Mediterranean Journal of Hematology and Infectious Diseases

Scientific Letter

# Spirometric Evaluation of Pulmonary Function in Nigerian Children underwent Bone Marrow Transplantation for Sickle Cell Anemia

**Keywords:** Sickle cell anemia, children, spirometry, transplant, asthma.

**Published: April 15, 2017** **Received: January 8, 2017** **Accepted: March 14, 2016**

**Citation:** Isgro' A., Marziali M., Paciaroni K., De Angelis G., Alfieri C., Ribersani M., Olowoselu F. O., Lucarelli G., Gaziev J. Spirometric evaluation of pulmonary function in nigerian children underwent bone marrow transplantation for sickle cell anemia. Mediterr J Hematol Infect Dis 2017, 9(1): e2017030, DOI: http://dx.doi.org/10.4084/MJHID.2017.030



Sickle cell anemia (SCA) and its complications result in significant morbidity and mortality, posing a significant public health challenge worldwide. SCA and its societal costs disproportionally affect Africa. A strong geographical link between the highest HbS allele frequencies and high malaria endemicity was observed at the global scale, but this observation is influenced primarily by the relationship found in Africa.[1] Nigeria, in particular, has the largest population of children and adults with SCA in the world. Approximately 150,000 children are born with SCA each year in Nigeria, compared to approximately 1,100 children born in the US each year. A greater understanding of the pulmonary factors contributing to morbidity and mortality among children with SCA may lessen the public health burden of SCA worldwide.

The prevalence of asthma in patients with SCA is higher than in normal population (30-70% versus 20%).[2] Asthma increases the risk of morbidity and mortality in patients with SCA.[3] It has been shown that there is an association between the presence of bronchial hyperactivity and the onset of acute chest syndrome (ACS):[3-11] children with SCA and asthma have more frequent episodes of ACS and/or veno-occlusive crisis (VOC). Asthma is also a risk factor for early second hospitalization after discharge from hospital.[12] Therefore, it seems that asthma is an additional factor that aggravates some manifestations of SCA.

Often in a patient with SCA, it is difficult to distinguish from the beginning the symptoms of an asthma attack from that of an initial ACS. Children with SCA are prone to invasive infections caused by *S. pneumonia*, *H. influenzae*, and *Plasmodium falciparum*. Like thalassemia, allogeneic hematopoietic stem cell transplantation (HSCT) is curative in most individuals with SCA.[13] We analyzed pulmonary function in SCA patients underwent BMT through high-resolution computed tomography (HRCT) scan and spirometry, before and after transplant.

This study included 37 consecutive SCA patients who underwent bone marrow transplantation from human leukocyte antigen (HLA)-identical sibling donors between 2010 and 2015 following a myeloablative conditioning regimen. The patients were referred to Mediterranean Institute of Hematology for transplantation, and none of them were followed previously in Italy. The median patient age was 10 years (range 2–17 years). Patient characteristics at the time of transplantation are summarized in **Table 1**. Patients Lansky/Karnofsky performance score varied between 90-100% at the time of transplantation. None of these patients had a splenectomy before transplantation. Only two patients received chronic blood transfusions, and the serum ferritin level before transplantation was 278 $\pm$ 231 ng/mL (mean $\pm$ SD). Before transplantation, eighteen patients had recurrent, painful, vaso-occlusive crisis (VOC); thirteen patients had VOC in association with acute chest syndrome (ACS); five patients experienced ischemic stroke with or without association with VOC; two patients exhibited leukocytosis, and

dactylitis and one patient exhibited priapism. Twelve patients were on hydroxyurea therapy before transplantation. Repeated and severe VOC, stroke, acute chest syndrome, in association with a not easy availability of hydroxyurea and/or transfusion therapy in their Country, were indications for HSCT. The patients were subjected to instrumental examinations in pre-transplant phase with HRCT and spirometry. Patients received fludarabine (30 mg/m$^2$/d) for 5 days followed by conditioning regimen including targeted intravenous busulfan and cyclophosphamide (200 mg/kg total dose). They received cyclosporine A, low-dose methylprednisolone, and a short course of methotrexate as graft-versus-host disease (GVHD) prophylaxis. All patients received BM from HLA-identical sibling donors 36 h after the final dose of cyclophosphamide. HRCT scan revealed parenchymal consolidation with nodular thickening in 19 out 37 patients, as active or residual pneumonia. Twenty-five out 37 patients had evaluable standard spirometry before transplantation. The following parameters were included: forced vital capacity, forced expiratory volume in the first second (FEV1), the ratio FEV1/FVC, and the total lung capacity (TLC). Spirometry results (FVC, $FEV_1$, $FEV_1$/FVC, TLC) were expressed as percent of the predicted value based on gender, age, and ethnic appropriate reference standards. Spirometry was performed according to standard protocols using European Respiratory Society/American Thoracic Society acceptability and repeatability criteria, adapted for children where appropriate (normal value: FVC>75; $FEV_1$/FVC>80).[14] Eleven out of 25 patients had a restrictive respiratory pattern (FVC <75%), one patient had a restrictive/obstructive pattern (FVC <75% and $FEV_1$/FVC <80%) and 13 of 25 patients had normal respiratory function tests. Six out 12 patients with restrictive respiratory pattern had ACS and bronchial hyperactivity (**Table 1**). All 37 patients had sustained engraftment after transplant. After 3-6 months of transplantation, we found no significant changes in spirometry values (**Table 2**). In particular, four out of nine patients had unchanged respiratory pattern, three patients experienced worsening, probably due to post-transplant infectious complications and/or the occurrence of acute GVHD (UPN 207, acute GVHD; UPN 213 and UPN 234, *Aspergillus fumigatus* pneumonia; UPN 237, *Klebsiella pneumonia* pneumonia) and two patients showed an initial amelioration.

Pulmonary complications are leading causes of morbidity and mortality in SCA.

Airway obstructions and repeated pulmonary infections are among the primary causes of pulmonary involvement, and they result in obstructive or restrictive respiratory disorders, which can result in pulmonary hypertension. Moreover, this population often presents with acute chest syndrome, which is characterized by chest pain, prostration, cough, dyspnea and hypoxia.[2]

When assessing pulmonary function, individuals may exhibit either normal function or altered ventilatory patterns, which are classified as obstructive, restrictive or mixed. Obstructive ventilatory patterns (OVPs) are characterized by disproportionately decreased peak flows (PEF) when compared to the volume that can be eliminated, and the $FEV_1$ and $FEV_1$/FVC are the major measures by which to characterize OVPs. Restrictive pulmonary patterns (RVPs) are characterized by decreased FVC. It should be noted that RVP cannot be measured by spirometry. However, RVP values can be inferred when the vital capacity (VC) and FVC are decreased, and the $FEV_1$/FVC ratio is normal or increased. Finally, mixed ventilatory pattern (MVP) is characterized by having both obstruction and restriction simultaneously. In the present study, the lung function tests (LFTs) obtained from 48% of the patients revealed changes in the pulmonary function (i.e., RVP or MVP). Our results indicate that RVP is a common finding in this disease. The presence of RVP in this population might result from episodes of vaso-occlusion in the lung, which is an organ that is prone to suffer from this condition because of its anatomical characteristics. This can result in pulmonary infarctions, necrosis of the alveolar wall with consequent airway remodeling, pulmonary fibrosis and progressive loss of lung function. In addition, RVP may be a result of fibrosis after many infection diseases in pulmonary districts.[15] In fact, the HRCT often in these patients showed fibrotic outcomes, expression of recent or past lung infections. RVP has been observed in our patients with bronchial hyperactivity instead of a typical asthma attack. Airway hyper-responsiveness is another feature of sickle cell lung disease. Various studies have defined hyper-responsiveness either as a decrease

**Table 1.** Spirometry in SCA patients before transplant. The standard spirometry was performed according to the Guidelines of American Thoracic Society/European Respiratory Society (ATS/ERS 2005 and Gold 2009). Normal value: FVC>75% of theoric value; FEV1/FVC>80%; TLC >80%. In bold are reported the SCA patients with restrictive respiratory pattern, ACS and bronchial hyperactivity.

| UPN. | Age/Sex | HbS pre TMO | Clinical conditions | Spirometry pre TMO | | | | |
|---|---|---|---|---|---|---|---|---|
| | | % | | %FVC | %FEV1 | FEV1/FVC | %TLC | Resp. patt. |
| **166** | **14/M** | **76** | **VOC ACS Stroke** | **58** | **64** | **100** | **62** | **R** |
| 191 | 6/F | 70 | VOC ACS | // | // | // | // | n.e |
| **192** | **9F** | **75** | **VOC ACS** | **67** | **59** | **83** | **63** | **R** |
| **195** | **11/F** | **71** | **VOC ACS Stroke** | **65** | **65** | **96** | **72** | **R** |
| 199 | 15/F | 86 | VOC ACS | 86 | 78 | 86 | 101 | N |
| 201 | 17/M | 89 | VOC | // | // | // | // | n.e |
| 202 | 3/M | 85 | VOC | // | // | // | // | n.e |
| 204 | 12/M | 92 | VOC | 64 | 45 | 100 | 75 | R |
| 205 | 5/M | 79 | VOC | // | // | // | // | n.e |
| 206 | 7/F | 83 | VOC | // | // | // | // | n.e |
| 207 | 13/M | 88 | VOC ACS | 76 | 68 | 81 | 103 | N |
| 210 | 3/M | 73 | VOC Stroke | // | // | // | // | n.e |
| 213 | 16/M | 91 | VOC | 82 | 76 | 85 | 89 | N |
| 215 | 2/M | 87 | Dactylitis | // | // | // | // | n.e |
| **216** | **14/F** | **92** | **VOC ACS** | **62** | **54** | **82** | **72** | **R** |
| 219 | 15/M | 91 | VOC | 59 | 50 | 78 | 62 | O/R |
| 221 | 4/F | 83 | VOC | // | // | // | // | n.e |
| 222 | 16/M | 91 | VOC | 49 | 45 | 86 | 70 | R |
| 224 | 5/F | 61 | VOC ACS | // | // | // | // | n.e |
| **229** | **17/M** | **82** | **VOC ACS** | **52** | **51** | **89** | **62** | **R** |
| 231 | 5/M | 88 | Stroke | // | // | // | // | n.e |
| **234** | **15/F** | **94** | **VOC ACS** | **57** | **51** | **86** | **64** | **R** |
| 235 | 8/F | 77 | Stroke | // | // | // | // | n.e |
| 236 | 17/M | 63 | Priapism | 82 | 75 | 83 | 95 | N |
| 237 | 10/F | 85 | VOC | 87 | 85 | 89 | 93 | N |
| 239 | 13/F | 73 | VOC | 71 | 68 | 90 | 70 | R |
| 240 | 12/F | 80 | VOC | 72 | 67 | 88 | 69 | R |
| 252 | 8/F | 88 | VOC | 65 | 55 | 82 | 68 | R |
| 258 | 17/M | 79 | VOC ACS ABN | 83 | 76 | 84 | 92 | N |
| 261 | 4/M | 80 | VOC | 93 | 79 | 97 | 93 | N |
| 263 | 8/M | 78 | VOC | 70 | 72 | 94 | 90 | N |
| 271 | 5/M | 80,9 | VOC | 80 | 73 | 95 | 93 | N |
| 273 | 13/M | 91,5 | VOC | 66 | 71 | 97 | 92 | N |
| 285 | 12/M | 79,7 | VOC | 93 | 79 | 97 | 94 | N |
| 289 | 17/M | 84,7 | VOC + ACS | 86 | 78 | 86 | 93 | N |
| 291 | 14/M | 70,2 | VOC + ACS | 85 | 79 | 85 | 95 | N |
| 297 | 2/M | 63,4 | VOC + dactylitis | // | // | // | // | n.e |

*Abbreviations:* UPN, unique patient number; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; TLC, total lung capacity; n.e, not evaluable; O, Obstructive ventilatory pattern; R, Restrictive ventilatory pattern; HbS, hemoglobin S; VOC, vaso-occlusive crisis; ACS, acute chest syndrome; ABN, avascular bone necrosis.

**Table 2.** Spirometry in SCA patients post transplant. The standard spirometry was performed after 3-6 months of transplant.

| UPN. | Age/Sex | Spirometry pre-TMO | | | | | Spirometry post-TMO | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *% FVC* | *% FEV1* | *FEV1/FVC* | % TLC | Respiratory pattern | *% FVC* | *% FEV1* | *FEV1/FVC* | % TLC | Respiratory pattern |
| 166 | 14/M | 58 | 64 | 100 | 62 | R | 57 | 61 | 97 | 64 | R |
| 207 | 13/M | 76 | 68 | 82 | 103 | N | 72 | 59 | 75 | 100 | N/O |
| 213 | 16/M | 82 | 76 | 85 | 89 | N | 68 | 72 | 84 | 89 | N/R |
| 219 | 15/M | 59 | 50 | 78 | 62 | O/R | 59 | 55 | 85 | 80 | R |
| 229 | 17/M | 52 | 51 | 89 | 62 | R | 54 | 54 | 91 | 80 | R |
| 234 | 15/F | 57 | 51 | 86 | 64 | R | 54 | 54 | 91 | 80 | R |
| 236 | 17/M | 82 | 75 | 83 | 95 | N | 83 | 74 | 83 | 95 | N |
| 237 | 10/F | 87 | 85 | 89 | 93 | N | 52 | 57 | 92 | 83 | R |
| 239 | 13/F | 71 | 68 | 90 | 70 | R | 79 | 76 | 91 | 85 | N |

*Abbreviations:* UPN, unique patient number; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; TLC, total lung capacity; O, Obstructive ventilatory pattern; R, Restrictive ventilatory pattern.

in lung function after exercise, cold air, or methacholine challenges or increase after administration of a bronchodilator and up to 70% of children with sickle cell disease have airway hyperresponsiveness.[4] After 3-6 months of transplant, we do not observe significant changes in spirometry value. In such a short time from the transplant, lung function may still be influenced by infectious events during transplant or the possible occurrence of acute GVHD. Our findings indicate that routine spirometry, before and after transplantation, is an important adjunct to the clinical in this patient population with a high prevalence of pulmonary disease and lung dysfunction.

Antonella Isgro'[1], Marco Marziali[1], Katia Paciaroni[1], Gioia De Angelis[1], Cecilia Alfieri[1], Michela Ribersani[1], Festus Olusola Olowoselu[2], Guido Lucarelli[1] and Javid Gaziev[1]

[1] International Center for Transplantation in Thalassemia and Sickle Cell Anemia. Mediterranean Institute of Hematology, Policlinic of the University of Rome "Tor Vergata", Rome, Italy.
[2] Dept. of Haematology and Blood Transfusion, College of Medicine, Lagos University Teaching Hospital, Lagos, Nigeria.

**Competing interests:** The authors have declared that no competing interests exist.

Correspondence to: Antonella Isgrò, M.D. International Center for Transplantation in Thalassemia and Sickle Cell Anemia. Mediterranean Institute of Hematology. Policlinic Tor Vergata, Rome, Italy. Viale Oxford, 81. Rome-00133, Italy. Phone: (+39) 06 20661300. Fax: (+39) 06 20661302. E-Mail: a.isgro@fondazioneime.org

## References:

1. Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Williams TN, Weatherall DJ, Hay SI. Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. Nat Commun. 2010;1:104. https://doi.org/10.1038/ncomms1104 PMid:21045822 PMCid:PMC3060623
2. DeBaun MR, Strunk RC. The intersection between asthma and acute chest syndrome in children with sickle-cell anaemia. Lancet. 2016;387(10037):2545-53. https://doi.org/10.1016/S0140-6736(16)00145-8
3. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with increased mortality in individuals with sickle cell anemia. Haematologica.2007;92:1115-8. https://doi.org/10.3324/haematol.11213 PMid:17650441
4. Sylvester KP, Patey RA, Rafferty GF, Rees D, Thein SL, Greenough A. Airway hyperresponsiveness and acute chest syndrome in children with sickle cell anemia. Pediatr Pulmonol. 2007;42:272-6. https://doi.org/10.1002/ppul.20571 PMid:17262858
5. Sylvester KP, Patey RA, Broughton S, Rafferty GF, Rees D, Thein SL, Greenough A. Temporal relationship of asthma to acute chest syndrome in sickle cell disease. Pediatr Pulmonol. 2007;42:103-6. https://doi.org/10.1002/ppul.20430 PMid:17186507
6. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with acute chest syndrome and pain in children with sickle cell anemia. Blood. 2006;108:2923-7. https://doi.org/10.1182/blood-2006-01-011072 PMid:16690969 PMCid:PMC1892235
7. Bryant R. Asthma in the pediatric sickle cell patient with acute chest syndrome. J Pediatr Health Care. 2005;19:157-62. https://doi.org/10.1016/j.pedhc.2004.12.003 PMid:15867831
8. Knight-Madden JM, Forrester TS, Lewis NA, Greenough A. Asthma in children with sickle cell disease and its association with acute chest syndrome. Thorax. 2005;60:20610 https://doi.org/10.1136/thx.2004.029165 PMid:15741436

9. Nordness ME, Lynn J, Zacharisen MC, Scott PJ, Kelly KJ. Asthma is a risk factor for acute chest syndrome and cerebral vascular accidents in children with sickle cell disease. Clin Mol Allergy. 2005;3:2 https://doi.org/10.1186/1476-79612
10. Boyd JH, Moinuddin A, Strunk RC, DeBaun MR. Asthma and acute chest in sickle-cell disease. Pediatr Pulmonol. 2004;38:229-32. https://doi.org/10.1002/ppul.20066 PMid:15274102
11. Bernaudin F, Strunk RC, Kamdem A, Arnaud C, An P, Torres M, Delacourt C, DeBaun MR. Asthma is associated with acute chest syndrome, but not with an increased rate of hospitalization for pain among children in France with sickle cell anemia: a retrospective cohort study. Haematologica. 2008;93:1917-8 https://doi.org/10.3324/haematol.13090 PMid:18815195
12. Frei-Jones MJ, Field JJ, DeBaun MR.Risk factors for hospital readmission within 30 days: a new quality measure for children with sickle cell disease. Pediatr Blood Cancer. 2009;52:481-5. https://doi.org/10.1002/pbc.21854 PMid:19058209 PMCid:PMC2730199
13. Isgrò A, Paciaroni K, Gaziev J, Sodani P, Gallucci C, Marziali M, Angelis GD, Alfieri C, Ribersani M, Roveda A, Akinyanju OO, Wakama TT, Olowoselu FO, Adediran A, Lucarelli G. Haematopoietic stem cell transplantation in Nigerian sickle cell anaemia children. Niger Med J. 2015;56(3):175-9. https://doi.org/10.4103/0300-1652.160355 PMid:26229224 PMCid:PMC4518332
14. Lum S, Bountziouka V, Sonnappa S, Wade A, Cole TJ, Harding S, Wells JC, Griffiths C, Treleaven P, Bonner R, Kirkby J, Lee S, Raywood E, Legg S, Sears D, Cottam P, Feyeraband C, Stocks J. Lung function in children in relation to ethnicity, physique and socioeconomic factors. Eur Respir J. 2015;46(6):1662-71. https://doi.org/10.1183/13993003.00415-2015 PMid:26493801
15. Walters MC, Hardy K, Edwards S, Adamkiewicz T, Barkovich J, Bernaudin F, Buchanan GR, Bunin N, Dickerhoff R, Giller R, Haut PR, Horan J, Hsu LL, Kamani N, Levine JE, Margolis D, Ohene-Frempong K, Patience M, Redding-Lallinger R, Roberts IA, Rogers ZR, Sanders JE, Scott JP, Sullivan KM; Multicenter Study of Bone Marrow Transplantation for Sickle Cell Disease. Pulmonary, Gonadal, and Central Nervous System Status after Bone Marrow Transplantation for Sickle Cell Disease. Biol Blood Bone Marrow Transplant. 2010; 16(2):263-272. https://doi.org/10.1016/j.bbmt.2009.10.005