The epidemiology of acquired aplastic anemia

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Aplastic anemia has been studied in many epidemiologic investigations, of which the current report from Barcelona[1] is the most recent. Rare diseases are not readily subject to population-based studies, but there are several reasons why aplastic anemia has been an exception. First, from its initial description in late nineteenth century in Ehrlich's brief but seminal case report, the disease has been observed in young persons; its sporadic occurrence and devastating consequences have invited speculation as to cause. Second, marrow failure early in its history was linked to environmental exposures, first among Swedish bicycle makers, followed by publication of many case series of other workers exposed to benzene, usually in open industries in which the chemical was aerated or uncontained. More idiosyncratically, aplastic anemia also has been associated with pharmaceutical drug use, most infamously with chloramphenicol. Third, anecdotal experience suggested a marked geographic variation in aplastic anemia rates, with comparatively large numbers of patients admitted to hospitals in Asia relative to Europe and the United States.[2] Early attempts to determine potential risk factors for this higher incidence included Custer's description, from the vantage point of Walter Reed Army Hospital in Washington during World War II, of many more cases of aplastic anemia among American soldiers in the Far East than in other theaters of war, which was suggested to be due to malarial prophylactic drug exposure,[3] and cited but not fully published investigations of aplastic anemia among Asians resident in Hawaii, that suggested that they experienced aplastic anemia at an American rate, against a genetic disposition and in favor of environment as a determinant.

A summary review of the epidemiology of aplastic anemia is informed by our present understanding of its pathophysiology, based on several decades of laboratory and clinical observations. Most aplastic anemia appears to be secondary to immunologic destruction of hematopoietic cells. The most important evidence for this hypothesis is the clinical response of the majority (but not all) patients to immunosuppressive therapies, in present practice usually a combination of antithymocyte globulin and cyclosporine, which in about two-thirds of cases yields sufficient improvement in blood counts to avoid transfusion of blood products and infections due to neutropenia. The uncertain mechanism(s) of action of a biologic like a polyvalent serum and multiple and unexpected additional activities of even well defined drugs like calcineurin inhibitors, necessarily makes such inferences conditional, but the exquisite sensitivity of blood counts to low doses of cyclosporine in a high proportion of responding patients and the successful extrapolation of conventional immunosuppressive regimens to alternative therapies such as high doses of a cytotoxic drug, cyclophosphamide, and to monoclonal antibodies directed to T cells, such as daclizumab and alemtuzumab, are highly supportive of the immune hypothesis.

The risk of development of autoimmune diseases has been linked to host genetics, and a few risk factors have been identified that affect the immune response and the susceptibility of the hematopoietic target cell. Aplastic anemia is associated with the class II histocompatabili-

ty antigen DR2,[4] especially in patients who respond to and are dependent on continued immunosuppressive drug therapy. Nucleotide polymorphisms in some cytokine genes also are more common in patients; for γ-interferon, a key regulator of the immune response and inducer of apoptosis in marrow target cells, differences in the gene's promoter would facilitate immune system activation.[5] Recently, inherited mutations in several of the telomerase complex genes have been found in patients with aplastic anemia. Deficiencies in telomere repair would increase susceptibility to marrow failure by quantitatively decreasing the size of the hematopoietic stem cell compartment and qualitatively diminishing its capacity to regenerate after stress. Telomere shortening and its effects on chromosome integrity may also underlie genomic instability and the transformation of aplastic anemia to myelodysplastic syndrome.[6]

Publication of the Barcelona study[1] prompts the consideration of three questions as to how epidemiologic investigation has contributed to our understanding of aplastic anemia: 1) how frequent is the disease? 2) what is the etiology of marrow failure in the community? and 3) what are implications of population surveys for the care of patients and overall clinical outcomes?

Incidence

The incidence reported by Montané *et al.* of 2.34/million[1] is similar to the rate of 2.0 for the International Agranulocytosis and Aplastic Anemia Study in Europe and Israel,[7] of which the Barcelona study is a partial continuation, and of smaller national studies in France,[8] the United Kingdom,[9] Scandinavia,[10] and Brazil.[11] These numbers should permanently replace older figures based on less reliable methodology that suggested a much higher incidence, as for example in Baltimore[12] (the large number of much older patients in that study suggests in retrospect confusion with myelodysplastic syndrome, now appreciated as a far more common diagnosis); in the absence of reliable studies in the United States, we can only assume that the rates are similar to those of Europe. The incidence rates in modern studies refer to both severe and moderate aplastic anemia, as determined by initial blood counts. While some moderate aplastic anemia patients show worsening pancytopenia, others remain stable and may never require treatment; this group may include individuals with constitutional marrow failure either mistakenly not tested for Fanconi anemia (based on the absence of physical anomalies) or with telomere complex mutations (for which diagnostic assays only recently have been available).

The incidence of aplastic anemia is higher in Asia than in the West. A large study from Thailand, conducted with the same methodology and some of the same personnel as the IAAAS, found a rate of 3.9/million for the Bangkok metropolitan area and 5/million in the northeast region of Khonkaen.[13] In the prospective Chinese Epidemiologic Study Group of Leukemia and Aplastic Anemia survey, 7.4/million was reported as a national incidence[14] (only limited methodological details have appeared in English; marrow biopsies were not required for diagnosis, possibly leading to overestimation of the number of cases). Other Asian studies of more limited scope have estimated similar incidence figures of about 5/million in Sabah, an ethnically distinct province of Malaysia[15] and 4.5/million for men in Ho Chi Minh City (*our unpublished data*). Therefore, aplastic anemia appears to be 2 to 3-fold more common in Asia than in Europe. Larger differences between the Orient and the West cited in the historical literature must be regarded as exaggerated due to dependence on personal experience or roughly enumerated hospitalizations, estimates particularly susceptible to differences in the centralization of health care systems and catchment areas. Marked variations in the frequency of aplastic anemia, among European cities or regions of Thailand or China in more recent papers, however, are largely unexplained.

In almost all modern studies of aplastic anemia, the sex ratio has been close to 1:1, which is unusual for immune-mediated diseases. In the largest studies, as in the current report from Barcelona[1] and in Thailand,[13] two patient age peaks of incidence are present, one among young adults and a second in the elderly.

Etiology

Among the potentially etiologic associations between environmental exposures and marrow failure, benzene is the oldest and most widely accepted. The relationship initially suggested by case series of workers exposed through their specific occupations[16] has been detected in some but not all population-based case-control studies, but even when an association was present, the proportion of cases that can be attributed to this chemical has been small. In Thailand, for example, benzene carried a relative risk of 3.5 but accounted for an etiologic fraction of only 1%;[13] in the IAAAS, the relative risk point estimate was of similar magnitude but of only borderline statistical significance.[7] Mild blood count abnormalities that occur with benzene exposure at one extreme, and myelodysplasia and leukemia at the other, may have been incorrectly equated with the diagnosis of aplastic anemia in some occupational surveys. Convincing associations between aplastic anemia and exposure to specific solvents other than benzene have been even more difficult to establish: despite early case reports implicating a variety of chemicals in the causation of aplastic anemia, the limited numbers of population-based studies have not confirmed the clinical literature for such diverse agents as hair dyes, glycol ethers or Stoddard's solvent. In rural Thailand, there were significant associations with several pesticides, including organophosphates, DDT, carbamates, and (borderline) with paraquat;[13] in the IAAAS, occupational insecticide

use also was a risk factor for aplastic anemia, although relatively few patients had been exposed.[7] Large numbers of cases have been collected less systematically. A dose effect has been suggested by lack of evidence of an association with household pesticide exposure, but dose-related toxicity in general has not been supported by surveys of individuals likely to be heavily exposed, including manufacturers and farm workers. The variety of chemical structures implicated is etiologically puzzling by a mechanism of direct toxicity, and agricultural pesticide exposure might be a surrogate for another exposure, as for example to an infectious agent transmitted by an insect, animals, in water or soil. A similarly diverse group of chemicals was implicated in a British case-control study of occupational and environmental exposures.[17]

Marrow failure, both aplastic anemia and agranulocytosis, is a severe idiosyncratic complication of the use of certain medical drugs. A reliable history of drug exposure is often difficult to obtain and susceptible to bias on the part of the questioning physician, the patient, the reporting academic author, and the legal system. Substantial efforts have been made to overcome this problem in studies that focused on drug use.[1,7,13,18] There is no discernible difference in the demographics or clinical behavior, including response to immunosuppressive therapy, between patients classified as having drug-induced versus idiopathic aplastic anemia.[19] Pathophysiologic mechanisms of action are lacking, due to rarity of the reactions and the absence of animal models. Usage of chloramphenicol, so prominently associated with aplastic anemia in the 1950s and following decades of consideration as the commonest cause of the disease, has declined to the point where it has not been a significant risk factor in any systematic epidemiologic study of aplastic anemia, even in Thailand where the need for such an effective and inexpensive antibiotic is substantial.[13] Relative risks for other classes of drugs were characterized in the IAAAS[7] and in the Thai study:[13] in Europe, sulfonylureas and sulfonamides, anticonvulsants, nonsteroidal anti-inflammatories, gold, allopurinol, and penicillamine; and in Thailand, sulfonamides and thiazide diuretics as well as mebendazole. It should be stressed that association is not equivalent to causation; for example, links between marrow failure and second diseases like rheumatoid arthritis are potentially confounding. A much higher proportion of aplastic anemia in the West appears attributable to medical drugs (etiologic fraction of 27% in the IAAAS) than in the East (etiologic fraction of 3% in Thailand).

For other factors, population-based approaches have been less definitive, either because the clinical association is too infrequent (as with eosinophilic fasciitis) or perhaps in reality only coincidental (suggested for pregnancy). Of particular interest is an infectious etiology, serving as a trigger for autoimmunity. Post-hepatitis aplastic anemia is a highly stereotypical syndrome, with pancytopenia following on seronegative liver inflammation, and accounting for about 5-10% of cases in series of patients. Aplastic anemia can similarly (and very rarely) follow on infectious mononucleosis, yet neither of these preceding episodes was significantly associated with aplastic anemia in either the large European or Thai reports. Some novel risk factors in the Thai study, including water source, animal exposure, use of animal fertilizers, and nonmedical needle exposures could account for a large proportion of cases, and they point to an infectious etiology.[13]

Clinical implications

A major contribution of the study of Montané *et al.*[1] is the detailed mortality data;[1] this type of clinical information is usually not provided in epidemiologic studies. Aplastic anemia was uniformly fatal in early case descriptions. Introduction of red blood cell and later platelet transfusions, plus antibacterial antibiotics, improved short term outlook in the mid-twentieth century. There are no accurate figures concerning spontaneous recovery of blood counts, which undoubtedly can occur but seems very infrequent. Cure of aplastic anemia first was accomplished by bone marrow transplantation from a histocompatible sibling and remains the preferred therapy for children and younger adults. More recent experience with alternative donors, usually marrow or mobilized peripheral blood from HLA-matched volunteers, suggests that outcomes in selected patients rival those of conventional allogeneic transplantation from siblings. Immunosuppression, introduced in Europe in the 1970s, is the major alternative and applicable in virtually all cases. Overall survival after antithymocyte globulin and cyclosporine is similar to survival after transplantation in the European registry database.[20] Chronic graft-versus-host disease is the major complication of transplant. For patients who respond to immunosuppression, relapse requiring further therapy is common, and a minority progress to myelodysplasia or develop clinical paroxysmal nocturnal hemoglobinuria. In nonresponders, continued transfusions and increased susceptibility to infection have affected quality of life and caused late mortality, with deaths from bacterial and fungal infections, secondary iron overload, and intracranial hemorrhage.

In the Barcelona series,[1] aplastic anemia remains a serious hematologic disease: mortality at two years after diagnosis (both severe and moderate pancytopenia) was over 40%, and higher in patients 45 years and older. Transplant conferred a better outcome, and those who received androgens did worse. Comparable cumulative long-term survival of about 60% also was found in patients at the National Institutes of Health with severe disease who were treated with immunosuppression in the 1990s[21] and in other recent published single institutional and multicenter or cooperative group experiences.[20]

However, the Barcelona group did note a marked improvement in survival with the era of treatment, with about a 20% increase between patients who were treated in the 1980s compared to the 1990s. This is good and important news for patients with aplastic anemia and the physicians who treat them. We recently have retrospectively analyzed survival in patients referred to National Institutes of Health for treatment. Remarkably, while hematologic response rates disappointingly have remained static, patients categorized as failing the first course of horse antithymocyte globulin have shown steady and marked improvement in survival; survival at five years post-immunosuppression of patients with primary "refractory" aplastic anemia has improved from less than 40% in the 1990s to about 80% in patients treated after 2003.[22] Multiple explanations are likely for why patients have much less likelihood of dying early and later from the consequences of pancytopenia, including better second therapies such as a repeat course of antithymoycte globulin or transplant from a matched unrelated donor (in children and young adults) and from matched sibling donors (in older adults); more facile utilization of platelet transfusions and iron chelation to prevent secondary hemochromatosis; and the introduction of less toxic and more effective antifungal drugs.

The future of epidemiologic studies of aplastic anemia

Future investigations of large populations must proceed beyond interviewer-administered questionnaires to molecular epidemiology. Two recent examples of such approaches will be cited as examples and for encouragement. In a hospital-based study of Canadian pediatric aplastic anemia, a much higher incidence of disease was found in children of Asian descent and correlated to HLA differences, both results by implication favoring genetic rather than environmental risk.[23] In large collaborative studies between the National Cancer Institute and American and Chinese institutions, susceptibility to benzene hematologic toxicity has been correlated to nucleotide polymorphisms in key drug metabolic pathways[24] and to cytokine gene polymorphisms.[25] We can anticipate that the epidemiologic studies of aplastic anemia in the future will reflect this good clinical news and also be more informative of the etiology and pathophysiology of the disease.

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