GENETIC COUNSELLING

IN SICKLE CELL DISEASE

Introduction:

Medical science was unaware of the premature death and crippling of many victims due to an unknown / unidentified disease before 1910, that is before the discovery of the Sickle cell disease. Development of medical science has a long history but a very slow evolution and has been rightly projected / observed in the discovery of this particular sickness.

After development of sophisticated instruments like microscope / x-ray / imaging system / various laboratory technique, medical science got better visibility and understanding about this disease.

By experimentations, observations and inferences which are the basis of a rationalized / scientific study i.e., from simple demonstration of a peculiar sickle shaped red cell to identification of abnormality in amino-acid coding inside D.N.A., with tracing out the origin of the disease has brought revolution in the field no doubt.

But it is most unfortunate that still the disease is posing serious threat / problem to mankind inspite of so many astrounding discoveries in the field of medicine.

Historical Review:

In the year 1910, J.B.Herrick demonstrated the presence of peculiar elongated sickle shaped red blood corpuscle in the blood of a young Negro student from Grenada of West Indies in a case of severe anaemia. Later, a second case of sickle shaped R.B.C. was found in a 25 year old black woman in a case of anaemia at the University of Virginia Hospital (Washburn-1911). **Cook and Mayer 1915** reported the clinical feature of a 3rd case, whose blood was demonstrated for sickling in vitro.

In 1922 the term “Sickle Cell Anaemia” was introduced by Mason. **(Hucks 1923) & Taliaferro (1923)** indicated the inherited nature of the disease and proposed that a single non-sex linked abnormal gene acting as Mendelian dominant, is probably controlling such inheritance. In the next year **Syndenstricker (1924)** described the active and latent phase of disease and attributed the anaemia to be due to the excessive blood destruction resulting from sickling. He also introduced the work ‘Crisis’ in association with **Sickle Cell** Anaemia.

Graham in 1924, observed recurrent paroxysm of acute illness characterized by fever, prostration, pain in extremities, joints and evidences of marked blood destruction.

In 1927 Hahn and Gillespie explained the basis of abnormal behaviour of the sickle cells to be due to abnormality of its haemoglobin in deoxygenated state and emphasized the intricate role diminished oxygen tension and reduced PH etc. In accelerating the sickling person. Hahn in 1928 proposed the term sickle trait where the red cells although susceptible to sickling is unaccompanied by anaemia.

Priapism was recognized as one complication of S.C.A. in 1934 (Diggs and Ching obendorf).

Sherman (1940) reported that sickling develops much more rapidly in blood maintained at body temperature and that the changes in shape occurred very slowly in preparation kept at low temperature. In 1945 Murphy and Shapiro noted increased prothrombin activity in Sickle Cell Anaemia which was further increased crisis.

In 1946 Cooley described haemolytic crises occurring in patients with Sickle Cell Anaemia in association with streptococcal infection. The relationship of sickle cell trait to Sickle Cell Anaemia was convincingly shown through generic study by Neel (1949) as heterozygote and homozygote respectively.

Gree-Burgh et. al. in 1957 had explained two chief manifestation of Sickle Cell Anaemia such as (i) chronic haemolytic anaemia (ii) painful crisis. He had also noted the increased fragility and diminished life span of R.B.C. in Sickle Cell Anaemia. In 1964 Klion F.B. et. al. described regarding cholestasis in Sickle Cell Anaemia. Saxenal et. al (1966) first described high fluid intakes and urinary volumes occur in 'SS' diseases in children and Noll et. al. (1967), marked the same in adults. In the other side enuresis and nocturia are common in children (Noll et. al.) nearly 71% and 67% in adult group as compared to 33% of control adult group (Kwak 1969).

Seeler and Shwiki (1972) reviewed the clinical feature of acute splenic sequestration and found that profound anaemia splenomegaly, high reticulocyte count, leucocytosis and thrombocytopenia are the common manifestation and immediate blood transfusion becomes highly essential.

The patients having 'SS' diseases are very much prone for human parvovirus infection which are responsible for aplastic crises of bone marrow first described by Pattison et. al. (1981) in Lond and Andersen et. al (1982)

Samuels-Reid and Scoot (1985) published through the studies that there is not clear relationship between the onset on painful crises before or during the menstrual cycle. But there is a clear increased risk of painful crises during the pregnancy especially in the third trimester and postpartum period being approximately have time that in the non-pregnant state for the same individual (Bacum et. al. 1978). Schumacher et. al. (1990) stated that muscle injury complicates sickle cell crises. In 1991 Valeriano market and Kerr desribed that myoneurosis and myofibrosis are seen as complication of Sickle Cell Anaemia.

Keeping pace with rapid progress in the field of biochemistry genetic and other advanced tools of investigation much knowledge have been added to this haemolytic disorder by many devoted workers conducting their studies in different part of the world during the last four decades.

Genetics of Sickling Disorder:

The genetic basis for sickling was first suggested by Cook & Meyer (1915). Later in 1923 Taliaferro and Huck led to the conclusion that the sickle cell phenomenon was inherited as a mendelian autosomal dominant character. When one parent is heterozygous for the sickle cell gene and the other parent is normal, the off spring would have one equal chance of having either the sickle cell gene i.e. sickle cell trait ('AS') or a normal 'AA' genotype. If both parents have the sickle cell trait, there is a 1 in 2 change of offspring having the sickle cell trait and 1 in 4 chance offspring being normal ('AA') or having 'SS' disease (Sergent, G.R. 1992).

Sickle Cell Anaemia and Sickle Cell Disease:

The term sickle cell disease is used to refer to any morbid condition that involves the possession of two abnormal allelomorphic genes (i.e. two alternative forms of a gene at corresponding site on homologous chromosomes which determine alternative character 'S' inheritance) related to haemoglibic formulation sickle cell diseases are therefore can be categorized as sickle cell disease ('SS') Sickle cell haemoglobin 'C' diseases ('SC'), Sickle cell & thalassaemia (S-thal), Sickle cell haemolobin 'D' diseases ('SD') etc. Therefore Sickle Cell Anaemia although a form of sickle cell desease is not a synonym.

Geographical Distribution:

Initially sickling disorder was thought to be confined to Negro race, but now it is clearly demonstrated to be global distribution with a highest gene frequency in equatorial Africa (Lehman, 1954 & Allison). In India, the Sickle cell anaemia gene was first recognized over 47 years ago among the tribal population in the Nilgiri Hills in southern India (Lehmann and Cutbrust, 1952).

The impression has remained that the gene is confined to small tribal groups despite of subsequent reports of wider distribution (Foi et. al., 1956; Sukhamaran, 1975). In India Sukla and Solanki in 1958 reported its prevalence in India, (Ray and Ray Choudhury (1967) in Madhya Pradesh and Nanda et. al. (1969) in Orissa i.e. Western Orissa.

Though it was believed that the disorder dominates only in the lower communities like Scheduled Castes and Tribes and the poor groups of population, still then later studies revealed that the population other than the above categories are not spared by this abnormal genes but have a widespread distribution through out the Indian society, irrespective of the tribe, caste, creed, language, geographical and political boundaries of our country. In recent years, it has been detected in India among the non-tribal and non-sanguinous groups widely distributed over Assam, Rajasthan, Uttar Pradesh, Bihar, West Bengal, Madhya Pradesh, Gujurat, Maharastra, Tamilnadu, Andhara Pradesh and Orissa. In Orissa, among all zone the Wester Zone holds the lions share of S-genes victims.

A study was undertaken at V.S.S. Medical College, Burla under the guidance of Prof. B.C.Kar in the Western part of the Orissa State, India from 1977 to 1982 and the data collected from the person suffering from Sickle Cell Anaemia is represented in the Table-1.

Table-I Regional distribution of sicklingtve cases in Orissa

Coastal Districts	**No. tested**	**No.**	**Sickling positive %**
Balasore (Bhadrak)	45	0	
Cuttack (J.S.Pur/ Kendrapada/ Jajpur)	247	2	(0.8)
Puri (Khurda/ Nayagarh)	105	2	(1.0)
Ganjam (Gajapati)	228	6	(2.6)
Hilly Districts	625	10	(1.6)
Mayurbhanj	48	4	(8.4)
Keonjhar	41	5	(12.2)
Phulbani or (Kandhamal / Bauda)	115	14	(12.2)
Sambalpur (Jharsuguda/ Deogarh / Baragarh)	5354	655	(12.3)
Sundergarh (Anugul)	356	48	(13.5)

Bolangir (Sonepur)	905	129	(14.3)
Dhenkanal (Anugul)	675	112	(16.6)
Koraput (Rayagada / Nawarangpur / Malkangiri)	18	3	(16.6)
Kalahandi	244	45	(18.4)
TOTAL	7756	1015	(13.09)
GRAND TOTAL	8381	1025	(12.23)

Distribution of sickle cell gene among different castes and social groupings in Orissa had been worked out and is presented in the Table-II.

Table-II- Distribution of sickle cell gene among different castes and social grouping in Orissa state.

Caste / Group	**No. Tested**	**No.**	**Sickling(%)**	**Positive 95% confidence intervals.**
Priest caste (Brahmin)	1510	20	(1.3)	(0.7, 1.9)
Warrior castes				
Kashatriyas	126	16	(12.7)	(6.9, 18.5)
Khandayat	290	18	(6.2)	(3.4, 9.0)
Agharias	396	(29.3)	(24.8, 33.8)	
Coomercial & Cultivators (Vaishyas)				
Cultivators	1575	304	(19.3)	
Kultia & Chasa	377	56	(14.9)	(17.4, 21.3)
Oilmen-Teli	738	95	(12.9)	(11.3, 18.4)
Milken-Dumel & Gouda	387	31	(8.0)	(10.5, 1533)
Weavers-Bhulia	26	2	(7.7)	(5.3, 10.7)
Carpenters-Badai	66	5	(7.6)	(0.0, 17.9)
Potters-Kumbhar	18	1	(5.6)	(1.2, 14.0)
Blacksmiths-Lubura	74	4	(5.4)	(0.0, 16.1)
Merchants-Bania	19	1	(5.3)	(0.3, 10.6)

Goldsmiths-Sunari	79	4	(5.1)	(0.0, 15.3)
Barbers-Bhandari	86	4	(4.7)	(0.2, 9.9)
Businessman-Sundhi	167	6	(3.6)	(0.2, 9.1)
Fisherman-Dhibar	354	4	(1.6)	(0.8, 6.4)
Clerks-Karan	81	1	(1.2)	(0.0, 3.1)
Florists-Mali	1442	288	(20.0)	(0.0, 3.6)
Scheduled castes (Shudras)	670	49	(7.3)	(17.9, 22.0)
Scheduled tribes			(1.3)	(5.3, 9.3)
Total:	**8381**	**1025**	**(12.2)**	**(11.5, 12.9)**

In the entire study it has been shown that shudras or scheduled castes has a much higher frequency (20%) than that observed among the scheduled tribes (7.3%).

Only the Brahmans of relatively low levels and the Aghrias were notable with the frequency of over 20% the Scheduled caste manifested a higher rate (20%) but the Scheduled tribes (primitive originals) has a frequency of 7%. In Orissa state therefore it seems most unlikely that the tribal population has acted as the reservoir of the gene from where it has permeated the rest of society.

Genetic counseling:

Emmal in 1917 discovered the phenomena of sickle cell anaemia who is called as the father of this disorder.

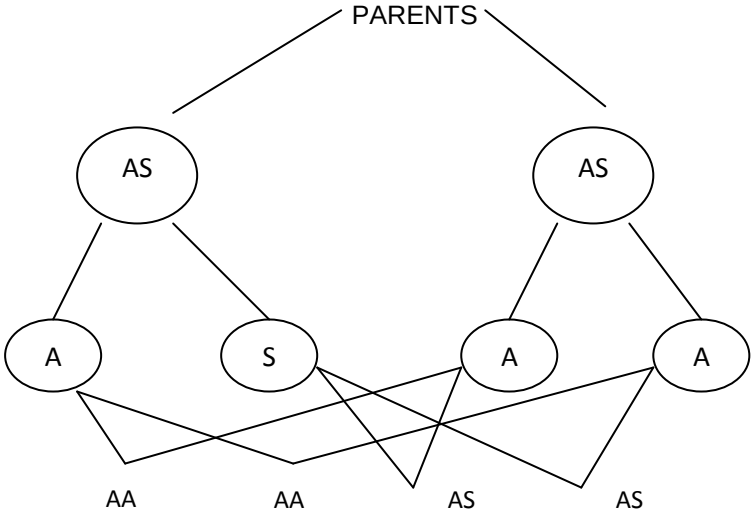
Cook and Mayer in 1915 at first suggested the genetic basis of sickling.

Both Hack and Sydenstriken et al. in 1923 noted the talent sicklers among relatives of parents with the disease and analysis of the pedigree of Hack's patient led to the conclusion that the Sickle phenomena was inherited as a 'mendelian autosomal dominant character'.

Digg et al in 1933 clearly differentiated symptomatic cases which the called **Sickle Cell Anaemia** from the latest a symptomatic cases which they terms the **Sickle Cell Trait**.

The inheritance of Sickle Cell Disease obeys the principle of Mendelia inheritance.

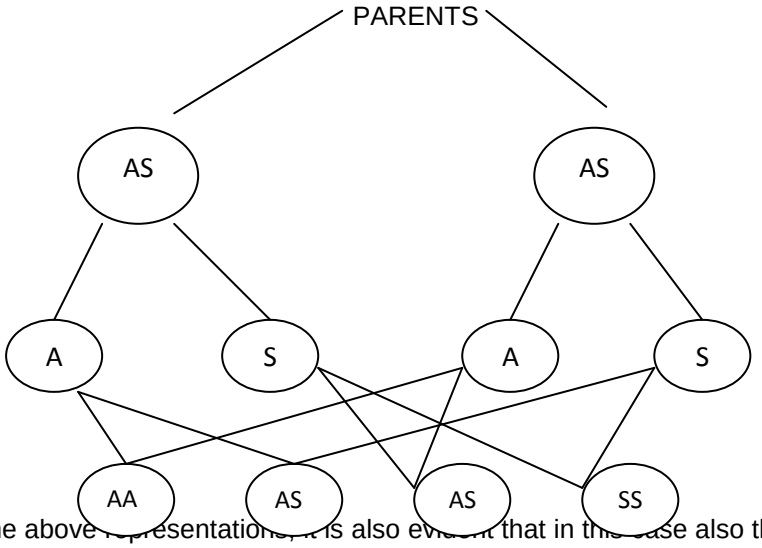
1. When one parent is heterozygous for the sickle cell gene and the other normal the offspings will have the equal chance of having either the sickle sell or a normal genotype. The progeny of which can be represented as follows:



From the above representation it is evident that when one parent is normal and the other is with heterozygous/sickle cell trait in the case there is fifty % chance of normalcy and fifty % of the offsprings will have sickle cell trait.

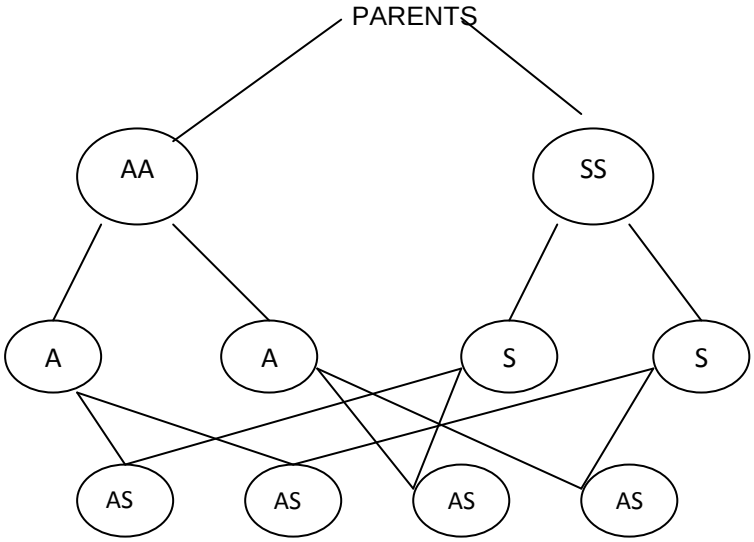
So, in that condition, it is advisable to the parent to go for the pregnancy.

2. If both the parents have the sickle cell trait there is 1 in 2, chance of offspring having the sickle cell trait and 1 in 4, chance of the offspring having normal AA and having SS disease which remains for each pregnancy regardless of the results of previous pregnancies which can be represented as follows :



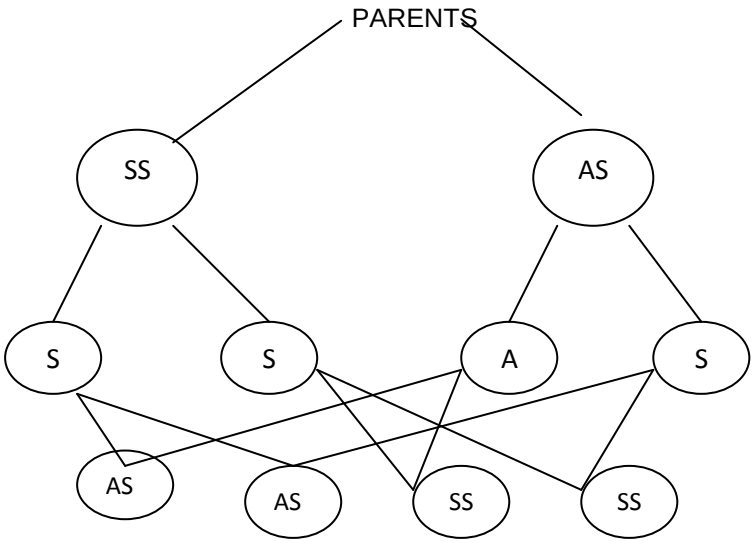
From the above representations, it is also evident that in this case also the pregnancy may be advisable as the parents want to take a chance that may be chance of normal progeny or there is 50% chances of offsprings having the Sickle cell trait.

3. When one parent is homozygous for the Sickle Cell gene and the other parent normal, then all the offsprings will have the Sickle Cell trait, which can be represented as follows:



From the above, it is evident that if one parent is having a homozygous gene and the other is a normal individual it is not advisable to go for pregnancy as there is no chane of normal offsprings and the sickle cell disease prevail for generations to come.

4. If one parent is homozygous for the sickle cell gene and other is having a trait for sickle gene then the progeny can be represented as follows:



From the above representations it is evident that it is not advisable to the parents to continue for pregnancy, as there is 50% offsprings may possess the homozygosity of the sickle cell disease and 50% will have the heterozygocity of the sickle cell trait.

At this present scientific era, the application of recombinant DNA technology has revolutionized prenatal which may now be made to detect examination of DNA from amniotic fluid cells.

From the above observations / discoveries available with us it is envisaged that the present human kind can be protected from this devastating / holocast possed by sickle cell disease.

Hence our aims / objectives should be to allow normal pregnancy to continue and condition to have normal pregnancy only.

Let us see how we can get offspring free for sickle cell disease / trait. Taking the responsibilities of genetic engineering into our hands it can be done.

Measures to be precisely undertaken are as follows:

1. Marriage counselling / Genetic counselling.
2. Advising mother carrying abnormal gene to go for abortion.

Each couple should undergo medical test before marriage and we should not allow (SS) to marry. (AS) group rather should marry with (AA) group; which is most ideal among all. If at all the (AS) group has married (AS) group they should be kept under surveillance to check up amniotic fluid for (AS) foetus and (AA) foetus. Person carrying (AS) abnormal gene or (SS) abnormal gene is to be advised for not holding conceptions.

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