INVITED COMMENTARY

Pulmonary Functions in Transfusion-Dependent Thalassemia

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Thalassemia is a genetic disorder which starts as a hemolytic anemia but during its course attains the dimension of a 'multi-system disease' [1]. Blood transfusion is the mainstay of treatment for individuals with transfusion-dependant thalassemia (TDT) as it improves anemia and also suppresses ineffective erythropoiesis. Each unit of packed red cells delivers an estimated 200 mg of iron. As body cannot excrete extra iron, complications resulting from iron overload become a major source of morbidity. Studies have highlighted importance of appropriate iron chelation in improving survival. A 2004 study of 977 patients from Italy had reported 68% patients being over 35 years. Patients with lower serum ferritin had a better probability of survival [2]. From India, a recent study of over one thousand patients reported 50% actuarial survival at 26.9 years with poor iron chelation being a significant risk factor for morbidity and mortality [3].

Iron overload in TDT is associated with saturation of transferrin in the body. The excess iron remains in the form of non-transferrin-bound iron. This labile iron is the predominant form of iron that causes tissue damage [4]. The involvement of other organ systems primarily results from iron overload related tissue injury; although, chronic hypoxia is also incriminated [5]. Involvement of heart, endocrine glands and liver has been extensively studied. Well stated guidelines are in place for assessment of these organs in patients with TDT and studies have shown their reversibility with intensive iron chelation with desfrrioxamine or combined oral chelation [6].

Pulmonary dysfunction resulting from iron overload has not been studied extensively in children. Studies done on adult TDT patients suggest that lung fibrosis and/or interstitial edema related to iron overload are the main cause of pulmonary dysfunction [7]. Pulmonary dysfunction in children with TDT is described to be restrictive, large airway obstruction, diffusion impairment, or small airway disease [8-12]. The differences among the published data may be due to the heterogeneity of the studies (different patient age, different iron chelation regimen), duration of transfusion received and level of serum ferritin along with the multifactorial nature of the pathogenesis of pulmonary dysfunction in these patients. Some have also reported that pulmonary dysfunction may be due insufficient anatomic and functional development of the lung during early infancy in patients with TDT. Reduced lung volumes in thalassemic patients were explained by the upward pressure on the diaphragm by the enlarged liver and spleen, when present, which is supported by an increase in the vital capacity and the expiratory reserve volume seen in patients after splenectomy [13]. Fortunately, moderate or massive splenic enlargement is not seen in adequately transfused patients. Although changes in pulmonary function have been attributed to iron overload, those that examined the link between somatic iron stores and pulmonary function had varying conclusions. On autopsy, iron was concentrated in bronchiolar epithelial and mucous glands. Hemosiderin-laden macrophages are present in bronchoalveolar lavage, often in quantities similar to those observed in idiopathic pulmonary hemosiderosis, as well as lymphocytic infiltrates suggestive of alveolitis [14,15].

This issue of the journal has two studies on the subject [16,17]. None of the patient in both the studies had any respiratory symptoms. In the study by Panwar, et al. [16], 50 (68.8%) patients had lung dysfunction, most commonly diffusional impairment (48; 96%), and 9 (81.8%) patients had restrictive defect with moderate to severely deranged DLCO. Baruah and Bhattacharjee [17] observed restrictive pattern on pulmonary function test in 71.2%. They did not perform tests for diffusion abnormalities. Both the studies stress upon adequate iron chelation. The cases had high prevalence of pulmonary dysfunction. Patients in the study by Panwar, et al. [16] were better chelated. However, pulmonary dysfunction was observed by them also in two-third of the patients. They have also shown reversibility in pulmonary dysfunction with intensive iron chelation as has been described for reversal of cardiac and endocrine dysfunction with intensive chelation [6,18,19]. Cases in study from Assam had high serum ferritin as only a few of the patients were on regular iron chelation. High serum ferritin resulting from poor compliance to chelation needs to be addressed through proper focused counseling. Non-

availability of iron chelators can be mitigated by organizing funds through National Health Mission [20].

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REFERENCES

1. Adamkiewicz TV, Abboud MR, Paley C et al. Serum ferritin level changes in children with sickle cell disease on chronic blood transfusion are nonlinear and are associated with iron load and liver injury. Blood. 2009;114,4632-8.
2. Borgna-Pignatti C, Rugolotto S, De Stefano P, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica. 2004; 89:1187-93.
3. Dhanya R, Sedai A, Ankita K, et al. Life expectancy and risk factors for early deaths in patients with severe thalassemia syndrome in South India. Blood Adv. 2020;4:1448-57.
4. Aydinok Y, Evans P, Manz CY, Porter JB. Timed non-transferrin bound iron determinations probe the origin of chelatable iron pools during deferiprone regimens and predict chelation response. Haematologica. 2012;97:835-841.
5. Piga A, Longo F, Duca L, Roggero S, et al. High nontransferrin bound iron levels and heart disease in thalassemia major. Amer J Hematol. 2009;84:29-33.
6. Cappellini MD, Farmakis D, Porter J, Taher A, eds. Guidelines for management of transfusion dependent thalassemia (TDT). 4th Ed. Nicocia Cy. Thalassemia International Federation. 2021.
7. Carnelli V, D'Angelo E, Pecchiari M, et al. Pulmonary dysfunction in transfusion-dependent patients with thalassemia major. Am J Respir Crit Care Med. 2003; 168:180-184
8. Arora M, Chandra J, Suri JC, et al. Pulmonary function tests in beta thalassemia. Indian J Pediatr. 2001;68:239-242.
9. Azarkeivan A, Mehrvar A, Pour HS, et al. Pulmonary function test in transfusion-dependent beta-thalassemia patients. Pediatr Hematol Oncol. 2008;25:598-606
10. Li AM, Chan D, Li CK, et al. Respiratory function in patients with thalassaemia major: relation with iron overload. Arch Dis Child. 2002;87:328-330
11. Alyasin S, Moghtaderi M, Amin R, et al. Pulmonary function test in transfusion-dependent beta-thalassemia major patients: a pilot study. Pediatr Hematol Oncol. 2011;28:329-333.
12. Keens TG, O'Neal MH, Ortega JA, et al. Pulmonary function abnormalities in thalassemia patients on a hypertransfusion program. Pediatrics. 1980;65:1013-1017.
13. Grant GP, Mansell AL, Graziano JH, et al. The effect of transfusion on lung capacity, diffusing capacity, and arterial oxygen saturation in patients with thalassemia major. Pediatr Res. 1986;20:20-23
14. Cooper DM, Mansel AL, Weiner MA et aI. Low lung capacity and hypoxemia in children with thalassemia major. Amer Rev Resp Dis. 1980; 121:639-646.
15. Priftis KN, Anthracopoulos MB, Tsakanika C, et al. Quantification of siderophages in bronchoalveolar fluid in transfusional and primary pulmonary hemosiderosis. Pediatr Pulmonol. 2006; 41:972-7.
16. Panwar N, Gomber S, Dewan P, Kumar R. Pulmonary dysfunction in transfusion-dependent thalassemia and response to intensive chelation therapy. Indian Pediatr. 2022;59:451-54.
17. Baruah A, Bhattacharjee J. Pulmonary function in children with transfusion-dependent thalassemia and its correlation with iron overload. Indian Pediatr. 2022;59:455-8.
18. Anderson LJ, Westwood MA, Holden S. Myocardial iron clearance during reversal of siderotic cardiomyopathy with intravenous desferrioxamine: a prospective study using T2* cardiovascular magnetic resonance. British J Haematol. 2002:127: 348-355.
19. Kontoghiorghes GJ, Kontoghiorghes C. Iron and chelation in Biochemistry and Medicine: New approaches to controlling iron metabolism and treating related diseases. Cells. 2020;9:1456.
20. Ministry of Health and Family Welfare, Government of India. Prevention and control of Hemoglobinopathies in India-Thalassemias, Sickle Cell Disease and other variant hemoglobins. National Health Mission Guidelines on Hemoglobinopathies in India. GoI,2016.