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Emerging insights in the management of hemoglobin E beta thalassemia

Nancy F. Olivieri,[1] Vivekanandan Thayalsuthan,[1] Angela O'Donnell,[2] Anuja Premawardhena,[3] Christopher Rigobon,[1] Giulia Muraca,[1] Christopher Fisher,[4] and David J. Weatherall[2]

[1]Hemoglobinopathy Research Program, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada. [2]Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Headington, Oxford, United Kingdom. [3]Faculty of Medicine, University of Kelaniya, Colombo, Sri Lanka. [4]MRC Molecular Hematology Unit, John Radcliffe Hospital, Headington, Oxford, United Kingdom

Address for correspondence: Nancy F. Olivieri, M.D., F.R.C.P.(C.), Professor, Pediatrics, Medicine and Public Health Sciences, University of Toronto, Canada; University Health Network, 200 Elizabeth Street, Eaton Wing North, 10th Floor, Room 225, Toronto, ON, Canada M5G 2C4. noliv@attglobal.net, nolivi@gmail.com

Globally, hemoglobin (Hb) E β thalassemia accounts for approximately half the severe forms of β thalassemia. Because of its wide clinical diversity and the ability of patients with this condition to adapt unusually well to low hemoglobin levels, the management of Hb E β thalassemia, particularly the decision to instigate regular blood transfusion, is particularly difficult. Here, we present a summary of our work in patients with this condition, which attempts to define clinical, adaptive, and genetic factors of possible value in determining the early management of this condition.

Keywords: hemoglobin; hemoglobin E beta thalassemia; β thalassemia

A recent population analysis suggests that hemoglobin E beta-thalassemia (Hb E β thalassemia) accounts for approximately half of all the cases of severe β thalassemia in the world population.[1] Hb E β thalassemia occurs widely throughout the eastern half of the Indian subcontinent, Bangladesh, Burma, and throughout Southeast Asia.[2] Hb E β thalassemia has a remarkably diverse phenotype, ranging from a transfusion-dependent disorder similar to β thalassemia major, to a condition characterized by relatively normal growth and development with survival into adult life in the absence of red cell transfusions.[2,3] Although the reasons for this clinical heterogeneity are still not fully understood, we and others have demonstrated that this in part reflects the coinheritance of genetic modifiers such as α thalassemia and genetic polymorphisms involved with elevated hemoglobin F production.[4–6] We have identified other genetic modifiers that influence the complications of the disease,[7] together with differences in adaptation to anemia,[8] and the effects of the environment, particularly exposure to malaria.[9]

The remarkable clinical diversity of this condition, which occurs against the background of coinheritance of Hb E with a wide variety of severe β thalassemia mutations,[4] together with its remarkable phenotypic instability during the early years of life,[5,10] presents difficult problems in the early management of this disease. These difficulties are compounded by the fact that it appears that the difference in hemoglobin levels between mild and severely affected patients are remarkably small, in the range of 1–2 g/dL.[5]

Here, we summarize findings obtained in a study of 115 patients with Hb E β thalassemia who had never received regular transfusions during the clinical course of their disease, or in whom regular transfusions had been stopped during the clinical course and in whom there was at least 5 years of followup after regular transfusions had been discontinued. This preliminary analysis attempts to define some clinical and genetic factors, which may assist in deciding whether to initiate regular transfusions, or to stop these when already initiated, in patients with Hb E β thalassemia.

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The study group was composed of patients with Hb E β thalassemia attending the National Thalassaemia Centre, Kurunegala, Sri Lanka, of whom approximately one-third had never been started on regular transfusions, while the remaining patients had been started on regular transfusions, but in whom a decision to stop regular transfusions had been made when the patient was first reviewed between 1996 and 2003. In each patient, it had been decided to stop regular transfusions because it was unclear why each patient had been recommended to begin regular transfusions, noting, in particular, that the pretransfusion hemoglobin concentrations showed little difference from hemoglobin concentrations in patients who had not been supported by regular transfusions. Folate, deferoxamine, and prophylactic penicillin continued to be prescribed as indicated. All these patients were reviewed at least four times a year for a minimum of five years.

The methods for clinical assessment, severity and grading on a scale of 1–5, hematologic and hemoglobin analysis, DNA analysis, serum ferritin and, in some cases, hepatic iron concentrations, and serial assessments of serum erythropoietin concentrations, have been described previously.[4,5,8]

We examined some clinical features, which might distinguish the patients who had never been transfused regularly, from those in whom regular transfusions had been started at some point during their clinical course. Several features suggested that the patients who had not been started on regular transfusions had a milder phenotype. For example, patients never started on regular transfusions were significantly older at diagnosis compared to those in whom regular transfusions had been started. Furthermore, there was a lower rate of splenectomy in the patients who had not been transfused regularly, compared with patients in whom regular transfusions had been initiated and patients in whom regular transfusions had been started had also been splenectomized at an earlier age, compared with those who had never been transfused regularly.

Currently, we are engaged in a detailed analysis of the factors that might underlie the difference in response of the patients in whom regular transfusions were terminated successfully, and those in whom this was unsuccessful and in whom regular transfusions needed to be resumed. Among others, the effect of genetic factors on response to transfusion withdrawal is currently being investigated, particularly with the recent recognition of the variety of different forms of nondeletion α thalassemia in the Sri Lankan population.

It may be possible successfully to stop regular transfusions in a substantial proportion of patients with Hb E thalassemia who have been placed, often for uncertain reasons, on such a regimen. Both genetic factors and the long-term adaptation to anemia may play a part in the successful or unsuccessful withdrawal of transfusions in these patients. We have previously suggested that some of the early phenotypic instability of Hb E thalassemia, including the decline in the rate of splenomegaly with age, might reflect the relatively high erythropoietin response in early life for a particular hemoglobin concentration. This response could certainly be implicated in the increasing spleen size, marrow expansion, and growth disturbances observed in this disorder during infancy and early childhood. Our previous findings that response to a given hemoglobin concentration declines throughout late childhood suggests the possibility arises that as patients with Hemoglobin E thalassemia age, it may be possible to stop transfusions in many.[8,10]

The management of Hb E β thalassemia is going to place an enormous burden on the limited health services of many of the poorer countries in Asia, particularly as they enter the epidemiological transition whereby, due to improved public health and social conditions, more affected children are surviving in early life. Undoubtedly, there are many children at the severe end of the spectrum of this disorder, who will require lifelong transfusions on a regular basis, along with a significant proportion of patients who may grow and develop relatively normally without ever being begun on such a regimen. Further work may help to define which patients of this type do require regular transfusions and who do not. Clearly, many such patients may be receiving unnecessary chronic transfusions because of its phenotypic variability during early life, and the difficulty of defining its future course.

It is possible that many patients might be spared the proliferative complications of the high erythropoietin response for a particular hemoglobin concentration in early life through the initiation of regular transfusions, which can then be stopped at or during early puberty. Given the vast numbers of patients with this disease in Asia, this approach

would lead to an enormous sparing of health resources. Further work is required to try to determine the factors, which might predict the successful cessation of transfusion in patients with Hb E β thalassemia.

Conflicts of interest

The authors declare no conflicts of interest.

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