Review Article

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Thalassemia: A Major Health Issue of 21st Century

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Abstract

Thalassemia was clinically described almost 100 year ago & treatment of this genetic disease has seen a great progress during this period.It is a inherited blood disorder,involving lower than normal amount of an oxygen-carrying protein.People who are suffering from thalassemia,they are not able to make enough hemoglobin and because of this,they have to suffer from anemia. Now days, thalassemia is a major health issue & according to data, 7% of world's population is a carrier of hemoglobin disorder & because of that 3 to 5 lacs children born each year with this disease. Origination of these disease are Mediterranean area,Middle east,Central Asia,South Asia & as well as Indian subcontinent.Apart from and thalassemia,beta thalassemia major is the most serve form & patient may needed regular blood transfusion. This kind of patient develop iron overload & they require chelation therapy to remove excess iron. A Patient with this disorder, for them it is necessary to go for genetic counseling.Symptoms like anemia,weakness,shortness of breath shows that patient is suffering from thalassemia. But with the proper treatment it can be cure.

What is Thalassemia? How it occurs & how it can be cured?

Thalassemia is a genetic blood disorder, which is inherited & human body makes an abnormal form of hemoglobin instead of normal form and here,hemoglobin is an oxygen carrying protein which is necessary to survive.RBc's in many of numbers get destroyed & this situation leads to anemia.Here,a person who is suffering from this disease, have a few number of RBC& their hemoglobin level is low than normal.Thalassemia minor,Thalassemia major,Thalassemia intermediate this are the types of it.

Here,a hemoglobin molecule has 2 sub-units & generally it is referred as 'alpha' & 'beta'.Both sub-units are necessary to bind oxygen.Normal hemoglobin is composed of 2 alpha & 2 beta globins.

Alpha Thalassemia caused by mutations in HBA2 gene.In Alpha Thalassemia,cells produce abnormal forms of hemoglobin called 'Hemoglobin Bart' or 'Hemoglobin H'.

Beta Thalassemia caused by a change in the gene for the beta globins component of hemoglobin.

In this case,DNA analysis is the must. The signs of thalassemia intermediate appear in early childhood of later in life.People with thalassemia trait in one gene are known as carriers or are said to have thalassemia minor.

Now,thalassemia is an inherited blood disorder in which the body produces abnormal form of hemoglobin.If excessive destruction of RBC occurs, it may further leads to anemia.It is most common single gene disorder.If one of your parents, either mother or father have thalassemia,than you may become a carrier of thalassemia automatically.

Patient with this disease make less hemoglobin.If both parents carry a hemoglobin trait,the risk is 25% for each pregnancy for an affected child.Intermediate form of thalassemia causes moderate anemia& major form of thalassemia causes severe anemia.Symptoms like paleness,jaundice,frequent infections,shortness of breath,fussiness,enlargement of organs,iron overload,weak bone has been seen while patient is suffering from thalassemia.If patient is suffering from thalassemia major,they need regular blood transfusions to live normal lives,however a cause remains to be found for this disease patient need blood transfusion if thalassemia is in major stage & it requires transfusion every 2-4 weeks,depending on individual's consumption of infused cells.Also it Is necessary to

remove excess iron by chelation therapy.Bone marrow transplant from a compatible donor may be an effective treatment in severe cases.Also a gene therapy is one of the effective treatment for thalassemia.

Recommendations for dietary supplementation should be made as indicated by nutritional history,complications of disease & of course in children growth status.If the child with thalassemia is transfused & he is on chelation medication,generally it is not recommended to avoid foods like high amount of iron.Hence,in other cases thalassemia patients should not be given iron rich food because it may lead other problems.Pork,Beans,Peas,Spinach,Green leafy vegetables these are the iron rich foods.In this case,thalassemia patient need calcium rich food because due to affliction,bones become weak & calcium rich food gives strengthen to muscles & bones.Foods like Cod-liver oil & Soya milk with vitamin-D helps in absorption.Folic acid rich foods like sweet potatoes& peaches helps to alleviate sign of thalassemia.If Patient is under the thalassemia treat they should avoid junk foods & carbonated drinks.At last, do more 'YOGA' or 'EXERCISE'.

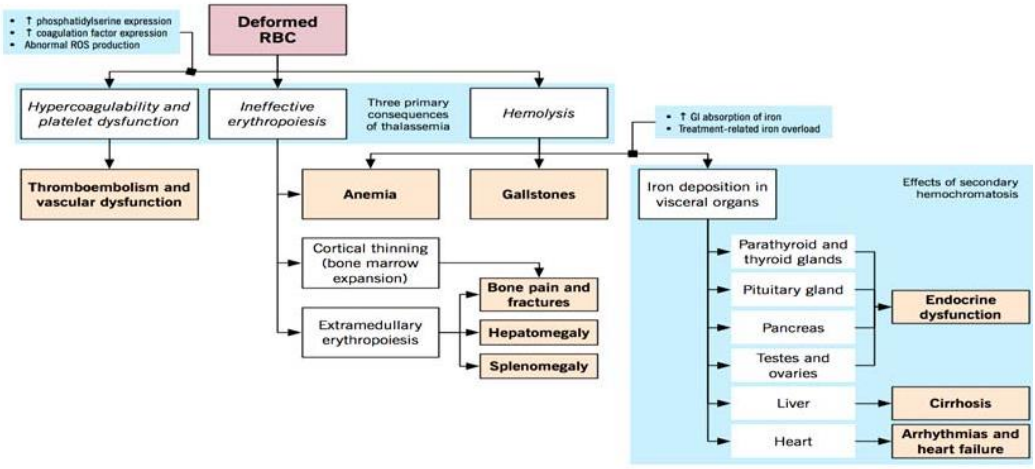

Fig-1 Mechanism of disease and complication

History of Thalassemia

Thalassemia was first described in 1925 in USA by American pediatrician Cooley & Lee,who studied Italian children with severe anemia,poor growth &huge abdominal organs.The name

thalassemia was coined by the NobelPrize winning pathologist George Hoyt Whipple.Whipple & Bradford studied about erythroblast anemia of Cooley & associated pigment anomalies stimulating hemochromatosis.

According to the Mende's law,thalassemia has been verified through the vast familiar case of histories picked up by Silvestroni & Bianco in more than 1100 families of heterozygotes & over 200 of homozygotes for the 'Beta thalassemia'.For more than 60 years, the Cooley's anemia foundation,a 50/(c)(3) nonprofit organization,has been a strong & supportive partner for families living with thalassemia.In 1946, the cause of thalassemia was found to be an abnormal hemoglobin structure.Destroyed RBC causing anemia by reaction with human body.In 1960,doctors started treatment of thalassemia Patient by transfusion of RBC every month.At the end of 1980,more& more application of DNA studies evidenced an enormous variety of molecular thalassemic defects & proposed again the problem of prevention based on new strategies.

Thalassemia in Indian Population

In India Beta thalassemia is frequently shown & Alpha thalassemia is shown rarely.It is most common in communities like Sindhis, Gujaratis, Punjabis, Parsis, Jains &etc. Central& Punjab government's NGO's,Societies,Patients, can work together to intervene at each stage of thalassemia care giving process & reduce the burden of thalassemia in Punjab.Centers for care of thalassemia were started in 1970s in Mumbai & Delhi.For blood transfusion,Indian Red Cross society played an important role in arranging donation of blood.In 1939,there are 3 reports which is appeared in India by Coelho in two Muslim sisters from Mumbai& in Brahmin boy of 5 years.However,the first case of Beta-thalassemia in India was reported by Chatterjee & sickle cell disease by Naik & Colleagues.The IVs-1-5 mutation is the common mutation found in Indian population & it's prevalence varies form 22.8 to 81.4% & it is shown highest in South-eastern India.The exact magnitude of disease in India is still obscure.So if we want to know the exact spectrum of mutations causing this disease,all we have to collect the reported data. Yearly 10,000 children born with thalassemia major in India. InMumbai, a very famous 'Hinduja Hospital' have that facility for the screening of hemoglobin variants by CE-HPLC system which is currently the method by choice.Shobha Tuli of thalassemia india & IS Arora of federation of indian thalassemics have

played an important role in improving care of thalassemia patients in india by arranging workshops & educational programs by bringing experts to examine & treat thalassemia patients.

Thalassemia in Abroad

In Srilanka,population is around 19 million & here birthrate is 18/1000.People carries 'BETA' thalassemia 2.2%.In children, it is <10.5/dl:56% from 6 months to 1 year &<11/dl:29.9% from 1 year to 5 years.Thalassemia prevention is so important now a days,because it relieves burden on families & it costs effectiveness.Patients with thalassemia in USA,they are planning to do international traveling,it should be aware that the health care delivery system in other countries may differ significantly from USA.Thalassemia is relatively rare in Northern Asia,including Japan.Japan has peculiar mutation spectrum & characteristics.Most of in Japan Beta-thalassemia patients are heterozygote & minor thalassemia are as a phenotype.More than a half of patients with Alpha-thalassemia are from Southeast Asia. Thus Japanese thalassemia have dual origin. Around 8000 children born every year with thalassemia major in Pakistan. Thalassemia major came from AFTP & other cities in Pakistan, specially in Karachi. The estimated requirement for treating a birth chart for 1 year is 90,000 units of blood & desferrioxamine; an iron chelator worth 22 million dollars. During last 3 years, PBM has provided financial assistance to 1500 thalassemia patients. In UK, the main causes of death were thalassemia infections, complications in bone marrow transplantation etc.. Due to iron overloaded from 1980 to 1999 there were 12.7 deaths from all causes per 1000 patients years. And in England, all pregnant women & newborn babies are now offered thalassemia test.

Now days, it is necessary to do thalassemia test before marriage, because if both thalassemia carriers marry & propose to have child, than there is a 100% chance of having a thalassemic baby at every conception. By born babies carrying hemoglobin with low level of oxygen. They need than frequently blood transfusion.parenatal diagnosis can be done by chorionic villus sampling. This test is done during 10th & 12th week of pregnancy. The issue of test Aries when both of them are thalassemia carriers & in some cases they may decide to not to have a child. Tests like HIV & other sexual transmitted disease, fertilitytest, gene testing are also important before marriage.So,it is advisable to those who are getting married, they should go for a blood test.

Year	Milestone	Current status
1925	Cooley's clinical description	DNA-based mutational diagnosis
1946	First transfusion clinic for thalassemia	Routine transfusions widely available
1973	Parenteral chelation: desferrioxamine	Parenteral and oral chelation widely available; hepcidin modulation for prevention of iron overload
1975	Liver biopsy as indicator of transfusional hemosiderosis	No longer needed
1976	Second trimester DNA-based prenatal diagnosis for certain genotypes	First trimester DNA-based diagnosis widely available for virtually all genotypes; investigational noninvasive diagnosis at 9 to 10 weeks using maternal blood sample
1982	Allogeneic BMT	Routinely available for suitable patients
1984	MRI for liver iron overload	MRI simultaneous measurement of heart, liver, and pancreatic iron content
1985	Pharmacologic HbF induction	Butyrates in clinical trials, novel agents under development
1989	Preimplantation genetic diagnosis	Available for selected cases
2005	Gene therapy	Clinical trials with improved vectors
2014	Novel therapies: activin ligand traps, JAK-2 inhibitors	In early clinical trials
2016	Additional novel therapies	Under development

Dates are approximate in some cases and refer to the earliest approved human (not animal) use.

Table 1 Thalasemia : From early milestone to the present and Future

The Future of Thalassemia: Will Modern Medicine Win the Battle?

In summary, there are many exciting new developments in the field of thalassemia at the diagnostic but more importantly, at the therapeutic level. The pace at which new diagnostic and therapeutic developments have been developed and clinically applied is rapidly increasing (Table I). Over the last four decades, the life expectancy for thalassemia patients in the industrialized world has increased dramatically. In the United Kingdom, the average life expectancy in 1970 was 17 years, in 1980 it was 27 years and in 1990, it was 37 years, more than doubling of the life expectancy in two decades [42]. Since 2000, over 80% of thalassemia patients in the United Kingdom could be expected to live longer than 40 years and the actual upper lifespan limit cannot be defined due to continued improvements over time [42]. Lifespan and hopefully, quality of life, should continue to improve in the industrialized world. Unfortunately, most of the techniques for diagnosis, proper treatment, and prevention of thalassemia, utilize sophisticated technology and/or are very costly. It is well known that the world's distribution of thalassemia patients is predominantly in developing countries which do not have the resources (financial and technological) to adopt the use of most of these modalities. Tragically, there are many countries in which the most basic routine care of transfusion and chelation are either nonexistent or woefully underutilized due to financial constraints. To those in the industrialized world, it is shocking to read that only about 12% of children born

with thalassemia worldwide are transfused and of these, only about 40% are adequately chelated. Therefore, the survival of thalassemia patients in low income countries at present is similar to that in the Europe and the United States 50 years ago . Annually about 1.33 million pregnancies worldwide are at risk for thalassemia but only a small fraction have access to genetic counseling and prenatal diagnosis. Furthermore, the problem of prevention and treatment of thalassemia is presently a worldwide issue, due to migration of individuals from higher prevalence regions to areas of lower prevalence [88]. Since infection has always been a cause of death of thalassemia patients [42,88], antibiotic therapy has prevented many deaths of children with thalassemia syndromes. More patients are surviving into late childhood and adulthood [88], thus increasing the number of thalassemia patients requiring long term therapy. All of these factors increase the likelihood that thalassemia will constitute a global health problem in the coming decades Modern medicine can partially alleviate the suffering of thalassemia patients and increase the implementation of prevention in regions where the standard of care is already high. However, it cannot vanquish thalassemia on a global basis. Thalassemia is, now more than ever, a disease of imbalance. At the cellular level, there is chain synthesis imbalance, and at the societal level, there is a critical imbalance between resource availability and resource need. Ultimately, social policy makers and public health practitioners must enact measures to maximize prevention of the disease, and provide optimal care for thalassemia patients.

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