identify subgroups of patients who are more likely to benefit from an adapted conditioning regimen or from early post transplant therapeutic strategies such as preemptive/prophylactic donor lymphocytes infusion and/or hypo-methylating agents.

This analysis is hampered by the limited number of patients analyzed and by the usual limitations related to its retrospective nature. However these data, considering very high-risk features of disease in more than 50% of patients and elevated median comorbidity index are encouraging and deserve further studies. A larger prospective trial of haploidentical transplant in higher risk MDS patients fitting with the procedure and lacking an HLA identical donor is warranted.

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CONFLICT OF INTEREST

Nothing to report.

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REFERENCES

[1] Malcovati L, Hellström-Lindberg E, Bowen D, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. *Blood*. 2013;122(17):2943–2964.

[2] Santini V, Alessandrino PE, Angelucci E, et al. Clinical management of myelodysplastic syndromes: update of SIE, SIES, GITMO practice guidelines. *Leuk Res*. 2010;34(12):1576–1588.

[3] Alessandrino EP, Della Porta MG, Malcovati L, et al. Optimal timing of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic syndrome. *Am J Hematol*. 2013;88(7):581–588.

[4] Della Porta MG, Alessandrino EP, Bacigalupo A, et al. Predictive factors for the outcome of allogeneic transplantation in patients with myelodysplastic syndrome stratified according to the revised International Prognostic Scoring System (IPSS-R). *Blood*. 2014;123(15):2333–2342.

[5] Cutler CS, Lee SJ, Greenberg P, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. *Blood*. 2004;104(2):579–585.

[6] El-Jawahri A, Kim HT, Steensma DP, et al. Does quality of life impact the decision to pursue stem cell transplantation for elderly patients with advanced MDS?. *Bone Marrow Transplant*. 2016;51(8):1121–1126.

[7] Mishra A, Anasetti C. Selection of Patients With Myelodysplastic Syndrome for Allogeneic Hematopoietic Stem Cell Transplantation. *Clin Lymphoma Myeloma Leuk*. 2016;16(suppl):S49–S52.

[8] Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106(8):2912–2919.

[9] Raiola AM, Dominietto A, Ghiso A, et al. Unmanipulated haploidentical bone marrow transplantation and posttransplantation cyclophosphamide for hematologic malignancies after myeloablative conditioning. *Biol Blood Marrow Transplant*. 2013;19(1):117–122.

[10] Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120(12):2454–2465.

[11] Bacigalupo A, Tong J, Podestà M, et al. Bone marrow harvest for marrow transplantation: effect of multiple small (2 ml) or large (20 ml) aspirates. *Bone Marrow Transplant*. 1992;9(6):467–470.

[12] Dalla Porta MG, Galli A, Bacigalupo A, et al. Clinical effects of driver somatic mutations on the outcomes of patients with myelodysplastic syndromes treated with allogeneic hematopoietic stem-cell transplantation. *JCO*. 2016;34(30):3627–3637.

[13] Lindsley RC, Saber W, Mar BG. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. *N Engl J Med*. 2017;376(6):536–547.

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Adrenal insufficiency: An emerging challenge in thalassemia?

To the Editor:

Due to dramatic improvements in disease management, thalassemia major patients are now surviving into their fifties and sixties, and face new unexpected medical issues that may require urgent recognition and treatment.

Iron overload, due to blood transfusion and to increased iron absorption from ineffective erythropoiesis, still remains the principal cause of morbidity in patients with transfusion-dependent thalassemia (TDT).[1] Endocrine functions are markedly affected by iron overload, with the most frequent deficiency being hypogonadotropic

hypogonadism, followed by diabetes mellitus, hypothyroidism, and hypoparathyroidism. The hypothalamic–pituitary–adrenal (HPA) axis is generally considered to be an infrequent target of chronic iron toxicity.[2] Since adrenal insufficiency may have dramatic consequences in conditions of stress such as sepsis, acute diseases, trauma, and surgery, an early diagnosis is crucial.

We report here three cases of adrenal insufficiency diagnosed in an acute setting, in TDT patients. Interestingly, none of them had previously shown symptoms and clinical signs of adrenal insufficiency and all had previously normal basal serum cortisol and ACTH values.

Case 1: A 52-year-old male patient was admitted to the Intensive Care Unit in November 2015 for septic shock due to bacterial pneumonia, complicated by atrial fibrillation and heart failure. He was on oral iron chelation therapy with deferasirox (DFX), and the last T2* cardiovascular magnetic resonance (CMR) didn't show liver or cardiac iron overload (Table 1). He had hypogonadotropic hypogonadism, type 2 diabetes, and hypoparathyroidism, all treated with good compliance and results. With the septic shock being unresponsive to intravenous norepinephrine, an adrenal crisis was suspected, and subsequently confirmed by the prompt reversal of hypotension following IV administration of hydrocortisone. The diagnosis was later confirmed by low serum cortisol and ACTH values.

Case 2: A 44-year-old male patient was admitted to the Intensive Care Unit in February 2015 for severe sepsis associated with hyponatremia, hypoglycemia, and altered mental state. He was on chelation therapy with DFX and had no liver or heart iron overload at the last T2* CMR (Table 1). The only known endocrine deficiency was hypogonadotropic hypogonadism. A severe hypoglycemia unresponsive to continuous IV glucose administration led to the clinical suspicion of adrenal insufficiency; after IV administration of hydrocortisone, blood glucose levels normalized. Once clinical conditions stabilized, an ACTH stimulation test confirmed the diagnosis of adrenal insufficiency.

Case 3: In a 40-year-old male patient, a giant myelolipoma originating in the right adrenal gland was surgically removed.[3] He was on iron chelation with DFX with no liver or heart iron overload detected at the last T2* CMR (Table 1). The only known endocrine deficiency was hypogonadotropic hypogonadism, on testosterone replacement. Basal adrenal function was normal; however an ACTH stimulation test prior to surgery was positive for adrenal insufficiency. Replacement with cortisone acetate was immediately started, and surgery was uneventful.

Published data about adrenal insufficiency in adult thalassemic patients are scarce, since most studies include patients in their early decades of life.[4,5] The reported prevalence of this complication is extremely variable, depending on iron overload severity, available treatments, and diagnostic criteria.

Iron toxicity can affect the HPA axis at different levels. The presence of high ACTH serum concentrations is consistent with direct damage to the adrenal glands, which can be confirmed by magnetic resonance imaging (MRI).[6] Lower than normal ACTH levels suggest secondary (central) adrenal insufficiency due to pituitary iron deposition, although combined central and peripheral impairments cannot be ruled out.

Adrenal insufficiency develops gradually, and symptoms, such as fatigue, may be aspecific and overlapping with those of chronic anemia. The main risk of undetected disease is that it may present with a life-threatening acute crisis. The hypothesis that subclinical adrenal impairment may be more common than expected in TDT patients, and sometimes revealed by conditions of stress, has been formulated by Scacchi et al.[7] In 2010, they described a subnormal response to low-dose tetracosactide test in 32.1% of adult thalassemia patients with normal basal cortisol and ACTH values. At our Rare Disease Center, the annual endocrinological assessment of TDT patients always included basal adrenal function evaluation (ACTH and cortisol basal levels). Since a normal basal function cannot rule out a reduced functional reserve, we are now reconsidering new criteria for performing or repeating the stimulation test. Recently, De Sanctis et al., in a survey on hematologists and endocrinologists, showed poor knowledge in the diagnostic criteria for secondary adrenal insufficiency among hematologists, while higher awareness and knowledge of proper diagnostic criteria were

TABLE 1 Clinical parameters of described patients

	Patient 1	Patient 2	Patient 3
Age (years) at diagnosis of adrenal insufficiency	52	44	40
Ferritin (ng/mL)	450-850	200-400	300-400
Cardiac T2* (msec)	32	43	73
Liver T2* (msec)	8	17	21
Chelation therapy Dose	Deferasirox 20 mg/kg/day	Deferasirox 15 mg/kg/day	Deferasirox 15 mg/kg/day
Basal serum ACTH (pg/mL)	26.5	75	21.9
Basal serum cortisol (mcg/dL)	6.0	9.3	6.6
ACTH test: Basal cortisol (nv 6.2-19.4 mcg/dL) Cortisol peak (nv > 18 mcg/dL)	 6.0 10.6	 7.2 13.6	 5.7 13.2

found in centers with a dedicated endocrinologist and an established multidisciplinary approach.[8] Further studies on larger thalassemic populations, including non-transfusion dependent thalassemia patients, are needed to establish criteria leading to the decision of performing dynamic tests of adrenal functions, as well as the appropriate use of these tests to inform clinical decisions.

CONFLICT OF INTEREST

Nothing to report.

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REFERENCES

[1] Borgna-Pignatti C, Gamberini MR. Complications of thalassemia major and their treatment. *Expert Rev Hematol.* 2011;4(3):353–366.

[2] De Sanctis V, Skordis N, Soliman AT, Cohen A. Chapter 8: Endocrine disease. In: Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V, eds. *Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT).* 3rd ed. [Internet]. Nicosia (CY): Thalassaemia International Federation; 2014.

[3] Motta I, Boiocchi L, Delbini P, et al. A giant adrenal myelolipoma in a beta-thalassemia major patient: does ineffective erythropoiesis play a role? *Am J Hematol.* 2016;91(12):1281–1282.

[4] Matin S, Jahromi MG, Karemizadeh Z, et al. The frequency of adrenal insufficiency in adolescents and young adults with thalassemia major versus thalassemia intermedia in Iran. *Mediterr J Hematol Infect Dis.* 2015;7(1):e2015005.

[5] Huang KE, Mittelman SD, Coates TD, Geffner ME, Wood JC. A significant proportion of thalassemia major patients have adrenal insufficiency detectable on provocative testing. *J Pediatr Hematol Oncol.* 2015;37(1):54–59.

[6] Guzelbey T, Gurses B, Ozturk E, Ozveren O, Sarsilmaz A, Karasu E. Evaluation of iron deposition in the adrenal glands of β thalassemia major patients using 3-tesla MRI. *Iran J Radiol.* 2016;13(3):e36375.

[7] Scacchi M, Danesi L, Cattaneo A, et al. The pituitary–adrenal axis in adult thalassaemic patients. *Eur J Endocrinol.* 2010;162(1):43–48.

[8] De Sanctis V, Soliman AT, Elsedfy H, et al. The ICET—a survey on current criteria used by clinicians for the assessment of central adrenal insufficiency in thalassemia: analysis of results and recommendations. *Mediterr J Hematol Infect Dis.* 2016;8(1):e2016034.

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A comment on improving transcranial Doppler ultrasonography screening in children with sickle cell anemia

To the Editor:

Regular screening with transcranial Doppler ultrasonography (TCD) is a crucial component of primary stroke prevention for children with sickle cell anemia (SCA).[1] Despite being the standard of care for nearly two decades, TCD screening rates remain low.[2] In a paper recently published in the *American Journal of Hematology*, Adams et al. reported TCD re-screening rates for 1896 eligible children receiving care at 19 of the 26 original sites that participated in the pivotal STOP and/or STOP II trials.[2] Only 57% of eligible patients had any follow-up TCD screening performed over a five year period, with significant variation by site (18-91%). The authors expressed concern that TCD screening protocols were not fully implemented even in these experienced centers. Other sickle cell centers have reported similar experiences with TCD screening among children with SCA, with rates ranging from 22% to 45%.[3,4]

For the past six years, we have utilized systems-based processes to achieve high TCD screening rates. We offer our results to demonstrate the efficacy of these methods, as our screening rates among eligible children with SCA have been $\geq$70% since 2011. Approximately 200 children with sickle cell disease receive care in our pediatric hematology practice, which is based in an urban safety net academic institution. As an HRSA Sickle Cell Disease Newborn Screening grantee from 2011-2015, we implemented an electronic health record (EHR)-based patient registry and used a part-time patient navigator to work with providers and families to achieve consistently high TCD screening rates.[5] Even though our grant funding ended in 2015, we have maintained high TCD screening rates without additional staff, surpassing most screening rates reported to date (Table 1).

To achieve and maintain these results, we have made two significant changes to our approach to patient care. First, we have incorporated our EHR-based patient registry reporting functions into regular clinic workflow, which has enabled us to provide better care to our entire patient population. Population-based lists are generated weekly for all children seen in our clinic and reviewed at our multidisciplinary hematology team meetings that include both clinical and administrative staff. All patients who are overdue for TCD are identified and contacted by administrative staff to schedule necessary screenings. In addition, an "opportunity report" is generated prior to each clinic