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Hemoglobinopathies in Iran : molecular spectrum, prevention and treatment.

Yavarian, M.

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Summary.
The aim of this thesis

Over 20.000 patients affected by major forms of Hemoglobinopathies (HbP), mainly β-thalassemia major and sickle cell disease live in Iran. Such a large number of severely affected patients, in need of intensive supportive therapy and with little or no chances of being cured, represent an enormous human suffering for many families and a heavy economic burden for the country.
Supportive treatment by blood transfusion and chelation therapy is freely available in Iran and represents a great effort of the public healthcare. Primary prevention is allowed and encouraged by the country's authorities from 1998. The aim of this thesis is to approach some of the existing problems related to the implementation of treatment and prevention, possibly contributing to their solution.
The introduction of this thesis explains in some detail the evolution, function and biochemical and molecular background of the globin genes. Moreover, details on the multi-ethnicity of the country and elucidations on several aspects concerning the treatment and the diagnostic tools needed to achieve primary prevention are given. The following studies have been done, and are either published or in the process of being published.
A random population sample of β-thalassemia patients have been monitored to show the dramatic improvement in life expectation of the last years and to look for additional improvements (publication 5 in this thesis).
Molecular screening of a large number of thalassemia chromosomes in the Hormozgan and Shiraz area have been done to facilitate the diagnosis and herewith to allow prenatal diagnosis at the DNA level. (publication 1 in this thesis). This survey has revealed the occurrence of prevalent mutations and the occurrence of a large spectrum of less common defects, associable with the high multi-ethnicity of the Iranian populations.
To define modulating factors associated with the phenotype variability of the thalassemia major patients the prevalence and molecular background of α-thalassemia has been studied (publication 2 and 3 in this thesis). This survey has revealed a variety of common and specific defects that may cause α-globin gene related Hemoglobinopathies solely or in association with β-globin gene defects.
For the same reason the occurrence of G6PD deficiency was studied as a possible aggravating factor in thalassemia trait and thalassemia major (publication 7 in this thesis).
The occurrence of mutation causing Hereditary Hemochromatosis (HH) has been studied in a large population sample to define the effect of iron accumulation in poly-transfused β-thalassemia patients (publication 6 in this thesis).
To reduce the need for transfusion treatment and the complications of iron overload, the effect of alternative Hydroxyurea treatment has been studied on a large number of patients affected with transfusion dependent β- thalassemia (publication 4 in this thesis).
To inform the population on the importance of carrier identification and on the risk for HbP major in the progeny a leaflet has been produced which is now in use to inform of Farsi speaking immigrants in The Netherlands (Appendix).
To apply "state of the art" prenatal diagnosis, the protocols used at the reference laboratory at Leiden University Medical Center have been studied and made applicable for Iran.

In conclusion this thesis offers a number of data that may be useful in management and prevention of Hemoglobinopathy in Iran and for Iranians living abroad. Most significant data are: 1) the molecular spectrum of β- and α-thalassemia in representative areas of the country. 2) A number of technical approaches to obtain molecular analysis in a routine setting for post and prenatal diagnosis. 3) A therapeutical approach significantly reducing the need for transfusion/chelation in β-thalassemia intermedia patients. 4) The estimation of the actual life expectation to stimulate improvement of state of the art treatment. 5) The high prevalence of α-thalassemia in the Hormozgan region.