

Prevention of the hemoglobinopathies

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The inherited hemoglobin disorders not only cause suffering and unhappiness to the patients but they also absorb a large part of resources and human effort in several countries which harbor the deleterious genes. Numbers are frightening! Africa, with several millions patients with sickle cell anemia; India with millions of patients with sickle cell disease and thalassemia, South East Asia with more millions of patients with hemoglobin E and α - or β -thalassemia. The offered treatment is suboptimal or nil and, and, in several places, patients are dying at infancy not only because of their hemoglobinopathy but mainly because of infections and malaria; in this way, nature took care of her own faults and eliminated them before they enter productive life. However, now that improvements of sanitary conditions have already significantly decreased infant mortality, the problem of hemoglobinopathies emerges more pressingly, because an ever increasing number of newborns with sickle cell disease, thalassemia or other clinically severe hemoglobin disorders is continuously added to the patients who are surviving and will certainly demand a better and more expensive treatment. According to recent WHO statistics, the number of newborns with sickle cell disease which are expected to be born annually in Africa is of the order to 300,000 and that of newborns with Hemoglobin E and severe thalassemia in the South East part of the globe will be similar. The Mediterranean countries are not spared; here the numbers are smaller but the fact that patients are receiving better treatment, allows them to survive longer and thus it imposes a heavy burden on the respective national health budgets. According to the same statistics, the number of patients with thalassemia major in the countries around the Mediterranean sea is no less 300,000, while the yearly number of affected newborns if no other measures were taken is estimated to be around 30,000.

Under present conditions, the cost for providing an acceptable, be it suboptimal treatment to a thalassaemic child is estimated at 20,000 US dollars yearly. This sum comprises mainly the cost of blood processing (estimated from 50 to 150 US dollars per PBRC unit) and the cost of the used chelating agent, which will probably increase as a result of the introduction of newer agents in the market. Adding the expenses

for running the transfusion service, the salaries of the medical and mainly paramedical staff, the cost of treating the inevitable complications (bile stones, leg ulcers, enlarged spleen, cardiomyopathy and cardiac failure, endocrinopathies and bone disease and other) brings an expense which is difficult if not impossible to meet when the number of patients is large and further growing. Considering these numbers it is obvious that the only way to decrease the impact of the inherited hemoglobin disorders across all countries involved is prevention.

This statement is not new; it has been advocated several years ago by various Committees of the WHO and other International and National Organisations and has been put in effect in several countries, mainly Mediterranean, with very satisfactory results. However, the latter are representing a minute part of the global problem. Expanding the concept of prevention across all involved countries leaves a lot to be desired and requires a thoroughly planned approach and judicious use of the usually limited available resources.

Approaching the problem in a country or specific area starts from the evaluation of the impact of the diseases addressed. This requires a census (or a reliable, as close as possible, estimation) of the surviving patients, establishment of the frequency of heterozygous carriers and calculation of the number of affected newborns which are expected to be born each year. It requires also an assessment of the available resources (hospitals and day-care Units) and, whenever feasible, a rough estimate of the expenses associated with the treatment of patients. Further calculations may project the cost on a time scale taking in consideration the ever increasing number of patients and the expanded survival of those already surviving. In addition, the facts that patients may not be fully productive, are unable to meet school or work obligations, and cause great difficulties to their parents who must often spend many hours daily for their care will certainly be a major factor in projecting the impact of the hemoglobinopathies in the given area.

These data are absolutely necessary to convince the policy makers; further support may be obtained by promoting the formation of Parents' Associations and have them put pressure on the Governments to initiate programs of prevention of the inherited hemoglobin disorders. Accumulating experience in many countries confirms the value of this coordinated efforts. The argument to persuade the parents of affected children to collaborate and help is that by preventing more births of affected children will allow re-allocation of funds to their own, surviving children.

Once the decision to implement a prevention program is made, sensitization and information of the involved population is the next step. In the past, at least for thalassemia in the Mediterranean countries, the problem was spontaneously solved because the appearance of several untreated patients was impressively abnormal and ugly and could not be easily overlooked; however now, in the areas where both prevention and treatment are effectively provided, patients are not recognized anymore and most people of the present generation completely ignore what thalassemia means.

Mass Media have a significant role in informing people; the problem is how to persuade them donate some time to this effect. Posters and leaflets related to the problem are equally effective, but must be continuously available and renewed. In some countries the Church may

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play a significant role, especially when couples to be married apply for a pre-nuptial certificate. Be this as it may, there is little doubt that the major target for providing information is the School. This is not as easy as it may appear; experience shows that a major factor of success is not the inclusion of the topic of hemoglobinopathies in the books (usually in the secondary school) and other printed material, but the teachers who need to be adequately educated and enthusiastic to spread the concept to their pupils. Spread of information among various minority groups residing in foreign countries will not succeed unless educated social workers of the same origin and language are integrated in these communities.

Sensitization and information are expected to induce people to request carrier identification before they are married or, at last, before they give birth to children; this "prospective" approach is much preferable to offering the test to specific groups of people (school, army, university), but it requires a flawless operation, which comprises an easy access to the laboratories providing the test, no or minimal charge, technical competence, politeness and non-failure to provide a yes or no answer. Association of the latter with additional information if both partners happen to carry the noxious genes is also a prerequisite and should be offered on a strictly personal basis, in keeping with the basic rule of counseling, *i.e.* explain but not direct.

In the past, most of these procedures were carried out retrospectively, *i.e.* on parents who had already an affected child; the search expanded, wherever possible, to other members of the family. This approach enabled the couples at risk to have a well child but did not help the overall prevention program. However, there are instances where this approach is the only potential solution to the program. This applies to the broad neonatal screening programs which are now in effect in several countries who have admitted, now or in the remote past, large numbers of immigrant workers from Africa and the Indian Subcontinent, such as the United States, the United Kingdom, Bresil, the Carribean, and France, and now address the problem by indentifying the homozygous sickle cell newborns in the maternities and then retrospectively examine parents and families in order to offer them the appropriate guidance. Of course, this approach is also precious for the sickle cell child because it ensures proper care and treatment whenever necessary.

Choice of the appropriate methodology is of utmost importance. Detection of the hemoglobinopathies which create public health problems is simple and non-expensive; hemoglobin electrophoresis and/or chromatography along with a sickling test are adequate to identify the carriers of hemoglobin S; a clearly low MCH/MCV along with hemoglobin A2 determination on acetate strips or by chromatography will detect

beta-thalassemia in most cases. Measurement of iron and ferritin will easily exclude iron deficiency. For field studies an one tube solubility test or a one tube osmotic fragility test may readily identify the suspect cases; further investigation may then be completed in a proper reference laboratory. Applying complex molecular methods of acquiring sophisticated and very expensive apparatuses in small remote laboratories is disapproved because neither the staff can handle them well, nor the result which they are expected to provide justifies the expense. In addition, experience shows that whenever such an apparatus breaks down in a remote laboratory, the chances of having it repaired on time are minimal.

Carrier identification leads to the option of (a) not having children, (b) select another partner or (c) proceed to prenatal diagnosis. The choice depends on several very variable factors, such as the ethical, legal, social and family constraints which prevail in each population at risk as well as the technical feasibility of safely carrying out the procedure in the given environment. Under present conditions, prenatal diagnosis is carried out on fetal DNA extracted from chorionic villi cells which are obstetrically obtained at the 8-10th week of pregnancy. Identification of the noxious genes can be carried out usually following PCR amplification by allele specific hybridization or other molecular techniques.

Prenatal diagnosis has been accepted rather easily by most couples at risk in several communities and countries where the problem of thalassemia is pressing and it is gradually expanding wherever information and technical conditions make it possible. Prenatal diagnosis of sickle cell disease at large lagged behind for various reasons: fear of interfering with eugenics and lack of compliance in several African-American communities, religious constraints in the Islamic world, technical difficulties in Africa. However, the desire of having a well child is so universal that sooner or later this procedure will become the only realistic solution for the populations which harbor high frequencies of the deleterious genes.

Organization of a prenatal diagnosis service is more complex than what appears to be a technical issue. Prospective mothers need a lot of psychological support to relieve their feelings of being guilty to the affected sibling, to reinforce their decision to proceed when their spouse or his family do not concur, to relieve the fear for the examination, and to face selective termination of pregnancy when results show homozygosity. Be this as it may, evaluation of the so far obtained results leaves no doubt that the feasibility of prenatal diagnosis has been instrumental for the large scale acceptance of the concept of prevention because couples to be married know that even they both prove carriers there is a solution to giving birth to a healthy child.

Oral presentation

Oral presentation is available online