Comment on Gagne et al, page 437

Pearson syndrome in a Diamond-Blackfan anemia cohort

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In this issue of Blood, Gagne et al describe a cohort of 362 patients clinically classified as having Diamond-Blackfan anemia (DBA), in which 175 (48%) were found to have mutations and deletions in ribosomal protein genes or CAT/AL, and 8 of the remaining patients (2.2% overall) had mitochondrial gene deletions consistent with Pearson marrow-pancreas syndrome (PS). The authors propose that all patients with presumptive DBA should be tested for mitochondrial DNA (mtDNA) deletion during their initial genetic evaluation.1

Sometimes one syndrome turns out to be another: for example, newborn anemia that was first thought to be DBA (MIM #105650) is instead found to be PS (MIM#557000) on genetic evaluation. Should DBA and PS be distinguished clinically first?

About 25% of patients with DBA may have characteristic physical features, such as short stature, low birth weight, abnormal thumbs, cleft lip or palate, and congenital heart disease among others.2 These features are not commonly seen in PS (except low birth weight), and the patients in the Gagne article do not show a specific pattern of physical features. Although both DBA and PS present in infancy with anemia and erythroid hypoplasia, the former do not usually have neutropenia and thrombocytopenia, which were present in all of the PS patients described by Gagne et al. There is a reasonably sensitive and specific blood test for untransfused patients with DBA—red cell adenosine deaminase (ADA)—which is elevated in about 85% of patients with DBA;3 elevated ADA was reported once in PS but the type of specimen was not clear,4 and red cell ADA has not been examined systematically in PS.

Macrocytic red cells, low reticulocyte levels, and elevated hemoglobin F are common in any type of inherited bone marrow failure syndrome and do not distinguish DBA from PS; thus, bone marrow tests may be the most informative. In DBA, the marrow shows erythroid hypoplasia but is otherwise usually normal without significant dyspoiesis. In PS, however, the marrow is usually abnormal, with global hypocellularity and vacuoles in myeloid and erythroid precursors, as were found in the PS patients in the Gagne article (see figure). Vacuolated precursors are not a feature of DBA; they may be seen as an artifact or associated with infection, particularly infection due to parvovirus B19. Their absence in early marrows in the patients studied by Gagne et al is not clearly understood, because vacuoles were seen as early as 2 weeks of age in 1 of their patients. Another feature of marrow in mitochondrial disease is ringed sideroblasts resulting from iron deposition surrounding the nucleus of erythroblasts. The diagnosis of ringed sideroblasts requires at least 5 siderotic granules per cell surrounding at least one-third of the nucleus in at least 15% of erythroblasts (see figure). In general, patients who are heavily transfused and who have an overload of iron may have sideroblasts, but they are not ringed. The differential diagnosis of ringed sideroblasts includes genetic syndromes in addition to PS such as hereditary X-linked sideroblastic anemia, thiamine-responsive megaloblastic anemia, and autosomal recessive mitochondrial myopathy with lactic acidosis. Acquired causes are the myelodysplastic syndrome subtype, which is refractory anemia with ringed sideroblasts, alcoholism, chloramphenicol, and copper deficiency.

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1. Gagne et al. 362 BLOOD, 17 JULY 2014 • VOLUME 124, NUMBER 3

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Vacuoles
Wright-Giemsa

Sideroblast
(Prussian blue)

Bone marrow from a patient with PS. Left: vacuoles in myeloid precursors; right: a ringed sideroblast. See Figure 1E in the article by Gagne et al that begins on page 437.
Perhaps the absence of ringed sideroblasts in very young patients with PS reflects low iron stores and thus should not be used to rule out PS.

The differential diagnosis of pure red cell aplasia anemia in infancy is very short, either DBA or transient erythroblastopenia of childhood. The physical features mentioned earlier may point toward DBA in some cases. Careful examination of the marrow for vacuoles and ringed sideroblasts may suffice to suggest PS. Pancytopenia, as well as signs of liver or renal functional disorders, and particularly lactic acidosis, should point toward PS as well.

There is no doubt that patients need to be properly classified, since those with DBA may respond to treatment with steroids, may have a remission, or may benefit from a stem cell transplant. They need genetic counseling and counseling with regard to their risk of leukemia or solid tumors. Family members who have the same mutated DBA gene should not be used as transplant donors, even if they are not anemic. Conversely, patients with PS have a different prognosis, with probably lower risk of malignancies, but very high risk of development of acidosis, metabolic problems, pancreatic dysfunction, and shorter life expectancy, as well as evolution to Kearns-Sayre neurologic syndrome. PS patients may have improved blood counts and become transfusion independent in childhood, but a spectrum of nonhematologic problems of mitochondrial disease may develop. The median survival in DBA is ~40 years, although it is less than 5 years for PS patients in the literature and in the Gagne et al study. Molecular testing for mtDNA deletions should be used to confirm a clinical suspicion of PS, but it may not be necessary to include this test in the workup of patients who clearly have DBA, despite lack of molecular genetic evidence at this time, because ~30% of known DBA patients do not have mutations in known DBA genes. This will change rapidly in the near future. Thus, appropriate classification of patients is critical but may be apparent from clinical and marrow morphologic data, which may then be confirmed by molecular studies, without such studies being offered to all patients with early-onset anemia.

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**REFERENCES**


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Comment on Yee et al, page 445

**FVIII stabilization: VWF D’D3 will do**

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In this issue of *Blood*, Yee et al have demonstrated that expression or infusion of a truncated von Willebrand factor (VWF) fragment containing the factor VIII (FVIII)-binding D’D3 region of VWF is sufficient to stabilize endogenous FVIII levels in VWF-deficient mice. In the absence of the carrier function of VWF, FVIII is susceptible to rapid proteolysis and clearance resulting in markedly reduced plasma levels of FVIII that contribute to a bleeding diathesis.

VWF and FVIII circulate in the plasma in a tight noncovalent complex. The FVIII binding site of VWF (residues 767-1031), contained within the D’D3 region, interacts with several sites in the light chain of FVIII (acidic a3, C1, and C2 domains). Type 2N von Willebrand disease (VWD) involves mutations in the VWF D’D3 region that impair binding to FVIII, resulting in reduced plasma FVIII levels (5% to 30% of normal) but normal VWF. A recently solved solution structure for the VWF D’ region (residues 766-864), currently in press in *Blood*, describes D’ as being comprised of 2 independently folding domains termed TIL’ (trypsin-inhibitor-like, residues 766-827) and E’ (residues 829-864). It was observed that β-sheets in the TIL’ and E’ domains provide scaffold support to a flexible TIL’ loop. This conformation results in a dynamic TIL’ structure that contains a high positive charge density that may allow for binding to the negatively charged a3 domain of FVIII.

The majority of type 2N VWD mutations are localized to the D’ region, with a preponderance of severe type 2N mutations residing in the TIL’ domain and involving either a loss of cysteine residues or positive charge.

Treatment of quantitative FVIII deficiency is dependent on the biological mechanism by which plasma FVIII levels are reduced. For type 2N VWD, administration of exogenous VWF is required to stabilize levels of endogenous FVIII as a substitute for the dysfunctional mutant VWF. In contrast, in hemophilia A, the normal endogenous VWF is able to act as a carrier for intravenously administered FVIII replacement products. The mean circulating half-life of recombinant or plasma-derived FVIII is between 8 and 12 hours, necessitating prophylactic treatment regimens for hemophilia A patients that are both frequent and expensive. Recent strategies designed to prolong FVIII half-life have focused on chemical (PEGylation) or genetic modification (Fc-fusion) of the FVIII molecule. Although these strategies have resulted in 1.5- to 1.8-fold increases in FVIII half-life relative to the native molecule, it is likely that this observed ceiling on FVIII half-life extension is related to the dominant carrier influence of VWF.

In the studies described by Yee et al, the authors generated a series of truncated VWF variants containing the FVIII-binding region of VWF. These fragments were either expressed or infused into VWF deficient mice,
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