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State of the art

Management of delayed hemolytic transfusion reaction in sickle cell disease: Prevention, diagnosis, treatment

Hémolyse post transfusionnelle du patient drépanocytaire : prévention, diagnostic, traitement

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Abstract

Transfusion remains a key treatment of sickle cell disease complications. However, delayed hemolytic transfusion reaction, the most serious complication of transfusion, may be life-threatening if hyperhemolysis develops. This syndrome is generally underdiagnosed because its biological and clinical features resemble those of vaso-occlusive crisis, and red blood cell antibodies are frequently absent. Further transfusions may aggravate the symptoms, leading to severe multiple organ failure and death. It is therefore essential to prevent, diagnose and treat this syndrome efficiently. Prevention is based principally on the attenuation of allo-immunization through the provision of extended-matched RBCs or the use of rituximab. However, such treatment may be insufficient. Early diagnosis might make it possible to implement specific treatments in some cases, thereby avoiding the need for secondary transfusion. Diagnosis is dependent on the knowledge of the medical staff. Finally, many treatments, including steroids, immunoglobulins, erythropoietin and eculizumab, have been used to improve outcome. Improvements in our knowledge of the specific features of DHTR in SCD should facilitate management of this syndrome.

Keywords: Sickle cell disease; Hemolysis; Transfusion; Allo-immunisation

Résumé

La transfusion reste un traitement majeur de la drépanocytose, à titre préventif mais aussi curatif. Cependant, la réaction transfusionnelle la plus sévère est l'hémolyse post-transfusionnelle retardée qui peut se compliquer d'une hyperhémolyse entraînant dans certains cas une insuffisance multi-organe et le décès du patient. Ce syndrome est souvent sous diagnostiqué du fait de ses caractéristiques particulières au cours de la drépanocytose, essentiellement l'apparition ou la récurrence après une transfusion d'une crise vaso-occlusive, avec une absence d'anticorps anti-érythrocytaires détectables au bilan immun-hématologique. Une retransfusion peut être fatale par exacerbation du processus hémolytique. La prise en charge de cette réaction est basée sur la triade : prévention, diagnostic et traitement. La seule prévention connue est celle de l'allo-immunisation, avec dans certains cas une prévention par le rituximab. Mais cibler uniquement l'allo-immunisation semble insuffisant, puisque de nombreux cas se développent sans anticorps détectables. Le diagnostic est basé sur la formation et l'information de l'ensemble des acteurs médicaux. La reconnaissance de ce syndrome particulier est indispensable. Enfin, le traitement repose sur les thérapeutiques classiques des accidents transfusionnels : immunoglobulines, corticoïdes, mais aussi sur l'érythropoïétine, et plus récemment, l'éculizumab. Des efforts de recherche sont indispensables pour comprendre les mécanismes de cette réaction et adapter, en fonction des mécanismes physiopathologiques prévention et traitement.

Mots clés : Drépanocytose ; Hémolyse ; Transfusion ; Allo-immunisation

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Sickle cell disease (SCD) is the most frequent inherited disorder in France, predominantly affecting patients originating from Africa and the Caribbean. Transfusion is a life-sustaining therapy in this disease. It decreases morbidity and mortality, by treating acute chest syndrome, stroke, and splenic sequestration. Moreover, intensive transfusion therapy prevents cerebral vasculopathy in children with SCD [1–3].

Delayed hemolytic transfusion reaction (DHTR) classically results from the restimulation of clinically significant antibodies against the red blood cells (RBCs) transfused. Within three or four days of transfusion, the antibodies produced bind to the RBCs, destroying them by various pathways, including phagocytosis and complement-mediated hemolysis. Symptoms of hemolytic anemia are frequently observed in this setting. It is becoming increasingly apparent that DHTR is both frequent and life threatening in SCD patients. The risks of DHTR have been underestimated in SCD patients, mostly because of the specific clinical features of this syndrome in SCD. Several retrospective studies, observational studies and case reports have highlighted the characteristics of this syndrome in SCD [4–7].

DHTR generally occurs 5 to 10 days after transfusion, and its symptoms resemble those of vaso-occlusive complications. Anemia frequently becomes more severe than observed before transfusion, due to the destruction of both transfused and autologous RBCs, and some patients may develop profound reticulopenia. HbA, a marker of the transfused RBCs in patients producing only HbS, becomes markedly less abundant and may cease to be detectable. Further transfusions may exacerbate the hemolysis, and the clinical symptoms. Blood group polymorphism between donors of European ancestry and patients of African ancestry frequently accounts for the antibodies detected. However, in some cases, the antibodies detected may not be those classically considered significant, or there may be no detectable antibodies. This situation makes it particularly difficult to determine the mechanisms underlying this syndrome. Based on published findings and our own experience of following 3000 adult patients at a reference center, we review here the prevention, diagnosis and treatment of this severe condition.

1. Prevention

Given the current unpredictability of this reaction, there is an urgent need to identify the particular clinical and biological characteristics in the patients' history or condition associated with the occurrence of this transfusion reaction, so as to avoid transfusion or adapt the transfusion regiment according to the risk.

Many case studies have provided evidence to suggest that three factors are associated with a higher risk of the patient developing DHTR:

- the transfusion indication, the risk being higher for patients undergoing transfusion for an acute condition;
- high responder status for allo-immunization;
- a history of DHTR.

It may already be possible to prevent many cases of DHTR, by focusing on these factors, discussing the indication for transfusion in cases in which these three risks are encountered and proposing alternative treatments or taking measures to prevent allo-immunization in situations in which transfusion is absolutely necessary.

However, it would not be possible to prevent all cases by simply taking these three factors into account, as no antibodies are detectable in at least 30% of described cases. The mechanism underlying the reaction in such cases remain unknown.

Allo-immunization is currently the only pathophysiological risk factor for DHTR for which partial prevention is possible. The choice of units for transfusion may help to prevent allo-immunization. RH and KEL are known to be the most immunogenic blood groups. Antibodies against these systems are the most frequent in SCD patients [8–10]. The matching of RBCs for RH (D, C, E, c, e) and KEL (K) status should therefore be included in standard care, as is already the case in France, and many other countries. However, the importance of extended matching to other blood groups (FY, JK, MNS) and of matching partial RH phenotypes, as are frequently found in SCD patients, remains discussed. We have shown that SCD patients who are already immunized have a 61% higher risk of producing additional antibodies after subsequent transfusions [9]. It has also been shown that about half the SCD patients displaying immunization produced their first alloantibody before transfusion of the eighth unit [11]. There therefore seem to be two types of patients: low responders, who never become immunized, and high responders, who become immunized after minor transfusion exposure, and continue to develop new antibodies. The best approach might therefore be to apply measures to prevent allo-immunization only in high responders, but this would require patient characterization. It is relatively straightforward to classify patients as high responders in cases of positive screening tests, or a known history of immunization, or as low responders if they have a long history of transfusion without immunization. However, it is much harder to predict responder status in a new patient or a patient with no known history of transfusion. Certain inflammatory conditions have been shown to favor allo-immunization [12], and attempts have also been made to differentiate between high and low responders on the basis of the phenotype and function of competent immune cells, together with genetic markers [13–16]. However, confirmation of the results obtained is required, and no simple test for use in routine clinical practice has yet been developed. In France, we have already advised the extension of matching to minor blood groups (FY, JK, MNS) exclusively for patients already immunized. For patients seen for the first time or with no history of transfusion, we maintain the RH and KEL matching protocol, with close monitoring of allo-immunization, as for non-immunized patients who have undergone large numbers of transfusions. In all cases, RBC units are also serologically matched with the patient's plasma, to prevent immediate conflict between RBCs and antibodies against low-frequency antigens not detected with the screening test because of the absence of test RBCs carrying the corresponding antigen.