Delayed Hemolytic Transfusion Reaction/Hyperhemolysis Syndrome in Children With Sickle Cell Disease

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ABSTRACT. Objective. Alloimmunization in patients with sickle cell disease (SCD) has a reported incidence of 5% to 36%. One complication of alloimmunization is delayed hemolytic transfusion reaction/hyperhemolysis (DHTR/H) syndrome, which has a reported incidence of 11%. In patients with SCD, clinical findings in DHTR/H syndrome occur approximately 1 week after the red blood cell (RBC) transfusion and include the onset of increased hemolysis associated with pain and profound anemia. The hemoglobin (Hb) often drops below pretransfusion levels. In many reported adult cases, the direct antiglobulin test (DAT) remains negative and no new alloantibody is detected as the cause for these transfusion reactions. To date, few pediatric cases have been reported with this phenomenon. The objective of this study was to describe the clinical and laboratory findings of a case series in children who had SCD and experienced a DHTR/H syndrome at our institution.

Methods. An 11-year retrospective chart review of patients with discharge diagnosis of SCD and transfusion reaction was performed. DHTR/H syndrome was defined as the abrupt onset of signs and symptoms of accelerated hemolysis evidenced by an unexplained fall in Hb, elevated lactic dehydrogenase, elevated bilirubin above baseline, and hemoglobinuria, all occurring between 4 and 10 days after an RBC transfusion. Patient characteristics, time from transfusion, symptoms, reported DAT, new autoantibody or alloantibody formation, laboratory abnormalities, and complications were recorded. Patients with acute transfusion reactions were excluded.

Results. We encountered 7 patients who developed 9 episodes of DHTR/H syndrome occurring 6 to 10 days after RBC transfusion. Each presented with fever and hemoglobinuria. All but 1 patient experienced pain initially ascribed to vaso-occlusive crisis. The DAT was positive in only 2 of the 9 episodes. The presenting Hb was lower than it was at the time of original transfusion, suggesting the hemolysis of the patient’s own RBCs in addition to hemolysis of the transfused RBCs; a negative DAT and reticulocytopenia are often present. Severe complications including acute chest syndrome, congestive heart failure, pancreatitis, and acute renal failure were associated with DHTR/H syndrome in our patients. DHTR/H in the pediatric sickle cell population is a serious and potentially life-threatening complication of RBC transfusion. It is important to avoid additional transfusions in these patients, if possible, because these may exacerbate the hemolysis and worsen the degree of anemia. DHTR/H syndrome must be included in the differential of a patient who has SCD and vaso-occlusive crisis who has recently had a transfusion. Pediatrics 2003;111:e661–e665. URL: http://www.pediatrics.org/cgi/content/full/111/6/e661; delayed hemolytic transfusion reaction/hyperhemolysis, sickle cell disease.

ABBREVIATIONS. SCD, sickle cell disease; RBC, red blood cell; DHTR/H, delayed hemolytic transfusion reaction/hyperhemolysis; Hb, hemoglobin; DAT, direct antiglobulin test; IVlg, intravenous immunoglobulin.

Children with sickle cell disease (SCD) commonly require red blood cell (RBC) transfusions to manage complications including anemia, acute chest syndrome, stroke, and splenic sequestration. Alloimmunization in patients who have SCD and have had a transfusion has a reported incidence of 5% to 36% in the United States and Europe.1–3 One serious complication of alloimmunization has been termed the delayed hemolytic transfusion reaction/hyperhemolysis (DHTR/H) syndrome.3,4 In patients with SCD, clinical findings in DHTR/H occur approximately 1 week after the RBC transfusion and include the onset of increased hemolysis associated with pain and profound anemia. The hemoglobin (Hb) often drops below pretransfusion levels. In many reported adult cases, the direct antiglobulin test (DAT) remains negative and no new alloantibody is detected as the cause for the transfusion reactions.

The DHTR/H syndrome is thought to occur after alloimmunization to an RBC antigen(s) after a transfusion. Over time, the patient’s antibody levels fall to undetectable levels. Subsequent reexposure of the recipient to RBCs that possess the antigen triggers an anamnestic response and subsequent hemolysis. Accelerated hemolysis results in profound anemia and hyperbilirubinemia.5 The diagnosis of antibody-mediated RBC hemolysis is usually confirmed by a pos-
itive DAT and identification of a new red cell antibody directed against a specific red cell antigen in the patient. However, in the patient who has SCD and DHTR/H syndrome, the DAT is often negative and no antibody can be detected in the serum.\(^6\)\(^7\) Therefore, this syndrome poses a significant diagnostic challenge.

Cox et al\(^6\) reported a prevalence of recognized DHTR/H syndrome of 4\% in their patients with SCD. Nevertheless, the syndrome may go unrecognized and may have a much higher incidence. Petz et al\(^8\) described 8 severe cases of DHTR/H syndrome and defined a sickle cell transfusion reaction syndrome with a characteristic constellation of findings. These characteristics include sickle cell pain crisis, laboratory manifestations of hemolysis, life-threatening anemia more severe than before the transfusion, and reticulocytopenia. The DAT can be negative (50\% of the time in Petz’\’s series), and identification of a new red cell antibody is often absent. The aforementioned series were adult patients; there are few reports of DHTR/H in children with SCD.

In this retrospective chart review, we report 7 pediatric patients who had SCD and developed evidence of accelerated hemolysis 6 to 10 days after an RBC transfusion. Each of these patients previously had a transfusion. In this report, we describe the clinical and laboratory characteristics of 9 episodes of DHTR/H syndrome in 7 children with SCD.

**METHODS**

Before 1995, all patients who had SCD and received a transfusion at our center received RBCs matched only for Rh D and ABO. Since 1995, patients with a diagnosis of SCD have received units of RBCs that are partially phenotype matched for the Rh (C, E, c, e) and Kell antigens in addition to routine blood bank cross-matching protocols.

We performed a retrospective chart review of patients at the Children’s Hospital of Wisconsin who had SCD from 1990 to 2001 with the discharge International Classification of Diseases, Ninth Revision code of Sickle Cell Disease and transfusion reaction. Patients who experienced an acute transfusion reaction were excluded. We defined an acute transfusion reaction as occurring within 24 hours after the initiation of the transfusion. Criteria to meet DHTR/H included the abrupt onset of signs and symptoms of accelerated hemolysis as evidenced by an unexplained fall in Hb, an elevated lactic dehydrogenase (LDH), elevated bilirubin and reticulocytopenia. These must have occurred between 4 and 10 days after an RBC transfusion. Clinical and laboratory data were collected on these patients and included patient characteristics and clinical findings, onset of symptoms after RBC transfusion, type of transfusion, previous transfusion history (including number of partial phenotype matched units), DAT results, new autoantibody or alloantibody formation, other laboratory abnormalities, complications, and treatment.

**Statistical Analysis**

Changes in laboratory results were compared using paired Student t test. \(P < .05\) was considered statistically significant. Before the data collection, the study was approved by the Institutional Review Board.

**RESULTS**

Each year, our center transfuses approximately 1000 units of RBCs to a population of 162 pediatric patients with SCD. Using the criteria described in "Methods," we identified 7 patients with 9 episodes of DHTR/H. None of the patients was on a chronic transfusion program. Clinical characteristics of these episodes are depicted in Table 1.

One patient had 3 separate episodes of DHTR/H (UPN 7.1, 7.2, 7.3). The second and third episodes of DHTR/H in this specific patient occurred when additional transfusions were given approximately 6 and 12 months after the original DHTR/H. The original DHTR/H was managed with transfusion of a completely phenotypically matched unit of RBC without additional complications. The 7.2 and 7.3 events were managed conservatively, and the patient’s Hb recovered spontaneously without the need for additional transfusions.

As depicted in Table 1, 6 patients had Hb SS and 1 patient had Hb SC disease. Their ages ranged from 6 to 18 years. There were 5 girls and 2 boys. Of note, all patients presented with fever and hemoglobinuria. All but 1 episode presented with symptoms of pain that was initially ascribed to vaso-occlusive crisis (in the back, abdomen, and/or legs). The number of days after transfusion to presentation ranged from 6 to 10 days with a median of 6 days. As shown in Table 2, the bilirubin increased from baseline in all patients \((P = .003)\) and the peak bilirubin ranged from 1.7 mg/dL to 10.1 mg/dL with a median of 4.2 mg/dL. The LDH increased from baseline in all patients \((P = .006)\) with the peak LDH ranging from 2667 IU/L to 17 274 IU/L with a median of 6039 IU/L. The Hb decreased from pretransfusion level in 8 of 9 episodes \((P = .0001)\). The nadir Hb ranged from 4.0 g/dL to 5.9 g/dL with a median of 4.5 g/dL. The net drop in Hb from posttransfusion to nadir in 6 episodes in which an immediate posttransfusion Hb was available ranged from 1.8 g/dL to 9.5 g/dL, with a median of 7.7 g/dL. The reticulocyte count at

**TABLE 1.** Clinical Characteristics of DHTR/H in SCD Patients

<p>| Patient Gender Age Hb type Previous No. of DAT Onset After RBC Transfusion Symptoms |</p>
<table>
<thead>
<tr>
<th>UPN</th>
<th>Gender</th>
<th>Age (Years)</th>
<th>Hb type</th>
<th>No. of Previous RBC</th>
<th>Previous Allo-Ab</th>
<th>DAT</th>
<th>Transfusion (Days)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 F</td>
<td>9 SS</td>
<td>6 SS</td>
<td>4 None</td>
<td>4 None</td>
<td>+</td>
<td>6</td>
<td>Pain, fever, hemoglobinuria</td>
<td></td>
</tr>
<tr>
<td>2 F</td>
<td>9 SS</td>
<td>6 SS</td>
<td>4 None</td>
<td>4 None</td>
<td>−</td>
<td>7</td>
<td>Pain, fever, hemoglobinuria</td>
<td></td>
</tr>
<tr>
<td>3 F</td>
<td>18 SS</td>
<td>23 Anti-C, S, Jk(^b)</td>
<td>11 None</td>
<td>6 None</td>
<td>+</td>
<td>10</td>
<td>Pain, fever, hemoglobinuria</td>
<td></td>
</tr>
<tr>
<td>5 M</td>
<td>15 SC</td>
<td>&gt;6 None</td>
<td>&gt;6 None</td>
<td>&gt;6 None</td>
<td>−</td>
<td>7</td>
<td>Pain, fever, hemoglobinuria</td>
<td></td>
</tr>
<tr>
<td>6 M</td>
<td>17 SS</td>
<td>&gt;6 None</td>
<td>&gt;6 None</td>
<td>&gt;6 None</td>
<td>−</td>
<td>6</td>
<td>Pain, fever, hemoglobinuria</td>
<td></td>
</tr>
<tr>
<td>7.1 F</td>
<td>9 SS</td>
<td>&gt;8 None</td>
<td>&gt;8 None</td>
<td>&gt;8 None</td>
<td>−</td>
<td>6</td>
<td>Pain, fever, hemoglobinuria</td>
<td></td>
</tr>
<tr>
<td>7.2 F</td>
<td>9.5 SS</td>
<td>&gt;10 None</td>
<td>&gt;10 None</td>
<td>&gt;10 None</td>
<td>−</td>
<td>6</td>
<td>Pain, fever, hemoglobinuria</td>
<td></td>
</tr>
</tbody>
</table>

Allo-Ab indicates alloantibody.
the time of nadir Hb ranged from 0.8 to 19.1% with a median of 4.3%. The corrected reticulocyte count accounting for the patient’s degree of anemia ranged from 0.2% to 5.6% with a median of 1.16%. Five of the 9 episodes had severe reticulocytopenia with a corrected reticulocyte count of <2%.

As seen in Table 1, only 2 of the 9 events had a positive DAT at the presentation of the DHTR/H. One patient had previous alloantibodies present, and 4 patients developed new identifiable antibodies, which included a warm autoantibody in 1 patient, anti-E and anti-Lea in a second patient, anti-E in a third patient, and anti-Fy in the fourth patient. The new alloantibodies appeared at the time of the event in 2 patients but were not detected for 1 month after the DHTR/H in a third patient. The number of previous transfusions ranged from 4 to 43. Since 1995, all RBC transfusions in patients with SCD at our institution are phenotypically matched for Rh (C, E, D, c, e) antigens and Kell to help reduce alloimmunization. In our series, only 2 of the patients had past transfusions that all were phenotypically matched RBCs for Rh and Kell. Both patients had no previous alloantibodies, and 1, who had a positive DAT at the time of the DHTR/H, had developed a warm autoantibody. The remainder of the patients (4 with 6 DHTR/H) received transfusions before 1995 and did not receive solely Rh and Kell phenotypically matched RBCs. This subset of patients received 6 to 43 previous transfusions.

Severe complications were observed after the onset of DHTR/H. Three patients developed acute chest syndrome 1 to 2 days after their admission for DHTR/H. Pancreatitis occurred in 1 patient approximately 1 week after the DHTR/H was recognized. In another patient, congestive heart failure was recognized 1 day after the DHTR/H was diagnosed. Finally, acute renal failure occurred 2 days after diagnosis of DHTR/H in 1 individual.

For stimulating erythropoiesis and suppression of the immune response, as well to avoid additional transfusions, corticosteroids and erythropoietin as described by Telen and Combs were administered to 6 patients. Most patients were placed on erythropoietin and corticosteroids for 1 to 2 weeks during their acute illness and hospitalization for the DHTR/H. One patient used erythropoietin and corticosteroids for approximately 2 months after DHTR/H during multiple subsequent hospitalizations for vaso-occlusive crises. This patient successfully avoided additional RBC transfusions. Three of the 6 patients received additional RBC transfusions that were completely phenotypically matched during their acute illness. One of the 3 patients (UPN-1) experienced severe additional hemolysis; the other 2 patients tolerated the transfusion without any additional hemolysis.

### TABLE 2. Laboratory Characteristics of DHTR/H in SCD Patients

<table>
<thead>
<tr>
<th>Patient UPN</th>
<th>Pre-Tx Hb (g/dL)</th>
<th>Post-Tx Hb (g/dL)</th>
<th>Nadir Hb (g/dL)</th>
<th>Fall in Hb (g/dL)</th>
<th>Retic Count (%)</th>
<th>Corrected Retic Count (%)</th>
<th>New Ab Formed</th>
<th>Increase in LDH (IU/L)</th>
<th>Increase in Bilirubin (mg/dL)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.6</td>
<td>11.9</td>
<td>4.2</td>
<td>7.7</td>
<td>8.4</td>
<td>4.1</td>
<td>Warm Auto Ab</td>
<td>16 302</td>
<td>0.9</td>
<td>ACS</td>
</tr>
<tr>
<td>2</td>
<td>7.2</td>
<td>NA</td>
<td>4.5</td>
<td>—</td>
<td>9.6</td>
<td>2.9</td>
<td>None</td>
<td>4401</td>
<td>4.3</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>7.7</td>
<td>5.9</td>
<td>1.8</td>
<td>2.5</td>
<td>1.16</td>
<td>None</td>
<td>4954</td>
<td>3.1</td>
<td>ACS, pancreatitis</td>
</tr>
<tr>
<td>4</td>
<td>5.8</td>
<td>9.3</td>
<td>4.1</td>
<td>5.2</td>
<td>19.1</td>
<td>5.6</td>
<td>Fy b</td>
<td>1955</td>
<td>2.1</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>12.1</td>
<td>14.8</td>
<td>5.3</td>
<td>8.5</td>
<td>1</td>
<td>0.35</td>
<td>None</td>
<td>16 156</td>
<td>2.5</td>
<td>ACS, ARF</td>
</tr>
<tr>
<td>6</td>
<td>9.6</td>
<td>12.5</td>
<td>4.7</td>
<td>7.9</td>
<td>12</td>
<td>3.8</td>
<td>E</td>
<td>5949</td>
<td>1.8</td>
<td>—</td>
</tr>
<tr>
<td>7.1</td>
<td>7.7</td>
<td>NA</td>
<td>4.8</td>
<td>—</td>
<td>2.1</td>
<td>0.67</td>
<td>None</td>
<td>5785</td>
<td>9.3</td>
<td>CHF</td>
</tr>
<tr>
<td>7.2</td>
<td>7.2</td>
<td>NA</td>
<td>4.5</td>
<td>—</td>
<td>4.3</td>
<td>1.29</td>
<td>None</td>
<td>3041</td>
<td>0.9</td>
<td>—</td>
</tr>
<tr>
<td>7.3</td>
<td>9.1</td>
<td>13.5</td>
<td>4.0</td>
<td>9.5</td>
<td>0.8</td>
<td>0.2</td>
<td>E, Le a</td>
<td>4905</td>
<td>3.7</td>
<td>—</td>
</tr>
</tbody>
</table>

Tx indicates transfusion; Retic, reticulocyte; Ab, antibody; ACS, acute chest syndrome; ARF, acute renal failure; CHF, congestive heart failure.

We have identified 7 pediatric patients who had SCD and experienced a DHTR/H event 6 to 10 days after an RBC transfusion. All of the patients presented with fever and hemoglobinuria. Vaso-occlusive pain in the back, abdomen, or legs was present in all but 1 patient. These symptoms could be easily mistaken for a simple vaso-occlusive crisis in the sickle cell population. Therefore, the clinician must have a heightened awareness of DHTR/H in a patient who has recently had a transfusion.

Unfortunately, there is no single test to diagnose DHTR/H. The direct antiglobulin test is often negative, and in our series, only 2 episodes had a positive DAT at presentation. Also, a new alloantibody may not be identified. Only 3 patients developed detectable alloantibodies, and 1 patient developed an autoantibody. However, the presence of a fall in Hb, often below pretransfusion levels; reticulocytopenia; and elevated LDH and bilirubin with fever, pain, and hemoglobinuria within 10 days of a previous transfusion constitute the major findings in this group of patients.

Friedman et al published an abstract that described hyperhemolysis associated with red cell transfusion in 3 pediatric patients with SCD. All 3 patients had severe hemolysis that required additional transfusions. However, the subsequent transfusions resulted in worsening anemia. Serial Hb electrophoreses showed clearance of Hb A cells within 1 to 14 days from the onset of the transfusion. Serologic evaluations revealed new alloantibodies in only 1 of the 3 patients. One patient died with severe hemolysis and anemia as a contributing factor leading to death. One can speculate that these cases were delayed hemolytic transfusion reactions. Vichinsky et al reported 2 cases of DHTR/H occurring in the stroke-prevention trial in pediatric patients with

http://www.pediatrics.org/cgi/content/full/111/6/e661
sickle cell anemia among the 1830 transfused units. Both patients had no previous identified antibodies. One patient developed anti-E, and the other patient developed multiple antibodies (anti-Fy$, -Le$, -Le$, -S). An unexpected drop in Hb and a paradoxical rise in % HbS was observed.

Recently, Aygun et al\textsuperscript{4} reported on 4 pediatric patients and 1 adult patient who had SCD and developed DHTR/H after receiving an RBC transfusion. Of the 4 pediatric patients, 2 had identifiable antibodies before the DHTR/H; 3 developed new antibodies. The episodes of DHTR/H occurred in 2 patients 5 to 8 days posttransfusion. However, in the remaining 2 patients, the DHTR/H occurred between 3 and 6 weeks posttransfusion. It remains unclear whether these represent isolated DHTR/H events or, alternatively, the concurrent pneumonia in patient 3 and splenic sequestration in patient 4 contributed to their hemolysis.

Other published reports have described delayed hemolytic transfusion reactions in the adult sickle cell population. Diamond et al\textsuperscript{12} reported 3 patients who had SCD and all experienced a DHTR/H 6 days after a partial exchange transfusion. All 3 patients had disappearance of transfused cells documented by Hb electrophoresis and differential agglutination. Two patients developed antibodies to the Kidd (Jk$\textsuper{x}$) antigen. One patient had no detectable antibodies. Petz et al\textsuperscript{8} described 5 patients who were aged 16 to 47 years with SCD and experienced 8 episodes of severe DHTR/H. He found characteristic manifestations including symptoms suggestive of a sickle cell pain crisis, marked reticulocytopenia, and more severe anemia after transfusion than was present at the time of diagnosis. Through Petz’s calculations of daily red cell production and senescence, he proposed that the combination of accelerated hemolysis and decreased erythropoiesis resulted in severe posttransfusion anemia when donor red cells are hemolyzed during a DHTR/H. In his series, phenotypically matched RBCs did not prevent DHTR/H from occurring in 2 patients.

We instituted a protocol in 1995 to provide partially phenotypically matched RBCs for our sickle cell population in hope of preventing alloimmunization and DHTR/H. All patients undergo complete phenotyping at presentation to our institution. Nevertheless, 2 patients who had received only partially phenotypically matched RBCs for Rh and Kell still experienced DHTR/H. Aygun et al\textsuperscript{4} likewise found that 2 patients who had received antigen-matched packed RBCs still experienced severe DHTR/H.

The Hb level in DHTR/H is often lower than pretransfusion levels. King et al\textsuperscript{13} demonstrated the phenomenon of bystander hemolysis whereby the patient hemolyzes both the transfused RBCs and his or her own cells, resulting in the nadir Hb often lower than pretransfusion levels. He described 2 patients who had a decrease in Hb S after DHTR/H documenting the destruction of autologous red cells. This is a consistent finding in our series in which 8 of the 9 DHTR/Hs had lower Hbs than the starting pretransfusion level. Bystander hemolysis may occur by the development or augmentation of RBC auto-antibodies (epitope spreading) as a result of alloimmunization from the transfusion. Garratty\textsuperscript{14} suggested another possible mechanism that may worsen the hemolysis by the reaction of alloantibodies with transfused RBCs, which leads to the attachment of activated complement components to autologous RBCs resulting in their lysis. Conversely, he proposed, in the absence of RBC alloantibodies, that other antibody reactions with transfused foreign antigens (eg, HLA and plasma proteins) may cause complement activation. These antibodies may be present in patients who have received multiple transfusions, which may lead to immune complex formation.

In our series, inappropriately low reticulocyte counts were seen in the majority of the DHTR/H. The mechanism of the reticulocytopenia remains unclear. Erythropoiesis can be suppressed by the transfusion or concurrent illness (viral infection), which can exacerbate the anemia. Other possible mechanisms of reticulocytopenia include accelerated destruction of reticulocytes as a result of selective antibody targeting of reticulocytes or decreased levels of erythropoietin secondary to kidney damage.

Various strategies have been used to avoid additional transfusions and decrease the amount of hemolysis. Cullis et al\textsuperscript{15} reported on an adult patient who had SCD and had a life-threatening DHTR/H that resulted in a Hb level of 3.0 g/dL. An additional transfusion was successfully given in conjunction with corticosteroids (100 mg intravenously every 6 hours) and high-dose intravenous immunoglobulin (IVIg) 1 g/kg without any evidence of additional hemolysis. Win et al\textsuperscript{7} reported on 2 adult patients who had SCD and were treated with IVIg (0.4 g/kg) for 5 days and corticosteroids (0.5 g) for 2 days. Our approach, mirrored after Telen et al\textsuperscript{9} used corticosteroids and erythropoietin with some success. However, the experience of using both erythropoietin and corticosteroids, as well as IVIg and corticosteroids in DHTR/H, is limited and needs to be confirmed by additional trials.

Severe complications were associated with the DHTR/H in our case series. They included acute chest syndrome, pancreatitis, congestive heart failure, and acute renal failure. Aygun et al\textsuperscript{4} also noted severe complications, including subarachnoid hemorrhage, acute respiratory distress syndrome, pneumonia, and splenic sequestration.

Our study is limited because it was retrospective in nature and may have missed additional cases of DHTR/H. Because the diagnosis must be made with a high index of suspicion, we may be underrepresenting the incidence of DHTR/H. Conversely, in the absence of a positive DAT, it is possible that we are overestimating the frequency of DHTR/H as there may be some other unknown cause of accelerated hemolysis such as glucose-6-phosphate dehydrogenase deficiency. However, all of the patients in our series had normal baseline glucose-6-phosphate dehydrogenase levels.

DHTR/H in the pediatric sickle cell population is a serious and potentially life-threatening complication of RBC transfusion. Recognition of this compli-
cation of transfusion is crucial because additional transfusions in such patients may exacerbate the hemolysis and resultant anemia. Optimal methods for prevention or treatment of DHTR/H syndrome remain to be determined.

REFERENCES
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