Tricuspid regurgitant velocity elevation in a three-year-old child with sickle cell anemia and recurrent acute chest syndromes reversed not by hydroxyurea but by bone marrow transplantation

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Abstract

Elevated Tricuspid Regurgitant Velocity (TRV) has been related to higher mortality in adults and to hemolysis, lower oxygen saturation during 6-minute walk test and acute chest syndrome (ACS) in children with sickle cell disease (SCD). Hydroxyurea (HU) has reduced TRV value in children and adults. We describe a three year old HbSS child with recurrent ACS -resulting in lung hypoperfusion-, mild hemolysis and TRV elevation since age two. He did not improve after HU treatment but 1 year after undergoing BMT from an HbAA HLA-related sibling, presents no signs of hemolysis and normal TRV, although lung damage remained.

Case Report

A 21-months Nigerian male was diagnosed with HbSS in occasion of the first ACS presenting with infiltration in the left lung and pleural effusion. At 23 and 26 months he experienced a second and third ACS with infiltration of the left lobe. Steady state hematomatological parameters are shown in Table 1, while steady state Blood Pressure (BP) and SatO2 were above the 90th percentile and 97-98%, respectively. Steady state TRV at 28 months was 2.8 m/sec.

At 30 months he began HU 10 mg/kg, gradually increased to 30 mg/kg in four months. The treatment was well tolerated.

At 42 months, 1 year after starting HU, despite improvement of hematological parameters, TRV was still 2.82 m/sec. BP had dropped to normal values. ECG and cardiac ultrasound (including Tissue Doppler) at 21, 38 and 43 months were normal. He never presented with obstructive sleep apnea or asthma. Transcranial Doppler (TCD) velocities remained conditional before HU and after HU -time averaged mean velocity of maximum blood flow (TAMM) of 185 cm/sec and 189 cm/sec, respectively.

Having experienced recurrent ACS and persistent high conditional velocities on TCD, due to unavailability of an HbAA HLA- matched sibling he was offered BMT.

As part of the BMT work-up he underwent lung CT scan showing numerous perihilar strie dense in the lower left lobe, with increased density of the parenchyma, interpreted as lung scars due to the recurrent ACS, and pulmonary perfusion scintigraphy revealing hypoperfusion of the entire left lung, mainly of the left lower lobe respectively (Figure 1).

At 47 months he received BMT with the following conditioning regimen: Thiopeta 8 mg/kg/day (70 mg x2 times on day -7), Treosulfan 14 g/m2/day (9.8 gr on day -6, -5 and -4), Fludarabine 40 mg/m2/day (28 mg on day -6, -5, -4 e -3), antithymocyte globulin 175 mg/day (on day -4,3 and -2). Polymorphonuclear leukocytes and platelet engraftment occurred at day +20 and +22 respectively. No transplant related complications were observed.

One year after BMT he presents with 100% chimerism, no HbS on electrophoresis and is currently well, having experienced no SCD-related complications. Hematological and bio-

Introduction

Tricuspid Regurgitant Velocity (TRV) has become a reliable marker to screen for doppler-defined pulmonary hypertension (PH) in sickle cell disease (SCD).1 Elevated TRV has been related to higher mortality in adults2 and to hemolysis, lower oxygen saturation during 6-minute walk test3 and acute chest syndrome (ACS)4 in children, even though it’s clinical relevance, especially in the paediatric age, is not yet clearly defined. It remains to be determined whether TRV, and its association with mortality, reflects true PH or is a biomarker of disease severity and systemic vasculopathy in SCD.5 In fact, even if TRV measurement on echocardiography can be a first tool to screen for PH in patients with SCD, recent studies have clearly shown that only a limited number of patients with TRV elevation have PH as confirmed on cardiac catheterization6 and that different factors could play a role in leading to TRV elevation in different subsets of patients.7,8 Moreover, the causes involved in the genesis of elevated TRV (role of hemolysis and vaso-occlusive thromboembolic factors) and of PH in SCD are still under investigation.5,9,10 Clinical management of TRV elevation is also not clear even if Hydroxyurea (HU) has been demonstrated to lower TRV value in children and adults.11,12 The effect of bone marrow transplantation (BMT) on TRV value and Doppler-defined PH in SCD has not yet been reported. We describe a three year old HbSS child with recurrent ACS -resulting in lung hypoperfusion-, mild hemolysis and TRV elevation since age two. He did not improve after HU treatment but 1 year after undergoing BMT from an HbAA HLA-related sibling, presents no signs of hemolysis and normal TRV, although lung damage remained.

Conflict of interest: the authors report no conflicts of interest.

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Key words: sickle-cell disease, pulmonary hypertension, tricuspid regurgitant jet velocity, hydroxyurea, bone marrow transplantation.

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chemical values are within normal range for
age (Table 1) and TRV dropped to 2.01 m/sec. A pulmonary perfusion scintigraphy performed 1 year after BMT still shows persistence of hypoperfusion of the left lung (unchanged from pre-BMT perfusion scintigraphy).

Table 1. Laboratory values before HU treatment, after 1 year of HU treatment and 1 year after bone marrow transplantation.

| Variable                        | Before HU | 1 year After HU | 1 year After BMT | P   |
|---------------------------------|-----------|-----------------|------------------|-----|
| Aspartate aminotransferase (U/L) | 80.67±21.03 | 53.88±7.02      | 57.25±13.52      | 0.021 |
| Indirect bilirubin (mcg/dL)     | 49.95±7.28 | 25.67±2.05      | 5.10±1.41        | 0.000 |
| White Blood Cells (x10⁹/L)      | 15840±4343.15 | 9704.17±2245.44 | 4745.83±1739.31  | 0.000 |
| Hemoglobin (g/dL)               | 7.08±0.46  | 8.10±0.49       | 12.29±0.64       | 0.000 |
| Hb F (%)                        | 5.10±0.62  | 17.31±1.96      | 2.15±2.76        | 0.000 |
| Platelets (x10⁹/L)              | 550600±223882.97 | 383769.25±170796.94 | 270909.91±34725.94 | 0.006 |
| Reticulocytes (x10⁹/L)          | 422500±32809.75 | 345016.67±113780.79 | 18300±10137.96   | 0.001 |

Discussion

Our case represents, to our knowledge, the first reported case of a very young SCD child with TRV elevation that did not reduce after HU treatment, but normalized after BMT.

Several factors contribute to the increase in TRV in SCD children, including increased pulmonary flow volume (cardiac output), increased left ventricular filling pressures, increased blood viscosity, and increased pulmonary vascular resistance.8 SCD children can also experience systemic hypertension, left-sided volume overload, and abnormal diastolic function, all of which lead to elevated left ventricular filling pressures and secondary elevation of pulmonary artery pressures. Our patient had several of the above-mentioned factors.

The lack of response of TRV values to HU has been described in only one older patient with severe PH12 and HU efficacy in reducing TRV values is still open. In fact, while some studies demonstrated the protective effect of HU on the development of PH in adults13 and children,11 others have not and HU-induced high haemoglobin F levels have, on the contrary, been related to higher TRV velocities.13 HU has reversed Doppler-defined PH in SCD children11 and adults12 probably due to the combined reduction of hemolysis and red cell adhesion, and to the improvement of vascular function,14 even when the increase in haemoglobin concentration was modest (from 8.3 to 8.7 g/dL and from 7.52 to 7.98 g/dL).11,12 But HU was not effective in reducing TRV in our patient, despite the increase in Hb level (from 7.08 to 8.1 g/dL), the significant increase of HbF% and the reduction of hematologic parameters related to hemolysis (reticulocytes, AST) and to blood viscosity (platelets, white blood cells). Additive effect during HU treatment was not effective in reducing TRV in our patient, despite the increase in HbAA donor-elimination of hemolysis and systemic vasculopathy5 instead of true PH and only prospective trials evaluating pulmonary vascular resistance could aid in clarifying this issue.

Nevertheless, our case shows that TRV reduction in young patients, having experienced recurrent ACS with mild hemolysis and persistent TRV elevation resistant to HU treatment, can be a positive concomitant effect of BMT.

References

1. Ambrusko SJ, Gunawardena S, Sakara A, et al. Elevation of tricuspid regurgitant jet velocity, a marker for pulmonary hypertension in children with sickle cell disease. Pediatric Blood and Cancer 2006;47:907-13.
2. Gladwin MT, Sachdev V, Jison ML, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med 2004;350:886-95.

3. Minniti CP, Sable C, Campbell A, et al. Elevated tricuspid regurgitant jet velocity in children and adolescents with sickle cell disease: association with hemolysis and hemoglobin oxygen desaturation. Haematologica 2009;94:340-7.

4. Colombatti R, Maschietto N, Varotto E, et al. Pulmonary hypertension in sickle cell disease children under 10 years of age. Br J Haematol 2010;150: 601-9.

5. Morris CR. Vascular risk assessment in patients with sickle cell disease. Haematologica 2011;96:1-5.

6. Parent F, Bachir D, Inamo J, et al. A hemodynamic study of pulmonary hypertension in sickle cell disease. N Engl J Med 2011;365:4639-44.

7. Chaudry RA, Cikes M, Karu T, et al. Paediatric sickle cell disease: pulmonary hypertension but normal vascular resistance. Arch Dis Child 2011;96:131-6

8. Dham N, Ensing G, Minniti C, et al. Prospective echocardiographic assessment of pulmonary hypertension and its potential etiologies in children with sickle cell disease. Am J Cardiol 2009;104:713-20.

9. Bunn HF, Nathan DG, Dover GJ, et al. Pulmonary hypertension and nitric oxide depletion in sickle cell disease. Blood 2010 May 14 [Epub ahead of print]

10. Hebbel RP. Reconstructing sickle cell disease: A data-based analysis of the "hyperhemolysis paradigm" for pulmonary hypertension from the perspective of evidence-based medicine. Am J Hematol 2001;66:123-34.

11. Pashankar FD, Carbonella J, Bazzy-Asaad, A, Friedman A. Longitudinal follow up of elevated pulmonary artery pressures in children with sickle cell disease. Br J Haematol 2009;144:736-41.

12. Olness M, Chi A, Haney C, et al. Improvement in hemolysis and pulmonary arterial systolic pressure in adult patients with sickle cell disease during treatment with hydroxyurea. Am J Hematol 2009;84:530-2.

13. Gordeuk VR, Campbell A, Rana S, et al. Relationship of erythropoietin, fetal hemoglobin, and hydroxyurea treatment to tricuspid regurgitation velocity in children with sickle cell disease. Blood 2009;114:4639-44.

14. Rees DC. The rationale for using hydroxyurea in the treatment of sickle cell disease. Haematologica 2011;96:488-91.

15. van Beers EJ, van Eck-Smit BL, Mac Gillavry MR, et al. Large and medium-sized pulmonary artery obstruction does not play a role of primary importance in the etiology of sickle-cell disease-associated pulmonary hypertension. Chest 2008;133:646-52.

16. Connors P, Veys P, Amrolia P, et al. Pulmonary hypertension in children with Evans syndrome. Pediatric Hematology Oncology 2008;25:93-8

17. Steen RG, Helton KJ, Horwitz EM, et a. Improved cerebrovascular patency following therapy in patients with sickle cell disease: initial results in 4 patients who received HLA-identical hematopoietic stem cell allografts. Annals of Neurology 2001;49:222-9

18. Bernaudin F, Socie G, Kuentz M, et al. Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease. Blood 2007;110:2749-56.

19. Walters MC, Hardy K, Edwards S, et al. Pulmonary, gonadal, and central nervous system status after bone marrow transplantation for sickle cell disease. Biol Blood Marrow Transplant 2010;16:263-72.

20. Lanaro C, Franco-Penteado CF, Albuquerque DM, et al. Altered levels of cytokines and inflammatory mediators in plasma and leukocytes of sickle cell anemia patients and effects of hydroxyurea therapy. J Leuk Biol 2009;85:235-42.

21. Sata M. Role of circulating vascular progenitors in angiogenesis, vascular healing, and pulmonary hypertension: lessons from animal models. Arteriosclerosis Thrombosis and Vascular Biology 2006;26:1008-14.

22. Manci EA, Culberson DE, Yang YM, et al. Investigators of the Cooperative Study of Sickle Cell Disease. Causes of death in sickle cell disease: an autopsy study. Br J Haematol 2003;123:359-65.