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ORIGINAL PAPER

Delayed haemolytic transfusion reaction in paediatric patients with sickle cell disease: A retrospective study in a French national reference centre

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Summary

Delayed haemolytic transfusion reaction (DHTR) is a life-threatening haemolytic anaemia following red blood cell transfusion in patients with sickle cell disease, with only scarce data in children. We retrospectively analysed 41 cases of DHTR in children treated between 2006 and 2020 in a French university hospital. DHTR manifested at a median age of 10.5 years, symptoms occurred a median of 8 days after transfusion performed for an acute event (63%), before surgery (20%) or in a chronic transfusion programme (17%). In all, 93% of patients had painful crisis. Profound anaemia (median 49 g/L), low reticulocyte count (median 140×10^9/L) and increased lactate dehydrogenase (median 2239 IU/L) were observed. Antibody screening was positive in 51% of patients, and more frequent when there was a history of alloimmunisation. Although no deaths were reported, significant complications occurred in 51% of patients: acute chest syndrome (12 patients), cholestasis (five patients), stroke (two patients) and kidney failure (two patients). A further transfusion was required in 23 patients and corticosteroids were used in 21 to reduce the risk of additional haemolysis. In all, 13 patients subsequently received further transfusions with recurrence of DHTR in only two. The study affords a better overview of DHTR and highlights the need to establish guidelines for its management in children.

KEYWORDS
children, corticosteroids, haemolysis, sickle cell disease, transfusion

INTRODUCTION

Sickle cell disease (SCD), a frequent inherited disease worldwide, leads to the production of abnormal haemoglobin S (HbS), which causes vaso-occlusion, haemolytic anaemia, inflammatory state and chronic vascular injuries.[1] Despite broad use of hydroxycarbamide and the development of news drugs,[2,3] red blood cell (RBC) transfusion is essential to manage certain complications of SCD in children, including acute chest syndrome (ACS), acute splenic sequestration or cerebral vasculopathy. Delayed haemolytic transfusion reaction (DHTR) is a rare and potentially life-threatening complication leading to destruction of both transfused and autologous RBCs. It is characterised

by severe haemolytic anaemia with Hb levels below pre-transfusion levels and inappropriately low reticulocyte counts, usually within 6–10 days after RBC transfusion.[4] The incidence in patients with SCD ranges from 4% to 7% after ABO Rhesus (Rh) Kell-matched RBC transfusion.[4–6] Most studies have described DHTR in adult patients and only a few small paediatric cohorts have been reported.[6–10] DHTR manifests as painful crisis (PC) and haemolysis with dark urine and jaundice.[6,7,10] DHTR is frequently followed by an ACS, kidney or liver failure and an increased risk of mortality (~10%).[6,7] Several risk factors for DHTR have been identified in a prospective study in adults, and include history of DHTR, alloimmunisation or low number of RBC transfusions.[5] Antibody screening is positive in 50%–60% of cases,[6,7,10] frequently with antibodies of unclear significance.[7,10] Although the pathophysiology is not fully understood, identification of alloantibodies suggests involvement of the immune system[4] and complement activation.[11–14] According to recently published guidelines,[15] if anaemia is well tolerated, RBC transfusion should be avoided due to the risk of exacerbating haemolysis. Immunomodulatory treatment, including corticosteroids (CSs), intravenous polyvalent immunoglobulins (IVIGs), rituximab and/or eculizumab, should be considered especially if RBC transfusion is required. In this retrospective single-centre study, we describe the clinical and laboratory features of DHTR in 41 children with SCD, with a focus on management, as only scarce data are reported in children.

METHODS

All children with SCD experiencing DHTR and treated at Robert Debré University Hospital in Paris, a tertiary centre with intensive care unit, between January 2006 and May 2020, were consecutively included in this retrospective study.

Definition

A DHTR was defined as: (i) anaemia with Hb equal to or below the Hb level immediately before the triggering RBC transfusion and, (ii) onset of symptoms within 3–30 days after the triggering RBC transfusion and, (iii) presence of symptoms including asthenia, PC affecting ≥one bone,[1] dark urine and/or jaundice, and (iv) with or without the development of antibodies against RBCs.[4,15] Complicated DHTR was defined as the occurrence of at least one of the following complications after the diagnosis of DHTR: (i) stroke; (ii) ACS, defined as respiratory symptoms with new infiltrates on chest X-ray[16]; (iii) kidney failure, i.e., increased plasma creatinine ≥26.5 μmol/L or >1.5-fold above baseline[17]; (iv) heart failure with left ventricular ejection fraction <50%; (v) severe cholestasis, i.e., elevated total bilirubin >100 μmoL/L with conjugated/total bilirubin ≥50% or liver failure with a prothrombin time of <50% below normal in the absence of vitamin-K deficiency. Acute splenic sequestration was defined as acute anaemia with increased spleen size and thrombocytopenia.[18]

Transfusion protocol

All patients received phenotypically cross-matched RBC transfusions compatible for ABO, Rh (D, C, E, c, e) and Kell blood antigens. Patients with a history of alloimmunisation received extended phenotype (EP) RBC transfusion matched to the antibody specificity and to other immunogenic common antigens such as Duffy (Fya, Fyb), JK (Jka, Jkb), and MNS (Ss).

Data collection

The data collected from medical records included sociodemographic and SCD characteristics, DHTR features (clinical symptoms, laboratory features, complications), acute management and DHTR recurrence during follow-up.

Blood groups, antibody screening by direct and indirect antiglobulin tests and antibody identification by indirect antiglobulin test and enzyme technique (papain) were retrospectively collected from the French Blood Agency (EFS). The RBC panel was produced by National Blood Service Reagents (CNRGS, Paris, France) and Diamed (ID-Diapanel).

Statistical analysis

Quantitative variables are expressed as median and first and third quartile (Q1–Q3) and qualitative variables as numbers and frequencies (%). Pearson's chi-squared test using R software (Version 4.2.0) was used to compare frequencies, with a $p < 0.05$ considered as statistically significant.

The study obtained a positive opinion (N°IRB00006477) from the local Ethics Committee and complied with the General Data Protection Regulation (N°20 200 721 093 713). Parents and patients were informed in writing and oral consent was collected.

RESULTS

Baseline characteristics before DHTR occurrence

During the study period, 41 children with SS/Sβ0 SCD were treated in our hospital for DHTR and were included, representing a prevalence of DHTR of 5% in SS/Sβ0 children transfused in the Robert Debré Hospital cohort. Baseline characteristics are presented in Table 1 and Table S1. Four patients (10%) had glucose-6-phosphate dehydrogenase deficiency. All patients had already received RBC transfusion for acute events before the transfusion associated with DHTR,

TABLE 1 Baseline characteristics before delayed haemolytic transfusion reaction occurrence in the 41 patients

Characteristic	Value
Baseline characteristics before DHTR occurrence	
Age at DHTR, years, median (Q1–Q3)	10.5 (7–15)
Female, *n* (%)	24 (59)
G6PD deficiency (*n* = 40), *n* (%)	4 (10)
Baseline Hb, g/L (*n* = 40), median (Q1–Q3)	75 (70–85)
Born in Africa, *n* (%)	11 (27)
RBC transfusion in Africa, *n/N* (%)	6/11 (55)
Hydroxycarbamide treatment[a], *n* (%)	12 (29)
Splenectomy[b], *n* (%)	4 (10)
Past RBC transfusion history before DHTR occurrence, median (Q1–Q3)	
Number of RBC transfusions received	3 (2–6)
Number of RBC units received	4 (2–9)
Age at first RBC transfusion	4 (2–7)
Indication for RBC transfusion, *n/N* (%)	
Acute events[c]	35 (85)
Acute events and chronic transfusion programme[d]	6 (15)
History of alloimmunisation, *n* (%)	11 (27)
With ≥1 classical antibodies[e]	9/11 (82)
With ≥1 other antibodies[f]	6/11 (55)
With ≥1 auto-antibodies	2/11 (18)
Number of antibodies, *n* (%)	
1	2/11 (18)
2	5/11 (46)
3	3/11 (27)
4	1/11 (9)

Abbreviations: DHTR, delayed haemolytic transfusion reaction; G6PD, glucose-6-phosphate dehydrogenase; Hb, haemoglobin; RBC, red blood cell.

[a]For repeated painful crisis, acute chest syndrome and/or low baseline Hb.

[b]For repeated acute splenic sequestration.

[c]For acute anaemia, painful crisis or acute chest syndrome.

[d]For cerebral vasculopathy, painful crisis despite hydroxycarbamide use or acute splenic sequestration.

[e]'Classical' antibodies, known to be pathogenic: anti-Rh (three of 11 patients), anti-Fya (one of 11), anti-Jkb (three of 11) or anti-S (five of 11).

[f]'Other' antibodies are antibodies not known to be pathogenic (anti-Lea/Leb: three of 11 patients, anti M: one of 11) or directed against high frequency RBC antigens (anti HI: one of 11 patients) and/or antibodies of unknown specificity (AUS, three of 11 patients).

and six patients (15%) were also included in a chronic RBC transfusion programme. In all, 11 patients (27%) had a history of alloimmunisation, nine of whom developed at least one alloantibody known to be pathogenic. The other two developed only antibodies against Lewis antigens.

DHTR features

The DHTR features are presented in Table 2 and Table S1. An inflammatory context (acute event, surgery) was present at the time of the triggering RBC transfusion or a few days after in most patients (83%). In the seven patients who had DHTR while on a chronic RBC transfusion programme, DHTR after 1 or 2 months in three patients and after 12–36 months in the other four. Almost all patients displayed PC (93%), requiring morphine (76%) and ketamine adjuvant treatment (45%), and three patients also had acute splenic sequestration. The median nadir of Hb was 49 g/L. HbA levels were available for 15 patients and were consistently low (median 8%), reflecting loss of transfused RBCs. No deaths were reported. Complications occurred in 21 patients (51%), including ACS (29%), severe cholestasis (12%), kidney failure not requiring dialysis (5%) and stroke (5%).

Immunohaematological features are summarised in Figure 1. During DHTR, patients with a history of alloimmunisation more frequently developed antibodies than patients without previous alloimmunisation (82% vs. 40%, $p = 0.017$). In all, 62% of patients who developed antibodies (13/21 patients) developed more than one: two antibodies (eight patients), three antibodies (three) or more than four antibodies (two). Partial antigens in *RHD* and *RHCE* gene loci were tested in 15 patients (37%) and were identified after DHTR by molecular analysis in four patients, two of whom developed antibodies associated with these partial antigens and one who also developed other classical antibodies. Of note, 17 patients out of 38 (45%) had a positive direct antiglobulin testing, mostly with immunoglobulin G (Table 2).

Initial management of DHTR

Initial management of DHTR is described in Figure 2 and Table S1. In all, 25 patients (61%) were admitted to the intensive care unit. Six patients (15%) did not receive any treatment and reached Hb levels ≥70 g/L in 2–14 days (4/6 patients) after onset of symptoms. RBC transfusion was required in 23 patients (56%) due to poorly tolerated anaemia, including seven patients transfused twice for poor RBC transfusion yield. RBCs were either EP-RBCs in 17 patients (74%) or phenotypically cross-matched RBCs compatible for ABO, RH and KEL antigens in six patients (26%). RBC transfusion was less frequent in the latter years of the study, 14 out of 18 DHTRs (78%) occurring before 2013 and nine out of 23 (39%) after 2013. DHTR management included erythropoietin (EPO; 22 patients [54%]), CSs (21 [51%]), rituximab (six [15%]), IVIGs (three [7%]) and eculizumab (two [5%]). CSs were always used with RBC transfusion, including three patients in whom they were used after the failure of a first RBC transfusion without CSs. CSs were used either with (9/21 patients) or without (12/21 patients) other immunomodulatory drugs and were usually administered as an intravenous bolus at a dose of 2 mg/kg/day (maximum 80 mg/day), followed by progressive oral CSs tapering over 10–15 days, with median 11.5 days after 2013. Rituximab was used in association with CSs and RBC transfusion (5/6 patients), mainly for

TABLE 2 Delayed haemolytic transfusion reaction features

Variable	Value
Triggering RBC transfusion, *n* (%)	
Acute event[a]	26 (63)
Preoperative RBC transfusion[b]	8 (20)
Chronic RBC transfusion programme[c]	7 (17)
Clinical features	
Timeframe between triggering RBC transfusion and onset of symptoms, days, median (Q1–Q3)	8 (6–10)
Fever (*n* = 40), *n* (%)	25 (62)
Painful crisis, *n* (%)	38 (93)
Requiring morphine, *n/N* (%)	29/38 (76)
Requiring ketamine, *n/N* (%)	17/38 (45)
Clinical jaundice, *n* (%)	39 (95)
Dark urine, *n* (%)	21 (51)
Acute splenic sequestration, *n* (%)	3 (7)
Complications during DHTR, *n* (%)	
Death	0
Acute chest syndrome	12 (29)
Requiring non-invasive ventilation	7/12 (58)
Severe cholestasis	5 (12)
Acute kidney failure	2 (5)
Stroke	2 (5)
Length of hospital stay, days, median (Q1–Q3)	11 (7–18)
Laboratory features	
Nadir of haemoglobin, g/L, median (Q1–Q3)	49 (37–57)
Loss of haemoglobin, g/L[d] (*n* = 37), median (Q1–Q3)	47 (32–57)
Haemoglobin A, % (*n* = 15), median (Q1–Q3)	8 (2–18)
Nadir of reticulocyte count, $\times 10^9$/L, median (Q1–Q3)	140 (104–230)
Nadir of platelet count, $\times 10^9$/L (*n* = 40), median (Q1–Q3)	231 (166–335)
Maximum of leucocyte count, $\times 10^9$/L, median (Q1–Q3)	23.9 (16.6–29.62)
Plasma lactate dehydrogenase, IU/L (*n* = 33), median (Q1–Q3)	2239 (1382–3240)
Total bilirubin, μmol/L (*n* = 40), median (Q1–Q3)	91 (66–147)
Conjugated bilirubin, μmol/L (*n* = 38), median (Q1–Q3)	18 (11–57)
Plasma AST, iu/L (*n* = 40), median (Q1–Q3)	108 (79–187)
Plasma ALT, iu/L (*n* = 40), median (Q1–Q3)	44 (27–74)
Nadir of prothrombin time, % of control value (*n* = 29), median (Q1–Q3)	65 (55–71)
C-reactive protein, mg/L, median (Q1–Q3)	125 (45–241)
Nadir of natraemia, mmol/L, median (Q1–Q3)	134 (131–136)
Positive direct antiglobulin test[e] (*n* = 38), *n* (%)	17 (45)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DHTR, delayed haemolytic transfusion reaction; RBC, red blood cell.

[a]For painful crisis or acute chest syndrome.

[b]Cholecystectomy (five patients), tonsillectomy (three).

[c]Abnormal transcranial Doppler ultrasound without cerebral stenosis (four patients), low baseline haemoglobin (two), frequent painful crisis (one).

[d]Between haemoglobin level post-RBC triggering transfusion and nadir of haemoglobin during DHTR.

[e]Positive for immunoglobulin G (12/17 patients), positive for complement C3d (one of 17) and positive for both (four of 17).

a second RBC transfusion (4/6 patients). IVIGs were used with CSs and RBC transfusion (2/3 patients), including one patient with a second RBC transfusion. Eculizumab was used in two patients after 2018 always with RBC transfusion, CSs and EPO: one with profound anaemia (Hb 27 g/L) and one with severe cholestasis.

Evaluation of RBC transfusion yield

In the absence of quantification of HbS/HbA in all patients, we used a 'practical' definition of RBC transfusion yield. We defined efficient RBC transfusion yield as an increase in Hb concentration of >20 g/L, for at least 21 days, with no need for a second RBC transfusion and with no clinical signs of haemolysis (dark urine, jaundice). Poor transfusion yields were observed in 61% of patients (14/23 patients) for the first RBC transfusion, including 80% of patients transfused with no immunomodulatory treatment (4/5 patients), 55% of patients treated with CSs (10/18 patients) and no patients treated with eculizumab. Five of the six patients transfused with non-EP-RBCs had a good transfusion yield: they had received CSs and one of whom had also received eculizumab. All seven patients requiring a second RBC transfusion received CSs and EP-RBCs, as well as rituximab (4/7 patients), and three of the patients also underwent emergency total splenectomy for concomitant acute splenic sequestration. Efficient RBC transfusion yields were observed in all three patients who underwent splenectomy (two also receiving rituximab) and in one patient on rituximab alone. The course of individual Hb concentrations after DHTR is provided in Figures S1–S3. Overall immunomodulatory treatments and EPO were well tolerated in most patients; however, two patients who received CSs for >3 months experienced PC. Moreover, stroke occurred in two patients without clinical sequelae. One had reversible cerebral vasoconstriction syndrome in the absence of underlying vasculopathy and in the context of a sudden and major increase in Hb from 27 to 114 g/L after eculizumab. In the other patient, stroke revealed undiagnosed

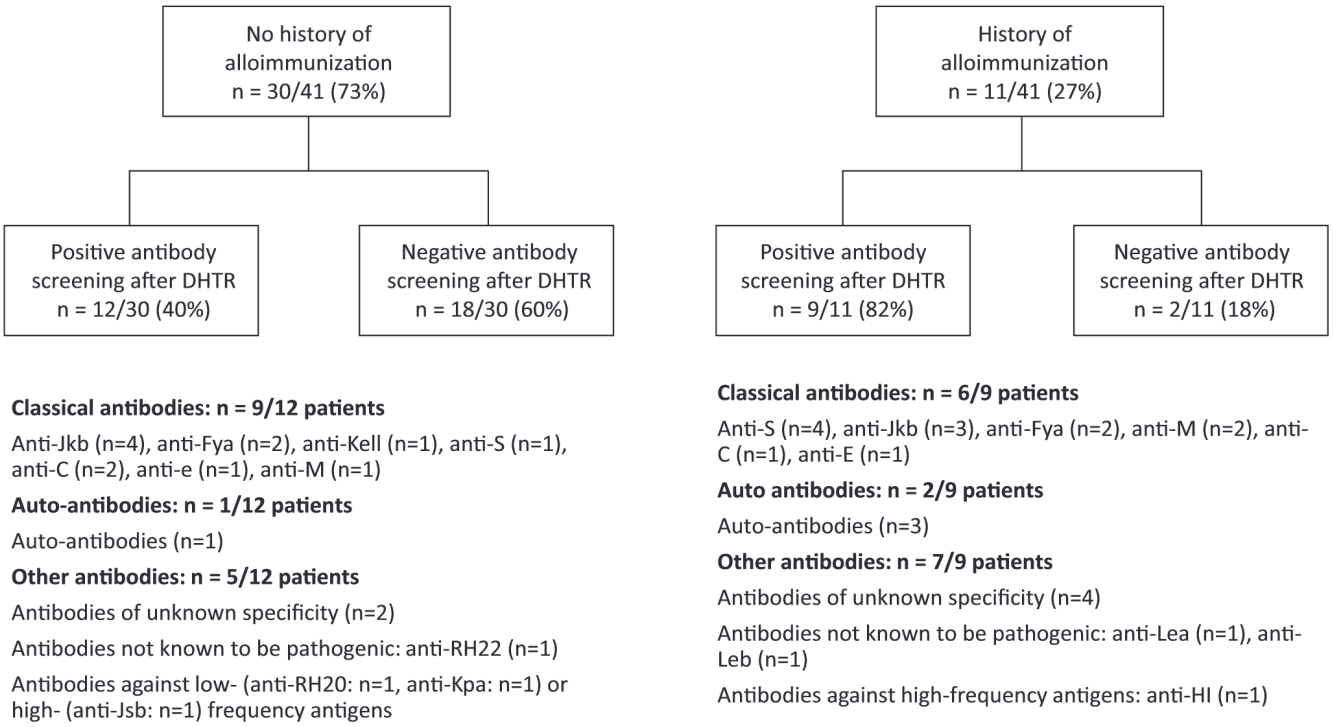

FIGURE 1 Immunohaematological parameters before and after delayed haemolytic transfusion reaction (DHTR). Red blood cell (RBC) antibody screening by indirect antiglobulin test

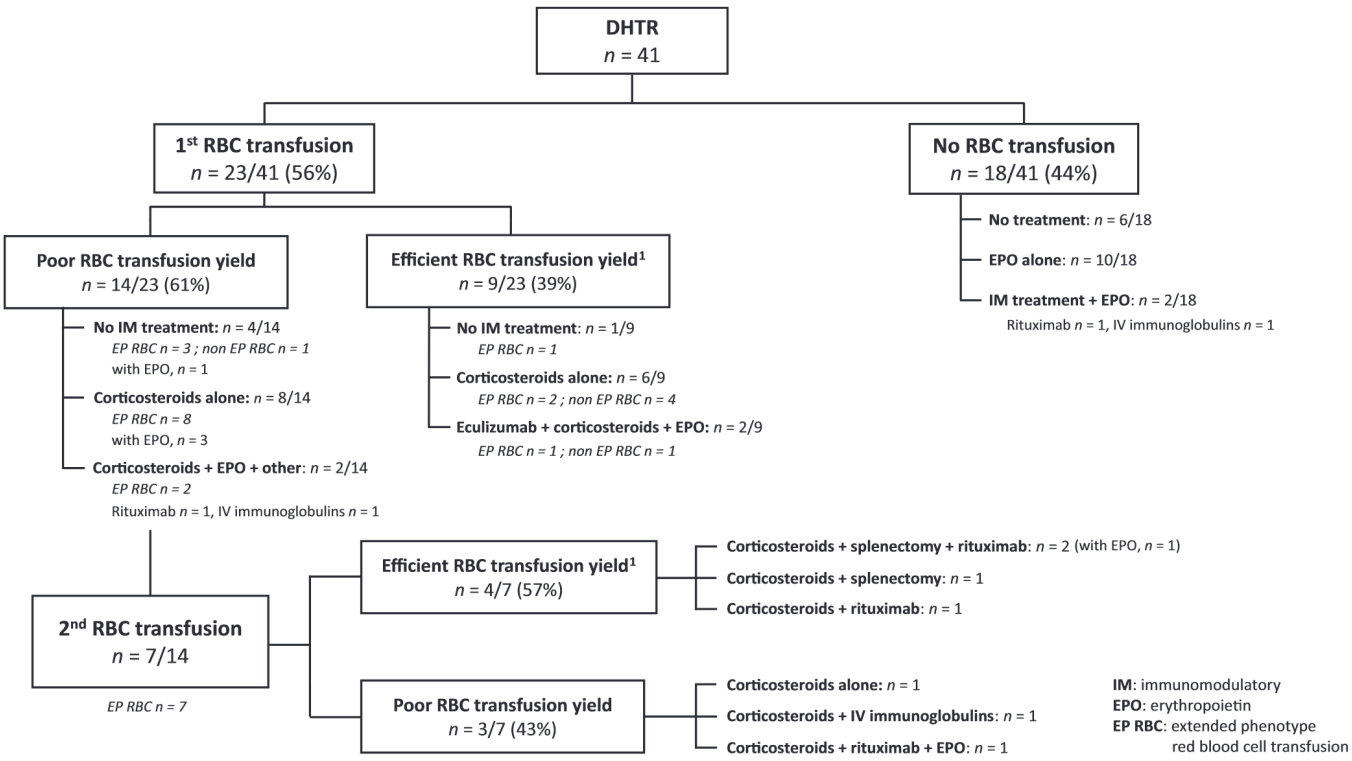

FIGURE 2 Initial management of delayed haemolytic transfusion reaction (DHTR). [1]Increase in haemoglobin concentration of >20 g/L for ≥21 days with no second transfusion and without clinical sign of haemolysis

cerebral vasculopathy with tight stenosis of the right intracavernous carotid artery 1 day after CSs treatment and RBC transfusion followed by rapid haemolysis of the transfused RBCs.

Long-term follow-up after DHTR

The median (Q1–Q3) follow-up after DHTR was 3.7 (2–7) years, with 18 patients having reached adulthood.

Hydroxycarbamide was introduced or continued in all patients except five due to parental refusal. Two patients with matched sibling donors underwent haematopoietic stem cell transplantation (HSCT) preceded by exchange transfusion with EP-RBCs, rituximab and CSs. During later follow-up, 13 patients (32%) required RBC transfusion for an acute event in eight (PC, ACS) or planned RBC transfusion in five (HSCT, 2/5 patients; cholecystectomy, 1/5 patient; parotidectomy, 1/5 patient; chronic RBC transfusion programme, 1/5 patients). Overall, 12 of the patients received CSs and EP-RBCs, and six also received rituximab, including all five patients with planned RBC transfusion. Only two patients had recurrence of DHTR (15%): one after RBC transfusion for ACS despite CSs treatment and one during an RBC transfusion programme before HSCT despite four injections of rituximab. HSCT was postponed, and the patient received azathioprine and sequential rituximab, which led to successful HSCT 2 years later. Of note, one patient in a chronic RBC transfusion programme for cerebral vasculopathy is currently receiving cross-matched RBCs phenotypically compatible for ABO, Rh and Kell antigens, with no recent immunomodulatory treatment 10 years after initial DHTR and with no recurrence of DHTR.

DISCUSSION

This study, describing 41 children with SCD with DHTR, is the largest paediatric cohort of this rare complication.[8–10]

In most patients, DHTR occurred in an inflammatory context, such as acute events or surgeries, as described in the literature.[5–8,10] Nonetheless, in 17% of patients, DHTR occurred within a chronic RBC transfusion programme, with no inflammatory event. However, these patients were at their first or second transfusion in the chronic protocol. Therefore, DHTR should not be overlooked at protocol initiation and the use of RBC transfusion before cholecystectomy should be discussed.

Contrary to adult cohorts, we reported no deaths and fewer complications, likely attributable to less underlying chronic organ damage in children compared to adults.[6,7] However, we also reported several as yet undescribed complications such as stroke and acute splenic sequestration, both of which are 'classical' complications of SCD in children.[18,19] Specifically, acute splenic sequestration increases anaemia due to RBC trapping, making DHTR diagnosis more challenging.[18] Marked haemolysis, low reticulocyte counts, positive RBC antibody screening and, more importantly, the context of recent RBC transfusion should suggest DHTR. In children with SCD, stroke can occur due to cerebral vessel stenosis and/or poor arterial vessel adaptation and can be aggravated by profound anaemia. On the other hand, increased blood viscosity with a rapid rise in Hb can also lead to stroke.[19] This issue, avoiding both profound anaemia and rapid correction of Hb, is illustrated by our two patients with stroke.

Monitoring HbA and HbS levels is extremely useful for DHTR diagnosis, using the nomogram established by Mekontso Dessap et al.,[20] with a drop in HbA and a sharp rise in HbS levels reflecting destruction of transfused RBC. Unfortunately, this monitoring was available in only a few patients in our cohort, in line with a study recently published.[10]

We reported previous alloimmunisation in 27% of the patients, which is lower than reported in other cohorts (40%–60%).[5–8,10] This could be due to the young age of the patients and/or to failure to identify antibodies if RBC antibody screening was not performed at the proper time. Half of the patients developed antibodies after DHTR, most of whom had a history of alloimmunisation, and they often developed several antibodies with at least one 'classical antibody', as previously described.[6–10] These data are consistent with a 'high responder' phenotype described in the literature, with a high risk of alloimmunisation after RBC transfusion.[21] Polymorphisms of genes involved in immune response are believed to partially explain this phenotype.[22–25] Importantly, absence of antibodies was frequent (49%) and should not exclude the diagnosis of DHTR. A recently published study showed that late screening up to 3 months after the occurrence of DHTR could identify antibodies that were not detected at the onset of DHTR.[10] These antibodies need to be taken into account for future transfusion to avoid immune reactivation.[4] These data regarding antibody screening tests and monitoring of HbA levels, advocate in favour of the need to establish standardised guidelines for the monitoring of patients with SCD after RBC transfusion, as well as for establishing a national transfusion database for patients with SCD.[26] Partial antigens in *RHD* and *RHCE* loci are frequent in people of African origin.[27] In our cohort, very few patients had screening for partial antigens; however, the relevance of antibodies against missing epitopes of a partial antigen in the pathogenesis of DHTR is questionable, especially if multiple antibodies are present.[27,28] Nonetheless, systematic RBC genotyping in patients with SCD should be considered, especially in patients transfused in Africa, where phenotyped RBC transfusions are frequently unavailable.

Recent guidelines are primarily based on expert opinions and case reports.[4,15] RBC transfusion during DHTR is not recommended to avoid haemolysis exacerbation. In our cohort, 56% of the patients received RBC transfusions for poorly tolerated anaemia or undiagnosed DHTR, particularly in cases during the initial study period. As reported, RBC transfusion yield was often poor despite extensive use of EP-RBCs and associated immunomodulatory treatments.[6,7,10] If RBC transfusion is needed, recommended first-line treatments are CSs and/or IVIGs,[15] and CSs were mostly used in our centre. Although our study is retrospective, some important elements concerning acute management of DHTR should be highlighted. First, RBC transfusion yield was almost always poor in the absence of immunomodulatory treatment (4/5 patients), suggesting that this management strategy is not safe if RBC transfusion is required. Moreover, half of the patients transfused with CSs had efficient yield, and CSs were well tolerated for short regimens. Side-effects were only observed in the first cases in our study where CS use was prolonged based

on the protocol for management of acute haemolytic autoimmune anaemia. This suggests that CSs are both safe and effective in association with RBC transfusion in line with a recent study.[10] Eculizumab, a monoclonal antibody blocking complement activation, is recommended for severe forms of DHTR and its use for milder form is currently debated.[4,15,29] It was successfully used in two severe patients. However, one patient presented a sharp rise in Hb followed by onset of stroke, probably partially due to hyperviscosity. Hb concentrations should therefore be closely monitored after eculizumab use. Guidelines have suggested that rituximab use in the initial phase of DHTR can prevent the formation of additional antibodies if RBC transfusion is required.[4,15] Rituximab has also been used successfully to prevent the occurrence of DHTR in adult patients with a history of either DHTR or RBC alloimmunisation.[30,31] In our cohort, although some patients had efficient RBC transfusion yields with rituximab, they also required concomitant splenectomy making the specific effect of rituximab difficult to analyse. When acute splenic sequestration occurs, emergency splenectomy seems to be a reasonable option to control anaemia. The use of immunomodulatory treatments in the absence of RBC transfusion to reduce haemolysis of both transfused and autologous RBCs is debated.[15] In these patients, the use of EPO to support haematopoiesis could be beneficial, although there is no consensus on administration modalities.[15] In our cohort, patients most often received one or two subcutaneous injections. EPO was very well tolerated and should therefore be used early, especially in patients with inadequate reticulocytes count or if the Hb concentration is <70 g/L.

Lifelong restriction of RBC transfusion use after DHTR is a matter of debate. If required, it should be discussed with both haematologists and blood experts. In our study, RBC transfusions after DHTR were well tolerated with a rate of recurrence of DHTR lower than in other published cohorts.[6,7,10] In our cohort, we used almost exclusively EP-RBCs and immunomodulatory treatments such as CSs and rituximab, including in patients with negative antibody screening. This might explain this lower rate of DHTR recurrence.

In conclusion, we report a large cohort of children with DHTR in a French SCD reference centre and our experience of acute management. DHTR should be suspected in patients with SCD if an acute event occurs during the month after RBC transfusion. Although less severe than in adults, DHTR in children can be associated with specific complications such as stroke and acute splenic sequestration. EP-RBC transfusion with a short course of CSs may be a reasonable option if anaemia is poorly tolerated or if complications arise, highlighting the need for standardised management guidelines.

AUTHOR CONTRIBUTIONS

Marica Rossi performed the research, wrote the paper, and revised the final manuscript. France Pirenne analysed all immune-haematological features, wrote the original draft of the paper and revised the final manuscript. Enora Le Roux helped design the study, reviewed the original draft of the paper, and revised the final manuscript. Djamel Smaïne, Marie Belloy, Stéphanie Eyssette-Guerreau and Nathalie Couque helped in data collection and reviewed both the original draft and final version of the paper. Laurent Holvoet, Ghislaine Ithier, Malika Benkerrou, Valentine Brousse, Bérengère Koehl and Albert Faye reviewed both the original draft and the final version of the paper. Florence Missud designed the research study, wrote the paper and revised the final version. All authors contributed to the interpretation of data.

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CONFLICT OF INTEREST

All authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

All data used and/or analysed during the study can be made available on reasoned request by email to the corresponding author, subject to the agreement of the data owner (AP-HP).

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REFERENCES

1. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, et al. Sickle cell disease. Nat Rev Dis Primer. 2018;4(1):18010.
2. Ataga KI, Kutlar A, Kanter J, Liles D, Cancado R, Friedrisch J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. N Engl J Med. 2017;376(5):429–39.
3. Howard J, Ataga KI, Brown RC, Achebe M, Nduba V, El-Beshlawy A, et al. Voxelotor in adolescents and adults with sickle cell disease (HOPE): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Haematol. 2021;8(5):e323–33.
4. Pirenne F, Yazdanbakhsh K. How I safely transfuse patients with sickle-cell disease and manage delayed hemolytic transfusion reactions. Blood. 2018;131(25):2773–81.
5. Narbey D, Habibi A, Chadebech P, Mekontso-Dessap A, Khellaf M, Lelièvre JD, et al. Incidence and predictive score for delayed hemolytic transfusion reaction in adult patients with sickle cell disease. Am J Hematol. 2017;92(12):1340–8.
6. Vidler JB, Gardner K, Amenyah K, Mijovic A, Thein SL. Delayed haemolytic transfusion reaction in adults with sickle cell disease: a 5-year experience. Br J Haematol. 2015;169(5):746–53.
7. Habibi A, Mekontso-Dessap A, Guillaud C, Michel M, Razazi K, Khellaf M, et al. Delayed hemolytic transfusion reaction in adult

sickle-cell disease: presentations, outcomes, and treatments of 99 referral center episodes: DHTR in SCD patients. Am J Hematol. 2016;91(10):989–94.
8. de Montalembert M, Dumont MD, Heilbronner C, Brousse V, Charrara O, Pellegrino B, et al. Delayed hemolytic transfusion reaction in children with sickle cell disease. Haematologica. 2011;96(6):801–7.
9. Talano JAM, Hillery CA, Gottschall JL, Baylerian DM, Scott JP. Delayed hemolytic transfusion reaction/hyperhemolysis syndrome in children with sickle cell disease. Pediatrics. 2003;111(6):e661–5.
10. Falguière C, Allali S, Khazem B, Kamdem A, Arnaud C, Belloy M, et al. Delayed hemolytic transfusion reaction in children with sickle cell disease: first five-year retrospective study in mainland France. Haematologica. 2022. Online ahead of print.
11. Thein SL, Pirenne F, Fasano RM, Habibi A, Bartolucci P, Chonat S, et al. Hemolytic transfusion reactions in sickle cell disease: underappreciated and potentially fatal. Haematologica. 2020;105(3):539–44.
12. Stowell SR, Winkler AM, Maier CL, Arthur CM, Smith NH, Girard-Pierce KR, et al. Initiation and regulation of complement during hemolytic transfusion reactions. Clin Dev Immunol. 2012;2012:1–12.
13. Merle NS, Boudhabhay I, Leon J, Fremeaux-Bacchi V, Roumenina LT. Complement activation during intravascular hemolysis: implication for sickle cell disease and hemolytic transfusion reactions. Transfus Clin Biol. 2019;26(2):116–24.
14. Arthur CM, Chonat S, Fasano R, Yee MEM, Josephson CD, Roback JD, et al. Examining the role of complement in predicting, preventing, and treating hemolytic transfusion reactions. Transfus Med Rev. 2019;33(4):217–24.
15. Chou ST, Alsawas M, Fasano RM, Field JJ, Hendrickson JE, Howard J, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. Blood Adv. 2020;4(2):327–55.
16. Vichinsky EP, Neumayr LD, Earles AN, Williams R, Lennette ET, Dean D, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. N Engl J Med. 2000;342(25):1855–65.
17. The International Society of Nephrology. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2(1):1.
18. Brousse V, Buffet P, Rees D. The spleen and sickle cell disease: the sick(led) spleen. Br J Haematol. 2014;166(2):165–76.
19. Stotesbury H, Kawadler JM, Hales PW, Saunders DE, Clark CA, Kirkham FJ. Vascular instability and neurological morbidity in sickle cell disease: an integrative framework. Front Neurol. 2019;10:871.
20. Mekontso Dessap A, Pirenne F, Razazi K, Moutereau S, Abid S, Brun-Buisson C, et al. A diagnostic nomogram for delayed hemolytic transfusion reaction in sickle cell disease. Am J Hematol. 2016;91(12):1181–4.
21. Yazdanbakhsh K, Ware RE, Noizat-Pirenne F. Red blood cell alloimmunization in sickle cell disease: pathophysiology, risk factors, and transfusion management. Blood. 2012;120(3):528–37.
22. Chiaroni J, Dettori I, Ferrera V, Legrand D, Touinssi M, Mercier P, et al. HLA-DRB1 polymorphism is associated with Kell immunisation: HLA-DRB1 polymorphism and Kell immunisation. Br J Haematol. 2006;132(3):374–8.
23. Yazdanbakhsh K. FcγR and SCD alloimmunization: a nonclass(ical) act. Blood. 2017;130(19):2051–2.
24. Godefroy E, Zhong H, Pham P, Friedman D, Yazdanbakhsh K. TIGIT-positive circulating follicular helper T cells display robust B-cell help functions: potential role in sickle cell alloimmunization. Haematologica. 2015;100(11):1415–25.
25. Pal M, Bao W, Wang R, Liu Y, An X, Mitchell WB, et al. Hemolysis inhibits humoral B-cell responses and modulates alloimmunization risk in patients with sickle cell disease. Blood. 2021;137(2):269–80.
26. Covington ML, Cone-Sullivan JK, Andrzejewski C, Lu W, Thomasson RR, O'Brien K, et al. Unmasking delayed hemolytic transfusion reactions in patients with sickle-cell disease: challenges and opportunities for improvement. Transfusion (Paris). 2022;62(8):1662–70.
27. Chou ST, Jackson T, Vege S, Smith-Whitley K, Friedman DF, Westhoff CM. High prevalence of red blood cell alloimmunization in sickle cell disease despite transfusion from Rh-matched minority donors. Blood. 2013;122(6):1062–71.
28. Silvy M, Tournamille C, Babinet J, Pakdaman S, Cohen S, Chiaroni J, et al. Red blood cell immunization in sickle cell disease: evidence of a large responder group and a low rate of anti-Rh linked to partial Rh phenotype. Haematologica. 2014;99(7):e115–7.
29. Floch A, Morel A, Zanchetta-Balint F, Cordonnier-Jourdin C, Allali S, Grall M, et al. Treatment of delayed hemolytic transfusion reactions in sickle cell disease patients by an anti-C5 antibody. Blood. 2019;134(Suppl 1):2458–8.
30. Zanchetta-Balint F, Pirenne F, Michel M, Mekontso-Dessap A, Mahevas M, Guillaud C, et al. Rituximab for preventing delayed hemolytic transfusion reaction (DHTR) in sickle cell adult patients: outcome of transfusion and side effects in 58 cases. Blood. 2019;134(Suppl_1):3687–7.
31. Noizat-Pirenne F, Habibi A, Mekontso-Dessap A, Razazi K, Chadebech P, Mahevas M, et al. The use of rituximab to prevent severe delayed haemolytic transfusion reaction in immunized patients with sickle cell disease. Vox Sang. 2015;108(3):262–7.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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