Acute Splenic Sequestration in Female Children with Sickle Cell Disease in the North of Jordan

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Summary

The objective of this study was to evaluate the rate of acute splenic sequestration (ASSC) in patients with sickle β-thalassaemia and sickle cell anaemia, the risk of recurrence in those who survive the first episode, and the relationship between ASSC episodes and subsequent hypersplenism. All patients with confirmed diagnosis of sickle cell disease at a tertiary referral teaching hospital, between January 1994 and December 2002 were interviewed and had their medical records reviewed. Seventy-seven patients with sickle cell disease were identified. Their ages ranged between 2 and 18 years (mean, 10.1 years). There were 35 females and 38 males. Thirty-seven (50.6%) had sickle β-thalassaemia, and 36 (49.4%) had homozygous sickle cell anaemia. Of these, 26 had high level of Hb F and 11 had normal level of fetal haemoglobin (Hb F).

Twenty-one patients (28%) had 63 episodes of acute splenic sequestration. Thirty-seven episodes were experienced by 12 patients with sickle β-thalassaemia; of these 11 were major attacks with one fatality. Twenty-six episodes were experienced by nine patients with sickle cell anaemia. Splenomegaly and hypersplenism were greater in the acute splenic sequestration group than in the rest of the sickle cell anaemia patients, and the differences were extremely significant. ASSC was found in nine siblings of sickle β-thalassaemia group, while none were found in the sickle cell anaemia group. The mean age of the first episode was significantly higher in sickle β-thalassaemia, with significant differences in the levels of Hb F, Hb S, size of spleen and severity of crisis between both groups.

In the sickle cell anaemia group the only significant difference between patients with and these without acute splenic sequestration was the difference in the size of spleen. In this study, the rate of ASSC in the sickle β-thalassaemia patients was 32%, in contrast to 25% in the sickle cell anaemia patients. The risk of recurrence was about 70% in those who survived their first episodes. There was a close relationship between ASSC and subsequent hypersplenism. Important predictable factors for ASSC in sickle β-thalassaemia patients were the presence of splenomegaly of more than 5 cm below the costal margin, history of acute splenic sequestration in siblings and high Hb F. Most of first episodes in sickle cell anaemia occur under the age of 2 years, while in sickle β-thalassaemia the majority of patients have their first crisis at the age of ≥3.5 years.

Keywords: acute splenic sequestration, sickle cell disease, sickle thalassaemia, female, Jordan

Introduction

ASSC is one of the most important causes of morbidity and mortality in infants and young children with sickle cell disease (SCD). The spleen suddenly enlarges, trapping circulating red cells, causing an acute fall in haemoglobin level and subsequent circulatory collapse. The attacks constitute minor episodes with increasing anaemia and spleen enlargement, or in contrast are extremely rapid, progressing to death, even before reaching the hospital [1, 2]. Although ASSC is most commonly described in children with homozygous sickle cell anaemia (SS), it has also been reported in heterozygous SS and sickle β-thalassaemia (Sβ-th).

In Jordan, SS and Sβ-th are among the commonest chronic haemolytic anaemias. Therefore, the possibility of finding patients with double heterozygous SS-Sβ-th is high, where, moreover, the interaction of SS and Sβ-th and its effect on ASSC has never been addressed. This study aimed at evaluating the
frequency and severity of ASSC with special emphasis on the deference between SS and Sβth in Jordan.

Patients and Methods

All patients with the diagnosis of SCD at Princess Rahma Teaching hospital between January 1994 and December 2002 had their medical records reviewed and were interviewed. A record was made of their date of birth, age at diagnosis of SCD, age at first episode of ASSC, number and severity of crises, spleen size before and after each crisis, history of splenectomy, haematological indices, glucose-6-phosphate dehydrogenase level and the results of haemoglobin electrophoresis of patients, parents and SCD siblings.

The haemoglobin (Hb) genotype was determined by cellulose acetate and citrate agar electrophoresis and by quantitation of fetal haemoglobin (Hb F) and haemoglobin A2 levels. The haematological indices were performed by an automated coulter counter and light microscopy of blood smears.

The diagnosis of homozygous SS was made if the level of Hb S by electrophoresis was ≥50%, with the presence of sickle cell trait in both parents, irrespective of whether the patient’s Hb electrophoresis demonstrated normal or high level of Hb F (SS-HF). The diagnosis of Sβth depended on the presence of Hb S in electrophoresis with one parent with SS trait and the other with Sβth trait, with haematological parameters indicating microcytic hypochromic anaemia.

ASSC attacks were divided into minor and major types. Minor attacks were defined as a decrease in Hb level of ≥25% from baseline accompanied by an increase in spleen size of at least 2 cm with mild transient thrombocytopenia. Major episodes were defined by sudden drop of Hb to <3 g/dl, an increase in spleen size with evidence of hypovolaemia.

The diagnosis of hypersplenism was based on the presence of splenomegaly with accompanying anaemia and an increased need for blood transfusion to more than 250 ml/kg of packed red blood cells per year, or a drop of Hb level of >0.5 g/dl per week and thrombocytopenia with platelets count of <100,000/mm³ or leucocyte count of <4000/mm³, either singly or in combination [3].

A comparison was conducted between the deferent SCD groups (Sβth, SS, SS-HF) with regard to frequency and severity of ASSC, age of first episode and presence of hypersplenism. The deference between SCD patients with ASSC and those without ASSC was studied too.

For statistical analyses, Fisher’s exact test for proportion and two-sample t-test for means were used. The results were expressed as mean (SD). A p-value ≤0.05 was considered statistically significant.

The study was approved by the Ethics Committee of the Medical Faculty. Informed consent was obtained from patients’ guardians.

Results

Over the 8 year period, 73 patients with SCD were attended to. Their ages ranged between 2 and 18 years (mean, 10.1 years). There were 35 females and 38 males. Thirty-seven (50.6%) had Sβth, 36 (49.4%) had homozygous SS. Of patients with SS, 26 had SS-HF genotype and 10 had SS with normal level of Hb F. Their mean corpuscular volume (MCV) haemoglobin concentration (MCH), Hb electrophoresis, age and male-to-female ratio are summarized in Table 1. There were significant differences between the three groups in the mean corpuscular volume, mean Hb concentration and the percentage of Hb S and Hb F.

Twenty-one patients (28%) had 63 episodes of ASSC (37 minor and 26 major). Thirty-seven episodes were experienced by 12 patients with Sβth (seven females and five males), of these 11 were major attacks with one fatal case of a 2.5-year-old girl, who died of acute circulatory collapse shortly after arrival to the hospital. Twenty-six episodes were

<table>
<thead>
<tr>
<th>Variable</th>
<th>S-βth No. 37</th>
<th>SS-HF No. 26</th>
<th>SS-NF No. 10</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/Male</td>
<td>19/18</td>
<td>10/16</td>
<td>5/6</td>
<td>0.3</td>
</tr>
<tr>
<td>Age/years, range (mean)</td>
<td>2–18 (11.4)</td>
<td>1.5–18 (7.4)</td>
<td>3–18 (10.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>MCV (fl), mean (SD)</td>
<td>66.9 (13.8)</td>
<td>82.7 (9.3)</td>
<td>85.7 (8.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MCH, Mean (SD)</td>
<td>21.6 (5.05)</td>
<td>28.3 (3.4)</td>
<td>26.3 (4.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Percentage of Hb S, mean (SD)</td>
<td>59.8 (12.3)</td>
<td>67.1 (10.6)</td>
<td>85.9 (12.9)</td>
<td>0.014</td>
</tr>
<tr>
<td>Percentage of Hb F, mean (SD)</td>
<td>25.5 (12.4)</td>
<td>24.7 (9.7)</td>
<td>0.39 (1.3)</td>
<td>0.77</td>
</tr>
<tr>
<td>Percentage of Hb A2, mean (SD)</td>
<td>2.7 (1.7)</td>
<td>1.7 (1.18)</td>
<td>2.6 (0.8)</td>
<td>0.007</td>
</tr>
<tr>
<td>Percentage of Hb A, mean (SD)</td>
<td>11.3 (12.8)</td>
<td>7.4 (10.7)</td>
<td>19.0 (22.5)</td>
<td>0.19</td>
</tr>
</tbody>
</table>
experienced by nine patients with SS (three females and six males). Of these, 15 were major with no fatalities. A comparison between patients with ASSC and those without was performed. The results are summarized in Table 2. There was no significant difference between the two groups in the mean corpuscular volume, mean haemoglobin concentration and Hb electrophoresis. On the other hand, splenomegaly and hypersplenism were higher in the ASSC group than the rest of SCD patients, the differences being extremely significant.

When patients with ASSC in the Sβth group were compared with those in the SS group, nine of the Sβth group were siblings while there were none in the SS group. There were significant differences in the levels of Hb F, Hb S, size of spleen and severity of crisis (Table 3). The mean age at the first episode was higher in Sβth patients. All Sβth patients had their first episode at the age of 2 years or over, nine were between 3.5 and 5 years and one at the age of 10 years. None of the SS group had their first crisis above an age ≥ 5 years. Five were less than 1 year of age, and three were under 2.5 years of age. These differences were statistically significant.

In the SS group, the only significant difference between patients with ASSC and those without ASSC was the presence of splenomegaly (Table 4).

**Discussion**
Acute splenic sequestration crisis is a potentially life-threatening event that is characteristic of SCD. The prevalence of crises differs significantly between countries. It is found in 30% of Jamaican SCD children [4, 5], 11.75–14.6% in France [6], 7.5% in USA [7, 8], 1.7–7% in Saudi [9, 10] and in about 1% of Omani children [11]. In this study, 21 children (28%) experienced ASSC. This is considered high compared with what was reported in neighboring Middle Eastern countries [9–11]. This high rate could be related to the presence of larger number of patients with Sβth in this study, with many affected siblings and easy access to the hospital, thus increasing the chances of making the diagnosis of ASSC.

It has been reported that the mortality rate at first attack of ASSC may reach 12% [1], and recurrences are common, occurring in approximately 50% of those who survive the first episode [1, 4, 9], with a mortality rate that may reach 20% [1]. In this study, 16 patients had major crisis with one fatality (6% mortality). Recurrence was observed in 15 cases with diminishing intervals between attacks that reached five to six episodes in some patients, with no fatalities. As there is always the potential of a fatality at first attack and any subsequent attack,
it is important to educate parents regarding the symptoms of ASSC to aid the early recognition of a crisis, thus allowing early institution of therapy.

The most significant deference between SCD patients with ASSC and those without ASSC was the presence of splenomegaly. Twenty patients with ASSC had splenomegaly, and only one child with ASSC had no palpable spleen before his first ASSC. The same significant difference was noticed when SS patients with ASSC without ASSC were compared. Moreover, 20 (43%) out 46 patients with enlarged spleens had ASSC, in 13 (70%) of them the spleen size was more than 5 cm below the costal margin. This suggested that 43% of patients with SCD and splenomegaly were at risk of developing ASSC, particularly those with Sβth.

Topley, et al. [1] described a close relationship between episodes of ASSC and subsequent development of hypersplenism, which occurred in one-third of his patients. Similar finding were described by Chopra, et al. [12], who reported that 39 of their 44 patients with hypersplenism had history of minor ASSC attacks. Fourteen of our patients (66.6%) developed hypersplenism after crisis compared with (31.4%) patients without ASSC. The difference was statistically very significant. This finding adds further support to previous reports.

Bailey, et al. [13] and Stevens, et al. [14] suggested that the lower the Hb F level in SS patients, the higher the possibility of ASSC, and that high Hb F level protected against attacks of ASSC [4]. In contrast, our study showed that the mean Hb F level was higher in ASSC compared with those without ASSC, but the difference was not statistically significant. Similarly, Moll, et al. [15] speculated that high Hb F levels and α-thalassaemia may be important aetiological factors in causing persistence of splenomegaly and predisposing patients to ASSC.

On studying the difference between patients with ASSC with Sβth genotype and those with SS genotype, there was a significant deference in the level of Hb S and Hb F, as expected in patients with Sβth. Moreover, there was significant difference between the two groups in the severity of crises. They were minor in 70% of Sβth patients, while these episodes were major in 57% of patients with SS. There was no significant difference in the recurrence rate of ASSC, mean number of crises and the number of patients with hypersplenism.

The mean age at first episode of ASSC was 3.9 years in the Sβth group and 2.1 years for the SS group. Seventy-five percent of patients with Sβth had their first crisis when over the age of 3.5 years, and in one of them the first crisis was at the age of 10 years, while 77% of patients with SS had their first crisis below the age of 2 years, and none of them had their first crisis after the age of 5 years. These finding are similar to those reported by others. Topley, et al. [1] and Bainbridge, et al. [16] reported that almost 30% of their patients had their first attack before the age of 2 years. Dickerhoff, et al. [2] reported that none of their SS patients had ASSC attacks after the age of 6 years. On the other hand, late presentations in some patients with Sβth suggest that they may remain at risk of ASSC even as adolescents and adults. This suggestion is supported by other reports that described a fatal ASSC in adults with Sβth [17–19].

The risk of ASSC in sibling with SCD was high in patients with Sβth. Nine out of the 19 sibships with Sβth had ASSC, while none of the 20 sibships with SS had ASSC. This suggests that if one of Sβth has ASSC, the risk to a sibling with SCD would be around 47%. Emphasizing this difference in the risk of ASSC in Sβth patients and those with SS is very important when counseling families with Sβth. An increased awareness among caregivers regarding this aspect is vital in combating this potentially fatal complication.

This study concluded that the rate of ASSC in Sβth patients was 32% and was 25% in SS patients. The risk of recurrence was about 70% in those who survived their first episode, and there was a close relationship between ASSC episodes and subsequent hypersplenism. The most important predicting factors for ASSC in Sβth patients were the presence of splenomegaly and presence of minor crises.

### Table 4
Comparison between patients with SS with ASSC and SS without ASSC

<table>
<thead>
<tr>
<th>Variable</th>
<th>SS with ASSC No. 26</th>
<th>SS without ASSC No. 11</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen size/cm, mean (SD)</td>
<td>4.18 (1.39)</td>
<td>1.69 (3.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Number of patients with hypersplenism</td>
<td>3</td>
<td>5</td>
<td>0.035</td>
</tr>
<tr>
<td>MCV values</td>
<td>84.56 (8.7)</td>
<td>85.5 (8.5)</td>
<td>0.76</td>
</tr>
<tr>
<td>MCH values</td>
<td>27.63 (3.6)</td>
<td>27.89 (3.8)</td>
<td>0.84</td>
</tr>
<tr>
<td>Percentage of Hb S</td>
<td>71.6 (13.34)</td>
<td>67.4 (2.36)</td>
<td>0.13</td>
</tr>
<tr>
<td>Percentage of Hb F</td>
<td>16.26 (14.5)</td>
<td>21 (12.5)</td>
<td>0.3</td>
</tr>
<tr>
<td>Percentage of Hb A2, range (mean)</td>
<td>1.86 (1.11)</td>
<td>1.95 (1.36)</td>
<td>0.8</td>
</tr>
<tr>
<td>Percentage of Hb A range (mean)</td>
<td>7.3 (10.65)</td>
<td>12.9 (16.1)</td>
<td>0.3</td>
</tr>
</tbody>
</table>
of splenomegaly of more than 5 cm below the costal margin, history of ASSC in siblings and high F Hb. In SS patients, most of the first episodes occurred when under the age of 2 years, while in Sβth patients the majority had their first crisis at age ≥3.5 years. It is suggested that any child with a history of major episode of ASSC needs long-term transfusion therapy if it is under the age of 5 years, and prompt splenectomy after a major first episode of ASSC if it is above the age of 5 years or where there is a minor episode that is followed by the development of chronic hypersplenism.

References