THE FACTORS UNDERLYING ACQUIRED APLASTIC ANAEMIA

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Abstract: *Aplastic anaemia, a very serious disease due to its morbidity and mortality, can be idiopathic (most cases), or acquired. The careful study of the causal factors involved is particularly important, because some of these factors can be avoided, while others provide valuable prognostic information, as well as information on treatment response. In this paper, we review the known etiologic factors of acquired aplastic anaemia, namely benzene and environmental toxins, radiation, drugs, viruses, pregnancy, malignant clonal diseases, malignancies, immune dyscrasias.*

Aplastic anaemia is a clonal disorder of the haematopoietic stem cell that is characterized by pancytopenia and bone marrow with varying degrees of hypocellularity. Its incidence is rare (1-2 cases per 1 million inhabitants), with a peak between 15 to 26 years, and a second peak above 60 years. There are several congenital diseases in which the incidence of aplastic anaemia is 25-50% (Fanconi anaemia, the Schwachman-Diamond syndrome, amegakaryocytic thrombocytopenia, dyskeratosis congenita). Most forms of the disease forms are acquired, idiopathic. Its secondary forms are caused by benzene and environmental toxins, drugs, viruses, ionizing radiation, pregnancy, malignant clonal diseases, malignancies, immune dyscrasias.

1.1 Benzene and other organic solvents

In the past, benzene was considered to be one of the etiologic factors commonly found in aplastic anaemia, while today it is considered that it plays a more significant etiologic role in leukaemia and myelodysplasic syndrome (MDS).(1) The exact magnitude of the risk of exposure to benzene is not known, but studies conducted in China show that toxic effects occur in 0.5% of those exposed to benzene, and the risk of developing aplastic anaemia is 6 times higher than in the general population.(2) The exposure dose is also important, as exposure at 100 ppm is followed by leucopoenia in 1/3 of the cases. With the introduction of the modern industrial standards limiting exposure to 1 ppm (1 ppm = 3mg/m^3), benzene is no longer one of the most important etiological factors. Aplastic anaemia is correlated with exposure to pesticides (organophosphates, carbamates, chlorinates) and insecticides. A study conducted in Brazil shows a relative risk of 2.7 for organophosphorus pesticides and of 3.0 for solvents / acetone.(3)

Prolonged exposure to oil or oil derivatives, as well as acute exposure to toluene can cause bone marrow aplasia.(4) Studies in Thailand show that young age and poor economic status are higher risk factors for aplastic anaemia than exposure to solvents and pesticides.(5)

1.2 Medication

A number of drugs have been incriminated as a cause of aplastic anaemia, but a direct cause-effect relationship is difficult to prove. Usually, interrupting the incriminated drug does not lead to haematological recovery, unlike in the case of agranulocytosis or drug-induced thrombocytopenia. The mechanism of the disease is idiosyncratic, directed against hematopoietic stem cells, and its treatment is similar to that for the idiopathic forms, except in the case of those who received high doses of chemotherapy, or people with deficient thiopurine methyltransferase (TPMT) - (these lead to bone marrow failure after low doses of thioguanine, azathioprine, mercaptopurine). PCR can help detect the major changes that lead to the inactivation of the TPMT locus.(7)

Chloramphenicol is the most studied drug that causes aplastic anaemia, and its effect is directly myelosuppressive in case of high doses, by mitochondrial toxicity. The risk of developing aplastic anaemia in patients treated with chloramphenicol is 1 in 20.000 or 10-50 times higher than in the general population.(8) The effect of chloramphenicol eye drops has also been studied, but it demonstrated the same incidence of the disease as in the general population.(9)

Atabrine (quinacrine), a prophylactic antimalarial, induces aplastic anaemia in 7 to 28 cases per 1 million of inhabitants.(10)

Many other drugs have been reported to increase the risk of aplastic anaemia, though perhaps the full spectrum of the drugs that can induce this disease is not yet fully understood, due to underreporting or infrequent association. Studies so far have shown an increased risk for gold salts, deltapenicillamines, colchicines, allo/tiopurinol, acetaminophen, salicylates, indole derivatives (11), sulphonamides, thiazides and mebendazole (12), azithromycin and chloramphenicol.(13)

1.3 Viruses

Like drugs, viruses are frequently incriminated, but rarely proven to be the cause of aplastic anaemia. They usually cause transient cytopenias, but only rarely aplastic anaemia. The mechanisms of cytopenia occurrence may be due directly to viral infection, or indirectly, to cytokine release, through an idiosyncratic mechanism directed against stem cells.(7)

Hepatitis viruses have been extensively studied as the cause of aplastic anaemia since 1970. Thus, although the involvement of hepatitis A, hepatitis B, hepatitis C, hepatitis E and G is also mentioned, their incidence is low. Other viruses

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can cause aplastic anaemia, besides hepatitis, namely: parvovirus B19, cytomegalovirus, Epstein Barr virus, echovirus 3, torque teno virus, SEN virus, and non A-E hepatitis.

Hepatitis associated to aplastic anaemia is a distinct clinical syndrome, which occurs up to 6 months after an episode of acute hepatitis, is documented in 2-5% of aplastic anaemia cases, it usually occurs in young males, and it has a severe or fulminant evolution and response to immunosuppressive therapy and bone marrow transplantation.(14) The pathogenetic mechanism is immune-mediated, activating T1 lymphocytes as cell effectors, with the primary target being the liver.(15) Aplastic anaemia occurs in up to 30% of patients after orthotopic liver transplantation for fulminant seronegative hepatitis.(16)

Parvovirus B19, which has also been intensively studied, infects the proerythroblast and causes transient red series aplasia, especially in people with chronic haemolytic anaemia. Parvovirus can also cause pancytopenia, especially in immunocompromised individuals. The receptor for the virus is the erythrocyte P antigen (globoside), which is found on the erythroid progenitors, erythrocytes, and in low concentrations in other tissues as well (foetal myocardium, placenta etc.).(17)

In rare cases, the Epstein Barr virus can also cause aplastic anaemia, which occurs 4-6 weeks after acute infection, by a mechanism that is still uncertain (direct or immunologic effect). HIV infection often causes varying degrees of cytopenias, and rarely aplastic anaemia, by a viral suppression mechanism and / or by effect of antiretroviral drugs.(10)

1.4 Ionizing radiation

Ionising radiation is toxic to the bone marrow, acting on stem cells / bone marrow progenitors, and the effects are dose dependent.(6) High doses of > 1.5 Gy per body are followed by severe pancytopenia occurring 2-4 weeks after exposure. The lethal dose is of 10 Gy, while the LD50 is 4.5 Gy.(7) Although pancytopenia occurs after a single exposure to a high dose, there is no evidence to support an increased incidence of aplastic anaemia in survivors of the atomic bombings.

1.5 Pregnancy

The literature describes several cases of pregnancy-associated aplastic anaemia, although the relationship is still uncertain.(18,19) The effect of haematopoiesis suppression by the oestrogens secreted during pregnancy, the maternal-foetal microchimerism (the presence of foetal or placental CD34 +, CD38 + cells in the maternal blood), as well as by the increased synthesis of maternal stem cells during pregnancy.(20)

Aplastic anaemia may occur during pregnancy or shortly after birth, and in this case the pregnancy aggravates the disease, which may improve after birth (21); or pregnancy may occur in a patient with aplastic anaemia, in which case relapses of the disease in subsequent pregnancies are possible.(22) A retrospective study conducted in Europe on 36 pregnant women with aplastic anaemia who received immunosuppressive treatment, shows that it is possible to have a healthy newborn after immunosuppressive treatment, with complications occurring more frequently in patients with low platelet counts and who associate paroxysmal nocturnal haemoglobinuria (HPN).(23) The treatment consists in termination of pregnancy (in the early pregnancies), supportive care and immunosuppression treatment (in advanced pregnancies) and bone marrow transplantation (after birth).(24)

1.6 Malignant clonal diseases

The association of aplastic anaemia with PNH is well known, and it is believed that 50% of cases of aplastic anaemia have small PNH clones detectable by flow cytometry, and that 25% of cases of PNH evolve into aplastic anaemia.

1.7. Among malignant diseases that can evolve into aplastic anaemia, the most common are hairy cell leukaemia and acute lymphoblastic leukaemia, as well as the graft versus host disease and thymoma as representatives of immune dyscrasias (more frequently, it causes pure red cell aplasia, but it can also cause aplastic anaemia).(25)

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