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RAMPANT ERYTHROCYTIC GENETIC DISORDERS IN INDIA: WHO CARES?

R.S.Balgir

As we know the population of India is composed of many subgroups, divided by geography, language, religion, castes (patrilineages), and scheduled tribes with endogamous norms of marriage. The net effect of these practices has been the creation of multiple genetic isolates with individual profile of erythrocytic genetic disorders, but to date the clinical consequences of this highly complex differentiation have been largely ignored[1]. In contrast, the topic of consanguinity continues to attract attention among medical and population geneticists, clinicians, biological anthropologists, social scientists and public health administrators in India[2]. The significant progress made in improving childhood nutritional status and combating infectious diseases means that genetic and erythrocytic disorders have assumed ever-increasing importance in India.

The primary prevention of human diseases in the context of medical genetics refers to prevention of disease entity for which the gene or genes in question play a major role. How can that occur? While gene therapy may become appropriate to correct certain deficient gene products leading to human disease, primary prevention of many multifactorial human diseases will entail understanding and interruption of the environmental cofactors among individuals who inherit genetic susceptibility (polymorphisms or disease mutations). The ultimate and powerful realization could be the driving force in medicine, public health and society at large to accept once and for all our genetic make-up and direct our focus and attention to the prevention of human diseases and suffering by targeting our disease prevention strategies to modifiable risk factors (e.g. dietary factors) according to each and everyone's unique biological susceptibilities. Such a realization could also be the engine that drives the much-needed reform in our health care system.

The advent of molecular testing has been a great boon for the people, as

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this has enabled antenatal diagnosis of many burdensome disorders, which were earlier not identifiable in the fetus. Molecular diagnosis is now possible for a large number of genetic disorders. Although the health infrastructures and treatment facilities are inadequate in India, it is further marred by the lack of any Medical Genetics faculty and facilities.

HEMOGLOBIN

Human blood contains a remarkable variety of cells, each precisely tailored to its own vital function. Blood is made up of erythrocytes or red blood corpuscles (RBC) in a slightly yellowish-coloured liquid called plasma. These RBCs are constantly produced in the bone marrow of the human body. RBCs contain hemoglobin, the messenger carrying oxygen essential for life from the lungs to all parts of the body. Hemoglobin contains iron. RBCs are constantly broken down due to wear and tear and the remaining iron left over in the process is reutilized by the bone marrow to reproduce fresh RBCs. Sometimes this unutilized iron in circulation leads to hyperbilirubinemia and damage to the liver, kidney and other vital body organs. Therefore, the elimination of this excess iron overload by chelation therapy after 10-15 blood transfusions is highly essential.

COMMON GENETIC DISORDERS

Among the various common genetic diseases such as cancer, cardio-vascular diseases, diabetes, hemophilia, colour blindness, chromosomal aberrations, congenital malformations, inborn errors of metabolism, psychiatric anomalies, etc. among others prevalent in India[3], the sickle cell anemia, β-thalassemia syndrome and glucose-6-phosphate dehydrogenase (G-6-PD) enzyme deficiency are the most dreadful ones. These ailments in the children are accounted for defective genes inherited from the parents. The patient has to undergo various trials and tribulations including frequent blood transfusions and painful injections from time to time for the normal survival of the affected offspring.

STRATEGY OF MANAGEMENT OF GENETIC DISEASES

With the ever-increasing disorders of blood like sickle cell disease, β-thalassemia and G-6-PD deficiency in the populations of India, the detection, treatment and management of these cases of genetic disorders have become a cause of worry for the medical practitioners, researchers as well as state's health policy makers, administration and the welfare organizations including the NGOs. In India as a tradition and convention, the horoscopes of both to be partners are generally matched before the finalization of a marriage of a couple. But now it has been over emphasized and realized that rather than the horoscope, the blood of the couple should be matched to prevent the severe hereditary disorders in the offspring/family and community[4-6].

For the strategy of management of genetic diseases, the intake of patients into the program will occur by two routes: through planned genetic screening and through individual referrals for medical diagnosis and genetic counseling[4]. Genetic screening has three major objectives:

a) To provide opportunity for medical intervention (treatment)
b) To provide opportunity for counseling about reproductive options; and
C) To collect research data pertinent to public health policy and basic knowledge and natural history of a disease.

If any married couple comes to know through blood testing regarding the carrier status, he/she should advise immediately to the spouse to get tested for these genetic disorders. Carrier parents are generally advised to avoid producing their own children, but can adopt a child of his/her brother/sister, relative or friend. They are given genetic counseling at each pregnancy for prenatal diagnosis, adoption of a child of relative or of any friend[7]. This is because of the fact that repeated blood transfusions, chelation therapy, maintenance of the child under aseptic conditions, frequent travel and loss of working hours, exorbitant cost of medicines, expensive bringing up, etc. are too burdensome for an average or mediocre family.

MEDICAL GENETICS

Every individual carries two sets of genes inherited each from biological parents. If one set of genes were defective one, the person would be a sickle cell/thalassemia carrier or trait. It is surprising that the carrier parents are as normal as any other parent and these carrier can lead a healthy life. Such carriers are known as sickle cell trait/thalassemia minor. However, when a child has "carrier father" and "carrier mother", the chances of inheriting defective genes from both parents are 25 percent in every pregnancy resulting in the disease. Thus, the children of carrier parents have 25 percent chance of having a sickle cell disorder/thalassemia in every pregnancy. In this case, it is known as sickle cell disease/β-thalassemia major. The β-thalassemia is prevalent in Mediterranean countries and is also known as "Mediterranean anemia", whereas, the sickle cell disease is prevalent in African countries and other tropical and subtropical parts of the world.

The G-6-PD enzyme is one of the most important enzymes in the red cells, which protects the red cells from oxidative damage. It is an x-linked inherited enzyme in humans. A person who is deficient (X°) sometimes suddenly gets severe anemia and jaundice after exposure to certain infections or after taking certain drugs or medicines. Generally, the neonates deficient of this enzyme have risk of developing severe jaundice[5]. Some patients also excrete black urine after taking certain drugs/ antimalarials. This enzyme deficiency is a sex-linked (X) hereditary disorder, which is present at birth and cannot be corrected during lifetime of an individual. Gene is located on the X chromosome. Males have only one X chromosome, the other being Y chromosome, however, females have two X chromosomes, therefore, deficiency is expressed in hemizygous (X°Y) condition in males and heterozygous (X°X) or homozygous (X°X°) condition in females depending upon the number of X chromosome carrying defective gene. If a G-6-PDDeficient man marries a woman without defective gene, all his daughters will have only one defective X from father and one normal X from the mother. In This case, all daughters will be carriers and all sons will be normal (for details see Balgir[5]).

SYMPTOMS

In case of β-thalassemia major, which is a genetic blood disease, bone marrow fails to produce normal RBCs resulting in acute dearth of hemoglobin. In the case of sickle cell disease, altogether structurally defective hemoglobin (Hb S) is produced. Sometimes, the combinations of both these genetic abnormalities occur in an individual and it is known as sickle cell-β-thalassemia. The outcome of these hemoglobin abnormalities will be failure to maintain regular oxygen supply, resulting in early death. Defective formation of globin chain in hemoglobin molecule of human red blood cells causes β-thalassemia major, resulting in anemia, jaundice, yellow eyes, joint or abdominal pains, body ache, and weakness throughout life[5]. The imbalanced globin chain synthesis of hemoglobin molecule damages the red cells in blood quickly and results in anemia, dysfunction of vital organs and profound physical and mental deformities.

Children with sickle cell disease/β-thalassemia major are quite normal during birth. The symptoms manifest between three to twelve months of age. They turn pale (anemic) with jaundice and show little inclination for food. They also hardly sleep. Absence of timely medical intervention may prove fatal.

TREATMENT

At present, available treatment for thalassemia is regular blood transfusion. This kind of blood transfusion is known as "hyper transfusion". The sickle cell disease can be managed without repeated blood transfusions even under low concentration of hemoglobin by carefully taking the preventive measures[7]. As the iron produced during the breaking process of the transfused blood will not be reutilized due to malfunctioning of bone marrow, it gets deposited in vital organs like liver and heart causing immense damage to them. Hence, it is very essential that this iron must be removed from the body. Failure to do so will shorten the life span of the patient. The β-thalassemia major is a condition where patients need blood transfusions throughout their lives, as their bone marrow is unable to produce red blood cells. These transfusions result in

An iron overload on various organs and patient does not grow normally. The drug "Desferal" in the form of injection has to be administered everyday to eliminate the excess iron deposited in the body.

CURATIVE THERAPIES

Stem cell and bone marrow transplantations, and gene therapy are other possible alternatives mooted by the experts. Bone marrow transplantation seems to be a far fetched one as it can be carried out only on a limited number of patients for want of suitable donors. Cord Blood is an alternative to bone marrow transplantation. The blood cells develop from the master cell, the stem cell. Knowledge of these cells has opened the doors to promising therapies for dreaded diseases like Cancer, thalassemia, etc. The umbilical cord connects the baby to the placenta supplying blood and nutrients. After birth, it is usually discarded. However, stem cells from the cord blood are used for treating cancers and blood disorders. Cord blood comprises of red and white blood cells that carry iron, oxygen and as a result fight any infection. Stem cells are immature cells that can develop into red cells, white cells or platelets. Bone marrow is used for such transplants because it contains undifferentiated or immature cells.

Collecting and preserving a baby's cord blood properly is highly important. The procedure followed for collecting cord blood is simple. Immediately after a baby is born, the umbilical cord is clamped. The baby is then removed from the area and the placenta is placed in a sterile supporting structure in such a manner that the umbilical cord hangs through the support. The cord is cleansed with betadine and alcohol. Blood is drawn by inserting a needle into the umbilical vein and stored in a standard blood-collecting bag containing nutrients and anticoagulant. The average yield is approximately 75 millilitres.

Stem cells research is a promising field of biological research and medicine based on the potential of the cells, which theoretically can be directed to form any tissue in the human body. These cells represent a rich source of material that could be used for transplantation.

Gene therapy may be effective by implanting healthy genes into patient's bone marrow cells. Trials for such a therapy are still on. In future such a technology may yield promising results. Stem cells are a kind of master cell that have the potential to grow into various tissues. Sometimes, taken from embryos, their power to differentiate into various cell types is unlimited. Embryonic stem cells are unusual in being much less immuno-genic than other cell types. They also appear not to cause potentially deadly transplant responses such as rejection. Although the potential is there to grow new tissues and even organs to treat diseases such as Parkinson's disease, Alzheimer's disease or cancer, no one quite understands how to do it yet. Some people want them only to become pancreatic beta cells that make insulin to cure children with type-1 diabetes. But opponents and some religious and anti-abortion groups say that any use of a human embryo, however, tiny, amounts to murder and is unethical.

PRENATAL DIAGNOSIS

The β-thalassemia major can be prevented during prenatal stage if the biopsy study of fetus, chorionic villi or amniotic fluid is done between 11-12weeks of the pregnancy[5,7]. This tissue sample taken is studied for genetic abnormalities. If the genes of the tissue indicate that the baby is going to suffer from the disease, then the couple is advised to terminate the pregnancy. If the genes tested to be are carrier or normal, then the pregnancy is allowed to continue. However, such facilities are available only in Metro cities in India.

ACKNOWLEDGEMENTS

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Dr. R. S. Balgir - Scientist F (Bio-Chemistry)

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Conference/Workshop/ Meeting Attended

Dr. Neeru Singh

- Attended Indo-US VAP Workshop on 'Development of Vaccines for P. vivax Malaria' held on June 17th - 18th, 2008 at Hyatt Regency, New Delhi.
- Attended Second meeting of Technical working group of NIH on 27th & 28th July 2008 in Washington USA.

Dr. V. G. Rao

- Presented a paper at 13th International Congress on Infectious Diseases held at Kuala Lumpur, Malaysia during 19th - 22nd June, 2008.
- Presented a paper at First International conference of South East Asia Region(The Union) & 63rd National conference on Tuberculosis & Chest Diseases (SEAR, NATCON 2008) held at New Delhi during 8th -10th September, 2008.

Dr. T. Chakma

- Attended as key resource person and delivered lectures at "Workshop on Research Methodology" Organised by Dept. of Physiology, MGM Medical College, Indore., during 1st to 5th July 2008.
- Attended as key resource person and delivered a lecture at "Fluorosis sensitization workshop for Administrator, Health Professionals and Policy Makers of West Bengal" organized by Directorate of Health services and Unicef West Bengal on 30th July, 2008.

Dr. K.B. Saha

- Attended as resource person the Review Meeting of Short Term Training Programme on Research Methodology, organized by Indira Gandhi National Open University, Regional Centre on 8th May 2008 at Jabalpur.
- Attended Ethics Committee Meeting of NSCB Medical College at Jabalpur on 11th August 2008.
- Attended NIRD's Off-campus Training Workshop on Participatory Rural Appraisal for Development of Rural Infrastructure at Chhattisgarh State Institute of Rural Development, Raipur during 15th-20th September 2008.

Dr. C.K. Dolla

- Completed Master Degree in Public Health (MPH) from VIT, Netherland in September 2008.

Dr. Jyothi Bhat

- Presented a paper at 13th International Congress on Infectious Diseases held at Kuala Lumpur, Malaysia during 19th - 22nd June, 2008.

- Presented a paper at First International conference of South East Asia Region (The Union) & 63rd National conference on Tuberculosis & Chest Diseases (SEAR, NATCON 2008) held at New Delhi during 8th -10th September, 2008.

Dr. R.K. Sharma

- Attended a Training cum Workshop on Stochastic Models and their Applications, at Department of Statistics, Banaras Hindu University (BHU), Varanasi, during 22nd September - 4th October 2008.

Foreign Visits

Dr. Neeru Singh

- Washington USA during 27th- 28th July 2008.

Dr. V. G. Rao

- Kuala Lumpur, Malaysia during 19th- 22nd June 2008.

Dr. Jyothi Bhat

- Kuala Lumpur, Malaysia during 19th- 22nd June 2008.

Workshops/Training/Meetings Conducted

- Five day training was jointly organized by RMRCT and M.P. State AIDS Control Society, Bhopal for laboratory technicians of Primary Health Centre's on Testing of HIV during 28th July to 1st August 2008.



- A workshop was organized on "Integrated Fluorosis Mitigation" for medical officers of Mandla and Dindori District on 4th and 10th September 2008. The training was supported by Dept. of Tribal Welfare, Govt. of M.P.



Joining/Transfer/Recruitment

- Mr. R.K. Gupta , Section Officer resumed his duty after deputation on 12th May 2008.
- Dr. R.S. Balgir, Scientist 'F' joined the centre on 19th May 2008.
- Mrs. Tazia Anwar Ali, Laboratory technician joined the centre on 30th June 2008.
- Mr. Devprakash Dube, Chowkidar joined the centre on 29th August 2008.
- Dr. Dasarathi Das, Scientist 'C' transferred to RMRC, Bhubhaneshwar on 23rd May 2008.

Hindi Fortnight Celebrations

During this fortnight (1st-15th September 2008) various competitions were organized at the centre for the employees. The winners of the competitions were presented cash prize and certificate by the Director.



Visits



Dr. S.K. Bhattacharya, Add. DG, ICMR, New Delhi visited the Centre on 17th May 2008 and had Scientific discussion with centre's Scientists.



Shri. G.B. Mukherjee, IAS, Principal Secretary, Min. Of Tribal Affairs, GoI, New Delhi visited the Centre on 14th July 2008.



Dr. Rashmi Arora, Scientist F, ICMR, New Delhi and Dr. D. Gadkari, Former Director, NIV, Pune visited the centre on 21st August 2008.



Dr. Manju Sharma, Former Secretary, DBT, New Delhi visited the Centre on 12th September 2008.

