Clinical Manifestations of Paroxysmal Nocturnal Hemoglobinuria: Present State and Future Problems

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Abstract

The clinical pathology of paroxysmal nocturnal hemoglobinuria (PNH) involves 3 complications: hemolytic anemia, thrombosis, and hematopoietic deficiency. The first 2 are clearly the result of the cellular defect in PNH, the lack of proteins anchored to the membrane by the glycosylphosphatidylinositol anchor. The hemolytic anemia results in syndromes primarily related to the fact that the hemolysis is extracellular. Thrombosis is most significant in veins within the abdomen, although a number of other thrombotic syndromes have been described. The hematopoietic deficiency may be the same as that in aplastic anemia, a closely related disorder, and may not be due to the primary biochemical defect. The relationship to aplastic anemia suggests a nomenclature that emphasizes the predominant clinical manifestations in a patient. This relationship does not explain cases that appear to be related to myelodysplastic syndromes or the transition of some cases of PNH to leukemia. Treatment, except for bone marrow transplantation, remains noncurative and in need of improvement. Int J Hematol. 2003;77:113-120.

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1. Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is an uncommon disorder that was first described unequivocally in 1866 as present in a patient with bouts of dark urine, thought to be due to “hemitin,” that were worse in the early morning [1]. Since that time, the clinical and laboratory manifestations have been recorded in numerous works that now give a more complete account of the disorder. In parallel, considerable basic scientific endeavors have yielded information that explains many of these manifestations. Nevertheless, a great deal more needs to be known about the clinical and basic manifestations of this disorder so that therapy, which is at present inadequate, can be improved.

The major clinical manifestations of paroxysmal nocturnal hemoglobinuria can be classified into 3 categories: (1) hemolytic anemia, (2) venous thrombosis, and (3) deficient hematopoiesis. To define the future solutions to the appropriate treatment of the disease, we must consider each separately and all together.

2. Hemolytic Anemia

The cause of the hemolysis in PNH is well documented. Because of the defect in the construction of the glycosylphosphatidylinositol (GPI) anchor [2], 2 proteins important in the defense of the red cell against the hemolytic action of complement are missing—CD55 (decay accelerating factor [DAF]) [3] and CD59 (protectin, membrane inhibitor of reactive lysis, etc) [4]. The result is that the red cells (as well as the other blood cells) are more vulnerable to the hemolytic action of complement than are normal cells [5].

Of these 2 proteins, CD59 appears to be more important. Results of in vitro tests have shown that inhibition of this molecule on normal erythrocytes by antibody results in a susceptibility to complement of those cells nearly equal to the susceptibility of the most abnormal PNH cells (those completely lacking the GPI-anchored proteins), whereas similar inhibition of CD55 results in a modest increase in the susceptibility of normal red cells to the action of complement. The congenital absence of
CD55—the so-called Inab phenotype—results in little if any hemolysis in vitro or in the patient [6], whereas the congenital absence of CD59 results in a striking syndrome of hemolysis similar to that of PNH [7]. Thus if progress is to be made in the prevention of hemolysis, it should concentrate on inhibiting that part of the complement system involved in the formation of the membrane attack complex or on functionally replacing CD59.

Hemolysis becomes most evident when complement is activated. The nocturnal pattern of hemolysis from which the disease acquires its name may be due to the nocturnal absorption of lipopolysaccharide (LPS), a byproduct of the bacterial cell wall, from the gut. LPS markedly activates the complement system, possibly through the mannan-binding protein pathway [8]. LPS is normally bound by monocytes through a GPI-linked protein, CD14 [9], which is missing in PNH [10]. In many patients with PNH, this hemolysis is a minor inconvenience, whereas in others it is a major source of the loss of hemoglobin and other complications attendant upon it. Certainly the latter group would benefit from better knowledge of LPS metabolism and perhaps better ways of controlling its activation of complement.

Complement also is activated by concurrent inflammation or the immune reaction to infections. Most viral disorders will result in a burst of hemolysis, which often becomes day long rather than nocturnal. The most serious hemolysis results from gastrointestinal inflammation, usually viral gastroenteritis. This hemolysis may be due to increased absorption of LPS and the effect of the immune reaction against the virus. It is hemolysis in this setting that is most likely to result in acute renal damage [11].

Immune reactions that ordinarily entail little hemolysis may cause serious hemolysis in PNH. For example, most patients with infectious mononucleosis from Epstein-Barr virus infection generate a low level of cold agglutinin antibodies of anti-i specificity. Except in rare cases in which the titer is very high, these antibodies are not hemolytic to normal cells. In PNH, however, because of the characteristic sensitivity to complement, the presence of the antibodies may result in severe hemolysis (personal experience).

Immunizations and vaccinations are designed to cause limited immunological reactions, but these reactions may activate complement. Ordinarily, this activation is not enough to cause hemolysis of the patient's red cells; however, in patients with PNH, because of the sensitivity of the cells to complement, rapid hemolysis may occur in some cases. Great care should be taken in giving repeated doses of polysaccharide-containing vaccine against Streptococcus pneumoniae, because this treatment has been known to result in severe hemolytic reaction (personal experience).

Administration of a transfusion to a PNH patient may cause a burst of hemolysis of the patient's red cells. This reaction often is alarming because the hemoglobinuria that results is taken as a sign of an incompatible transfusion reaction with hemolysis of the transfused cells. The incidence and cause of the reaction are not certain, but the preponderance of evidence suggests that the reaction is due to activation of complement by immune reactions involving leukocytes or plasma proteins [12]. The problem usually can be avoided with thorough washing of red cells before transfusion, but this step probably is not necessary unless the patient has a history of such reactions [13].

The most direct and obvious result of intravascular hemolysis as seen in PNH is hemoglobinuria. The plasma hemoglobin level is nearly always elevated, and plasma haptoglobin (its binding protein) level is diminished even in a quiescent clinical state. Thus the binding capacity of haptoglobin is readily exceeded, and hemoglobin αβ dimers circulate in the plasma and are filtered by the glomeruli of the kidney. The dimers are resorbed in the proximal tubules, where they are degraded, and the iron is stored in ferritin in the epithelium of the proximal tubule. This iron is detected as urinary hemosiderin in almost all patients with PNH almost all the time, as observed by Marchiafava and Micheli [14,15].

Considerable hemolysis may occur without evidence of hemoglobinuria. As greater hemolysis occurs, the level of αβ globin dimers in the glomerular filtrate will rise to exceed the resorption capacity of the proximal tubules. The result is excretion of the dimers in the urine as hemoglobinuria. If the level of globin dimers becomes so great that the resorption capacity of the proximal tubule for other molecules normally resorbed by this epithelium, such as glucose and small peptides, is impaired, the other small molecules may appear in the urine in a form of temporary Fanconi syndrome of proximal tubular dysfunction.

In rare instances, the concentration of hemoglobin in the tubular filtrate becomes sufficiently high to impair renal function, and acute renal failure results [11,16,17]. This situation usually is seen with gastrointestinal illnesses and is complicated by the inability of the patient to take in water. Although there usually is good recovery if the condition is treated with hydration and careful monitoring of blood pressure, there often is residual renal impairment.

Chronic damage to the kidneys takes 2 forms: proximal renal tubular acidosis and chronic renal failure. The former is rarely recognized (acidosis with low serum bicarbonate level, low potassium level, increased calcuaria, etc). The latter usually is slowly progressive and may result in death. To date, no effective treatment has been found for progressive renal failure, the cause of death in approximately 8% of patients.

Hemoglobin binds nitric oxide (NO) with considerable avidity. However, when it is confined to the red cells, hemoglobin is too distant from the site of NO formation to affect organ function. When it is free in the plasma, on the other hand, hemoglobin is able to diffuse into tissues and sop up NO, causing a local deficiency manifest in contraction of smooth muscle. This effect is most evident in the esophagus; patients with hemoglobinemia frequently have substernal "tightness," especially early in the morning. Manometric studies have shown that the waves of muscular contraction are normal in initiation and propagation but are several times as strong as normal (personal experience). With the clearing of the hemoglobinuria, the spasms subside. Many patients gain benefit from sublingual or transdermal nitroglycerine during periods of heavy hemoglobinuria.

Removal of NO has been implicated in a frequent complication among men with PNH—penile erectile dysfunction during periods of hemoglobinuria. This symptom may be relieved with relatively large doses of sildenafil (Viagra), although this treatment is not always successful. More infor-
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3. Thrombosis

An excessive incidence of venous thrombosis has been noted almost since the first clinical descriptions of PNH and has been recognized both in Europe and in the United States as a leading cause of death since at least 1956 [18]. Results of recent epidemiological studies in Europe and in the United States suggest that the incidence is approximately 40% of all patients [19,20] (J.N. et al, unpublished data). It is curious that the incidence among East Asian patients (Chinese, Thai, and Japanese) and among Mexicans is considerably less than that in other groups. In a recent review, the incidence was found to be approximately 5% in a large Japanese population of PNH patients (J.N. et al, unpublished data).

Venous thrombosis can occur in almost any venous site. Hepatic veins and veins of the portal system are particularly affected [21,22]. Hepatic venous thrombosis can occur as sudden obliteration of major hepatic veins (the classic Budd-Chiari syndrome), often in the setting of severe hemolysis; this form is easily demonstrated with radiographic and sonographic techniques. Clinical examination shows the liver is large and painful to percussion. Ascites may accumulate acutely, and the patient may become jaundiced. Levels of the serum enzymes indicative of liver damage are elevated; care must be used to distinguish the elevations of lactic acid dehydrogenase and aspartate aminotransferase due to hemolysis (the level of alanine aminotransferase is not increased by hemolysis).

In other patients, hepatic venous thrombosis may gradually involve the small radicals of the hepatic vein, a situation much more difficult to demonstrate with radiographic or other techniques [22]. Clinically this disorder may manifest as pain in the right upper quadrant, enlargement of the liver, and the gradual onset of ascites. Signs of portal hypertension may be seen. “Liver enzyme” levels, notably serum alkaline phosphatase, usually are elevated.

Hepatic venous thrombosis may be accompanied by inferior vena caval thrombosis or renal vein thrombosis, which leads to lower body anasarca in the first case and renal dysfunction (proteinuria, renal failure) in the second. In both cases, the thrombus usually is easily visualized by radiographic or sonographic means.

Other veins of the abdomen may be affected with thrombosis, including splanchnic veins [17]; the result is a syndrome of recurrent abdominal pain and sometimes bowel necrosis [23]. Involvement of the portal vein may result in a syndrome of portal hypertension (ascites, esophageal varices, caput medusae, etc) [24]. Thrombosis of the splenic vein can cause massive splenic enlargement and even rupture [25].

Cerebral venous thrombosis is common among the sites in which thrombosis occurs [26,27]. The sagittal sinus is probably the most frequently involved. Thrombosis in this area may present as a history of severe headaches and evidence of increased intracranial pressure [28]. Thrombosis of the veins covering the cerebrum may cause neurologic syndromes consonant with the site affected (e.g., hemiparesis if over the motor strip, Gerstmann syndrome if over the dominant parietal lobe); the brainstem and cerebellum are seldom affected. Once thrombosis has occurred, there is a great chance of recurrence.

Venous thrombosis, both intraabdominal and cerebral [29,30], is a dreaded complication of pregnancy. Results of a retrospective survey study suggested that the rate of thrombosis is approximately 12% of all pregnancies [31]. The overall mortality rate in pregnancy was said to be 20% and the fetal death rate, 8%; more than half of the infants were premature. These figures are similar to those of Hartmann and associates [32]. The complication rate among women of Asian or Mexican origin is apparently less than the overall rate. Given the figures for women of European origin, pregnancy is usually undertaken with great caution.

Thrombosis can occur in dermal veins and lead to necrosis of the skin in some cases [33-35]. This complication is more likely to occur if there has been trauma to the area (one patient who was severely beaten lost large areas of skin and died of the complications [personal experience]) or if the area has been involved in an allergic reaction (one patient had a skin reaction to penicillin and had thrombosis and necrosis wherever the reaction had occurred) [36]. Again, thromboses are likely to be recurrent.

Thrombosis can occur in some unusual sites. Epididymal vein thrombosis results in a syndrome that is confused with epididymitis, orchitis, or torsion of the testicle. Thrombosis of the veins of the uterus can cause a syndrome resembling pelvic inflammatory disease. Thrombosis should be suspected in any instance in which it could account for the symptoms.

The cause of the excessive thrombosis in PNH is not entirely clear and is probably multifactorial. When they are deposited on the platelet membrane, the terminal complexes of complement (polymeric C9) are removed by exocytosis through vesicles that bud off from the cell, carrying the potentially lethal complexes with them [37]. The activation of complement produces many more C9 complexes on the membrane of PNH platelets than on normal platelets because the lack of CD59 means formation is not inhibited; consequently, PNH platelets produce many more of these microvesicles than do normal platelets in vitro [38]. These vesicles, which have been demonstrated in vivo in patients with PNH [39], have been shown to be very thrombogenic, because they externalize the acidic phospholipids that form the site for the prothrombinase complex [40]. Furthermore, PNH platelets are more sensitive to aggregation by thrombin than are normal platelets. Finally, the abnormal monocytes in PNH lack the receptor for plasminogen activator [41] and are thus less able to partake of fibrinolysis.

Why the splanchic and hepatic veins should be so subject to thrombosis is unclear. It is clear that the flow rate is somewhat retarded and may be sufficiently so as to permit the formation of platelet aggregates. Slowed circulation also may permit the activation of complement on the surface of the red cells that can be transferred to the neighboring endothelial cells; the results are expression of tissue factor and initiation of clotting. More work is needed to understand these phenomena.

The current treatments of thrombosis probably are inadequate. Severe thromboses certainly can occur in patients optimally anticoagulated with warfarin derivatives. Heparin...
is clearly useful in acute thrombosis. Low-molecular-weight heparin (LMWH) is simpler to use than and probably equally as effective as conventional heparin; however, sufficient experience has not been gained with the use of LMWH to lead to understanding of the advantages and limits of this agent.

It is important to institute thrombolytic therapy when acute thrombus formation is going on or is very recent. In acute Budd-Chiari syndrome, the use of tissue plasminogen activator has dramatically reduced the size of the liver and allowed the patient to survive without further episodes or progression of thrombosis (personal experience). The use of thrombolytic agents in chronic thrombosis has been suggested but not established [42].

The following suggestions have been made about the treatment of thrombosis in PNH after a metastasis of the problem [31]. It should be noted that these suggestions have not been tested prospectively.

1. Long-term anticoagulation with warfarin derivatives should be considered for patients of European descent who are not thrombocytopenic; alternatively, daily aspirin therapy may be considered.

2. Prophylaxis with heparin or LMWH should be used in the perioperative period, during prolonged immobilization, or during the prolonged use of an intravenous catheter. Prophylaxis with heparin (7,500-10,000 units twice a day) or LMWH (75-100 anti-Xa units/kg) should be started in the first trimester of pregnancy and maintained until 4 to 6 weeks postpartum.

3. Aggressive anticoagulation with heparin or LMWH should be pursued during any acute thrombotic episode. This therapy probably should be maintained for a long term because recurrence is likely.

4. If the platelet count is less than $10 \times 10^9/L$, anticoagulation is contraindicated. When the platelet count is greater than $50 \times 10^9/L$, the usual anticoagulation may be used. Between those platelet counts, care must be taken, and platelet transfusions may be needed.

It is clear from this discussion that the phenomenon of excessive thrombosis and its treatment are insufficiently understood. This is an area in which great aid could be given to patients with PNH, particularly those whose ancestry is European, by improvements in understanding and treatment.

4. Hematopoietic Deficiency

The relationship between bone marrow hypoplasia and PNH has been documented for some time but is still poorly understood. Lewis and Dacie pointed out 40 years ago that many patients with PNH had a history of aplastic anemia and that hematopoiesis appeared to be diminished to a greater or lesser extent in all patients with the disease [43,44]. This association became evident when it was realized that the survival of platelets and granulocytes in PNH was normal [45,46]; that two thirds of patients had thrombocytopenia or granulocytopenia or both [47] indicated there is commonly underproduction of these cells in these patients. As many as 50% of patients with aplastic anemia have a readily detectable population of GPI- (PNH-like) hematopoietic cells, particularly during and after recovery in response to antithymocyte globulin [48-50]. Finally, many patients with PNH develop aplastic anemia as the final stage of the disease [19,20] (J.N. et al, unpublished data).

When marrow culture methods became available, it was shown that the cells of patients with PNH did not grow well in vitro [51]. This finding was true of both the normal GPI+ [52,53] and the abnormal GPI- precursors. This lack of growth was shown not to be a fault of the stroma needed for long-term culture because the PNH cells grew poorly on normal or PNH stroma, and normal cells grew normally on either type of stroma. In these respects, the growth of marrow resembled that of the marrow in aplastic anemia [53].

These findings led to the current dominant hypothesis (the Young-Luzzatto hypothesis) for the explanation of the pathophysiology of PNH [54,55]. This hypothesis supposes that GPI- hematopoietic stem cells exist in very small numbers in the bone marrow of many healthy persons. This supposition has been indirectly confirmed by several laboratories [56]; approximately 1 in $10^6$ granulocytes or lymphocytes is found to lack the GPI anchor in many if not most healthy donors. These defective cells are thought have a growth disadvantage in the normal marrow environment and therefore remain in very small numbers. The fundamental and difficult challenge is to understand how the defective cells come to be expressed in large enough numbers to result in clinical PNH.

The hypothesis suggests that when the marrow is affected by aplastic anemia (thought to be an autoimmune reaction against marrow precursors) [57], these defective precursors are thought to be less suppressed than the normal GPI+ precursors and thus become, by Darwinian principles, the dominant source of hematopoiesis. The findings show that growth characteristics of marrow from patients with PNH are very similar to those of marrow from patients with aplastic anemia. There is marked diminution of colony formation in both cases, and long-term marrow culture is difficult. It is especially noteworthy that the GPI+ precursors in PNH marrow grow no better than the GPI- precursors, a finding consistent with the action of a suppressive element. However, the cause of selection and expansion of the PNH clone(s) is at the present time not at all clear.

An alternative hypothesis is that the dominance of the GPI- clone in PNH arises because of a decrease in apoptosis of the nuclear precursors in PNH marrow [58]. The specificity of this finding has been doubted, because the same phenomenon is seen in other disorders of the bone marrow, including aplastic anemia and myelodysplastic syndromes [59], and is not limited to the GPI- cells [60]. More understanding of the initiation and control of apoptosis is needed.

The GPI- precursors do not appear to have any proliferative advantage in vivo. In experiments in which the PIG-A gene was knocked out, fetuses completely lacking the GPI anchor did not survive to birth. The chimeric animals with a small proportion of GPI+ cells did survive, but the proportion of those cells did not increase with time [61]. These facts suggest that the Young-Luzzatto hypothesis is, in large measure, correct.

PNH is related to another class of bone marrow disorders, the myelodysplastic disorders. The association with
myelofibrosis was made many years ago [62,63]. The occurrence of myelodysplasia in the marrow of some patients with PNH was noted at about the same time [64]. The association with other myelodysplastic disorders has been made since that time [65,66]. Cells lacking GPI-linked proteins have been found in up to 20% of patients with myelodysplastic disorders [67]. These facts are difficult to reconcile with the Young-Luzzatto hypothesis on the basis of current knowledge.

A rare complication of PNH is its evolution into acute leukemia, first noted in 1969 [68-70]. Since that time, many more cases have been reported [71]. With few exceptions, the leukemia is acute nonlymphocytic in type. It is heralded by the disappearance of the abnormal PNH red cells and often by a period of dyserythropoiesis lasting several months. This form of leukemia has occurred in patients who presented with the hemolytic form of PNH as well as in those who presented with aplastic anemia [72,73] or myelodysplastic syndrome. The leukemic cells are invariably lacking GPI-linked proteins, a finding that indicates the origin of the cells in the abnormal clone. The only exceptions are cells seen in patients with myelodysplasia and PNH, in whom the leukemic cells may have GPI-linked proteins. This finding suggests that the cells arose from the myelodysplastic clone of cells [56,74,75]. It is not at all clear how the occurrence of leukemia in the abnormal clone fits with the Young-Luzzatto hypothesis. This association is an area of fruitful and interesting research.

5. Classification and Nomenclature

With the development of newer diagnostic tools, particularly the detection of cells lacking GPI-linked proteins with the use of monoclonal antibodies and flow cytometry, and the recognition that the disease has 2 components—abnormal cells and abnormal hematopoiesis, the diagnostic definition of PNH has become somewhat muddled. Does the patient with aplastic anemia with a very small population of GPI- cells have PNH? Does the patient with hemolytic anemia along with granulocytopenia and thrombocytopenia have only PNH? Where does myelodysplasia fit in? Perhaps a new system of nomenclature is in order.

Clinically, PNH has 2 sets of symptoms and signs—those due to the abnormality of the cells (hemolysis, thrombosis) and those due to the insufficiency of hematopoiesis (hypoplasia or aplasia of the marrow, granulocytopenia, thrombocytopenia). Many patients have a predominance of one or the other set of symptoms, and it is useful when treating the patients to emphasize the predominant abnormality. For these reasons, we propose the following nomenclature.

Aplastic anemia with detectable PNH cells (AA-(PNH)): The clinical syndrome is caused by bone marrow failure with the detection of fewer than 5% PNH granulocytes in the peripheral blood with standard monoclonal antibodies and flow cytometry (note: detection of the abnormal cells in the granulocytes is more reliable than detection in red cells or platelets [76]). This classification would flag patients who might develop overt PNH symptoms in the future.

Aplastic anemia—PNH (AA-PNH): The predominant clinical syndrome is that of bone marrow failure, but the presence of PNH cells (>5% of the granulocytes) might lead to some clinical symptoms.

PNH-aplastic anemia (PNH-AA): The predominant clinical syndrome is that of PNH (hemolysis, thrombosis) but with significant evidence of bone marrow hypoplasia, including granulocytopenia and/or thrombocytopenia.

PNH (classic PNH): The clinical syndrome is that of PNH without clinical evidence of bone marrow hypoplasia.

The presence of myelodysplastic hematopoiesis could also be indicated, either as MDS-PNH when PNH cells are present in the patient with predominantly myelodysplastic hematopoiesis or as PNH-MDS when the clinical syndrome is predominantly due to the abnormal cells of PNH but elements of MDS are significantly present.

At the risk of making more complex the nomenclature of these diseases, this suggested classification would focus therapy on the predominant abnormality and would be helpful in understanding the natural history of PNH.

6. Treatment of PNH

The treatment of PNH is aimed either directly at the abnormalities of the cells or of hematopoiesis or at the effects of the defect. In any case, treatment may be of benefit but is curative in only 1 case—bone marrow transplantation.

In the general care of patients with PNH or PNH-AA, iron supplementation usually is recommended because a large amount of iron is lost either as hemoglobin or as hemosiderin [77]. This supplementation may be accompanied by a burst of hemoglobinuria as first described by Strubing [78]; this effect was found to be due to the emergence of a cohort of defective red cells in the therapeutic response [79]. Supplementation with folic acid also is usually prescribed, although deficiency of this vitamin in this disease has not been reported. It is possible that the folic acid of red cells is reused when the red cells are lysed in the circulation.

The role of adrenocorticosteroids in PNH and PNH-AA is controversial. Reports of the utility of this form of treatment have circulated for many years; however, the doses required are high and cannot be continued on a daily basis. Approximately 60% of patients derive some benefit as measured by an increase in hemoglobin when steroids (0.3-0.5 mg/kg) are administered on an alternate-day basis. With this regimen most patients have few side effects, and none of these side effects is of a serious nature (personal experience).

Androgenic hormones have been advocated, presumably, as improving hematopoiesis [80]. This mode of treatment is not without androgenizing side effects and, in some cases, liver dysfunction. Because the hormones are useful to a minority of patients, a short (1-2 month) trial often is used. If no improvement in hemoglobin level is seen, the drug should not be used.

Treatments that improve hematopoiesis in aplastic anemia have been used in the care of patients with PNH, particularly those with a major aplastic component (AA-PNH and PNH-AA). Antithymocyte or antilymphocyte globulin affects remission in approximately 40% to 60% of patients with aplastic anemia. Remission is complicated in up to 10% of patients by the appearance or increase in the number of
GPI- cells [81]. This immunotherapy improves hematopoiesis in approximately the same proportions of patients with AA-PNH and PNH-AA (personal experience); however, the proportion as well as the number of PNH erythrocytes often increases, and hemolysis increases. Relapse can be treated with repeated administration of the drug, but great care must be taken to administer massive doses of prednisone (500 mg/d) or its equivalent to prevent anaphylaxis and massive hemolysis.

Cyclosporine also is immunosuppressive and has shown great utility in the treatment of aplastic anemia [82]. Use of cyclosporine in PNH has not been documented, but cyclosporine presumably would be useful in treating the hematopoietic deficiency in the disease.

Immunosuppression and subsequent remission of aplastic anemia have been achieved with very high doses of cyclophosphamide [83]. This treatment has been used in the care of patients with AA-PNH and PNH-AA with improvement of hematopoiesis but persistence of the abnormal clone of PNH cells.

Allogeneic and syngeneic bone marrow transplantation has been used successfully in the treatment of PNH when serious prognostic signs are present (onset of aplasia and thrombosis in particular) [84-87]. The complications encountered appear to be those encountered in bone marrow transplantation for other diseases—nonengraftment, graft-versus-host disease, infection, and so on. In almost all cases, the abnormal clone was eliminated. Survival has increased as treatment of the complications has improved, and this form of therapy is becoming more useful to patients with PNH. To date, the incidence of complications in transplantation of the marrow of HLA-identical but unrelated donors is several-fold higher than the incidence in transplantation from related donors, and this therapy generally is reserved for desperate situations. The use of nonablative regimens, which are more easily tolerated, is under preliminary investigation [88].

Because the abnormal gene is known and can be corrected, the role of gene therapy should be considered. In gene therapy, the normalized gene is inserted into hematopoietic precursors in the hope that normal cells or cells containing a corrected GPI- gene relative efficiently into hematopoietic precursors [89] with expression of the GPI-linked proteins. Thus in patients who have essentially replaced the normal hematopoietic stem cells with the defective ones, a clone of PIG-A-replete cells can be generated. It is not clear, however, that this gene transfer is all that need be done. If, as is supposed in the Young-Luzzatto hypothesis, a secondary insult to the marrow has occurred to suppress normal hematopoiesis, then the altered cells would presumably be under the same repression. Thus relief of the suppression of the normal marrow elements will be necessary before gene therapy can be successful.

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