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Anti-Ge3 causes late-onset hemolytic disease of the newborn: the fourth case in three Hispanic families

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Abstract

BACKGROUND—The Gerbich (Ge) blood group system consists of 11 antigens carried on red blood cell (RBC) membrane glycoproteins C and D; of these, Ge:3 antigen is of high prevalence, and the anti-Ge3 is found to be clinically significant.

CASE REPORT—A 34-week neonate born to a Hispanic mother with anti-Ge3 developed late-onset hemolysis with hyperbilirubinemia and was successfully treated with transfusions from her mother. Relevant clinical findings and laboratory results for this case are summarized and compared to three other previously reported cases; all babies were born from a mother of Hispanic ethnicity.

CONCLUSION—Hemolytic disease of the fetus and newborn associated with anti-Ge3 is rare but should be considered when working up a broadly reactive RBC antibody screen in women of Hispanic ethnicity. Early identification of pregnant women with anti-Ge3 is recommended for prenatal transfusion planning and close monitoring of the newborn infant for evidence of late-onset anemia.

Hemolytic disease of the fetus and newborn (HDFN) is a rare, but significant, cause of neonatal morbidity and mortality. HDFN occurs when a maternal immunoglobulin (Ig)G antibody, directed against an antigen on fetal red blood cells (RBCs), crosses the placenta and attacks fetal RBCs, causing hemolytic anemia. Maternal antibodies develop after exposure to foreign RBC antigens, for example, via blood transfusion or via transplacental fetomaternal hemorrhage. Historically, ABO antibodies have caused the majority of mild cases of HDFN, and D alloimmunization has caused the majority of severe cases.¹ The prevalence of HDFN associated with anti-D has declined with routine anti-D prophylaxis for all D– women.¹ Other antibodies, such as anti-K, anti-c, and anti-E, now cause an increasingly large percentage of severe HDFN cases, although anti-D still causes the

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CONFLICT OF INTEREST

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majority of them.^{1,2} IgG antibodies to any of the 300 RBC antigens other than ABO and Rh can also cause HDFN but are much rarer. Many of these antigens (e.g., Lu^b, Yt^a, and Vel) are not well developed on fetal RBCs or are of high prevalence so only a small percentage of the population is at risk for making these antibodies.

The Gerbich blood group system consists of 11 antigens carried on RBC membrane glycoproteins C (GPC) and D (GPD), proteins that help maintain RBC membrane shape and stability.³ Five of the Gerbich antigens (Ge5, Ge6, Ge7, Ge8, Ge9) are of low prevalence and have not been reported to be clinically significant.³ The other six Gerbich antigens (Ge2, Ge3, Ge4, Ge10, Ge11, Ge12) are high-prevalence antigens (found in >99.9% of the population).³ Three Gerbich-negative types have been identified: Ge:–2,3,4 (Yus type); Ge:–2,–3,4 (Gerbich type); and Ge:–2,–3,–4 (Leach type).³ Anti-Ge3 is usually IgG and reacts at the anti-human globulin phase of antibody detection tests, but IgM forms of anti-Ge3 have also been reported.³ Anti-Ge3 can cause autoimmune hemolytic anemia and alloimmune transfusion reactions^{3,4} but was not known to be associated with severe HDFN until recently. Two relatively recent reports described three infants who developed severe, late-onset anemia and hyperbilirubinemia up to 40 days after birth to mothers with anti-Ge3.^{5,6} We now report a fourth such case.

CASE REPORT

The patient was a girl born at 34 weeks at an outside hospital to a 29-year-old Hispanic woman (group O, D+). The baby was delivered via emergency cesarean section because of absent fetal movement. Her birth weight was 2075 g, with Apgar scores of 9 at both 1 and 5 minutes. Her mother had no transfusion history and an uncomplicated pregnancy with routine prenatal care. At 30 weeks' gestation, an antibody screen was positive for anti-Ge3. Her previous pregnancies were uncomplicated and included a broadly reactive RBC antibody screen with no specific antibody identified. One of her three other children (unknown blood type) had mild neonatal jaundice and received phototherapy. Relevant laboratory results for this case are summarized and compared to three other reported cases (Table 1); all babies were born from a Hispanic mother.

At birth, the baby's blood typed as group O, D+, with a positive direct antiglobulin test (DAT); her hematocrit (Hct) was 40.9%. On the first day of life (DOL) outside the uterus (DOL 1), she developed jaundice and a total bilirubin of 18.1 mg/dL, which required phototherapy. She received intravenous immunoglobulin (IVIG; 1 g/kg [DOL 9 and 10]) and epoetin alfa (Epogen, Amgen, Thousand Oaks, CA; 600 units on DOL 9) as her Hct decreased significantly from 40.9% to 20% by DOL 9. On DOL 10, her Hct decreased to 17.7%, and she developed tachycardia, prompting transfer to a neonatal intensive care unit (NICU). A double-exchange transfusion was planned, but no Ge:–3 RBCs were available in the United States.

The infant was then transferred (DOL 10) to Lucile Packard Children's Hospital (Stanford, CA) NICU for transfusion, using maternal Ge:–3 RBCs collected in AS5 and split into aliquots (approx. 40 mL each) for transfusion. She received four aliquots, one each on DOL 11, 12, 13, and 21. Continued hemolysis and persistent hyperbilirubinemia (12.6 mg/dL

[DOL 13]) was treated with phototherapy. She remained stable until her discharge on DOL 22 with a total bilirubin of 5.1 mg/dL and a Hct of 47%. Although her Hct decreased to 31.6% (DOL 72), she had not required additional RBC transfusions (Fig. 1). A comparison of all four cases of anti-Ge3-mediated HDFN reported is shown in Table 2, with a comparison of additional treatments shown in Table 3.

DISCUSSION

We describe a case of HDFN due to anti-Ge3 in an infant who presented with late-onset anemia and required transfusion. Only three cases of HDFN due to anti-Ge3 (two of these cases involved the same mother) have been reported previously.^{5,6} The common feature of the four cases of HDFN described is that the mothers were of Hispanic origin presenting with a broadly reactive RBC antibody. Although the frequency of occurrence of the Ge:3 antigen is known to be more than 99.9% in most ethnic groups,³ the Hispanic population appears to have the highest number of Ge:-3 individuals currently reported.

All four infants presented a similar course: born at or near term and appearing healthy, after otherwise uncomplicated pregnancies with standard prenatal care, and no transfusion history.⁵⁻⁷ The initial laboratory results for these infants at birth revealed near normal hemoglobin (Hb) levels, Hct, and reticulocyte counts, as well as no significant abnormality on the peripheral blood smears. Yet for each infant, the DAT and indirect antiglobulin test (IAT) were positive, with anti-Ge3 identified, and the total serum bilirubin level was sufficiently elevated to necessitate phototherapy. Additionally, they all developed severe anemia between DOL 10 and 40 and required one or more RBC transfusions. Overall the infants' Hb and Hct levels stabilized in the normal range and remained stable. Two of these babies (including the infant discussed here) received maternal Ge:-3 blood. The other two infants received blood from random (probably Ge:3) donors but the anti-Ge3 was not demonstrable in the serum of one of these two babies; the other baby receiving Ge:3-untreated blood had also received IVIG and tolerated the transfusion with no reaction and a reasonable response. The survival rate of the incompatible transfused RBCs is unknown but appears to have been sufficient to treat the severe phase of the HDFN (Table 1).

The neonate described here developed anemia requiring transfusion earlier (on DOL 10) than the other three neonates, whose anemia peaked on DOL 19, 29, or 40, respectively. Our patient, however, was born at 34 weeks and had not left the hospital before she developed severe anemia on DOL 10. The other three infants had been discharged and were subsequently readmitted to the hospital for severe anemia (on DOL 19, 29, and 17, respectively); consequently, they were not monitored as closely as our hospitalized patient.

In 1960, Rosenfield and coworkers⁸ first reported a new high-prevalence antigen, which they called Gerbich (Ge), in pregnant women. Very little evidence of HDFN was noted in the infants; one baby had slight jaundice. But in 2002, Arndt and colleagues⁵ described the first case of severe HDFN due to an anti-Ge3. This case was described in more detail, together with another baby born to the same mother, in 2005.⁶ In 2008 Blackall and colleagues⁷ described a further case of severe HDFN, with late anemia caused by anti-Ge3. All three case reports were very unusual and contrasted with the results encountered with Rh disease.

The authors noted that the course was more similar to HDFN associated with Kell antibodies (e.g., anti-K). Vaughan and coworkers⁹ and Weiner and Widness¹⁰ suggested that anti-K might be causing erythroid suppression, in addition to sensitizing circulating fetal RBCs with IgG as occurs with Rh antibodies. Vaughan and coworkers¹¹ supported their hypothesis by showing that anti-K, but not anti-D, specifically inhibited in vitro growth of K+ erythroid-forming units. Daniels and coworkers¹² extended these findings and confirmed earlier work from 1999,^{13,14} which showed that K appeared before D on developing RBCs in the marrow. Arndt and colleagues⁶ suggested that the same hypothesis could be used for the unusual clinical findings of Ge3-associated HDFN. Ge3 is found on GPC and GPD; GPC develops on RBC membranes earlier than Rh or K.^{14,15} Arndt and coworkers,⁵ Blackall and coworkers,⁷ and Denomme and coworkers¹⁶ were able to show that anti-Ge3, in contrast to anti-D, could have phagocytic and inhibitory effects on erythroid progenitors. Thus, fetal progenitor RBCs in the marrow can be affected by anti-K and anti-Ge3, leading to different clinical and laboratory findings than those found in Rh HDFN. For instance, with anti-K or anti-Ge3 HDFN, hyperbilirubinemia may be mild, if present at all, in the first few days of life. Additionally, antibody titers and amniocentesis, which are classic modalities for monitoring elevated bilirubin levels (as a marker of hemolysis) in fetal circulation in Rh alloimmunization, may give misleading results in patients with anti-K or anti-Ge3 HDFN, because erythroid hypoplasia, not hyperbilirubinemia, may be involved. Late-onset anemia was apparent in all four babies with anti-Ge3-induced HDFN.

Late-onset anemia has been well described in HDFN associated with anti-K as well as other RBC antibodies.^{17–23} Erythroid hypoplasia (or hyperplasia with a low reticulocyte count) has long been recognized to be a cause of late onset anemia (2 to 6 weeks after birth) in Rh antibody-mediated HDFN.^{17,21} Late-onset anemia, as Hurdle and Davis¹⁷ described in some patients with Rh-mediated HDFN, usually presents with a moderately low Hb and a positive DAT. Two mechanisms were thought to account for late anemia: continuing destruction of D+ cells by the specific antibody, combined with progressive disappearance of D– RBCs transfused perinatally.¹⁷ A third mechanism for late-onset anemia was related to “marrow exhaustion” after a phase of hyperproduction with insufficient folic acid or erythropoietin (EPO) synthesis in neonates.¹⁷ That group observed a “definite [direct] relationship” between Hb levels immediately after exchange transfusion and the appearance of late anemia (nadir Hb 15 to 58 days after birth).^{17,19} Our case, as well as the three prior anti-Ge3-mediated HDFN, demonstrate some of each of these three mechanisms in the development of late onset anemia. Hurdle and Walker¹⁷ found no correlation between late anemia and numerous other factors, including birth weight, cord serum bilirubin, neonatal hyperbilirubinemia, the number of exchange transfusions, cord serum anti-D titer, antibody specificity, or the length of time the substance persisted in the serum.

The efficacy of exogenous EPO and IVIG in the setting of anti-Ge3-mediated anemia is uncertain. Our patient and the baby from Case 1 both received IVIG, which possible mode of action is reticuloendothelial Fc receptor blockade, thus competing with the anti-Ge3-sensitized neonatal RBCs and preventing further hemolysis.²⁴ Our patient also received a single dose of epoetin alfa at the outside hospital (on DOL 9), similar to one of the other cases, without any apparent impact on reticulocytosis.⁵ The possibility that anti-Ge3 inhibits erythropoiesis explains, at least in part, the lack of significant response to exogenous EPO. A

recent study showed that RBCs incubated with anti-GPC are unresponsive to EPO because anti-GPC inhibits extracellular-regulated kinase 1/2, a protein kinase through which EPO achieves its effects.²⁵ In that study, RBC incubated (>24 hr) with anti-GPC progressively lost their ability to maintain the electrochemical gradient across their inner mitochondrial membrane, leading to cell death and apparent EPO resistance.²⁵ Exogenous EPO's utility for treating anti-Ge3 HDFN has not been established, and further research about EPO's efficacy is needed before it becomes part of the anti-Ge3 HDFN treatment regimen.

All four infants reported to have developed severe, late-onset anti-Ge3 HDFN were born to Hispanic mothers. Moreover, the one patient in whom an anti-Ge3-related acute mild hemolytic transfusion reaction has been described was a Hispanic woman,⁴ and one of the three women in which Ge antibodies were first reported was described as Mexican.⁸ American Red Cross Blood Services (Southern California Region) recently screened the RBC phenotypes of approximately 1000 of its Hispanic donors and did not identify any Ge:-3 individuals. Nevertheless Reid and Lomas-Francis²⁶ described the selected Yus phenotype (Ge:2,-3) to be more common in the Mexican population.

Planning and action during the prenatal period are necessary to mitigate the management challenges associated with a Ge:-3 mother and her likely Ge3+ baby. Ge:-3 blood is rare (<0.1% of potential donors) and banked blood may not be available for transfusion. Transfusion of the baby or mother with Ge:-3 RBCs may be required. A national search for these rare units may not yield compatible blood in a timely fashion for optimal patient care. The mother may require blood because of postpartum hemorrhage or may have developed a peripartum infection that renders her unable to donate blood. Indeed, one of the three mothers in the case reports summarized here required transfusion of several units of Ge:-3 RBCs after delivery.⁶ Finally, because of the likelihood that the infant will be transferred to a tertiary medical center NICU, distance might prevent the mother from being available to donate blood. Consequently, for expectant Ge:-3 mothers, identification of suitable directed donors (e.g., the mother's siblings) and collection of compatible blood (including maternal blood) before delivery provides the best chance of having compatible blood available when the neonate needs it. As illustrated in Case 1, incompatible Ge+ blood sometimes may have to be transfused in an emergency.⁶ The degree of clinical significance of Gerbich antibodies is not well documented. Much of the early literature uses the term Gerbich antibodies rather than anti-Ge2 and -Ge3, either because these subtypes had not yet been defined or because the appropriate testing was not performed. Thus, the relative clinical significance of anti-Ge2 versus -Ge3 is not clear in the literature. Arndt and colleagues²⁷ recently presented data supporting suggestions that anti-Ge3 is more clinically important than the more common anti-Ge2.

ABBREVIATIONS

DOL	day of life
GP	glycophorin
HDFN	hemolytic disease of the fetus and newborn

NICU neonatal intensive care unit

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Fig. 1.

Treatment course for neonate with anti-Ge3-mediated HDFN during hospitalization through first 3 months of life, showing the infant's Hct (%; ●) on DOL 0 through 121; total bilirubin (mg/dL; ■) on DOL 0 through 92; transfusion (TX) of RBCs; administration of epoetin alfa (star); administration of IVIG (triangles); and phototherapy (P).

TABLE 1

Comparison of laboratory results of four infants with anti-Ge3-mediated HDFN

	Index case	Case 1 (Sibling 1) ⁵	Case 2 (Sibling 2) ⁵	Case 3 ⁶
Mother				
Antibody screen	Positive (4+)	Negative → positive (3+)	Positive (3+)	Positive (3+)
Antibody ID	Anti-Ge3	Anti-Ge3	Anti-Ge3	Anti-Ge3
Subclass	Not tested	IgG1	IgG1	IgG1
Titer @ 37°C	IAT 512	IAT 256	IAT 256	IAT 32
Ethnicity	Mexican	Hispanic	Hispanic	Peruvian descent
Baby				
Gestational age (weeks)	34	37	34	Term
Birth weight (g)	2075			2670
Apgar scores (at 1.5 min)	9, 9	8, 9		
ABO/Rh	O, D+	O, D+	O, D+	O, D+
Initial laboratory results				
DAT/IAT (anti-IgG/anti-C3)	2+/0	2+/1+	3+/1+	2+/1+
Hb (g/dL)/Hct (%) (DOL)	14.8/40.9 (1)	11.8/33.8 (1)	17.5/52.7 (1)	15.6/44.8 (1)
Initial TBili (mg/dL) (DOL)	18.1 (1)	11.8 (1)	10.3 (1)	13.7 (1)
Peak TBili (mg/dL) (DOL)	18.1 (1)	13.5 (1)	21.7 (2)	19.9 (3)
Reticulocytes (%) (DOL)	7.3 (2)	2.4 (1)	4.9 (1)	8.3 (1)

ID = identification; TBili = total bilirubin.

TABLE 2

Comparison of transfusion treatment of four infants with anti-Ge3-mediated HDFN

	Index case	Case 1 (Sibling 1) ⁵	Case 2 (Sibling 2) ⁵	Case 3 ⁶
Anemia				
Nadir Hb/Hct (%)	6.2/17.7	1.8/6.2	6.9/20.8	5.8/16.2
Age at nadir (days)	10	19	29	40
RBC transfusion				
Pretransfusion DAT/IAT	2±/−	2+/3+	2+/0	3+/3+
Total volume (mL)	155	185	40	160
Number of transfusions (DOL)	4 (10, 12, 13, 21)	4 (19, 20, 25, 28)	1 (30)	4 (17,40[3])
RBC source	Mother	Random	Random	Mother
Posttransfusion Hb/Hct (%) (DOL)	10.7/31.3 (11)	13.3 (20)	11.1 (31)	−/36.2 (18)
	17/49.6 (14)	13.8 (21)	9.7 (36)	8.8/26.2 (40)
	17/52.2 (15)	8.6 (26)		
	15.2/47.0 (19)	9.1 (29)		
Discharge Hb/Hct (%) (DOL)	15.9/47.0 (22)	8.5/24.0 (37)	11.1/32.8 (30)	8.8/26.2 (40)
Follow-up Hb/Hct (%) (DOL)	14.1/46.1 (30)	8.8/24.5 (43)	9.7/27.7 (36)	“Stable” and “gradually normalized”
	10.5/30.6 (57)	9.0/25.0 (46)	9.7/29.0 (72)	
	12.9/37.6 (121)		13.0/35.6 (118)	

TABLE 3

Comparison of other treatments of four infants with anti-Ge3-mediated HDFN

	Index case	Case 1 (Sibling 1) ⁵	Case 2 (Sibling 2) ⁵	Case 3 ⁶
Phototherapy (DOL)	Yes (2–9, 11, 14)	Yes (1, 2, 4)	Yes (1–5, 8–11)	Yes (1–6)
Platelet transfusion	No	Yes	No	No
Plateletpheresis (DOL)	No	Yes (21, 22)	No	No
IVIG (DOL)	Two doses [*] (9, 10)	Four doses [†] (29, 30, 31, 32)	No	No
Epoetin alfa (DOL)	One dose [‡] (10)	Seven doses [§] (23, 25, 28, 30, 32, 35, 37)	No	No

^{*}Dose, 1 g/kg.

[†]Dose, 1500 mg.

[‡]Dose, 600 units.

[§]Dose, 500 units.