second patient, the sister of patient #1, presented in a similar fashion. However, at presentation, the platelet count was $112,000 \cdot m^{-3}$ and spinal anesthesia was provided without complication for Cesarean delivery. The same patient presented for a second delivery during which fetal bradycardia necessitated emergency C-section under general anesthesia. Despite administration of six units of platelets, blood loss was 5,200 mL. Her postpartum course was uncomplicated and she and the infant were discharged home on postoperative day #4.

Conclusion: The primary concerns for the anesthesiologist looking after patients with qualitative platelet defects are related to defective coagulation which influences the need for perioperative replacement of blood products and limits the use of regional anesthesia.

Objectif : Décrire les soins anesthésiques obstétricaux prodigués à deux sœurs atteintes d'un dérèglement plaquettaire rare, le syndrome des plaquettes grises (SPG).

Éléments cliniques : Les deux patientes présentaient une thrombocytopénie avant l'accouchement, sans antécédent de diathèse hémorragique ou d'autres anomalies de la fonction de coagulation. La première a subi une césarienne d'urgence à cause de la bradycardie fœtale. Étant donné la thrombocytopénie et l'urgence de l'intervention, on a réalisé une anesthésie générale. Pendant la césarienne, 1,5-2 litres de sang vieilli ont été notés dans la cavité abdominale et attribués à une ancienne rupture de la rate d'origine inconnue. L'examen de la thrombocytopénie a révélé de grandes plaquettes à la périphérie des prélèvements et une agrégation anormale lors de l'étude de la fonction plaquettaire. Les plaquettes examinées au microscope électronique montraient une absence de granules alpha, ce qui a amené le diagnostic de SPG. La seconde patiente, sœur de la première, présentait les mêmes signes. Cependant, au moment de l'accouchement, la numération plaquettaire était de $112,000 \cdot m^{-3}$ et la rachianesthésie pour une césarienne a été réalisée sans complication. Cette même patiente a connu un second accouchement pendant lequel la bradycardie fœtale a nécessité une césarienne d'urgence sous anesthésie générale. Malgré l'administration de six unités de plaquettes, la perte sanguine a été de 5 200 mL. La récupération du postpartum a été sans complications et la patiente et son enfant ont pu quitter l'hôpital au quatrième jour.

Conclusion : Dans des cas d'anomalie plaquettaire qualitative, l'anesthésiologiste est surtout préoccupé par les défauts de coagulation qui influencent les besoins de remplacement périopératoire par des produits sanguins et limitent l'utilisation de l'anesthésie régionale.

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THE Grey Platelet Syndrome (GPS) is a rare, inherited qualitative disorder of platelet function, originally described in 1971 by Raccuglia.¹ Presentation of the disorder includes a bleeding diathesis, thrombocytopenia and abnormal platelet morphology on both light and electron microscopy. Patients may give a history of easy bruising, ecchymosis, recurrent epistaxis, and menorrhagia but severe hemorrhage has most commonly been reported following surgical procedures.¹ Light microscopy examination of the peripheral smear after Wright staining reveals large platelets with a decreased number of cytoplasmic granules and increased vacuoles thereby giving them a grey appearance. Electron microscopy of the platelets reveals a deficiency in alpha granules.² The deficiency of alpha granules results in abnormalities of platelet secretion and secondary aggregation in response to various stimuli including collagen and thrombin. All other functions of the platelets remain normal.³ Male and female patients are equally afflicted although, due to the limited number of patients reported with this disorder, the sex prevalence is uncertain. There is some debate whether the condition is an autosomal dominant or recessive disease, as reports demonstrate afflicted children of normal parents as well as transmission in successive generations.

Due to abnormalities in both platelet number and function, serious perioperative complications related to the bleeding diathesis and other sequelae may occur. There are no previous reports in the anesthetic literature reviewing this disorder. We report two sisters from a large Mennonite family who developed peripartum complications.

Case reports

Patient #1

A 21-yr-old woman presented at 35 wk gestation with complaints of abdominal pain. Complete blood count revealed a hematocrit of 34.4% (normal 36-47%), a hemoglobin of 11.5 g·dL⁻¹ (normal 12-16 g·dL⁻¹) and a platelet count of 26,000·mm⁻³ (normal 130,000-400,000·mm⁻³). Ultrasound revealed good fetal movement. Subsequent platelet counts are listed in Table I. After two attempts at amniocentesis, grossly bloody fluid was obtained and a partial placental abruption was suspected. Uterine contractions increased and the patient was transferred to our institution. Past medical and surgical history revealed a clavicular abscess at 11 yr of age that required open irrigation and debridement. No perioperative complications were reported from that anesthetic and surgical procedure. However, at the time of that hospitalization the platelet count ranged from 81,000 to 114,000·mm⁻³. Work-up for the throm-

TABLE I Platelet counts of patient #1

<i>Time</i>	<i>Platelet count (1000·mm⁻³)</i>	
hospital day #1	26	40 mg prednisone·day ⁻¹
hospital day #2	22	
hospital day #3	25	60 mg prednisone·day ⁻¹
day of transfer	25	
day of surgery	28	6 units platelets
post-op day #1	58	
post-op day #2	50	
post-op day #3	77	
post-op day #4	83	
post-op day #6	110	

bocytopenia at that time was inconclusive. Family history revealed a sister who also had become severely thrombocytopenic during pregnancy (see second case report). There was an obstetrical history of spontaneous abortion the previous year without further work-up. An external fetal monitor was applied and oxytocin induction initiated. On artificial rupture of membranes, the fluid was clear without blood. The prothrombin and partial thromboplastin times were within normal limits. The next morning, the fetal heart tracing revealed bradycardia to 60-90 beats·min⁻¹ and late decelerations that did not improve with oxygen and repositioning.

Ranitidine, 50 mg, and 10 mg metoclopramide *iv* were administered and 30 ml of non-particulate antacid *po* were administered as the patient was transported to the operating room for emergency Cesarean section. She received preoxygenation with oxygen and rapid sequence intubation was performed following 375 mg thiopental and 125 mg succinylcholine.

On entry into the abdominal cavity, there were approximately 1.5 to 2 litres of dark red blood. A 14 gauge peripheral intravenous cannula and a 20 gauge radial arterial line were placed. Blood gas analysis revealed: pH 7.29, PCO₂ 40 mmHg, PO₂ 268 mmHg with a base deficit of -6.8 mEq·L⁻¹ and 50 meq of sodium bicarbonate were administered. Coagulation function and fibrinogen were within normal limits. The infant's APGAR scores were 5 and 9. The bleeding was determined not to be coming from the uterus and the uterine incision was closed. The general surgery team was consulted. A small non-bleeding splenic capsular tear was noted and repaired. Estimated blood loss for the procedure was 3500 mL. Fluids included two units of packed red cells, 500 mL albumin 5%, and 2900 mL isotonic crystalloid. At the completion of surgery, residual neuromuscular blockade was reversed and the patient's trachea was extubated. The remainder of the postoperative course was uncomplicated. Further work-up revealed abnormally

large platelets on the peripheral smear. Platelet aggregation studies revealed abnormal aggregation and electron microscopy revealed absent alpha granules diagnostic of grey platelet syndrome. The male infant had an uneventful newborn course. His platelet count normal and he underwent circumcision with without any bleeding problems.

Patient #2

The second patient, sister of patient number one, was a 22-yr-old woman at 34 ½ wk gestation, referred from a local hospital by her obstetrician due to thrombocytopenia. At her first prenatal visit, her platelet count was 60,000·mm⁻³ which was thought to be due to an immune-related process and 20 mg prednisone·day⁻¹ were started. By the seventh month of pregnancy, the platelet count was 75,000·mm⁻¹, but did not increase any further even with 60 mg prednisone·day⁻¹. There was no relevant past medical history. She had undergone a hysterosalpingogram for primary infertility without complications. She denied easy bleeding or menorrhagia, but had noted easy bruising for approximately six months. On admission, she was in no acute distress. Physical examination was unremarkable except for 3-4 ecchymotic areas on the right lower extremity. Laboratory evaluation revealed a PT of 12.4 sec (normal 12-15 sec), a PTT of 22.1 sec (normal 23.7-33.4 sec), fibrinogen 392 mg·dl⁻¹ (normal 157-345), Factor VIII assay 382% of normal (normal 50-200% of normal), bleeding time 15 min (normal 4-10 min). Platelet counts during the hospitalization are listed in Table II. A bone marrow biopsy on the second day of hospitalization revealed adequate megakaryocytes. On hospital day 14, fetal ultrasound revealed oligohydramnios and amniocentesis showed fetal lung maturity. It was decided to deliver the fetus via a primary Cesaerean section. Following ranitidine and metoclopramide *iv* and sodium bicarbonate *po*, the patient was transported to the operating room and routine monitors placed. Spinal anesthesia was accomplished using 15 mg bupivacaine and 0.2 mg preservative-free morphine. The infant's APGAR scores were 8 and 9. There were no post-partum complications and the patient was discharged on her fourth post-partum day. The infant was admitted to the NICU for routine group B streptococcal antibiotic prophylaxis due to a positive maternal culture. He underwent circumcision without complication.

Nineteen months after delivery of the first child, the patient presented again with a 38 wk estimated gestational age. She was referred with poorly controlled diabetes, which was attributed to prednisone therapy for thrombocytopenia, and oligohydramnios. The diagnosis of GPS had been made in her sister. At the time of

TABLE II Platelet counts of patient #2

Time	Platelet count (1000·mm ⁻³)	
hospital day #1	37	60 mg prednisone·day ⁻¹ IVIG 400 mg·kg ⁻¹ ·day ⁻¹
hospital day #4	27	
hospital day #6-10	100	
C-section, day #14	112	
post-op day #4	90	60 mg prednisone·day ⁻¹ 6 units platelets
hospital day #1	31	
post-op day #1	32	
post-op day #4	50	

TABLE III Qualitative defects of platelet function

Inherited intrinsic defects:
Glanzmann's disease
Bernard-Soulier syndrome
Ehlers-Danlos syndrome
Platelet storage pool diseases:
isolated defect
Chediak-Higashi syndrome
Wiskott-Aldrich syndrome
Hermansky-Pudlak syndrome
gray platelet syndrome
Inherited extrinsic defects:
von Willebrand disease
Hemophilia type A
Acquired extrinsic defects:
uremia
hepatic failure
fibrin degradation products
vitamin B ₂ deficiency
drug-induced:
dextran
hydroxyethyl starch
non-steroidal anti-inflammatory agents
phenothiazines
semi-synthetic penicillins - ticarcillin
phenothiazines
prostaglandin E

admission, medications were 60 mg prednisone·day⁻¹ and prenatal vitamins. The risks associated with vaginal delivery after a Cesarean section were explained and she elected vaginal delivery. Induction of labour was initiated. Pain management included butorphanol *iv*. Fetal heart tones were monitored via utero-fetal monitoring and remained reassuring with only intermittent mild variable decelerations noted. With an increasing probability that operative delivery would be necessary as there was no advancement in dilation and effacement and an episode of prolonged fetal bradycardia, six random donor units of platelets were infused. Subsequently, there was an arrest of dilation and the fetal heart tracing showed minimal reactivity. A Cesarean section was per-

formed emergently. Ten mg metoclopramide *iv* and 30 mL sodium bicarbonate *po* were administered and the patient transported to the operating room. Rapid sequence induction was accomplished following pre-oxygenation and the administration of 300 mg thiopental 300 and 120 mg succinylcholine *iv*. General anesthesia was maintained with sevoflurane (exhaled concentration 1-2.5%) in oxygen 100%. Nitrous oxide (50%) and fentanyl were given after the infant was born. Intermittent doses of cisatracurium were administered to provide neuromuscular blockade. Intraoperatively, the uterus was ruptured along the left lateral wall from the left uterine cornu down to the vagina. The infant was delivered with APGARs of 3 and 9. An abdominal hysterectomy and right salpingo-oophorectomy were performed. A posterior bladder wall rupture was also noted and repaired. Blood loss for the procedure was 5,200 mL requiring three units of packed red cells and a six units of random donor platelets. On postoperative day two, two units of packed red blood cells were transfused for a hemoglobin of 6.7 mg·dL⁻¹. She was discharged home on her fourth post-partum day with a platelet count of 58,000·mm⁻³. The male infant also did well and was discharged home with his mother. A diagnosis of GPS was subsequently confirmed by electron microscopy of the peripheral blood smear.

Discussion

We report two sibilings with GPS, a qualitative platelet disorder. As with other qualitative platelet disorders, spontaneous bleeding may be uncommon but bleeding may occur following surgical procedures or trauma. The primary issues relating to anesthetic care include the need for perioperative replacement of blood products or factors to correct the bleeding diathesis and limitations of the use regional anesthesia. Both patients required administration of several units of packed red blood cells to replace intraoperative losses as well as platelet transfusions to correct the coagulation defect. At initial presentation of the second patient, she had not been previously diagnosed and the thrombocytopenia was thought to be secondary to an immune process. With a platelet count greater than 100,000·mm⁻³ at the time of Cesarean section, it was decided to proceed with spinal anesthesia. Even with a platelet count greater than 100,000·mm⁻³, spinal or epidural anesthesia may not be recommended in patients with a qualitative platelet defect without demonstration of a normal bleeding time.

The inability to provide epidural anesthesia necessitates other options for labour analgesia. While we used butorphanol *iv* in our patients, others have demonstrated the efficacy of fentanyl or alfentanil delivered

via patient- controlled analgesia in providing labour analgesia while having limited adverse effects on neonatal respiratory function.⁴⁻⁶

Strict attention is suggested regarding any medications or products that may adversely affect platelet function. Although obvious offenders such as non-steroidal anti-inflammatory agents should be avoided, other agents including specific antibiotics (semi-synthetic penicillins), phenothiazines, and hydroxyethyl starch may adversely affect platelet function. Although these effects are generally not clinically relevant in patients with normal platelet function, there is a theoretical potential for adverse effects in patients with qualitative platelet defects.

The severity of bleeding and presentations in GPS is variable. Spontaneous, life-threatening bleeding is rare. Patients may give a history of excessive bleeding with minor surgical procedures such as tooth extraction or circumcision, easy bruising, heavy menses, or recurrent epistaxis, cutaneous and mucosal membrane bleeding. Some patients may deny any symptoms. Berrebi *et al.* reported a 68-yr-old man who had only a history of recurrent ecchymoses and thrombocytopenia in whom the diagnosis of GPS was made.⁷ His only major bleeding complication occurred following prostatectomy.⁷

Normal coagulation function results from the interaction of the vascular endothelium, platelets, and circulating coagulation factors of the intrinsic and extrinsic clotting cascades. Trauma to the vascular endothelium releases collagen and other factors which result in primary platelet aggregation through the interaction of platelet surface receptors and the endothelium. This interaction results in the release of intracellular compounds from cytoplasmic granules of the platelets such as ADP, serotonin and epinephrine that result in the secondary aggregation of additional platelets. Defects in any of these steps can result in a bleeding disorder (Table III).

Within the platelet cytoplasm there are several types of membrane enclosed bodies. When platelets are activated, these cytoplasmic granules release their contents into the surrounding area leading to further platelet aggregation. Defects in these steps may result from deficiency of cell surface receptors (Glanzmann's thrombasthenia, Bernard Soulier syndrome) or deficiency of the intracellular granules (GPS, storage pool diseases).⁸ In GPS, the primary defect is not the production of the material for the alpha granule, but rather its packaging.⁹ Proteins destined for the alpha granule are produced, but either do not reach the alpha granule or are lost after inclusion.

Clues to the diagnosis of GPS and other uncommon qualitative platelet disorders include a history of easy

bruising with recurrent ecchymosis, mucosal membrane bleeding, and/or heavy menses. Examination of the peripheral smear may reveal thrombocytopenia and the pathognomonic gray platelets. The diagnosis is supported by abnormal platelet aggregation studies and confirmed by the absence of alpha granules on electron microscopy.

Treatment includes platelet transfusions prior to major surgical procedures. Other attempts to increase the platelet count including splenectomy, corticosteroids, and intravenous gamma globulin have resulted in modest increases in the platelet count to levels that are inadequate to ensure adequate hemostasis during surgical procedures especially since these therapies do not affect the qualitative defect. As in our patients, these therapies are initiated because the thrombocytopenia is thought to be auto-immune prior to making the diagnosis of GPS. With abnormal platelet function, there may be shortened platelet half-life with platelet removal from the circulation by the reticuloendothelial system.¹⁰ This may provide a physiologic rationale for the use of immune-modulating therapy even when the primary disorder is not immune-mediated.

Agents such as desmopressin (DDAVP), aprotinin, and epsilon-amino caproic acid have been used to augment coagulation function in various bleeding diathesis.¹¹ Due to the limited number of patients with GPS, there has been limited clinical experience with these agents. Pfueller *et al.* reported an improvement in the bleeding time following the administration of DDAVP to a patient with GPS¹² while Kohler *et al.* noted no benefit.¹³ Kohler suggested that the varying responses may be related to the platelet count at the time of therapy.¹³ A similar phenomenon has been reported with the use of DDAVP in other platelet disorders.¹⁴

We noted the unusual occurrence of spontaneous organ rupture in our patients. Although this may have been from other factors (inadvertent trauma during the operative procedures or from the previous Cesarean section scar), there was a splenic rupture and placental abruption in our first patient and a uterine and bladder rupture in our second patient. Previous reports of GPS have not demonstrated such problems.

Grey platelet syndrome is generally an isolated deficiency although there are reports concerning its occurrence with other disorders including hemophilia A, Marfan syndrome, and Goldenhar syndrome.¹⁵ Breton-Gorius *et al.* demonstrated the presence of myelofibrosis in two patients with GPS which they postulated resulted from the release of platelet derived growth factor from the alpha granules of the megakaryocytes and its effects on fibroblast proliferation.¹⁶

In summary, we have reviewed the pathogenesis and anesthetic implications of the gray platelet syndrome, a qualitative platelet defect related to a deficiency of alpha granules. In patients with documented GPS, fetal scalp sampling for platelet count and morphology may be indicated prior to the decision to proceed with vaginal delivery *vs* operative delivery.¹⁷

References

- 1 Raccuglia G. Gray platelet syndrome. A variety of qualitative platelet disorder. *Am J Med* 1971; 51: 818-28.
- 2 Levy-Toledano S, Caen JP, Breton-Gorius J, *et al.* Gray platelet syndrome: alpha-granule deficiency. Its influence on platelet function. *J Lab Clin Med* 1981; 98: 831-48.
- 3 Greenberg-Sepersky SM, Simons ER, White JG. Studies of platelets from patients with grey platelet syndrome. *Br J Haematol* 1985; 59: 603-9.
- 4 Rosaeg OP, Kitts JB, Koren G, Byford LJ. Maternal and fetal effects of intravenous patient-controlled fentanyl analgesia during labour in a thrombocytopenic patient. *Can J Anaesth* 1992; 39: 277-81.
- 5 Howell PR, Gambling DR, Pavy T, McMorland G, Douglas MJ. Patient-controlled analgesia following Caesarean section under general anaesthesia: a comparison of fentanyl with morphine. *Can J Anaesth* 1995; 42: 41-5.
- 6 Ginsberg B, Gil KM, Muir M, Sullivan F, Williams DA, Glass PSA. The influence of lockout intervals and drug selection on patient-controlled analgesia following gynecological surgery. *Pain* 1995; 62: 95-100.
- 7 Berrebi A, Klepfish A, Varon D, *et al.* Gray platelet syndrome in the elderly. *Am J Hematol* 1988; 28: 270-2.
- 8 White JG. Inherited abnormalities of the platelet membrane and secretory granules. *Hum Pathol* 1987; 18: 123-39.
- 9 White JG. Ultrastructural studies of the Gray platelet syndrome. *Am J Pathol* 1979; 95: 445-62.
- 10 Köhler M, Hellstern P, Morgenstern E, *et al.* Gray platelet syndrome: selective alpha-granule deficiency and thrombocytopenia due to increased platelet turnover. *Blut* 1985; 50: 331-40.
- 11 Testa LD, Tobias JD. Techniques of blood conservation. Part II: autologous transfusion, intraoperative blood salvage, pharmacologic agents, and cost issues. *Am J Anesthesiol* 1996; 23: 63-72.
- 12 Pfueller SL, Howard MA, White JG, Menon C, Berry EW. Shortening of the bleeding time by 1-deamino-8-arginine vasopressin (DDAVP) in the absence of platelet von Willebrand factor in gray platelet syndrome. *Thromb Haemost* 1987; 58: 1060-3.
- 13 Kohler M. Treatment of gray platelet syndrome (Letter). *Thromb Haemost* 1988; 60: 123-4.

- 14 *Mannucci PM, Vicente V, Vianello L, et al.* Controlled trial of desmopressin in liver cirrhosis and other conditions with a prolonged bleeding time. *Blood* 1986; 67: 1148-53.
- 15 *Crowell EB Jr, Eisner EV.* Familial association of thrombopathia and antihemophilic factor (AHF, factor VIII) deficiency. *Blood* 1972; 40: 227-33.
- 16 *Breton-Gorius J, Vainchenkar W, Nurden A, Levy-Toledano S, Caen J.* Defective alpha-granule production in megakaryocytes from gray platelet syndrome. Ultrastructural studies of bone marrow cells and granulocytes growing in culture from blood precursors. *Am J Pathol* 1981; 102: 10-9.
- 17 *Scott JR, Cruikshank DP, Kochenour NK, Pitkin RM, Warenski JC.* Fetal platelet counts in the obstetric management of immunologic thrombocytopenia purpura. *Am J Obstet Gynecol* 1980; 136: 495-9.