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Review Article

Efficacy of Prolonged Implementation of National Programs for Prevention and Treatment of β-Thalassemia Patients. The Greek Experience

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Abstract

Greece is one of the few countries with high incidence of β-thalassemia trait in which prolonged national programs for prevention and treatment were implemented.

Evaluation of treatment program in 1979, demonstrated amelioration of the main clinical features of the disease, significant improvement in survival and quality of life and a continuous increase on patients' cohort and worsening of disease burden. Evaluation of combined implementation of the two programs in 2009 demonstrated: i) further amelioration of the clinical features and improvement in survival and quality of life , ii) a gradual reduction in the annual input of affected neonates and prevention of 4.329 births of affected fetuses versus 1,010 born, and iii) wide changes in the age distribution of thalassemia patients. In 2009 only 6.8% of patients were below 15years compared to 68% of adults above the age of 30 years.

The important conclusion is that a prolonged and efficient implementation of combined prevention and treatment programs can change the most common fatal genetic disease of childhood to a rare chronic one with prolonged survival and a reasonable quality of life, common in adults.

INTRODUCTION

β- Thalassemia was recognized as a serious public health problem in Greece in the late 60's, after extensive studies on the prevalence of β-thalassemia trait and the increasing burden of the disease by the rise in admissions of children with thalassemia for transfusions.

Epidemiological studies demonstrated that β-thalassemia heterozygotes were spread all over the country in a wide uneven distribution. There were areas with low incidence (< 5%), others with moderate (5-10%), with high (10-15%) and very high (>15%) especially in previously highly malarious areas. The overall incidence of β-thal trait in the Greek population is estimated to 8.0% [1-4].

Implementation of frequent transfusions in 1965 provoked a rapid increase of admissions of patients in hospitals that was aggravated from the improvement of survival and the continuous increase of the total population of patients. In our department the annual admissions increased from 62 in 1965 to 2.400 in 1975 and around 4.800 in 1980 [5].

The severe impact of the disease on public health stimulated authorities to take appropriate measures. To this end, two national programs were organized and implemented; the one for treatment started in 1965 and the other for prevention started in1980 combined with treatment program.

The main objective of this paper is to review in brief the prolonged application of national programs for treatment and prevention of patients with β-thalassemia in Greece based mainly on published data.

Initial period of treatment program (1965-1979)

Organization of treatment program proceeded rapidly and upgraded continuously. In this period the main landmarks of the program were: i) the frequent transfusions started in 1965 and ii) the chelation treatment with DFO in 1974, given at first as intramuscular injections and later by continuous subcutaneous infusions and occasionally by intravenous infusions ,using special pumps [6].

To cover the special and increasing demands of treatment and follow-up of patients, special Units were established. The

first Thalassemia Day Care Unit was established in 1975 in our Department.[5] Soon after, special Units were organized in other children hospitals or Pediatric Departments, as at this period, nearly all patients were children below 10 years of age. Thalassemia Units for adults were organized later, joint to Hematology or Internal Medicine departments. At present a total of more than 30 thalassemia units are operating within the National Health System (NHS) covering, the whole populations of patients, all over the country. All units follow a homogeneous regime of treatment that is continuously upgraded to meet the recommendations, proposed by International Scientific Committees.

The major beneficial effects of treatment evaluated in 1979, at the end of this period of exclusive implementation of treatment program were: i) the amelioration of the main clinical manifestations of the disease (anemia, splenomegaly, bone changes and growth retardation) and ii) the significant improvement of survival and quality of life. Prior to transfusions, Thalassemia major (TM) was fatal within the first decade of life. In 1979 more than 90% of treated patients had the possibility to survive above the age of 20 years [7].

This period was characterized by a high annual input of new patients that increased significantly and continuously the total number of thalassemia population, the prevalence, and the burden of disease. It is estimated that within 15years more than 3,500 patients were added to the cohort of thalassemia. This estimate represents the assessment of the expected number of births of affected newborns, based on the total number of live-born neonates and the incidence of thalassemia trait.

Combined prevention and treatment programs period (1980-2009)

This period is characterized by the organization and progressive implementation of prevention program jointly with treatment program. The prevention program is free of charge and is provided through a network of 23 prevention Units, distributed all over the country; these units cover the screening, the detection and the consultation of couples of risk, of child-bearing age population. The program is coordinated and supervised by the National Centre for Prevention in Athens; the Centre is also responsible for prenatal diagnosis and termination of pregnancy of affected fetuses [8]. During the last decades antenatal diagnosis is also applied in recognized private genetic laboratories and in special maternity units for tissue sampling and termination of pregnancy.

The main landmarks in the evolution of prevention program run in parallel to the evolution of prenatal diagnosis (PND). At the initial stage of the program, prenatal diagnosis was achieved by chain synthesis analysis of fetal blood obtained on the 15-17 weeks of gestation. Prenatal diagnosis improved gradually involving DNA analysis of blood and fetal tissues (mainly chorionic villi), obtained at the end of the 1st trimester of gestation. The recent most accurate and rapid PND is based on DNA analysis, utilizing reliable direct and indirect PCR based methodology [8,9]

The most recent evolution in the prevention program of β-thalassemia is Pre-implantation Genetic Diagnosis (PGD), started in 1999. It has the advantages of selection of healthy embryos for implantation and the option for simultaneous selection of an HLA compatible embryo, as a candidate of bone marrow donor in case of an affected sibling with thalassemia [10].

The major effect of the prevention program was the reduction in the annual input of new patients. Reduction increased gradually parallel to the expansion of screening for β-thalassemia trait in the at risk section of the population. The longitudinal process and the results of the program are summarized in Table 1. Table, demonstrates the longitudinal trends, on a 5 years intervals, of the expected versus absolute (observed) and prevented number of β-thal births. In 30 years of a total of 5,339 expected affected neonates only 1010 were born. The number of births of affected newborns was rapidly reduced from 458 in 1980-84 to 48 in 2005-09 [11].

During this period, efficiency on treatment program was also progressively upgraded. This was mainly due to: I. The successful implementation of bone marrow transplantation in patients with a compatible relative donor. Since 1990, 90% of nearly 150 transplanted patients are cured [12]. II. The approval of two oral chelators, Deferiprone (DFP) in 1999 and Deferasirox (DFX) in 2000, given either as monotherapy or combined with DFO ; both drugs facilitated compliance and efficacy of chelation [13]. III. The important contribution of blood bank services to provide high quality specific products for transfusion dependent patients. These products include: packed red blood cells (RBCs) free of leukocytes, neocytes, compatible blood for rare blood groups and blood free of infectious agents, mainly viruses of hepatitis B and C and immunodeficiency syndrome, tested by DNA methods. Advances in transfusion medicine reduced significantly

Table 1: Longitudinal trends of annual births with β-thal (in five years intervals) during 1980-2009, for expected versus observed and prevented births.*

Period	Number of newborns with β-thal		
	Expected	Observed	Prevented
1980-84	1096	458 (41.7%)	638 (58.3%)
1985-89	872	187(21.4%)	685(79.6%)
1990-94	823	145(17.3%)	678(82.7%)
1995-99	809	99(12.2%)	710(87.8%)
2000-04	831	73(8.7%)	758(91.3%)
2005-09	908	48(5.2%)	865(94.8%)
1980-2009	5,339	1,010(18.2%)	4,334(81.8%)

*Revised and supplemented data from Ref [11]

Table 2: Age distribution of patients with β-thal in 2009 in Greece.* Revised data of Ref [14].

Age Group	Patients	
	Number	%
Pediatric (1-14yrs)	220	6,7
Adolescents-Young Adults (15-29yrs)	790	24,3
Adults (30-52yrs)	2231	68,8
1-52yrs	3241	99,8

transfusions' complications as the frequency of fever (due to white cells), allo- immunization to rare blood groups antigens, and severe blood-borne diseases

Present status of β-thalassemia in Greece. Prevalence and burden

The longitudinal effects of the two national thalassemia programs had contradicted results on the prevalence of β-thal. These results can be accessed from the data of two recent publications: the national registry of hemoglobinopathies conducted by the Greek Society of hematology [14] and the data on prevention of hemoglobinopathies in Greece by the Greek Society of Pediatric Hematology [11]. Based on these data the total number of patients in 2010 was 3,241; 2,485 transfusion dependent with thalassemia major and 756 with thalassemia intermedia) [14]. Of interest are the changes in the pattern of age distribution of the whole population of thalassemia which showed a significant trend towards advanced ages. Of 3,241 patients only 220 (6.7%) belonged to the pediatric age groups (1-14yrs), 790 (24.3%) to adults and young adults and 2,231 (68.8%) in adults of older ages (30-52 yrs) Table 2 [14].

The influence of each of the two programs on the age distribution of thalassemia, could more clearly assessed comparing the age distributions (in 5 yrs intervals) of the number of patients born in the period of the combined programs to that of the number of expected , if only the treatment program was applied (Table 1). In contrast to the continuous tendency of reduction of annual input and tendency to older ages in the first group, in the expected cohort of patients on conventional treatment alone, the age distribution from 1 to 30 years of age is assumed to be homogeneous [11].

FUTURE PERSPECTIVES

In Greece the persistent gradual reduction of thalassemias and the persistent change in the age distribution towards older ages (above 30 yrs), create serious problems in the management of patients. Advanced aged patients have additional problems related to the age and the high incidence of chronic complications (endocrinopathies, myocardiopathies, bone and liver diseases and others). Clinical management of these patients necessitates reorganization of the structure and function of the thalassemia units which were established mainly to treat children, adolescents and young adults. To meet the health problems of the increasing older cohort of patients, in parallel to the considerable reduction of the cohort of young ages and the decreasing incidence and severity of complications, the thalassemia units are gradually modified to combined units to cover children, adolescents and adults; these units are in close collaboration with adult specialties units, for treatment of complications and hospitalization of patients. It is assumed that in the near future the thalassemia units for children and adolescents in Greece will be restricted to 2-4 reference units, thanks to the efficacy of prevention that changed "the most frequent monogenic disease of pediatrics in Greece to a very rare one", a common in adults".

The recent schedule of treatment is advancing rapidly. In the near future it is expected that complete cure with bone marrow transplantation will be available to an increasing proportion of patients, while upgraded of conventional treatment will improve further survival, health status and quality of life for the remaining patients. New oral chelators and precise monitoring of chelation on an individual base is expected to minimize the complications of transfusional hemosiderosis especially myocardiopathies and endocrinopathies [15].

CONCLUSION

The Greek experience on the efficacy of prolonged implementation of national programs for prevention and treatment of β-thalassemia is valuable for developing countries implementing programs on conventional treatment without or with partial implementation of prevention. The same holds true for a number of European countries with minorities of immigrants from countries with high prevalence of β-thalassemia trait. The implementation of conventional treatment alone in Greece, for the first 15 years, leaded to considerable amelioration of clinical manifestation of the disease and a significant improvement in survival and quality of life. However improvement of survival resulted in a continuous annual input of new patients, which in 15 years increased the base line cohort, by more than three times, aggravating accordingly the burden of the disease on health services. The same is expected to happen in countries involving only conventional treatment. The most interesting achievement of the treatment program was the modification of a fatal disease of childhood to a longstanding chronic disease of adults.

On the other hand, the Greek experience for combined administration of both prevention and advanced treatment program, resulted in a further amelioration of clinical findings and complications and improvement of survival and quality of life. In a recent study of survival in1, 044 patients with TM, an overall survival of 65% at the age of 50 years was found. Furthermore birth cohort had a significant effect on survival ($P<0.001$), with a negative trend towards past decades (prior 1970, 1970-79 and 1980-89). A significant negative trend was also detected in relation to severe, moderate and mild degree of hemosiderosis [7]. Survival studies have been recently reported from three countries (England, Italy and Cyprus) implementing advanced programs of conventional treatment with similar results [16-18].

In addition, there was a continuous reduction of the annual input of patients and during the last two decades to a negative balance of the number of annual input of new patients versus number of deaths (14) that leaded in a slow but steady reduction of the cohort of patients and the incidence and burden of disease. In 30 years of implementation of combined programs only 1010 patients were born, versus 5,339 expected. During this period there was a gradual reduction of the annual rate of births of affected neonates from 160 per 100,000 live births, prior to prevention to only 8-10 (a 95% reduction) during the last decade of the program.

A most interesting observation was the extreme changes in the age distribution of patients. In 2009 only 220 (6.7%), were below the age of 15 yrs versus 2,231(68%) above the age of 30 yrs. Thus, in Greece, the most common genetic disease of childhood turned to be a very rare chronic disease in children and common one in patients of older age.

These data clearly show that at present the control of homozygous β-thalassemia, could be achieved only on efficient

combined treatment and prevention programs. Conventional treatment alone will increase the incidence and burden of disease, unless methods for cure, as bone marrow transplantation and gene therapy in the near future could be generally applied.

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