The cohort of thalassemic adults described by Drs. Anupam Prakash and Ramesh Aggarwal is representative of an emerging problem in medicine: thalassemia major (TM) is no longer merely a pediatric disease, and the adult physicians should be acquainted with the morbidity these patients can develop in adulthood.

Thalassemia major is characterized by severe anemia, and survival depends on regular blood transfusion, with an unavoidable iron overload resulting in multiorgan damage due to free radical generation.[1] Iron chelation is mandatory in this condition, but not sufficient to avoid iron deposition in tissues. The introduction of modern therapeutic regimens, based on regular transfusion and intensive chelation, indubitably prolonged life expectancy: survival in compliant individuals with appropriate treatment extends now beyond the 40s, in comparison with previous occurrence of death before the second or third decade. However, this implies an increased time span for the long-term complications of the disease and its treatment to evolve.

The clinical findings usual in untreated or poorly transfused individuals, still present in some developing countries - growth retardation and skeletal deformities, jaundice, hepatosplenomegaly, leg ulcers, masses of extramedullary hematopoiesis - in the industrialized countries gave way to a less striking clinical picture, nonetheless remarkable. The patients described in the paper by Drs. Anupam Prakash and Ramesh Aggarwal did not follow optimal regimens for transfusion nor chelation, so a high risk for complications could be expected, despite the young age. However, iron overload-related complications appear even in optimally treated patients, especially with increasing age, and this is bound to have a significant social impact since thalassemias are the most common monogenic disease worldwide.

Late complications involve mainly the heart (dilated cardiomyopathy, sometimes arrhythmias), liver, and endocrine glands. Hypogonadism is still the most frequent endocrine defect, with a major impact on quality of life related to the delicate implications for fertility and ability to raise a family.[2] Nonetheless, sex steroid deficiency can be overcome with proper replacement, and today women with TM can achieve pregnancy, either spontaneously or by inducing ovulation, as ovarian function is commonly preserved until the 30s. This is an extraordinary success, unthinkable only two decades ago, which gives these patients the hope of a normal social and affective life.

Hypostaturism, described in this Indian population, is currently a less prominent problem in western countries, but GH deficiency is emerging in adults; this raises a crucial question about rhGH therapy, due to the deleterious consequences of this defect on several biologic functions, first of all cardiac morphology and function.[3] Other endocrinopathies become more common with increasing age.[4] In this cohort, as the authors correctly point out, the low prevalence of diabetes and hypothyroidism is probably due to the young age.

Liver disease secondary to iron burden and HCV infection is still a problem in adult thalassemic patients; besides the development of fibrosis and cirrhosis, the liver disease interferes with insulin action favoring deterioration of glucose metabolism over time. Virus negativization achieved by combined treatment with IFN and ribavirin may play a striking role in the immediate future not only in the reduction of hepatocellular carcinoma risk, but also in the prevention of diabetes with its sequelae. By analogy with liver disease, the iron deposition may raise the suspicion of its possible cancerogenetic role played by iron deposition in other organs. A recent report of malignant nodules in the thyroid of thalassemic patients is very alarming,[5] though these data need to be confirmed by controlled trials in larger populations.
Despite blood transfusion controlling bone marrow expansion and maintaining acceptable Hb levels, chelation treatment preventing bone iron toxicity, and adequate sex hormone replacement correcting hypogonadism, a wide spectrum of bone abnormalities still affect adult thalassemic. The entity defined as “thalassemic osteopathy” includes osteopenia/osteoporosis, fractures, spinal complications.[6] Osteoporosis is a potentially debilitating and progressive disease, so timeliness in detection, prevention, and treatment are essential to avoid progression to severe impairment of bone mineral density. Periodic follow-up of BMD starting from adolescence is crucial, and several general interventions must be taken: encouragement of physical activity, preferring moderate and high impact activities when not contraindicated by comorbidity, avoidance of smoking, early diagnosis, and replacement of hypogonadism. Vitamin D deficiency is quite common, and the administration of oral supplements in combination with an adequate calcium intake may have a huge role in preventing bone loss and fractures. Despite such interventions, many TM patients continue to lose bone mass. Based on findings of an increased bone turnover with prevailing resorptive phase, bisphosphonates have been used, and the best effects on BMD were obtained with alendronate, pamidronate, and zoledronate.[7] Their efficacy in reducing fracture risks needs to be confirmed with controlled trials in larger populations. Delay in diagnosis or intervention leads to pain, fractures, and spinal deformities, unfortunately common disabling occurrences in the poorly treated adult thalassemic.

Deferoxamine causes endplate deformation leading to platyspondyly and vertebral deformities; furthermore, it seems to negatively affect the integrity and strength of the annulus fibrosus. Also deferiprone, the first oral iron chelator introduced, can produce arthropathy as a side effect. We are now facing the clinical problems of the first generation of adult thalassemics. We need collaborative efforts and awareness on the part of all the physicians involved to overcome this new challenge.

References

1. Fibach E, Rachmilewitz E. The role of oxidative stress in hemolytic anemia. Curr Mol Med 2008;8:609-19.
2. Chatterjee R, Bajoria R. Critical appraisal of growth retardation and pubertal disturbances in thalassemia. Ann N Y Acad Sci 2010;1202:100-14.
3. Scacchi M, Danesi L, Cattaneo A, Valassi E, Pecori Giraldi F, Argento C, et al. Growth hormone deficiency (GHD) in adult thalassaemic patients. Clin Endocrinol (Oxf) 2007;67:790-5.
4. De Sanctis V, Roos M, Gasser T, Fortini M, Raiola G, Galati MC; Italian Working Group on Endocrine Complications in Non-Endocrine Diseases. Impact of long-term iron chelation therapy on growth and endocrine functions in thalassaemia. J Pediatr Endocrinol Metab 2006;19:471-80.
5. Poggi M, Sorrentino F, Pascucci C, Monti S, Lauri C, Bisogni V, et al. Malignancies in β-thalassemia patients: First description of two cases of thyroid cancer and review of the literature. Hemoglobin 2011;35:439-46.
6. Haidar R, Musallam K, Taher A. Bone disease and skeletal complications in patients with β-thalassemia major. Bone 2011;48:425-32.
7. Terpos E, Voskaridou E. Treatment options for thalassemia patients with osteoporosis. Ann N Y Acad Sci 2010;1202:237-43.