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Leukocytosis is a risk factor for lung function deterioration in children with sickle cell disease

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KEYWORDS
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FEV1;
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Summary
Background: The decline in lung volumes associated with sickle cell disease (SCD) may begin in childhood. Risk factors for early restrictive lung disease may include SCD severity markers such as leukocytosis.
Objective: We examined the relationship between early alteration of lung function and extra-pulmonary markers of SCD severity.
Methods: We analyzed pulmonary function test results for 184 SCD children (mean age 12.6 y) enrolled in a pediatric cohort.
Main results: Total lung capacity (TLC) and vital capacity (VC) were not associated with a history of acute chest syndrome. Lower TLC values were significantly associated with three independent factors: older age, previous acute episodes of anemia <6 g/dl, and higher baseline white blood cell counts. Only the baseline WBC count and age were independent risk factors for lower VC. Relative risks to have a TLC or a VC lower than the mediane value in our population were significantly associated to the baseline leukocytosis (per 10^9 G/L), after adjustment on age, sex, genotype, baseline Hb, and treatment (RR (95% CI) = 1.16 (1.04–1.29) $p < 0.009$, and 1.17 (1.06–1.29) $p < 0.002$, respectively). The obstructive pattern, defined by FEV1/FVC ratio, was not significantly associated to biological parameters.
Conclusions: Hemolysis and leukocytosis were independent risk factors for an early decline in lung volumes in this pediatric SCD cohort

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Introduction

Sickle cell disease (SCD) is the most common inherited disorder in African and Caribbean populations. It is due to homozygous point mutations in the β-globin gene, leading to a reduction in the solubility of deoxygenated hemoglobin.[1] The fundamental pathological processes in SCD include increased red cell fragility, hemolysis, and microvascular obstruction, leading to anemia and ischemia.

Pulmonary complications are responsible for significant morbidity and mortality, accounting for 21%–85% of deaths among SCD patients.[2–4] Chronic lung disease in adults with SCD is thought to result from repeated lung damage caused by pulmonary vaso-occlusion, and is characterized by abnormal lung function test values, chronic hypoxia, pulmonary hypertension, diffuse interstitial fibrosis and cor pulmonale.[3,5–9]

A restrictive pattern of impairment may also be observed in SCD children,[10] and longitudinal studies have shown that the decline in lung volumes begins in childhood.[11] However, the pathophysiology of restrictive disease is less well known in children than in adults. Changes in pulmonary function in SCD children have not been linked to a specific type of lung injury or disease.[11] However, sickle cell disease is characterized not only by repeated lung injury but also by general disorders such as hemolysis, endothelial cell dysfunction, vascular disorders and leukocytosis.[7] Biological markers such as leukocytosis have been linked to disease severity, but their relation to changes in lung function has not been studied.[2,12,13] A decline in DLCO with age has also been linked to markers of vascular disease, such as impaired hepatic and renal function.[14] Here we examined possible relationships between early alteration of lung function and extra-pulmonary markers of sickle cell disease in a pediatric SCD cohort.

Methods

Patient database

This study was based on the Creteil pediatric sickle cell anemia (SCA) cohort.[15] The cohort comprises children who were diagnosed at birth by neonatal screening, and children who were included later in childhood after moving from other region or country. All the children were born between 1978 and 2001.

All clinical events are prospectively collected in a database, together with the results of yearly evaluations performed during crisis-free periods. Vaso-occlusive crises (VOC) were considered here only if necessitating hospitalization. The acute chest syndrome (ACS) was defined as the occurrence of a new pulmonary infiltrate on chest radiography, usually accompanied by chest pain, fever, tachypnea, wheezing or cough.[16] The ACS rate was defined as the number of ACS episodes per year.

In this database, 184 SCD children had undergone lung function tests (LFT). We retrospectively analyzed the most recent LFT results for these children with a mean age (SEM) of 12.6 (0.3) years (range 4.8–20.0). One hundred fifty-nine patients had sickle cell SS or $S\beta_0$ -hemoglobin disease (155 SS and 4 $S\beta_0$), and 25 patients had sickle cell SC-hemoglobin or sickle cell β-thalassemia disease (17 SC and 8 Sβ-thal).

Among the 159 children with SS/Sβ0 SCD, 105 received treatment intensification with hydroxyurea (HU) ($n = 48$), a transfusion program (TP) ($n = 81$) or stem cell transplantation (SCT) ($n = 30$). Their mean (SEM) age at HU, TP, and SCT initiation was 7.9 (0.5), 9.2 (0.5), and 10.0 (0.6) years, respectively.

Lung function testing

Lung function tests (LFTs) were performed in steady-state clinical conditions, at least two months after the last acute event. Acceptance criteria for lung function tests were those recommended by the ATS/ERS task force.[17] Patients who were able to cooperate with testing had measurements of vital capacity (VC), forced expiratory volume in 1 s (FEV_1), functional residual capacity (FRC) measured by the helium washout technique, total lung capacity (TLC), and diffusing capacity for carbon monoxide (DLCO), measured with the single-breath technique. Reference equations from Quanjer et al. were used.[18] Reference values for TLC, FEV_1, and VC were increased by 12% to account for ethnicity.[19,20] The FEV1/FVC ratio was expressed as *Z* score according to recent guidelines.[18,21] The lower limit of normal is defined as the fifth percentile of the distribution that corresponds to a *Z* score of −1.64.[18,21] Adjustments for hemoglobin to the measurement of DLCO were performed as recommended.[22] DLCO was further adjusted to the alveolar volume in order to obtain the transfer coefficient of the lung for carbon monoxide (KCO).[22]

A restrictive pattern was defined as a reduction in TLC to less than 80% of the corrected predicted value.[20,23] An obstructive pattern was defined by a reduction in the FEV1/FVC *Z* score to less than −1.64. FEV_1 was measured before and 15 min after bronchodilator challenge (200 μg of salbutamol). A positive response was defined as an increase in FEV1 of at least 12%, with an absolute increase in volume > 200 ml.[20,23]

Biological values

Biological parameters recorded in the database include the white blood cell (WBC) count, the neutrophil count, the hemoglobin (Hb) level, the platelet count, the hematocrit (Ht), the hemoglobin F (HbF) level, the reticulocyte count and the lactate dehydrogenase (LDH) level. Baseline values were obtained in children older than 18 months who had had no intensive treatment, no transfusions within the previous 3 months, and no painful crises within the previous month. Values were also collected at the time of the pulmonary function tests. In our population, the mean time interval between baseline and contemporaryvalues was 5.5 ± 0.3 years, and the median value was 5.3 years. Only 159 patients had available baseline blood values.

Statistical analysis

Data are reported as means ± SEM. The Kolmogorov–Smirnov test was applied to test for a normal distribution. Analysis of variance was used to identify relations between systemic complications (acute chest syndrome,