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1 **Peripartum bleeding management in a patient with CalDAG-GEFI deficiency**

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3 Matthias Canault¹, Paul Saultier¹, Sixtine Fauré¹, Marjorie Poggi¹, Alan T Nurden², Paquita
4 Nurden², Pierre-Emmanuel Morange^{1,3}, Marie-Christine Alessi^{1,3*}, Jean-Christophe Gris^{4*}

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7
8 ¹ Aix Marseille Univ, INSERM, INRA, NORT, Marseille, France

9 ² Institut-Hospitalo-Universitaire LIRYC, Plateforme Technologique et d'Innovation Biomédicale,
10 Hôpital Xavier Arnoz, Pessac, France

11 ³ APHM, CHU Timone, French Reference Centre for Rare Platelet Disorders, Marseille, France.

12 ⁴ Laboratoire d'hématologie, Groupe Hospitalo-Universitaire Caremeau, Nîmes, France

13
14 * These authors contributed equally to this study

15
16 Correspondence to:

17 Matthias Canault

18 UMR Inserm 1062, INRA 1260, Aix-Marseille Univ

19 Nutrition, Obesity and Risk of Thrombosis (NORT) laboratory

20 Faculté de Médecine Timone, 27 boulevard Jean-Moulin

21 13385 Marseille Cedex 05

22 matthias.canault@univ-amu.fr

23 Tel: +33 491 324 507

24 Fax: +33 491 254 336

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27 **Essentials**

- 28 • Some platelet disorders increase risk of haemorrhage during pregnancy and delivery.
29 • Management of bleeding diathesis during the course of pregnancy in CalDAG-GEFI
30 deficiency.
31 • Severe bleeding occurred in the postpartum period similar to that in women with
32 Glanzmann's thrombasthenia.
33 • A planned bleeding prevention strategy is required for pregnant women with CalDAG-
34 GEFI deficiency.

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37 *To the editor,*

38 Pregnant women with inherited platelet disorders are at high risk of life-threatening
39 haemorrhage during delivery. Foetuses and newborns can also be affected, and be at risk of
40 bleeding complications (1, 2). Here we describe bleeding diathesis and its management during
41 the course of pregnancy in a young woman with severe mucocutaneous bleeding and platelet
42 dysfunction caused by calcium and diacylglycerol-guanine exchange factor I (CalDAG-GEFI)
43 deficiency recently characterised by several groups (3-6). The patient was explored after
44 informed written consent was obtained, in accordance with the Declaration of Helsinki.

45 The propositus was born in 1994 from asymptomatic consanguineous parents (cousins). She
46 experienced easy bruising and recurrent epistaxis from early childhood (Fig. 1A) with an
47 International Society on Thrombosis and Haemostasis (ISTH) bleeding score (7) of 5. She
48 carried a homozygous frameshift mutation c.199_200delAA (p.N67Lfs*24) within the
49 CalDAG-GEFI coding gene, *RASGRP2* (6). Westbury *et al.* recently described her clinical
50 features and platelet phenotypes, emphasising a platelet aggregation defect after stimulation
51 with intermediate- and low-dose agonists.

52 Western-blot analysis revealed absence of CalDAG-GEFI in the patient's platelets (Fig. 1B)
53 and in GripTite 293 MSR cells expressing the p.L67 variant compared with the p.N67 (wild-
54 type) and the p.G248W (previously reported (3)) variants (Fig. 1C).

55 Between ages 5 and 11 years the propositus was repeatedly hospitalised for intractable
56 mucocutaneous bleeding, with sometimes acute anaemia requiring platelet/red blood cell
57 (RBC) transfusions, recombinant factor VIIa (rFVIIa) injection (90 µg/kg), tranexamic acid
58 and iron supplementation (Fig. 1A). At menarche (age 11 years), she experienced severe
59 menorrhagia, treated with tranexamic acid. Severe autoimmune thrombocytopenia (6 G/l with
60 strongly positive anti-GPIIb/IIIa (anti- $\alpha_{IIb}\beta_3$ integrin) autoantibodies) was concomitantly

61 evidenced. Evans' syndrome was characterised one year later (haemoglobin 63 g/l, platelet
62 count 59 G/l) with further diagnosis of systemic lupus erythematosus (SLE) complicated by
63 lupus nephropathy at age 13 years. She was treated with initial γ -globulin infusion,
64 corticosteroids, hydroxychloroquine and enalapril.

65 At age 15 years she was hospitalised for acute anaemia (46 g/l haemoglobin) due to severe
66 menorrhagia. Her platelet count was 500 G/l, and bleeding was treated with platelet/RBC
67 transfusions and noregestrol. Treatment on exit was iron supplementation, prednisone,
68 enalapril, and hydroxochloroquine.

69 At age 19 years she received progestin oral contraception to treat hypermenorrhea. Her
70 chronic treatment was maintained.

71 A first pregnancy was diagnosed a few months later. She displayed normal blood pressure
72 values and no sign of oedema. Platelet count was 252 G/l, and she tested positively for
73 antinuclear antibodies 1/320, and negative for anti-DNA and antiphospholipid antibodies.
74 Creatinine level was 52 μ M (normal range 45–90 μ M) with no proteinuria. The patient had a
75 monthly follow-up, without emergence of any abnormal symptom (bleeding, SLE flare,
76 cytopenia or manifestation of renal disease).

77 She was hospitalised for spontaneous onset of labour at 38 weeks plus 6 days (platelet count
78 277 G/l, haemoglobin 145 g/l). Spinal or epidural anaesthesia was contraindicated, and
79 patient-controlled analgesia with remifentanil was initiated. As labour progressed,
80 prophylactic transfusion of 6 platelet concentrates and continuous intravenous tranexamic
81 acid infusion (10 mg.kg⁻¹ bolus, then 1 mg/kg/h) were prescribed. She gave birth after 8 h of
82 labour by vaginal delivery, to a healthy male newborn with normal neonatal blood cell counts.
83 Artificial placental delivery had to be performed under general anaesthesia. Sulprostone was
84 used to reverse uterus atony and prevent postpartum haemorrhage. No maternal or neonate
85 bleeding was evidenced. One prophylactic transfusion of 6 platelet concentrates was

86 performed early post-delivery. The patient was monitored for 5 days, and was released from
87 hospital without any haemostatic maintenance treatment.

88 Severe metrorrhagia occurred on day 11 *post partum*. A single emergency transfusion of 6
89 platelet concentrates was administered together with a continuous tranexamic acid infusion
90 (Fig. 1A), resulting in prompt positive clinical effects. The patient left the hospital on day 13
91 *post partum*; her treatment was prednisone (10 mg/d), hydroxochloroquine (400 mg/d), oral
92 tranexamic acid (1 g each 8 h for 3 days).

93 She underwent an emergency hospitalisation 38 days *post partum* for a severe haemorrhagic
94 first post-pregnancy menstrual period with expulsion of clots by the vaginal route. Platelet
95 count was within normal ranges. Platelets and RBC transfusions, intravenous tranexamic acid
96 and fluid infusions allowed haemodynamic stabilisation, but showed moderate haemostatic
97 efficacy. A single rFVIIa injection (90 µg/kg) stopped abnormal bleeding. The patient left the
98 hospital 4 days later.

99 This report is the first to describe the management of pregnancy and parturition in a patient
100 with homozygous CalDAG-GEFI deficiency. A deficit in CalDAG-GEFI leads to integrin
101 activation defects (3-5). However, unlike in Glanzmann's thrombasthenia (GT), CalDAG-
102 GEFI-deficient platelets achieve full aggregation when stimulated with high doses of strong
103 agonists (TRAP-6 and collagen). This suggests that the risk of bleeding complications in these
104 patients might be lower than in women with GT.

105 As in other inherited platelet disorders (1), the course of pregnancy in this context was not
106 altered despite the added diagnosis of SLE. Repeated platelet transfusions in the delivery
107 period prevented haemorrhage. Close follow-up and a preventive haemostatic strategy in
108 women with CalDAG-GEFI deficiency are required not only during the primary postpartum
109 period (within 48 h of birth), but also from 48 h to several weeks post-birth until menses
110 resume. Maintaining tranexamic acid treatment might be of benefit throughout this period.

111 The severe bleeding episode experienced at resumption of menses was only partially
112 controlled by platelet and RBC transfusions. Injection of single-dose rFVIIa demonstrated a
113 significant effect in stopping haemorrhage. Thus rFVIIa may be considered as a strategy to
114 manage the haemorrhagic risk in women with CalDAG-GEFI deficiency at delivery and
115 during the following days.

116 In conclusion, this case illustrates for the first time that CalDAG-GEFI deficiency carries an
117 increased risk of severe bleeding during the peripartum period. Prolonged monitoring and a
118 planned preventive haemostatic strategy are accordingly required to minimise bleeding in
119 these high-risk pregnant women.

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126 clinical characterisation of patients, analysed the data and wrote the paper. P. Saultier, S.
127 Faure and M. Poggi performed the research, analysed the data and wrote the paper. A.T.
128 Nurden, P. Nurden, P.E. Morange and M-C. Alessi designed the research study, analysed the
129 data and wrote the paper. The authors have no competing interests

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164 **Figure legends**

165 Figure 1: (A) Evolution of platelet count, haemorrhagic and autoimmune manifestations and
166 haemostatic treatments prior to and during pregnancy/delivery. (B) Representative Western-
167 blot for CalDAG-GEFI in platelet lysates from two healthy subjects (Controls), the patient,
168 her mother and her father. GAPDH expression was used as equal loading and electrophoretic
169 transfer control. (C) Representative Western-blot for CalDAG-GEFI in GripTite™ 293 MSR
170 cells transfected with vectors coding for the wild-type, p.G248W, and p.N67Lfs*24 variants

171 of CalDAG-GEFI. GAPDH expression was used as equal loading and electrophoretic transfer
172 control.