Clinical Study

Associated Factors of Acute Chest Syndrome in Children with Sickle Cell Disease in French Guiana

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A matched case-control study was performed in order to identify some associated factors for ACS or to confirm the published data. Controls were children hospitalized during the same period for pain crisis who did not develop an ACS during hospitalization. Between January 2006 and October 2010, there were 24 episodes of ACS distributed among 19 patients (8 girls and 11 boys). The median age was 7.5 years (range: 3 to 17 years) for the cases and 7 years (range: 3–18 years) for the controls. Four cases and 11 controls were treated with hydroxyurea (HU). In 75% of the cases, the ACS had arisen 24–72 hours following admission. The independent factors associated with ACS were average Hb rate <8 g/dL (OR = 4.96, 95% CI = 1.29–27.34, and \( P = 0.04 \)), annual number of hospitalizations >3 (OR = 5.44, 95% CI = 3.59–8.21, and \( P = 0.003 \)), average length of hospitalization >7 days (OR = 3.69, 95% CI = 3.59–8.21, and \( P = 0.003 \)), and a pathological transthoracic echocardiography (TTE) (OR = 13.77, 95% CI = 2.07–91.46, and \( P = 0.003 \)). Although the retrospective design and small sample size are weaknesses of the present study, these results are consistent with those of previous studies and allowed identifying associated factors such as a pathological TTE.

Sickle cell disease (SCD) is a major public health concern in French Guiana, a French region with 230,000 inhabitants located in South America [1]. The incidence of major SCD from birth screening is 1/227, and the overall frequency of AS carriers is 10% [2]. The major SCD groups include the three main genetic forms: hemoglobin (Hb) SS (68%), Hb SC (25%), and Sβ thalassemia (7%). The acute chest syndrome (ACS) is a complication of SCD characterized by pleuritic chest pain, fever, rales on lung auscultation, and pulmonary infiltrates on chest X-ray [3]. It is the most frequent cause of mortality in children with SCD [3–8]. In 1979, Charache et al. first suggested using the term acute chest disease (ACD) for this complication, acknowledging the difficulties in determining its pathogenesis [9].

We report here the results of a case-control study of risk factors for ACS in children with SCD in French Guiana, in order to find some associated factors for ACS or to confirm the published data. We hypothesized that HbSS, age, high Hb level, and high steady-state leukocyte count could be risk factors for ACS. This matched case-control study concerned all cases of ACS hospitalized in the pediatric unit in French Guiana from 2006 to 2010. The cases were children hospitalized between January 2006 and October 2010 for pain crisis and who developed an ACS. The controls were children hospitalized during the same period for pain crisis and who did not develop an ACS during hospitalization. Each episode of ACS was matched on age, gender, and year of diagnosis.

The transthoracic echocardiography (TTE) was performed by a single pediatrician cardiologist, at baseline when the child was in a healthy state, during the annual evaluation. Patients with a pathological TTE were followed every six months by the same pediatrician cardiologist. All the TTE were obtained at true baseline and not during admissions. These TTE showed the following anatomical pathologies: an enlargement of the left heart chambers associated with an elevation in blood volume in seven cases and two controls and elevation in left ventricular myocardial indices in two cases and two controls. The Commission Nationale Informatique et Libertés approved our data collection. The factors associated with ACS were analyzed by logistic regression based on odds.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>Bivariate analysis</th>
<th>Multivariate analysis</th>
<th>$P$</th>
<th>$P$</th>
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<tr>
<td></td>
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<td>Crude OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
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<td>Age (years)</td>
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<td>0–4</td>
<td>2 (8)</td>
<td>25 (33)</td>
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<tr>
<td>5–9</td>
<td>14 (59)</td>
<td>21 (27)</td>
<td>0.12 (0.02, 0.59)</td>
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<tr>
<td>10–14</td>
<td>6 (25)</td>
<td>15 (20)</td>
<td>0.2 (0.04, 1.12)</td>
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<td>15–19</td>
<td>2 (8)</td>
<td>15 (20)</td>
<td>0.6 (0.08, 4.72)</td>
<td>0.63</td>
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<td>Sex</td>
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<tr>
<td>M</td>
<td>13 (54)</td>
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<tr>
<td>F</td>
<td>11 (46)</td>
<td>33 (43)</td>
<td>1.1 (0.44, 2.77)</td>
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<td>Type of haemoglobin</td>
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<tr>
<td>SS</td>
<td>20 (83)</td>
<td>45 (59)</td>
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<tr>
<td>Sβ thal or SC</td>
<td>4 (17)</td>
<td>31 (41)</td>
<td>0.29 (0.09, 0.93)</td>
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<td>History of treatment by hydroxyurea</td>
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<tr>
<td>Yes</td>
<td>4 (17)</td>
<td>11 (14)</td>
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<tr>
<td>No</td>
<td>20 (83)</td>
<td>65 (86)</td>
<td>0.85 (0.24, 2.95)</td>
<td>0.79</td>
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<td>Duration of hospitalization (days)</td>
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<tr>
<td>&gt;7</td>
<td>14 (58)</td>
<td>12 (16)</td>
<td>4.23 (2.64, 6.3)</td>
<td>&lt;0.01</td>
<td>3.69 (2.30–5.56)</td>
<td>&lt;0.01</td>
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<tr>
<td>0–7</td>
<td>10 (42)</td>
<td>64 (84)</td>
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<td>Age during the first symptoms</td>
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<tr>
<td>1 year</td>
<td>5 (21)</td>
<td>34 (45)</td>
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<td>Before 1 year</td>
<td>19 (79)</td>
<td>42 (55)</td>
<td>3.08 (1.04, 9.09)</td>
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<td>History of &gt;3 annual hospitalisations</td>
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<td>Yes</td>
<td>19 (79)</td>
<td>26 (34)</td>
<td>7.31 (2.45, 21.8)</td>
<td>&lt;0.01</td>
<td>5.44 (3.59–8.21)</td>
<td>0.003</td>
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<td>5 (21)</td>
<td>50 (66)</td>
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<td>Basic haemoglobin level</td>
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<tr>
<td>&gt;8 g/dL</td>
<td>3 (12)</td>
<td>31 (41)</td>
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<tr>
<td>0–8 g/dL</td>
<td>21 (88)</td>
<td>45 (59)</td>
<td>4.82 (1.32, 17.58)</td>
<td>0.15</td>
<td>4.96 (1.29–27.34)</td>
<td>0.04</td>
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<tr>
<td>Basic S haemoglobin level</td>
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<td>≥80%</td>
<td>20 (83)</td>
<td>39 (51)</td>
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<tr>
<td>&lt;80%</td>
<td>4 (17)</td>
<td>37 (49)</td>
<td>0.21 (0.07, 0.68)</td>
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<td>Transthoracic echocardiography</td>
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<tr>
<td>Normal</td>
<td>15 (63)</td>
<td>70 (95)</td>
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<tr>
<td>Abnormal</td>
<td>9 (37)</td>
<td>4 (5)</td>
<td>10.5 (2.85, 38.65)</td>
<td>&lt;0.001</td>
<td>13.77 (2.07–91.46)</td>
<td>0.003</td>
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<td>Transcranial echo-Doppler</td>
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<td>Normal</td>
<td>19 (79)</td>
<td>72 (97)</td>
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<tr>
<td>Abnormal</td>
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<td>2 (3)</td>
<td>9.47 (1.7, 52.69)</td>
<td>0.01</td>
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</tbody>
</table>

* Obtained using conditional logistic regression with indicator variables for nonbinary variables.

Bold fonts: OR (95% CI) of multivariate analysis.

Italic fonts: $P$-value of multivariate analysis.
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ratios (OR). For all tests performed, a \( P \) value of 0.05 or
less was considered as statistically significant. The data were
entered into Microsoft Excel 2007 and analyzed using R 2.10.0
(R project, CRAN R 2.10.0 version 2010) statistical software.

All the factors numbered in Table 1 were included in this
analysis. We included in our final model the covariates that
were associated with the outcome in the univariate analysis
and other factors associated with ACS, according to the
literature.

Between January 2006 and October 2010, there were 24
episodes of ACS distributed among 19 patients (8 girls and 11
boys). One patient developed 3 events of ACS; 3 presented 2
events; and 15 patients presented 1 event of ACS. The median
age was 7.5 years (range: 3 to 17 years) for the cases and 7
years (range: 3–18 years) for the controls (Mann-Whitney
test). These two groups did not differ in age.

Four cases and 11 controls were treated with hydroxyurea
(HU). The results are shown in Table 1. Among the cases,
there were 20 HbSS, 3 HbS\(^{β}\) thalassemia, and 1 HbSC.
Among the controls, there were 45 HbSS, 12 HbS\(^{β}\) thala-
ssemia, 10 HbS\(^{β}\)+ thalassemia, and 9 HbSC. The more
frequent hospitalization, longer hospital stays, lower Hb,
higher % HbS, and earlier presentation in the cases may be
explained, at least in part, by the difference in genotype and
the severity of sickle cell anemia.

In 75% of the cases, the ACS had arisen 24–72 hours fol-
lowing admission. All patients received rehydration, oxy-
gen therapy, and pulmonary physiotherapy using stress spiro-
metry and triple antibiotic therapy (cefotaxime, aminoglycoside,
and a macrolide). In 16 cases, patients received a single
red blood cell transfusion and in six other cases, the red
blood cell transfusion was followed by a partial exchange
transfusion (removing the patient’s own blood and replacing
it with 0.9% NaCl volume for volume, which was followed
by a red blood cell transfusion). The target haemoglobin S
value was under 30% and haemoglobin level 80–90 g/L, and
in any of the cases, we obtained them. The more frequent
hospitalization, longer hospital stays, lower Hb, higher %
HbS, and earlier presentation in the cases may be explained,
at least in part, by the difference in genotype and the severity
of sickle cell anemia. Two cases died. The cases who died
did not receive a transfusion. The first was a 6-year-old girl
in severe vasoocclusive crisis with fever and severe anemia
(Hb of 4 g/dL), who presented 8 hours later with a frank ACS
and whom endotracheal intubation was unsuccessful. The
second was a 4-year-old girl also with frank ACS and bilateral
pleural effusion, who died despite successful endotracheal
intubation. The two cases who died had received a single dose
of ceftriaxone. The proportion of death was high and due
in part to low access to care in foreign patients. Although
health is free of charge in French Guiana, the prevention
is complicated by the fact that a number of persons are
illiterate or do not understand the language. However, the
health priorities of immigrants are often overridden by daily
struggles to obtain food, shelter, and papers. Due to the
low power of our study, certain factors such as lower Hb,
higher % HbS, and earlier presentation in the cases as well
as the transcranial Doppler, that were significant in bivariate
analysis, were not statistically significant in multivariate
analysis. However, the effect of including several episodes
in single individuals was not analysed because of the small
sample of our study.

Annual number of hospitalizations >3 (OR = 5.44,
95% CI = 3.59–8.21, and \( P = 0.003 \)), average length of
hospitalization >7 days (OR = 3.69, 95% CI = 3.59–8.21,
and \( P = 0.003 \)), average Hb rate <8 g/dL (OR = 4.96, 95% CI
= 1.29–27.34, and \( P = 0.04 \)), and a pathological TTE (OR =
13.77, 95% CI = 2.07–91.46, and \( P = 0.003 \)) were independent
associated factors for ACS. The TTE was performed to detect
any abnormalities such as left heart chambers abnormalities
and intracardiac shunts, including foramen ovale. According
to a few studies [10], intracardiac shunting could be a risk
factor for stroke in children with SCD because it predisposes
to thrombosis and elevations of right heart pressure, which
could promote paradoxical embolization across an intracar-
diac shunt. In our study, a pathological TTE was a strong
factor associated with ACS. However, the role of cardiac
abnormalities as associated factors for children with ACS
was unknown. Defining the role of intracardiac shunting in
pediatric ACS will require controlled studies with unified
detection methods in stratified populations. HU is efficacious
in children and adults with SCD, with an increase in Hb F%,
reduction in hospitalizations and pain crises, and prevention
of new episodes of ACS. However, in our study, because of its
low power, this variable did not appear as a protective factor.
Although the retrospective design and small sample size are
weaknesses of the present study, our results are consistent
with those of previous studies [3,4,9]. This study also allowed
us to identify associated factors such as pathological TTE.
Possible preventative measures consist of earlier use of red
blood cell transfusion and/or early use of HU. The role of
cardiac abnormalities in ACS deserves to be clarified by other
studies.

Conflict of Interests

The authors declare that they have no conflict of interests.

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