The Acute Chest Syndrome in Sickle Cell Disease: Incidence and Risk Factors

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The acute chest syndrome (ACS), a pneumonia-like illness in sickle cell patients, is one of the most frequent causes of their morbidity and hospitalizations. Repeated ACS events may predict the development of chronic lung disease. ACS is reported as a frequent cause of death in these patients. We examine here the incidence and risk factors of ACS in 3,751 patients with sickle cell disease who were observed prospectively for at least 2 years (19,867 patient-years [pt-yrs]) as part of a multicenter national study group. The ACS, defined by a new pulmonary infiltrate on x-ray, occurred at least once in 1,085 patients (2,100 events). ACS incidence was higher in patients with homozygous sickle cell disease (SS; 12.8/100 pt-yrs) and in patients with sickle cell-β thalassemia (9.4/100 pt-yrs), and lower in patients with hemoglobin (Hb) SC disease (5.2/100 pt-yrs) and patients with sickle cell-β thalassemia (3.9/100 pt-yrs). α-Thalassemia did not affect the rate of ACS incidence in SS patients. Within each Hb type the incidence was strongly but inversely related to age, being highest in children 2 to 4 years of age (25.3/100 pt-yrs in SS) and decreasing gradually to its lowest value in adults (8.8/100 pt-yrs in SS). In SS children (<10 years of age), we documented an age-related within-person reduction in ACS attack rates. Adults with a higher ACS rate had a higher rate of mortality (from all causes) than those with low ACS rates. This increased rate of mortality might also have contributed to the decline in ACS rate with age. In multivariate analysis, other factors affecting incidence in SS patients were degree of anemia (lower ACS rates in patients with lower steady-state Hb levels) and fetal Hb (lower rates in patients with high fetal Hb). There was also a positive association between ACS rate and steady-state leukocyte count. The relationship of ACS rate to higher steady-state Hb levels in SS patients is unexplained but might be caused by increased blood viscosity.

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San Francisco, CA). Patients in this group were diagnosed as having SS-α thalassemia if restriction endonuclease analysis showed that they lacked one α-globin gene.

**Definition of ACS.** For the purposes of this study, the diagnosis of ACS was made each time a patient (1) developed a new infiltrate on chest x-ray and/or (2) had a perfusion defect demonstrable on a lung radionuclide scan. However, because the performance of the isotope scan was not mandatory, only a very small number of ACS episodes (<0.9%) was diagnosed by this method.

**Statistical analysis.** The primary goal of the statistical analysis was the identification of variables with which ACS incidence varies. The relation between ACS rate and its potential predictors was examined using Poisson regression, with correction for overdispersion. Poisson regression is particularly useful for modeling counts of relatively rare events. Under the assumed model, the natural logarithm of expected ACS rate (events/pt-yrs) varies linearly with the independent variables. A multivariable approach to model construction was used to gain some control of confounding. First, a model was constructed that included all covariates of interest in an analysis. Then backward elimination was used to remove covariates that were not statistically significant. For Hb and Hb F, both linear and quadratic terms were considered, with the quadratic terms included to test for curvature in the relationship between the log of expected ACS rate and each of these variables. The linear and quadratic components were treated as separate variables in the stepwise model building. Categorical variables (age group and genotype) with three categories were included in the model as k-1 binary (0 or 1) variables. For example, four genotypes can be represented by three binary variables and five age groups by four variables. The 12 variables created by the product of the age and genotype variables were used to test the interaction between age and genotype. Model fitting was accomplished with the GLIM statistical package using an algorithm developed by Breslow.

**RESULTS**

**Incidence of ACS.** A total of 2,100 episodes of ACS occurred in 1,085 sickle cell disease patients during the study period. Most (606) of the patients with chest syndrome had only one such event, but four SS patients had at least 13 events each (Table 1).

Table 2 shows the distribution of these events by Hb genotype and age at the time that each event occurred. A Poisson regression model was developed to examine variation in ACS incidence with these two factors. Age at entry into the study (≤2, 2 to 4, 5 to 9, 10 to 19, or ≥20 years) was used in place of age at each event in this model. Both age and genotype made strong contributions to the model (P < .0001). For SS patients, the ACS rate at age less than 2 years was lower than that in the 2 to 4 year age group (although still higher than in adults and older children). The increase from ages greater than 2 to 2 to 4 years was not the result of differences in the patient population because the ACS rate also increased (from 21.5 to 25.8/100 pt-yrs) for the subset of 451 patients with follow-up in both age groups. The lower ACS rate in the less than 2 years of age group could have been an effect of higher Hb F concentrations in those patients. As shown below, the Hb F level strongly and independently influences ACS incidence. An age-genotype interaction was not statistically significant (P = .55). Thus, no variation among genotypes in age-related trends in ACS incidence was detected. The fitted model indicates that ACS incidence is higher in SS patients than in SC or S-β⁺ thalassemia patients, but the difference between SS and S-β⁺ thalassemia patients was not statistically significant. Additionally, the fitted model showed that S-β⁺ thalassemia patients had a higher incidence of ACS than either SC or S-β⁺ thalassemia patients. No statistical difference was found between the rates of ACS for SC and S-β⁺ thalassemia patients.

**α-Globin gene DNA analysis was performed in a subset of 1,852 SS patients to determine their α thalassemia status. There were 1,284 patients without α thalassemia (4 α-genes) and 568 with this abnormality (521 with 3 α-genes and 47 with 2 α-genes). A total of 1,462 ACS events occurred in this subset of SS patients with known α-gene status. Of these, 1,029 events occurred in patients without α thalassemia (4 α-genes), 393 in patients with 3 α-genes, and 40 in those with 2 α-genes. α Thalassemia had no apparent effect on ACS rate because the incidence of this event in patients with 4, 3, and 2 α-genes was similar (13.0, 12.4, and 13.6/100 pt-yrs, respectively). The effect of α thalassemia is considered further in the multivariable analysis described below.

**Factors affecting the relationship of age to ACS incidence.** The inverse association between ACS incidence and age could reflect underlying within-person changes in incidence or it could reflect a survival effect if high ACS incidence is associated with early mortality. These two explanations were examined using data from SS patients. The first explanation was tested by subtracting the incidence rate (events/year) for the first 3 years of each patient’s follow-up from his/her incidence rate for the remainder of their follow-up. Paired t-tests were used to determine whether the average change in incidence differed from zero. Only subjects with at least 6 years of follow-up were included (1,169 subjects; 46% of SS patients). Results showed that children entering the study before 10 years of age experienced declines in ACS incidence during the study observation period, but patients who were at least 10 years old at study entry did not do so (Table 3).

The second explanation, ie, that there is an association between ACS incidence and survival, was examined by comparing survival among those patients who experienced an ACS event during their first 2 years of follow-up with those who experienced no episodes of ACS in that time period.

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**Table 1. ACS in Sickle Cell Disease**

<table>
<thead>
<tr>
<th>No. of patients at risk</th>
<th>ACS 3,751</th>
<th>Patients with at least one episode of ACS</th>
<th>1,085 (29.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with a single ACS episode</td>
<td>605 (55.0%)*</td>
<td>With 2 episodes</td>
<td>253 (23.3%)</td>
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<tr>
<td></td>
<td></td>
<td>With 3 episodes</td>
<td>104 (9.6%)</td>
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<td>With 4 episodes</td>
<td>57 (5.2%)</td>
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<td></td>
<td>With 5 episodes</td>
<td>24 (2.2%)</td>
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<td></td>
<td></td>
<td>With 6 episodes</td>
<td>16 (1.5%)</td>
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<td></td>
<td></td>
<td>With 7 episodes</td>
<td>10 (0.9%)</td>
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<td></td>
<td>With 8 episodes</td>
<td>5 (0.5%)</td>
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<td></td>
<td></td>
<td>With 9 episodes</td>
<td>4 (0.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With 10 episodes</td>
<td>2 (0.2%)</td>
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<td></td>
<td></td>
<td>With 11 episodes</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With 13 episodes</td>
<td>1 (0.1%)</td>
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<td></td>
<td></td>
<td>With 14 episodes</td>
<td>1 (0.1%)</td>
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<tr>
<td></td>
<td></td>
<td>With 15 episodes</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With 16 episodes</td>
<td>1 (0.1%)</td>
</tr>
</tbody>
</table>

* One hundred percent is 1,085.

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The method used was a modified product-limit approach that used age at death (time since onset of disease) as the outcome. Patients were considered to be at risk after their time of the death. Subjects were also no longer considered to be at risk when they reached 40 years of age because there were very few patients above this age. A computer algorithm within the SAS program was developed to generate these curves. From Fig 1 it can be seen that mortality is comparable in the two groups until 20 years of age, at which time the mortality for patients with at least one ACS event begins to surpass that of patients with no ACS events. With similar methodology, a likelihood ratio test was developed to determine whether having at least one ACS event was a predictor of mortality in a Cox regression model. This test showed that having at least one ACS event was associated with reduced survival ($P = .943$). Thus, these results indicate that both within-patient changes in incidence rates and, to a lesser degree, higher mortality among patients with high ACS rates contributed to the negative association between ACS incidence and age at entry into the study.

Multivariable analysis of risk factors for ACS incidence. Potential predictors of ACS incidence were examined in multivariable models (see Materials and Methods). Age at study entry was controlled for in all models. The following risk factors were tested in both SS and SC patients in separate models: gender, α thalassemia status (SS only), Hb F level at study entry (after exclusion of patients <2 years of age because their Hb F levels are not yet stable), hematologic parameters (Hb, hematocrit [Hct], red blood cell [RBC] count, mean corpuscular RBC volume, leukocyte count, and platelet count), and smoking status and number of cigarettes smoked per day (patients >10 years of age). For most hema-
Smoking status was left out in the modeling because it was not found to be significant in SS patients. In this model, the only variable that was statistically significant was the steady-state white blood cell (WBC) count. The relatively small sample size for SC patients may have prevented detection of other risk factors for ACS in this group.

DISCUSSION

This prospective study of 2,100 episodes of ACS in a representative sample of sickle cell patients was undertaken to elucidate some factors influencing its incidence (risk factors). The incidence of ACS was strongly influenced by patient age, being most common in younger children with the disease and least frequent among adult patients. In the SS genotype, the effect of age on ACS incidence was explained by a within-patient decline in ACS rates in young children and possibly also by a preferential survival of patients with lower ACS incidence among adults. However, the higher mortality in patients with higher ACS rates does not mean that they died of this complication. In all probability, the increased mortality was associated with higher ACS rates because both are indicators of disease severity. As will be

Fig 1. Survival analysis in SS patient groups with no ACS events in the first 2 years (---, N = 1,784) and with at least one ACS event in the first 2 years (----, N = 419).

tologic variables, values were obtained by averaging the measurements made at annual exams during the study. Thus, the values should reflect long-term steady-state levels and not changes occurring during ACS.

Age ($P < .0001$), Hb F level ($P < .0001$), degree of anemia [Hb level] ($P < .0001$), and white blood cell (WBC) count ($P < .005$) were independent risk factors for ACS incidence in SS patients. The terms that were not statistically significant, and that were therefore dropped from the model, were gender, α thalassemia, both smoking variables, platelet count, erythrocyte mean corpuscular volume, and (because Hb was included in the model) RBC count and Hct.

The incidence of ACS varied inversely with Hb F levels in SS patients. Figure 2 shows the effect of the percentage of Hb F on ACS rates for 3 of our patient age groups as predicted by the Poisson model. An increase in Hb F from 5% to 15% corresponds to an approximate halving of ACS incidence. For example, for patients aged 5 to 9 years, the ACS rate decreases from 0.16 episodes/pt-yrs at 5% Hb F to approximately 0.09 episodes/pt-yrs at 15% Hb F.

The ACS rates were lower in SS patients with more severe anemia (lower Hb levels, Fig 3). For example, for patients 20 years of age and older, an increase in Hb from 8 to 12 g/dL corresponds to an increase in the ACS rate from approximately 0.06 to 0.14 episodes/pt-yrs.

Multivariable analysis of ACS risk factors in SC patients was also performed as described above for SS patients. α Thalassemia status was not determined for SC patients.

Fig 2. Effect of HbF level on ACS incidence in SS patients as predicted by Poisson modeling. Plots are shown for three age groups: 2 to 4 years (----), 5 to 9 years (----), and 20+ years (----). The plot for the 10 to 19 years age group (data not shown) was nearly the same as that for the 20+ years age group. In generating these plots, the other terms that were statistically significant in the Poisson model were held constant. Blood Hb level and WBC were set at their overall means for SS patients (8.42 g/dL and 12.06 x 10⁷/µL, respectively). ACS rate was plotted within the range of observed HbF levels for each age group.
predicted by Poisson modeling. Age groups are as in Fig 2. The WBC within the range of the observed Hb values for each age group.

discussed below, a high frequency of pain crises is also an indicator of disease severity (and a predictor of short survival) in this patient population.

Other factors associated with a high ACS incidence were the SS genotype and a high steady-state leukocyte count. For SS patients, risk factors also included high Hb level and low Hb F concentration. In all age groups of patients with sickle cell anemia (SS), the incidence of ACS was inversely related to Hb F level. Our data may explain why previous analyses of the protective effect of Hb F on the prevalence of ACS have given equivocal results. The influence of age on ACS incidence is so strong that the protective effect of Hb F, which is only relative, can be detected only by examining a narrow age range, particularly among younger patients. α Thalassemia did not affect ACS incidence in SS patients even though α thalassemia is known to lower these patients' hemolytic rate.21 The reasons for the association between high leukocyte count and ACS incidence are not clear. Preliminary analysis of the CSSCD patient survival data shows that higher leukocyte counts correlate with higher mortality rates. Therefore, the association of leukocytosis with ACS incidence could reflect the fact that both high WBC and high ACS rate are more frequent in patients with severe disease.

What do these risk factors suggest about the pathogenesis of ACS? The highest ACS incidence in young children is compatible with infection as an etiology because these patients have not yet developed antibodies to a variety of bacterial and viral microorganisms. However, recent reports, in which careful bacteriologic and virologic studies were performed, excluded an infectious etiology of ACS in most adults and children.3,6,22 The association of ACS with young age could also be explained by reasoning that the increased susceptibility to viral respiratory infection in young children could precipitate ACS if the latter had a vaso-occlusive pathogenesis. The within-patient decline in ACS incidence as these children age could then reflect a developing immunity to viral infections.

Sickle cell patients have a known predisposition to bacterial infection, particularly pneumococcal infection.23-25 Without invasive procedures it is very difficult to rule out conclusively a bacterial process as a cause of ACS. Bacteria could also superinfect an area of ischemic lung tissue. For these reasons, the ACS is almost always treated with antibiotics. On the other hand, reports of rapid resolution of severe ACS after exchange transfusions26-28 suggest that pulmonary vascular occlusion and ischemia/infarction play an important etiologic role in the syndrome. Indeed, vascular occlusion has been suggested by high resolution computerized tomography,29 and has been demonstrated in the isolated ACS cases in which pulmonary angiography was performed.30 The frequent finding of alveolar wall necrosis and marrow emboli31 at autopsy of sickle cell patients dying of various causes also suggests lung injury from vascular occlusion rather than infection. Other presumptive causes of ACS include viral infection, mycoplasma infection,32 thromboembolism,33 fat embolization syndrome,34 and hypoventilation-atelectasis due to rib infarctions.35

It is interesting to compare the ACS risk factors with those of the most common sickle cell complication, the vaso-occlusive (pain) crisis. Platt et al26 recently analyzed the risk factors for pain crises using the same CSSCD database and multivariable analysis. As was the case with the ACS data reported above, pain crises in SS patients were associated with higher Hb levels and they were inversely related to Hb F concentration. Among SS adults, mortality risk was positively associated with pain crisis rate. In adult SS patients, a high ACS incidence was an independent predictor of shorter survival, even after correcting for high pain crisis rate (data not shown but available on request). The similarities in the risk factors for ACS and painful events (crises) suggest, but do not prove, that vascular occlusion is the process underlying both of these complications. Additional insights may be gained after completing the analysis of the clinical presentation and clinical course of ACS in this large patient population (manuscript in preparation). In any case, our data indicate that therapeutic measures that increase Hb F should lower the risk for both pain crisis6 and sickle cell chest syndrome.

APPENDIX

The Cooperative Study of Sickle Cell Disease is funded by the Sickle Cell Disease Branch of the Blood Division of the National Heart, Lung, and Blood Institute, National Institutes of Health. The following are cooperating clinics and senior investigators in the study.
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Chairman of Steering Committee: Dr Wendell F. Rosse. 

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