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*Review:*

# Health Care Challenges of Hereditary Common Hematological Disorders in Odisha, India

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**Abstract::** Medical Genetics over the past few decades have emerged as an important and powerful medical specialty with increasing appreciation of its role and function in the biomedical sciences. This emergence is related to a great extent to the progress in the Human Genome Project, which promises wide-ranging applications in the diagnosis, treatment and prevention of human diseases. Nevertheless, the discussion on the role of genetics as the preventive medicine and public health care also lead to ethical, legal and social concerns about general applicability of genetic testing in the ethnic communities. The interpretation of prevention in the context of genetic diseases leads to the unavoidable discussions of genetic engineering, stem cell transplantation, prenatal diagnosis and selective termination of pregnancy, as well as broader concerns about discrimination in health care coverage, gender bias, employment and insurance in the society. In Indian communities where consanguineous marriage is widely practiced, recessive/x-linked genetic disorders such as sickle cell disease and beta-thalassemia, will continue to gain greater prominence in the overall spectrum of ill health. Developing an understanding of these changes will require a wide-ranging and multidisciplinary investigative approach for which public health genetics is ideally suited to conditions in Odisha.

**Key Words:** Medical Genetics; Sickle Cell Disease; b-Thalassemia; G6PD Deficiency; Public Health Burden; Odisha.

**Introduction:**

The human population of the state of Odisha is comprised of many subgroups, divided by geography, language, religion, castes (patrilineages), and scheduled tribes with endogamous norms of marriage. The net effect of endogamous practices has been the creation of multiple genetic isolates with individual profile of genetic and erythrocytic disorders (1,2), but to date the clinical consequences of this highly complex differentiation have been largely ignored.(3,4) 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 the state of Odisha.(5,6) 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 the state of Odisha.

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.(7) 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.(8, 9)

The advent of molecular testing has been a great boon for the people, as 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. At present, there are three established medical colleges at Cuttack, Burla and Berhampur in the state of Odisha. Medical colleges located at Berhampur and Cuttack cater to the health care needs of coastal Odisha, whereas, at Burla it covers the whole of Western Odisha. The 11$^{th}$ Five Year Plan is being implemented to open a branch of All India Institute of Medical Sciences, Bhubaneswar and three medical colleges at Rourkela, Bhawanipatna and Koraput in Odisha. Although the health infrastructures and treatment facilities are inadequate in Odisha (10), it is further marred by the lack of any Medical Genetics faculty and facilities in the state.

**Common Genetic Disorders:**

Among the various common genetic diseases such as cancer, cardio-vascular diseases, diabetes, hemophilia, color blindness, chromosomal aberrations, congenital malformations, inborn errors of metabolism, psychiatric anomalies, etc. among others prevalent in Odisha (11), the sickle cell anemia (12-14), β thalassemia and glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency are the most dreadful ones.(15) These ailments in the children are accounted for defective genes inherited from the parents.(16-18) 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.(3,12-14)

With the ever-increasing disorders of blood like sickle cell disease, β thalassemia and G6PD deficiency in the populations of

Odisha, the detection, treatment and management (12-14) of these genetic disorders have become a cause of worry for the medical practitioners (16,17), researchers as well as state's health policy makers, administration and the welfare organizations including the NGOs.(19,20)

In Odisha 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.(7,21,22)

**Strategy of Management of Genetic Diseases:**

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 (7, 21).

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.

**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 carrier or trait for sickle cell disease/ beta-thalassemia. It is surprising that the carrier parents are as normal as any other parent without this genetic defect. In this case, as another set of genes is normal, the carrier can still 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/β-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. If any married couple comes to know through testing the blood 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.(21-23) This is because of the fact that repeated blood transfusions, chelation therapy, maintenance 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.(4)

The G6PD 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 ($X^o$) 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.(22,23) Some patients also excrete black urine after taking certain drugs/antimalarials.(15) 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 ($X^oY$) condition in males and heterozygous ($X^oX$) or homozygous ($X^oX^o$) condition in females depending upon the number of X chromosome carrying defective gene. If a G6PD deficient 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 references.(15,22,23)

**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 slightly yellowish-colored 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 after 90-120 days due to wear and tear and the remaining iron left over in the process is reutilized by the bone marrow to reproduce fresh RBCs.(24) 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.(22,23,25)

**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 sickle 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 (3). 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.(23,26) 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.(21-23) 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.(12-14) 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 beta-dine 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 milliliters. 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 immunogenic 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 10-12 weeks of the pregnancy.(21-23) 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.

**Thalassemic Woman May Become Mother!**

Musharat Wahab, the first thalassemic woman in the country to conceive, who has delivered a baby girl after a Caesarian section at the St. George's Hospital, Mumbai on 1st December 2000. Her baby brings hope to thalassemic patients across India as experts say that there is a slim chance of female patients conceiving at all as they fail to develop secondary sexual characteristics. Musharat was married in February and conceived a couple of months later. Throughout her life, she had been taking regular transfusions at the blood bank in this hospital and all care was taken to see that her hemoglobin level was normal. This resulted in her greater maturity and her pregnancy.

**Odisha Scenario:**

Studies have revealed that the tribal populations of Western and Southern parts of Odisha are prone to sickle cell anemia and G6PD deficiency; the coastal region is mostly vulnerable to β-thalassemia and G6PD deficiency. Communities such as Khandayat, Chasa, Kulita, Agharia, Brahmin, Karan, Teli, Gauda, Dhoba, Pano, Ganda, Dom, Gond, Kharia, Paraja, Bhatra, Munda, Santal, etc. are at risk and highly vulnerable to these genetic disorders in Odisha state. Most of these communities practise consanguinity (27), which further increases the homozygosity and severity. This also leads to high morbidity, mortality and fetal wastage in Odisha.(4,26) Initial studies in Odisha state pertaining to sickle cell disease were carried out by anthropologists.(28,29)

Although the High Performance Liquid Chromatography (HPLC) machine used for the detection of sickle cell disease or beta-thalassemia is less time consuming and reliable to some extents over the traditional method of electrophoresis, but it is not confirmatory test over molecular techniques, which determine the exact defect in an individual. Moreover, it is costly to poorer sections of the society who are at high risk, most vulnerable and cannot afford to pay money. These genetic disorders are rampant among the poor section of the people.(19,20)

It is deplorable that cases of sickle cell anemia and β-thalassemia major require repeated blood transfusion to maintain their survival under healthy conditions. The total life span of the RBCs on an average varies from 90 to 120 days. Unfortunately in the state of Odisha, these patients are given blood transfusions before the actual diagnosis is made. The amount of blood transfused is also sometimes influences the laboratory investigation report. Sometimes, the attending doctors refer the suspected cases of above blood disorders for electrophoresis and hematological investigations immediately after the blood transfusion. The transfused blood interferes with the accurate diagnosis of the patient. This leads to misdiagnosis of the cases where the past history is not taken. Sometimes the parents of the affected child are also the blood donors for the child. Since these disorders are hereditary in nature that means both of the parents are carriers for the disease. Hence parents' blood is also partly defective one and should not be given to the patient, in general. In most of the cases, the investigation reports vary from laboratory to laboratory due to this fact, which create confusion to the attending physician. These are technical and very important aspects, which should be taken care of. Therefore, it is advisable that the patient should be sent for hematological laboratory investigations at least one month after the blood transfusion or immediately before blood transfusion.

It is pathetic that the adequate treatment and management facilities are not available for the sickle cell disease, β-thalassemia major and G6PD deficiency cases even in the capital city of Bhubaneswar. Adequate treatment and management facilities need to be extended to at District Headquarters Hospital level for hereditary hemolytic disorders in the state. The accumulated genetic data have enhanced the rapid advancement of clinical genetics in Odisha.(21-23)

Currently in India, the emphasis is on the small family norms and the socio-economic constraints have created a desired in all the eligible couples that every child born should be normal. Thus, it has been emphasized that medical genetics play a pivotal role in the clinical practice, therapy, innovative developments, prevention, and the management of genetic diseases.

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