Birth Control Necessary to Limit Family Size in Tribal Couples with Aberrant Heterosis of G-6-PD Deficiency and Sickle Cell Disorders in India: An Urgency of Creating Awareness and Imparting Genetic Counseling

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Abstract

Objectives: (i) To study the outcome of ignorance and lack of awareness about sickle cell disease and G-6-PD deficiency among Dhelki Kharia tribal families of Orissa, and (ii) to study the reproductive output in relation to clinical genetics and pathophysiological implications.

Methodology: A random genetic study of screening for hemoglobinopathies and G-6-PD deficiency among Dhelki Kharia tribal community in Sundargarh district of Orissa was carried out for intervention during the year 2000-2004. A total of 81 Dhelki Kharia families were screened and six families with double heterozygosity for above genetic anomalies were encountered. About 2-3 ml. intravenous blood samples were collected in EDTA by disposable syringes and needles after taking informed consent from each individual in the presence of a doctor and community leaders and sent to laboratory at Bhubaneswar for hematological investigations. Analysis was carried out following the standard procedures after cross checking for quality control.

Results: There were 12 (about 52%) children out of 23 who were either suffering from sickle cell trait or disease in concurrence with G-6-PD deficiency in hemizygous/heterozygous/homozygous condition in Dhelki Kharia tribal community of Orissa. There were on an average 3.83 number of surviving (range 2-6) children per mother in families of G-6-PD deficiency and sickle cell disorders. The average number of children (3.83) born (range 2-6 children) per mother to carrier/affected mother was much higher than the average for India (2.73).

Conclusions: It is very difficult to maintain the normal health of an affected child with aberrant anomalies due to exorbitant cost of treatment, frequent transfusions and huge involvement of economy. One of the implications of aberrant heterosis is its adverse affects on routine individual physiology and hard activities. It is suggested to limit the family size in carrier couples to avoid aberrant heterosis of hereditary hemolytic disorders in their offsprings.

Introduction

Despite impressive gains in economic investment and output, India faces pressing problems such as significant overpopulation, increased burden of preventable diseases, environmental degradation, extensive poverty, and ethnic and religious strife. As per recent estimate (July 2008), the population of India was 1,147,995,904 with a growth rate of 1.38% having fertility rate of 2.73 children born per woman and infant mortality of 54.63 deaths per 1,000 live births. Population growth has long been a concern of the government of India and has a lengthy history of explicit population policy. In the 1950s, existing hospitals and health care facilities were made available for birth control information, but there was no aggressive effort to encourage the use of contraceptives to limit the family size. The National Population Policy adopted in 1976, reflected the growing consensus among policy makers that family planning would enjoy only limited success unless it was an integrated part of program aimed at improving the general welfare of the population. The policy makers assumed that excessive family size was the part and parcel of poverty and had to be dealt with as an integral to a general development strategy. Many of the goals and assumptions of National Population Control programs did not correspond exactly with local attitudes toward birth control. India's high infant mortality and elevated mortality in early childhood remained significantly stumbling blocks to population control. The local voluntary groups either provided or secured sites suitable as distribution depots for condoms and birth control pills and also made arrangements for the operation of sterilization camps for birth control.

The family planning concept has significantly improved the status of women, involving and empowering them to bring about change in the families and communities. This contribution is important because of the way in which the deeply entrenched inferior status of women in many communities in India negates official efforts to decrease the fertility rate. It requires more time to educate masses through direct contact with a couple for the idea of family planning to gain acceptance. In India, most elite couples, in fact, regard family planning positively. However, the common fertility pattern in India has diverged from the two-child family that policy makers hold as an ideal one. Women still continue to marry young; their average age at marriage is just over eighteen years. When women choose to be sterilized, financial inducements, although helpful, are not the principal

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incentives. On an average, those accepting sterilization already have four living children, out of whom two are the sons. The strong preference for sons was a deeply held cultural ideal based on economic roots. Sons not only assist in farm labor as they are growing up (as do daughters) but they provide labor in times of illness and unemployment and serve as parents’ only security in old age.

Modern science has helped us to understand how blue eyes or baldness—as well as other inherited traits, whether helpful, harmless or harmful—can run in a family, or appear without precedent in a family. Genes, which give us these traits, are tiny packets of information that contain instructions for how our bodies develop and function.

Genetic disorders differ from medical afflictions because of the high risk of recurrence of anomaly in other family members and, subsequent impact on the family life. This impact is also dependent on the educational level, psychosocial mindset, economy, transport and communication facilities, availability of health care and practices, and many other aspects of the community behavior. Heterosis, also called hybrid vigor or boost in performance, is the increase in growth, size, fecundity, function, yield, or other characters in hybrids over those of the parents. In other words, heterosis is increased strength of different characteristics in hybrids, the possibility to obtain a “better” individual by combining the virtues of its parents. Aberrant heterosis is antagonistic to heterosis, i.e. combination of ill effects or abnormal qualities in an individual. Therefore, it is not always true that the heterosis increases the strength of different characteristics in hybrid. Aberrant heterosis may occur with severer ill effects or abnormal qualities, lethal for the survival of an individual.

Hereditary hemolytic disorders like hemoglobinopathies, thalassemia syndrome and glucose-6-phosphate dehydrogenase (G-6-PD) enzyme deficiency are important genetic and public health problems in India. The sickle cell anemia especially affects 60-70 million people all over the world. The victims include the growing children, adolescent girls, pregnant women and a large chunk of ignorant people. Inherited disorders of hemoglobin cause high degree of hemolytic anemia, clinical jaundice, painful crisis, frequent infections, splenomegaly, growth retardation, etc. and are responsible for high infant morbidity and mortality, maternal mortality and fetal wastage in India. However, practically no step has been taken towards imparting information, education and genetic counseling to the vulnerable individuals, families and communities in India.

In India, mothers usually get the blame for poor reproductive outcome, whether it is infertility or a handicap in the child. The problem gets further compounded, if the woman is by chance found to be the carrier of a disease. Although both hemoglobinopathies and G-6-PD deficiency are prevalent in malaria endemic areas but to the best of our knowledge, no study has ever reported combined conditions in a single individual from India. The present study highlights six Dheiliki Kharia tribal families with compound occurrence of sickle cell hemoglobinopathy and G-6-PD deficiency in a randomly conducted study in Sundargarh district of North-Western Orissa. This study is focused on the outcome of ignorance and lack of awareness about the common genetic and public health problems like sickle cell disease and G-6-PD deficiency among the rural under-privileged people (like Dheiliki Kharia tribal communities) of Orissa; study the reproductive outcome in relation to clinical genetics and patho-physiological implications and the need of dissemination of knowledge and information about genetic counseling in India.

### Material and Methods

This study was a part of our large project carried out for randomly screening of major tribal communities (Bhuyan and Kharia) for G-6-PD deficiency and hemoglobin variants in Sundargarh district of North-Western Orissa for intervention during the period from July 2000 to September 2004. Ethical clearance from Ethical Committee of Regional Medical Research Centre (ICMR), Bhubaneswar was obtained prior to conducting the study and informed consent was taken before taking the blood sample from subjects. A total of 81 families with 345 Dheiliki Kharia (181 males and 164 females) tribals belonging to all age groups were screened. Out of the screening, a total of six families of sickle cell hemoglobinopathy with G-6-PD deficiency reported in the present study were encountered.

### Blood Collection

About 2-3 ml. intravenous blood samples were collected using ethylene diamine tetra acetic acid (EDTA) as anticoagulant by disposable syringes and needles from each individual after obtaining the informed/written consent in the presence of a doctor and community leaders. Any other ailment present was treated/referred to local health facilities. Blood samples so collected were transported to laboratory at Bhubaneswar under ice-cold conditions within 24 hours of collection. Laboratory investigations were carried out following the standard procedures after cross checking for quality control from time to time. Hematological parameters were studied by using an automated Blood Cell Counter (Model-MS4, Melet Schloesing Laboratories, Cergy-Pontoise Cedex, France).

### Laboratory Analysis

The sickling test for all the blood samples was performed on red cells by using freshly prepared sodium metabisulphite solution as reducing agent to determine the presence or absence of sickle hemoglobin. The routine hemoglobin electrophoresis was carried out on cellulose acetate membrane (CAM) in Tris-EDTA-Borate buffer at pH 8.6 and quantification of A fraction of hemoglobin by elution method. The value more than 3.5% of A fraction of adult hemoglobin was taken as cut off point for determining β-thalassemia trait. Estimation of fetal hemoglobin was done following the procedures of Betke and coworkers as modifications described by Weatherall. Hemoglobin variant (Made for Bio-Rad Diagnostics Group, Hercules California, USA) analysis was carried out to confirm the doubtful cases. Family studies were carried out to confirm the diagnosis of probands only, wherever it was felt necessary.

The G-6-PD enzyme deficiency was primarily detected by using Dichlorophenol Indophenol (DCIP) dye as described by Bernstein. Females heterozygous for G-6-PD deficiency have two populations of cells, one with normal G-6-PD activity and the other deficient. This is the result of inactivation (Lyon’s hypothesis) of one of the two X chromosomes in individual cells early in the development of the embryo. All progeny (somatic) cells in females will have the characteristics of only the active X chromosome. The total G-6-PD activity of blood in female will depend on the proportion of normal to deficient cells. In most cases, the activity will be between 20 and 80% of the normal. However, a few heterozygotes (about 1%) may have almost only normal or almost only G-6-PD deficient cells. The present study has not at all encountered any such ambiguity; therefore, there were either 60-80% of the cells normal or deficient in all cases. Subsequent confirmation was done by following the Beutler
et al.8 and WHO procedures9 in case any doubt arose for the detection of G-6-PD deficiency.

Results

In the present study, out of six Dhelki Kharia families having G-6-PD deficiency with concurrent occurrence of sickle cell hemoglobinopathy, 4 fathers and one mother were normal, 2 fathers were hemizygous (affected), 4 mothers were heterozygous (carrier) and one mother was homozygous (affected) for G-6-PD deficiency (Table 1). For sickle cell disorders, all fathers were carriers of sickle cell disease and all mothers except one mother (sickle cell carrier) were normal (Table 1). Of the 23 children of carriers of sickle cell disease and all mothers except one mother (sickle cell carrier) were normal (Table 1). Of the 23 children of carriers of sickle cell disease and all mothers except one mother (sickle cell carrier) were normal (Table 1). Of the 23 children of s
other words, only six (about 26%) children were normal and 17 (74%) children were either carriers or affected for G-6-PD enzyme deficiency. On the other hand, out of these 23 children, only 9 (39.1%) were normal, 13 (56.5%) were carriers and one (4.4%) was suffering from sickle cell disease. There were 12 (about 52%) children out of 23 who were either suffering from sickle cell trait or disease in concurrence with G-6-PD deficiency in hemizygous/heterozygous/homozygous condition in Dhelki Kharia tribal community of Orissa. There were on an average 3.83 number of surviving (range 2-6) children per mother in these affected families of G-6-PD deficiency and sickle cell disorders, regardless of the number of abortions, miscarriages, still births and neonatal deaths due to neonatal jaundice/hereditary hemolytic anemia. Thus, the average number of children (3.83) born (range 2-6 children) per mother to carrier/affected mothers are much higher than the average for India (2.73). In the six families represented in the Table 1, there have been 1-3 abortions, miscarriages, still births or neonatal deaths in each of these families in Sundargarh district of Western Orissa in Central-Eastern India.

It is apparent from table 1 that the values of normal cases without G-6-PD deficiency/sickle cell hemoglobinopathy for most of the hematological indices, in general, were lower in Dhelki Kharia scheduled tribe of Orissa than the standards. This may be due to the prevalence of iron deficiency anemia, folate deficiency, vitamin B₁₂ deficiency, parasitic (malaria) infection and infestations, hepatic disease, bone marrow malignancy or wild food-induced toxemia. A high prevalence of iron deficiency anemia, folate deficiency, vitamin B₁₂ deficiency, parasitic (malaria) infection and infestations, hepatic disease, bone marrow malignancy or wild food-induced toxemia. Therefore, the other aspects of hemolytic anemia in these subjects were not studied in details.

It was observed that both the heterozygote and homozygote females with G-6-PD deficiency with co-existence of sickle cell hemoglobinopathy showed reduced values of almost all hematological indices especially the level of hemoglobin (Hb), corpuscular volume (MCV), corpuscular hemoglobin (MCH), corpuscular hemoglobin concentration (MCHC) and red blood cell count (RBC) in comparison to the normals. The red cell indices were found further reduced in male G-6-PD deficients with co-existing sickle cell hemoglobinopathy in homozygous condition (Hb SS), i.e. sickle cell disease (Table-1). However, the red cell indices picture was variable in males with G-6-PD deficiency with co-existing heterozygous (carrier) sickle cell disease in comparison to normals. However, some cases did show normal indices or identical to the normals, whereas, the others showed reduced values under natural (field) environmental conditions (Table-1). The values of hematological indices were slightly better in sickle cell trait (Hb AS) than the sickle cell disease cases.

The values of MCV, MCH and fetal hemoglobin were lower and that of hemoglobin level, RBC counts, HCT, MCHC and WBC counts, higher in male G-6-PD deficients with co-existing sickle cell trait in comparison to normals. The values of hematological indices were much lower in both heterozygous and homozygous female G-6-PD deficients with concurrent sickle cell trait in comparison to counterpart males and normals (Table 1). The interaction effect of G-6-PD deficiency with sickle cell gene (trait) in lowering the red cell indices was more marked in females than in males. However, almost all the hematological indices were significantly lower except WBC counts and fetal hemoglobin level in male G-6-PD deficiency with co-existing homozygous sickle cell disease in comparison to counterpart sickle cell trait and normals.

Distribution of ABO and Rhesus (D) blood groups in individual cases is presented in Table 1 as an additional parameter of hemolytic anemia, although it was not directly related to the present study.

**Discussion**

The prevalence of sickle cell hemoglobinopathy and G-6-PD deficiency in Dhelki Kharia tribe was recorded to be 12.4% and 30.7%, respectively in Sundargarh district of Northern Orissa. This high prevalence of hereditary hemolytic disorders implicates the clinical manifestations and physiological complications related to day to day daily life in infants, children, adolescents, pregnant women and elderly people in the community. These disorders constitute a major genetic and public health problem in the state of Orissa. It is apparent from the present study that apart from the high prevalence of hemato-genetic disorders, the cases of double heterozygosity (heterosis) are encountered in the community which further exaggerate the clinical manifestations and adversely affect the general health of an individual and, consequently, the community as a whole. It is very difficult to maintain the normal health of an affected child with the said abnormalities due to exorbitant cost of treatment, repeated transfusions and the huge involvement of economy. The poor illiterate tribal communities, which are at the verge of extinction, can not afford even the minimum standard of living and the treatment of an affected child is beyond their expectation in India.

The ignorance, illiteracy, and poverty including overall backwardness in all spheres of life have further complicated the survival of tribals in the remote geographical and ecological niches of the country. The practical deprivation of infrastructural health facilities, lack of adequate resources for treatment and lack of any source of entertainment in their isolated habitat in the dense forest cover are the added disadvantages of the tribal communities in India. Reproductive pleasure and sex life is the only entertainment source under such environmental conditions. This is evident from the present study that the tribal people go on producing children (2-6 children) regardless of their resources. If the couple inherits any defective gene(s), those abnormal genes go on multiplying in the community because of a large number of offspring productions. Since the mortality is equally high as that of fertility in tribals, to ensure the adequate number of offspring survival out of them, they produce more children. This is exactly what is reflected by the Dhelki Kharia tribal community of Sundargarh district of Orissa.

**Family Planning and Birth Control**

The Family Planning Program provides men and women with the ability to decide if they want to have children and if so, how many and how far apart they want to space them.

A Primary Health Centre (PHC) provides a broad range of acceptable and effective family planning birth control methods and services. This includes natural family planning methods, infertility services and services for teens. One has to decide which one is the best suited.

Family Planning/Birth control services are located in a local PHC of each Block of the District in any of the states of India.

A PHC provides services to everyone regardless of the race, caste/tribe, age, citizenship status or income status.

All services are confidential. No information can be given to another person without the informed/written consent of the person who receives the services.

All services are affordable and provided at low cost. The
service providers include skilled clinicians, nurses, social workers and the supporting staff.

To overcome this situation, there is an urgency of creating awareness about genetic disorders and imparting of genetic counseling through audio-visual aids/pamphlets, booklets, cassette diskettes (CD), TV films, etc. among the tribal communities of India. There is an urgent need to contain the spread of preventable hereditary hemolytic disorders in the underprivileged tribal communities of India.

**What is Genetic Counseling?**

Genetic counseling is a service to help individuals and families translate scientific knowledge into practical information. A genetic counselor works with a person or family that may be at risk for an inherited disease or abnormal pregnancy outcome, discussing their chances of having children who are affected.

Providers of genetic counseling include:

- Individuals who have followed a specific educational curriculum and who are certified genetic counselors (CGCs)
- Doctors or nurses with special training in the subject
- Those who have, or are concerned that they might have, an inherited disorder or birth defect.
- Women who are pregnant or planning to be pregnant after 35 years of age.
- Couples who already have a child with mental retardation, an inherited disorder or a birth defect.
- Couples whose infant has a genetic disease diagnosed by routine newborn screening.
- Women who have had babies who died in infancy or three or more miscarriages.
- People concerned that their jobs, lifestyles or medical history may pose a risk to the outcome of pregnancy. Common causes of concern include exposure to radiation, medications, illegal drugs, chemicals or infections.
- Couples who would like testing or more information about genetic conditions that occur frequently in their ethnic group.
- Couples who are first cousins or other close blood relatives.
- Pregnant women whose ultrasound examinations or blood testing indicate that their pregnancy may be at increased risk for certain complications or birth defects.

**What does the Genetic Counselor do?**

When one goes to a genetic counselor (he or she):

- Will record the family history (for instance, if parents, grandparents or siblings had heart disease, diabetes, sickle cell disease, G-6-PD deficiency, etc.) and medical background.
- May arrange appointments for blood tests, physical exams, or amniocentesis.
- Will try to put together a picture of how family’s health may affect the children.
- Will help interpret medical information about any risks present and explain the role of genetics in these conditions.

Often genetic counselors can determine the risk of occurrence or recurrence of a condition and the availability of tests for it.

Evaluation of tests results usually is coordinated between the genetic counselor, the person or couple and the doctor. In the occasional case of troubling results, the counselor will provide information to help make decisions (for instance, on the risk of having a child or more children). The counselor or the doctor can refer to resources in community that deal with a specific genetic condition, or to medical specialists, educational specialists or family support groups.

**Referred Services for a Genetic Counselor**

These may be provided by the Private Clinics, Nursing Homes, Government/Private Hospitals in the State.

A family can seek genetic counseling directly or be referred by a physician. Comprehensive genetic services centers are available, usually located within large medical centers or teaching hospitals. Smaller areas may be served by satellite clinics.

Knowing more about genetic makeup also should lead to a more individualized approach to preventive medicine. One may be able to be tested to learn whether one is especially susceptible to certain diseases so that one can take steps to prevent them.

**Indian Scenario**

In India, genetic counseling is a communication process directly related to client or the patient. Prevention of genetic diseases is a recently emerging concept for disease management and is considered equivalent to the technological services. The main objectives of the genetic counseling are:

1. To bring awareness of genetic diseases in the society,
2. To offer information for prevention and control of genetic diseases through screening, carrier detection and prenatal diagnosis, and
3. To proffer information for clinical aspects, prognosis and treatment of the disease.

On many occasions, it has been observed that mainly the ignorance of parents is responsible for the birth of a defective child. The birth of a child with thalassemia major or sickle cell disease brings mental stress on parents, family members, and society and also on the health care system. Treatment strategies such as bone transfusion, iron chelation therapy, stem cell or bone marrow transplantation, etc., although available in India, but add to economical, psychological and social burden and stress. Since about 60-70% of the families in India come from the low-income strata, to give proper treatment to affected children is beyond their means. Bone marrow or stem cell transplantation is so expensive in India that the most of the parents cannot afford it.

Therefore, prevention is the only “mantra” (solution), which can ultimately control the birth of a thalassemia major or sickle cell anemia child. Thus, the genetic counseling comes into the picture that is, a technology that is economical, less stressful and ultimately plays the significantly key role in prevention and further spread of genetic diseases in the family and the communities.

Genetic counseling in India is generally given to the following categories of the clients/people:

*Individuals, families, relatives and to the high risk
communities like Punjabi Khatri, Sindhi, Lohana, Agharia, Khoja, Jain and many scheduled castes and tribes, etc.

- Parents and relatives of thalassemia major or sickle cell disease child.
- Carriers or traits of sickle cell and thalassemia who have/do not have family history of sickle cell disease or thalassemia major.
- Couples at high risk (husband and wife being both carriers)
- Married and unmarried individuals with trait status.
- Voluntary social workers, educational institutes and welfare organizations

Genetic counseling should be given in different languages keeping in mind the educational and economic background, marital practices, social and cultural status, customs and traditions, psychological aspects, social attitude and perception of the individual and family.

Conclusions

In Indian population where consanguineous marriage is widely practiced, recessive/x-linked genetic disorders 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 community genetics is ideally suited to conditions in India.

The polymorphism of hemoglobin variants and G-6-PD deficiency is advantageous to community against lethal effects of malaria especially against Plasmodium falciparum at population level, but their combination is harmful at individual level because of low levels of red cell indices to cope with the routine human physiology.

It is a rare occasion when an individual is afflicted together with two independently inherited hemolytic defects, resulting in severe clinical and hematological manifestations.

Implications of the study are that prior adequate knowledge and awareness of hemoglobinopathies/G-6-PD status of a patient can prevent hemolysis associated morbidity and mortality especially in pregnancy and neonates in a state like Orissa, which has a dubious distinction for the highest infant mortality rate (73 per 1000 live births in the year 2007) in the country.

Currently in India, the emphasis is on the small family norms and the socio-economic constraints have created a desire in all the eligible couples that every child born should be normal.

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References

2. Balgir RS, Dash BP and Das RK. Fetal outcome and childhood mortality in offspring of mothers with sickle cell trait and disease. Ind J Pediatr 1997; 64:79-84.