

ANTENATAL SCREENING FOR SICKLE CELL DISEASE

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I. INTRODUCTION

- **1949** : Pauling, Itano and associates: Identification of the abnormality in Sickle Cell Disease (SCD)
- **1978** : Kan and Dozy: first DNA-based diagnosis
- **1998** : No efficient treatment available

II. EPIDEMIOLOGY

Worldwide

- Sickle cell disease is the most frequent hemoglobinopathy world wide. It affects an estimated 50 000 Americans and affects people of different racial and ethnic background.
- According to many authors, compared to blacks in general population, the average life expectancy of homozygous patients is decreased by 25 to 30 years.
- 1/500 African American couples in the US is at risk of giving birth to a child with SCD.

II. EPIDEMIOLOGY

In Cameroon

- The prevalence of heterozygous cases for SCD is as high as 35,5 %
- Children between 1 to 6 years are among those who paid a high tribute to sickle cell disease (4-6 hospital consultations/month)
- Symptoms severity and life expectancy vary considerably with patients surviving beyond middle age, and others dying during infancy and child hood.
- 4 hyphotypes are encountered
 - Bantu haphotype
 - Benin
 - Senegal
 - Kenya
- The 5th type, ARAB-India, does not exist in Cameroon

II. EPIDEMIOLOGY

HbS and Malaria

As shown in the Africa map :

- The distribution of the β^s gene in Africa corresponds closely to that of *Plasmodium falciparum*, the organism causing the most severe form of human malaria.
- J.B.S. Haldane (1949) : Individuals with various red cell disorders might be protected against malaria infection
 - This protection applies almost entirely for infants.
 - Infants with sickle cell trait become infected with *plasmodium falciparum*, but the infections occur less frequently and are milder than those of AA infants.

III. PATHOPHYSIOLOGY

Normal hemoglobin

- The Adult hemoglobin = tetramera composed of either :
$$A \rightarrow \alpha_2 \beta_2$$
$$A \rightarrow \alpha_2 \delta_2$$
- The α gene cluster : 141 Amino Acids - Chromosome 16p (25-kb region)
- The β gene cluster : 146 Amino acids - 16 p (60-kb region)
- Genetic mechanisms which allow equal output of α and non- α genes

III. PATHOPHYSIOLOGY

Hemoglobin structural variants

- Caused by a variety of mutational events affecting a given hemoglobin gene
- Most hemoglobin mutations, regardless of whether they do or do not affect electrophoretic charge have no effect on hemoglobin function and are compatible with normal health
- Variants that cause hemolytic anemia (sickling globin and HbC) do so because they have an unusual rigid structure

III. PATHOPHYSIOLOGY

Pathogenesis of sickle cell disease

- HbS is formed as a result of a single gene defect, causing substitution of the Codon GAG (Glutamic Acid) → GTP (Valine) Under low oxygen pressure, HbS polymerizes and causes red blood cells to take on a "sickle" shape.
- The deformity of red blood cells leads to the fact that they cannot squeeze in single file into the capillaries, there by blocking the blood flow and causing the symptoms of sickle cell disease.

IV. ANTENATAL SCREENING

- **Screening** Presumptive identification of a given disease or defect.
- **Aim** To reduce the incidence of SCD
- **Objective** To reduce risk of death from SCD

Laboratory analysis

2 main lab test are performed:

- Polymerase Chain Reaction + Enzyme detection of the Mutation or
- Polymerase Chain Reaction + Oligonucleide Hybridization

The use of restriction enzyme Mst II for the diagnosis of sickle cell anemia.

DNA is isolated from a β globin gene after specific application. The exact status of the fetus can be predicted according to the presence or absence of the Mst II recognition site at Codon 6 of the β globin gene.

V. PERSPECTIVES FOR SCREENING PROGRAMS IN CAMEROON

- Screening programs for SCD : Not available in Cameroon so far.
- Existing difficulties in applying these programs:
 - Poor financial resources and low economic status of the country
 - Lack of counselors that may be able to present the pertinent information clearly and thoughtfully, so that the prospective parents can make a rationale and guilt free decision
 - We keep in mind the importance of ethical problems these programs can lead to, considering that termination of pregnancies, which is the intended course of action, remain taboo in our society

VI. CONCLUSIONS

Prenatal DNA-based diagnosis is not a screening test in normal circumstances.

Because of the high frequency of sickle cell disease among our population and the high morbidity rate associated to it, (up to 6 hospital visits per homozygous child per month), the importance of an early antenatal diagnosis among parents that are both carriers is clear.

Still, the decisions made as a result of screening are affected by cultural, moral and ethical standards as well as practical considerations.