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Letter to the Editor

ICET-A an Opportunity for Improving Thalassemia Management

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The treatment of patients with β-thalassaemia major (β-thal) has considerably changed over the past few decades, with advances in red cell transfusion and the introduction of iron chelation therapy. Iron overload can be fatal as its tissue accumulation can result in progressive dysfunction of the heart, liver and endocrine organs. In patients receiving transfusion but not chelation therapy, symptomatic cardiac disease has been reported within 10 years of the start of transfusion. Regular Red Blood Cell (RBC) transfusions eliminate the complications of anaemia, compensatory bone marrow expansion, permit normal growth throughout childhood, and extend survival. The most important consequence of these life saving transfusions is the inexorable accumulation of iron within tissues.

Stunted growth, delayed puberty, hypothyroidism and diabetes mellitus are well-recognized complications of iron overload.

Iron is normally stored intracellular in the form of ferritin, a protein whose synthesis is induced upon influx of iron, when the storage capacity of ferritin is exceeded, pathological quantities of metabolically active iron are released intracellular in the form of hemosiderin and free iron within an expanded labile pool. This metabolically active iron catalyzes the formation of free radicals, which damage membrane lipids and other macromolecules, leading to cell death and eventually organ failure. The heart and pituitary are very sensitive to the toxicity of free iron.

An additional factor is the effect of L-Type Ca^{2+} Channels (LTCCs). These channels play a role in the excitation-secretion coupling properties of osteoblasts, pancreatic β-cells, thyrotrophs, corticotrophs and parathyroid hormone producing cells. LTCCs cause a membrane depolarization, thereby mediating the opening of LTCCs which allow iron to pass in the cell membrane of endocrine glands.

Other factors contributing to the variability of cellular iron overload are cell surface transferring receptors and the capacity of the cells to deploy defence mechanisms against inorganic iron. Liver disorders, chronic hypoxia and associated endocrine complications, such as diabetes may be additional factors.

Thus iron overload constitutes the most important complication in thalassaemia major and is the major focus of clinical management. Effective chelation reduces or prevents iron accumulation and iron-mediated organ damage, resulting in a consistent decrease of morbidity and mortality.

Combined therapy (use of two chelators on the same day), may induce negative iron balance and may reverse hypogonadism and endocrine complications in severe iron overloaded β-thal subjects. Long-term studies have shown that deferiprone and Deferoxamine (DFO) accelerate iron chelation by rapidly reducing liver iron, serum ferritin, and myocardial siderosis. Combination chelation therapy with deferasirox and DFO has also been shown to be beneficial.

The major difficulties reported by hematologists or pediatric endocrinologists experienced in thalassaemias in following growth disorders and endocrine complications were: lack of familiarity with medical treatment of endocrine complications (40%), interpretation of endocrine tests (30%), costs (65%), absence of pediatric endocrinologist for consultation on growth disorders and endocrine complications (27%), facilities (27%), other [e.g. lack of collaboration and on-time consultation between thalassaemic centers supervised by hematologists and endocrinologists] (17%) .

Therefore, there is a clear need to encourage endocrinological follow up of multi-transfused patients and to train more endocrinologists and attract them to this interesting and important field. There is also room for collaborative research, especially since both epidemiological and clinical data are based on relatively small numbers of patients.

Because any progress made in research into growth disorders and endocrine complications in thalassaemia should be passed on to all those suffering from these conditions, on the 8th of May, 2009 in Ferrara (Italy) the International Network on Endocrine Complications in Thalassaemia (I-CET) were founded.

The team of doctors who have taken the initiative and have formed the initial core group include endocrinologists: Vincenzo de Sanctis (Italy), Ashraf Soliman (Qatar), Nicos Skordis (Cyprus), Mohamed El Kholy (Egypt), Heba El Sedfy (Egypt), Giuseppe Raiola (Italy), Ploutarchos Tzoulis (UK). In addition doctors experienced in thalassaemia care are supporting the group. These include: Christos Kattamis (Greece), Mohamed Yassin (Qatar), Mehran Karimi (Iran), Praveen Sobti (India), Bernadette Fiscina (USA), Duran Canatan and Yurdanur Kilinç (Turkey), Michael Angastiniotis (Cyprus), Hala Rimawi (Jordan), Ludmila Papusha. (Russia), Soad K Al Jaouni (Saudi Arabia), Shahina Daar (Oman), Maria Concetta Galati, Saveria Campisi and Salvatore Anastasi (Italy) [1-6].

From March 2014, the I-CET acronym has changed and extended to International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine (ICET-A).

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The practical objectives of ICET-A are to encourage and guide endocrinological follow up of multi-transfused patients in developing countries, to promote and support collaborative research in this field, to encourage and guide endocrinological follow up of multi-transfused patients, and to educate and train more endocrinologists and other pediatricians/physicians to prevent and improve management of the growth and endocrine complications in these patients.

The final goal of the ICET-A program is to train Pediatricians and Hematologists to:

1. Acquire adequate knowledge and ability to problem solves and interprets data originating from laboratory investigations.
2. Reach an international acceptable standard on growth disorders and endocrine complications in thalassaemia
3. Become competent and maintain the optimal care provided to individuals suffering from endocrine disorders due to thalassaemia
4. To encourage research in the field of growth disorders and endocrine complications in thalassaemia
5. In order to offer to the participants or to doctors taking care of thalassaemic patients material that can be easily used and applied to practical clinical situations encountered by pediatricians or haematologists, the Ludhiana Booklet on Growth disorders and Endocrine complications in thalassamia , published by Scripta Manent Editions of Milan and prepared by the ICET-A Group will be distributed.

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