Sickle cell chronic pulmonary disease among Africans: the need for increased recognition and treatment

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Abstract

The pulmonary complications of sickle cell disease (SCD) among adults are expected to increase since more of them are expected to survive into adulthood with improved healthcare delivery systems. Such complications, especially the chronic ones, which are usually collectively referred to as SCCLD (sickle cell chronic lung disease), are often under-appreciated by healthcare providers in sub-Saharan Africa. However, results of recent work in Nigeria show that SCCLD might not be as uncommon as previously thought. It is very important to detect SCCLD at an early stage, which is usually asymptomatic; the late stages are not usually responsive to conventional treatment. In Africa, outline spirometry can be used as a screening test for asymptomatic SCCLD in the follow-up of SCD. Patients with asymptomatic SCCLD should be offered measures that can prevent further deterioration of their condition, while those with more advanced symptomatic disease are treated symptomatically.

Introduction

Sickle cell disease (SCD) is one of the most common genetic disorders among Africans.[1] Of the children born annually with haemoglobinopathies worldwide, 61.4% have SCD and are from Africa.[2] With improved standards of living and healthcare delivery systems many patients will survive into adulthood. Therefore, the complications of the disease will be seen more frequently.

Although acute and chronic pulmonary complications of SCD are common, they are often under-appreciated by healthcare providers, in particular the chronic complications.This article aims to review the chronic pulmonary complications of SCD in order to increase awareness of these problems to healthcare providers.

Chronic pulmonary disease in SCD

Prevalence

The chronic pulmonary complications of SCD are usually collectively referred to as sickle cell chronic lung disease (SCCLD). Although the exact prevalence and methods of diagnosis of SCCLD have not been established, owing to lack of detailed epidemiological studies, a recent study done in Nigeria showed a prevalence of 18.9%.[3] This shows that SCCLD may not be as uncommon as was previously thought.

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Definition of SCCLD

SCCLD is defined by radiological and clinical features of ventilatory dysfunction (restrictive or obstructive) and pulmonary hypertension which may later progress to cor pulmonale.[4] The pulmonary hypertension is most frequent in older children and adults, often following recurrent acute chest syndrome (ACS).

Clinical features

Although the early stages of SCCLD are usually asymptomatic,[5] it may later be characterised by progressive disabling dyspnoea, exercise limitation, hypoxaemia, and chest pain of increasing severity. The chest X-ray shows diffuse interstitial markings and pulmonary function tests reveal decreased lung volumes and a restrictive functional pattern without significant airway obstruction in the advanced stage.[6]

Pathogenesis of SCCLD

The concept has emerged that SCCLD may result from pulmonary scarring due to repeated episodes of ACS.[7] Other factors proposed include: a sickle cell-related vasculopathy,[8] chronic oxygen desaturation and/or sleep hypoventilation,[9] and recurrent episodes of thromboembolism.[10]

Jaja et al[11] have said that the reduced lung function in sickle cell patients may also be related to their smaller stature. However, SCCLD is not seen in all patients with sickle cell anaemia. Powars et al[7,12] reported that the variability of the clinical expression of sickle cell anaemia (SCA) (including SCCLD) is the result of the interaction of the β^s-gene-cluster haplotype and the α-gene status, with the Benin haplotype being associated with decreased severity.

Investigations in SCCLD

The investigations in SCCLD can be grouped into two main types as follows:

- pulmonary function tests (PFTs)
- other investigations

Pulmonary function tests
PFT derangement in patients with SCCLD usually affects the ventilatory and gas exchange functions.

Derangement of ventilatory function
A test of ventilatory function in stable patients with SCCLD usually reveals decreased lung volumes with restrictive functional pattern without significant airway obstruction. Elegbeleye[13] observed small lung volumes in a group of stable patients with SCA.

Many workers have also reported lower lung volumes and restrictive pattern of ventilatory defect in stable patients with SCA.[7,11] Reasons given by these workers for the observed impaired ventilatory function in these patients include the smaller stature in some of them[11,14] and a reduction of lung compliance which may be due to repeated episodes of ACS[7] or sickle cell-related vasculopathy.[15]

Some workers have demonstrated obstructive ventilatory defect; mostly in the early part of the disease process. Santoli et al[16] observed obstructive defect in ventilatory function in a group of stable patients with recurrent ACS. They noted that the obstructive defect was accompanied by an increase in diffusing capacity and suggested that it might have been related to an increase in lung blood volume. The authors did not explain the mechanism of increase in airway resistance by increased lung blood volume.

A similar result was observed by Koumbourlis et al[17] in a group of children with SCA. They suggested that obstructive lung disease possibly precedes the development of restrictive lung disease, and that airway reactivity may be part of the pathogenic mechanism. However, no other known published series has validated this. Spirometry is an important screening test for asymptomatic SCCLD that should become part of the routine follow-up of SCD patients in Africa.

Derangement of gas exchange
Hypoxaemia is the hallmark of pulmonary abnormality in SCA patients of all age groups. This was first documented by Klinefelter[18] and has since been corroborated by other workers.[7,15,19] The hypoxaemia of stable SCA patients is said to result from the combined effects of both a perfusion and diffusion defect. Most studies examined however, revealed that perfusion defect was the most important mechanism producing hypoxaemia in these patients.

Sproule et al[19] noted hypoxaemia among asymptomatic patients and identified a perfusion defect, showing venoarterial admixture within the pulmonary parenchyma. Their data also suggested a minor diffusion defect. Similar results were later documented by other workers.[20,21] Elegbeleye,[13] however, documented a disproportionately high pulmonary diffusing capacity in all the SCA patients he studied. He suggested that it might be due to a chronically expanded pulmonary capillary blood volume in these patients.

Other investigations
Chest X–ray (CXR)
The lungs show multiple scars, which cause a generalised loss of translucency of the lung fields. This, according to Lagundoye,[22] presumably results from the numerous small scars left by previous infarcts and infections over the years, which are individually too tiny to be discernible at the active stage. There is often a cardiomegaly with a globular configuration.[22] This is a result of the chronic anaemic state. In adults, left ventricular enlargement is almost constant and right ventricular enlargement is common.[23] The right ventricular enlargement may be due to pulmonary hypertension. However, since right ventricular enlargement may also be found in the early stages of SCA due to chronic anaemia, it is important to assess further for features of pulmonary hypertension.

Electrocardiography (ECG)
There may be evidence of right ventricular hypertrophy (RVH) and right atrial enlargement due to pulmonary hypertension. However, voltage criteria for ventricular hypertrophy must be applied cautiously, since there is some evidence that higher voltages may occur as a normal racial variation in black populations and the lack of skin fat and thin chest wall in these patients may also contribute to high recorded voltages.[24] Thirty-eight (48%) of Nigerian SCA children and adolescents studied by Aluko[25] had LVH, 1 (1.3%) had RVH while 14 (17.9%) had biventricular hypertrophy.

Echocardiography
This may show right ventricular chamber enlargement and wall hypertrophy as well as tricuspid regurgitation with increased pulmonary artery pressure as a result of pulmonary hypertension. There may also be right atrial enlargement.

Cardiac catheterisation
This is a very important investigation where facilities are available because it is the gold standard test for the diagnosis of pulmonary hypertension. Although Castro[26] suggested that it should be done unless echocardiography shows tricuspid regurgitation with increased pulmonary artery pressure, it is invasive and is also not readily available in many African countries.

Management of SCCLD
Since recurrent episodes of the ACS are the most important risk factor for SCCLD,[7] prevention and prompt treatment of this process are the main therapeutic focus. The treatment of ACS has been documented elsewhere.[27]

Prevention of ACS
Measures that have been designed to prevent recurrent episodes of ACS include:

Hydroxyurea (droxial) therapy[28]
This agent is the first widely available agent to show

promising activity and to be piloted in phase III studies in adults. It was the least toxic of agents investigated in the treatment of SCA prior to the introduction of Nicosan. The exact mechanism of action is unclear but it appears to regulate the expression of γ-globin genes and hence increase fetal haemoglobin (HbF).[29,30] HbF has been shown to confer some protection on SCA sufferers by binding more strongly to oxygen than haemoglobin A, thus preventing hypoxia and sickling in the sickle cell patient.[11] It may also exact beneficial effects on red cell hydration, vascular wall adherence, and suppression of the granulocyte and reticulocyte counts. It is said that white cells and reticulocytes may play a major role in the pathogenesis of sickle cell crisis; their suppression may be an important benefit of hydroxyurea therapy.[30] It should only be used in severely affected patients because of theoretical risk of teratogenicity and leukaemogenesis.[29] This drug may have an important role in developing countries where strategies such as safe transfusion and bone marrow transplantation may not be readily available.

Institution of long-term transfusion programmes[31]
It has been shown that patients with recurrent episodes of ACS may benefit from regular exchange transfusion to maintain the HbS concentration below 30%.[32] This option may not be the best in many African countries where there is no easy access to properly screened blood.

Bone marrow transplantation[33]
Though this can provide definitive cure, it is known to be effective and safe only in children.[30] Despite the fact that it is a feasible option in SCD where facilities are available; it is not readily available in Africa where the bulk of patients with SCD reside.

Various other measures such as gene therapy, and the use of agents blocking red cell dehydration (like clotrimazole) or vascular adhesion (like monoclonal antibodies), are still undergooing trials.

The newly introduced non-toxic phyto-pharmaceutical product (Nicosan) seems to be the miracle drug for prophylactic management of SCD. It is an herbal mixture consisting of four active agents (*Piper guineense*, *Pterocarpus osun*, *Eugenia caryophyllum* and *Sorghum bicolor*) which have been shown to have antisickling effects in separate studies. The real mechanism of action of Nicosan is not yet confirmed but it has been shown to inhibit cell sickling by increasing solubility of haemoglobin S. However, there is urgent need for further local studies to corroborate findings from earlier studies.

The most important effort in managing SCCLD is the prompt treatment and prevention of ACS as highlighted above. Other modalities like transplantation of lung or heart–lung are probably too risky in SCA.There are no proven treatments for sickle cell-related pulmonary hypertension.[26] Vasodilators such as prostacyclin and calcium- channel blockers like nifedipine and diltiazem that have been shown to improve pulmonary artery pressure and survival in patients with primary pulmonary hypertension may be tried. Continuous or nocturnal oxygen therapy, which is also known to decrease pulmonary artery pressure in patients who are hypoxaemic from a variety of lung disorders, can also be given especially if it lowers the pulmonary pressure at cardiac catheterisation (where available).[26] However, there are no known published reports describing the use of any of these drugs in sickle cell-related pulmonary hypertension.

Conclusion

More African patients with SCD are expected to survive into adulthood and many of them will develop chronic pulmonary complications of their disease. Efforts to reduce these complications should be aimed at prevention and prompt treatment of ACS. PFTs should be carried out routinely on all patients with SCA for early detection of the asymptomatic stage. Such asymptomatic patients should be offered treatment modalities that have been shown to improve outcomes of SCA to prevent further deterioration. Those with more advanced symptomatic disease should be treated symptomatically. African pulmonary specialists have to pay more attention to the chronic pulmonary complications of SCD.

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Pan African Thoracic Society Methods in Epidemiologic Clinical and Operations Research 2008

The Pan African Thoracic Society (PATS) exists to promote respiratory health in Africa (www.africanthoracic.org). Supported by the Nuffield Foundation (UK) and the American Thoracic Society, PATS has set a goal of establishing regular research training workshops in Africa for health professionals, primarily doctors, interested in respiratory research. These workshops are modelled on a successful and expanding programme established 14 years ago in Latin America (MECOR). The first PATS-MECOR Level 1 workshop was held in 2007. Young investigators are encouraged to apply for the second workshop, which will be held in Blantyre, Malawi in September 2008. Building on last year's experience, this year there will be two workshops: Level 1: Introduction To Clinical Research Methods and Level 2: Developing Your Research.

Who should apply?

Doctors with an interest in respiratory medicine who wish to improve their skills in clinical research and investigation. No prior experience with research is needed for Level 1. Applicants for Level 2 should have research experience or have attended PATS-MECOR Level 1. We will emphasize methods for quantifying the burden of respiratory disease in Africa, so preference in selecting applicants and providing travel bursaries in 2008 will be given to individuals with a specific interest in this area of research.

What will MECOR graduates gain?

MECOR will provide annual training workshops, ongoing mentorship and a forum in which graduates will be able to present their research findings. We anticipate that PATS-MECOR graduates will form the research backbone of PATS.

Why is research training useful to respiratory doctors?

Research training helps in all aspects of a career in clinical medicine, academic medicine and research. Research data provide the impetus and momentum for change in health care methods, priority setting, local and national budget allocation and training.

How does the application process work?

Initial enquiries should be addressed to patsmecor2008@africanthoracic.org. An application form will be sent to qualified candidates. Successful candidates will be given details of travel bursaries and the logistical arrangements for the 2008 MECOR Courses in Blantyre, Malawi.