INTRODUCTION
Sickle Cell Disease

Sickle Cell Disease (SCD) is an autosomal recessive disease and is a common genetic disorder worldwide. In this disease patients have hemoglobin S (HbS) which contains valine instead of glutamic acid in the 6th position of the β chain. Most often, the patients suffer from chronic symptoms like anemia, growth retardation, chronic leg ulcer and various organ dysfunctions like chronic renal failure and stroke. In addition to this they have life threatening acute complications called crisis which may be fatal.

SCD was first recognized in South India Veddoids in 1952. SCD is highly prevalent in Central Indian states with a gene frequency ranging from 5-40%. It has been reported from various states like Chattishgarh, Maharastra, Gujurat, Kerala and Andhra Pradesh. In Orissa this disease is most prevalent in the Western part and is more common in certain castes like Agharia, Chasa, Kulita, Teli, Scheduled Castes, Scheduled Tribe and is less common in Bramhin and Karan.

SCD behaves clinically as a multigenic trait with exceptional phenotypic variability (Steinberg 2005). Some patients are absolutely asymptomatic and remain so even up to 6th or 7th decade of life, whereas some have repeated attack of vaso-occulsive crisis from childhood. In some persons the disease remains asymptomatic in early period of life and later on manifests with increasing severity.

The various factors responsible for variable clinical expressions are genetic and environmental factors. Increasing numbers of genetic loci have now been identified that can modulate SCD phenotype from nucleotide motif within the β globin cluster to gene located on different chromosome. The various genetic factors which modulate the phenotypes are:

i. Genotype of the Sickle cell disease

ii. Linked β⁸ haplotype

iii. XmnI polymorphism
iv. Fetal hemoglobin level (Hereditary persistence of fetal hemoglobin/ δβ Thalassemia)

v. X-linked locus that regulates the production of the F-cell production (FCP)

vi. Coinheritance of α-thalassemia

vii. Association of other Hb variants and thalassemias

Environmental factors like malaria and tuberculosis also modulate the disease severity.

The phenotypic expression of SCD depends upon the genotype of Sickle Cell Syndrome. Inherited abnormalities of Hb may be divided into two groups: those characterized by structurally abnormal Hb variants termed as hemoglobinopathies (HbS, HbC, HbD, HbE disease) and those in which one or more of the normal polypeptide chains of Hb are synthesized at a reduced rate, considered as thalassemias. The Thalassemias have a significant role in pathophysiology of sickling disorder by reducing the rate of production in one or more of the globin subunits of Hb. This leads to modification of α/β chain ratio and thus modulates the HbS polymerization.

Phenotypic expression of SCD is influenced by inheritance of other β- globin gene abnormalities along with the sickle cell gene. Sickle Cell β- thalassemia (Sβ-thalassemia) is due to inheritance of thalassemia gene from one parent and sickle gene from the other parent. When there is no production of HbA, the condition is Sickle Cell β⁰ thalassemia (Sβ⁰ thalassemia) where as partial production of HbA results in Sickle Cell β⁺ thalassemia (Sβ⁺ thalassemia). Phenotypic expression of Sβ⁰ thalassemia is similar to severe form of SCD where as the phenotypic expression of Sβ⁺ thalassemia ranges from mild to severe form (Serjeant & Serjeant 2001; Weatherall et al, 2001).

Alpha thalassemia (α- thalassemia) is a condition characterized by the absence of one or more α gene. Deletion of one or a pair of α genes result in mild α-thalassemia where as deletion of both the genes result in severe α-thal. Mild α⁺ thal is a common inherited disorder in South East Asian population. The phenotypic expression of SCD is modified in presence of α-thalassemia. Association of α-thalassemia in SCD leads to increase in the RBC count, reduction of hemolytic rate, mean cell volume (MCV), mean corpuscular Hb concentration (MCHC), reticulocyte count...
and bilirubin level. Clinically there is fewer incidences of leg ulceration and acute chest syndrome. The role of α-thalassemia in modulating the clinical course of SCD is not clear.

Sickle Cell hemoglobinopathies is a common blood genetic disorder in Western Orissa with the sickle gene frequency of 15.1% (Patel et al, 2007). There is extreme inter-individual variation in phenotypic expression of the disease in this part of Orissa. However there is very limited data on the variable phenotypic expression of SCD. There is no detailed study regarding the effect of genotype on phenotypic expression of SCD in Western Orissa. In view of this, the study entitled “Study of Genetic Diversity of Sickle Cell Disease and its Phenotypic Expressions in Association with other Inherited Globin Gene Disorders in Western Orissa, India.” was undertaken at Sickle Cell Clinic and Molecular Biology Laboratory, V.S.S. Medical College Hospital, Burla.

Aim and Objectives:

A. To study the sickle cell mutation in Western Orissa by
   i) ARMS PCR for genotype detection
   ii) β-globin cluster haplotype by RFLP

B. To study the prevalence of Sβ-thalassemia in Western Orissa by ARMS PCR

C. To study the prevalence of α-thalassemia in patients of Sβ-thalassemia and Sickle Cell Disease by Multiplex PCR.

D. To study the phenotypic expressions of Sβ-thalassemia with age, sex matched Sickle Cell Disease.

E. To study the influence of α-thalassemia on phenotypic expressions of Sβ-thalassemia and Sickle Cell Disease.