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Review article

Relevance of alloimmunization in haemolytic transfusion reaction in sickle cell disease

Impact de l'alloimmunisation sur les hémolyses post-transfusionnelles au cours de la drépanocytose

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Abstract

Transfusion remains a key treatment in sickle cell disease. The occurrence of a delayed haemolytic transfusion reaction is not rare and is a life-threatening event. The main cause of delayed haemolytic transfusion reaction is production of alloantibodies against red blood cell antigens. The high rate of alloimmunization in sickle cell disease patients is mainly due to the differences of red blood groups between patients of African descent, and the frequently Caucasian donors. From an immuno-haematological point of view, delayed haemolytic transfusion reaction in sickle cell disease patients has specific features: classical antibodies known to be haemolytic can be encountered, but otherwise non significant antibodies, autoantibodies and antibodies related to partial and rare blood groups are also frequently found in individuals of African descent. In some cases, there are no detectable antibodies. As alloimmunization remains the main cause of delayed haemolytic transfusion reaction, it is extremely important to promote blood donation by individuals of African ancestry to make appropriate blood available.

Keywords: Sickle cell disease; Alloimmunization; Haemolysis; Transfusion; Autoantibodies; Partial RH

Résumé

La transfusion est un des traitements majeurs de la drépanocytose. Les réactions d'hémolyse post-transfusionnelles retardées ne sont pas rares chez les patients drépanocytaires, et peuvent mettre en jeu le pronostic vital. La principale cause est la production par ces patients d'alloanticorps antiérythrocytaires. La fréquence élevée d'alloimmunisation est surtout due au polymorphisme des antigènes de groupes sanguins entre donneurs d'origine caucasienne et patients d'origine afro-antillaise. Sur un plan immuno-hématologique, ces accidents présentent des caractéristiques au cours de cette maladie : les alloanticorps classiques, aux propriétés hémolytiques bien connues sont les plus souvent rencontrés, mais des anticorps non classiquement significatifs, des auto-anticorps, des anticorps liés à un antigène « partiel » du patient ou à la présence d'un sang rare peuvent aussi être retrouvés au cours de ces accidents. Dans un tiers des cas, aucun anticorps n'est retrouvé. L'alloimmunisation restant la cause majeure de ces accidents, il est primordial de promouvoir le don de sang dans les populations d'origine afro-antillaise.

Mots clés : Drépanocytose ; Alloimmunisation ; Hémolyse ; Transfusion ; Auto-anticorps

1. Introduction

Sickle cell disease is the most frequent inherited disorder in France. There are about 10,000 patients suffering from sickle cell disease in France, mostly originating from Africa and the West Indies. Transfusion is a life-sustaining therapy for these patients: it decreases morbidity and mortality by treating acute chest syndrome, stroke, and splenic sequestration. Intensive transfusion therapy also prevents cerebral vasculopathy in children with sickle cell disease [1].

However, transfusion has side-effects in patients with sickle cell disease, mainly iron overload and alloimmunization. In this review, we will explore the consequences of alloimmunization in these patients and more specifically the life-threatening reaction known as the delayed haemolytic transfusion reaction.

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2. Alloimmunization in patients suffering from sickle cell disease

Within the general population of transfused patients, patients suffering from sickle cell disease are among those most frequently alloimmunized [2]. The substantial polymorphism of immunogenic antigens between donors of European descent and these patients mostly of African descent is clearly the major factor contributing to the high prevalence of red blood cells alloimmunization. Indeed, the incidence of alloimmunization is lower when donors and patients have similar ethnic origins [3,4]. Although it could be argued that the low rate of alloimmunization reported in countries with ethnically homogeneous populations may reflect the less extensive use of transfusion in these countries, for many patients, alloimmunization occurs early during transfusion treatment. Also, the red blood cells alloimmunization rates in the general population of two African countries are about the same as those in patients suffering from sickle cell disease in these countries (1–6%) [5].

Antibodies produced by patients suffering from sickle cell disease are determined by both the differences between donors and recipients, and the relative immunogenicity of the foreign antigens, closely associated with the degree of histocompatibility promiscuity. The antibodies most frequently observed in transfused patients with sickle cell disease are against C, E, Fy^a, Jk^b and S [6,7]. Some less frequent antibodies are also found when patients carry a partial antigen or have a rare blood group. The antibodies linked to these situations are more difficult to manage, because the partial status is not always recognizable, and also because supply of rare blood types may not be sufficient.

Interestingly, despite identical transfusion protocols, some patients become immunized and others do not. This suggests the involvement of immunogenetic and acquired factors. Mouse models have been used for investigating alloimmunization risk factors, and in particular, inflammation, which is likely to be a major factor [8].

It is clear that alloimmunization leads to transfusion becoming both more complicated and more dangerous for the patient. The first consequence is the delay before transfusion due to the difficulty of finding blood units that match the antibodies produced. The results of screening tests can be also difficult to resolve when many antibodies are present, or when antibodies are produced in a patient with a partial or a rare blood group. The most serious consequence of alloimmunization in patients suffering from sickle cell disease, however, is the risk of a delayed haemolytic transfusion reaction with hyper haemolysis. This side effect of transfusion has consequences for the outcome of the disease and can be life-threatening. Alloimmunization is also a risk factor for the production of autoantibodies against red blood cells [9]. Autoantibodies can enhance the haemolytic reaction, participating in the so-called bystander haemolysis and explaining in some cases, the destruction of both the patient's own and transfused red blood cells. Autoantibodies also complicate screening tests, as specific and time-consuming techniques are required to detect relevant alloantibodies that can be masked by autoantibodies.

3. Haemolytic transfusion reaction in sickle cell disease: the most harmful effect of transfusion

3.1. Classic situations of haemolytic transfusion reactions

Haemolytic transfusion reactions are a well-known complication in multiply transfused patients. This reaction generally results from a conflict between antigens expressed on donor red blood cells and antibodies produced by the recipient. For ABO blood group incompatibilities, the antibodies are naturally occurring rather than being the result of previous exposure to the antigens. In such situations, applying ABO compatibility rules is sufficient to prevent transfusion reactions. In cases of error, the haemolytic accident is immediate, and frequently dramatic, involving intravascular haemolysis through complement activation (membrane attack complex). More frequently, transfusion reactions are delayed. Such delayed reactions result from a secondary immune response in a previously transfused or pregnant patient in whom an alloantibody has developed. Screening tests are intended to detect these antibodies which can then be taken into account by giving red blood cells free of the particular antigen. In some cases, however, the alloantibody titre may be below detectable levels at the time of pre-transfusion testing and the antibody is therefore ignored. Upon repeat transfusion, alloantibodies are restimulated, with increased cytotoxic capacities, and a switch to immnunoglobulin gamma 1 (IgG1) and IgG3 subclasses; the titre, affinity, and capacity to bind complement all increase. The haemolytic transfusion reaction develops within 4 to 6 days. Screening tests of patient plasma and direct antiglobulin tests (which characterize the in vivo sensitization of donor red blood cells by the recipient antibodies) will then give positive results. Donor red blood cells are mostly destroyed by macrophages expressing immunoglobulin (Ig)Fc receptors in the spleen and in the liver. Complement opsonization may synergise IgG-mediated haemolysis through a C3b receptor on macrophages. Prevention of accidents of this type is currently based on taking any previously detected antibodies into account, and avoiding alloimmunization against the major immunogenic antigens carried by red blood cells. Initially, these antigens are the RH and KEL antigens; when patients become immunized, they also include FY, MNS and JK antigens.

3.2. Specific features of the delayed haemolytic transfusion reaction in patients suffering from sickle cell disease

The characteristic features of delayed haemolytic transfusion reaction in sickle cell disease are a delayed accident (more than 6 days after transfusion), a dramatic drop in post-transfusion haemoglobin to below pre-transfusion levels caused by destruction of both donor and recipient red blood cells, the presence of sickle cell disease-related manifestations, and exacerbation haemolysis on further transfusion. Profound reticulopenia is frequent and may contribute to the drop in the haemoglobin concentration.

Various serological features may be associated with this post-transfusion hyperhaemolysis syndrome. The antigen differences between donor and recipient can lead to patients developing