

Gender Differences in Sickle Cell Crises: Implications for Genetic Counselling and Psychotherapy

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Abstract

Painless and painful crises are common phenomena in sickle cell crises. People with Sickle Cell Disorder (SCD) do experience both chronic and acute pain throughout life. The painful crisis is unpleasant with wide variation in intensity, quality, duration and persistence. It accounts for over 60% of hospital admissions in any given year of persons affected with SCD. Little attempt has been made to survey gender differences in frequency and intensity of pain as well as types of crises often experience by individuals suffering SCD. Thus researches focusing on gender differences in SCD crises are rare despite the fact the two men often report lower pain thresholds, higher pain ratings, and lower tolerance for pain. Men affected by SCD also experience low nitric oxide. Psychologically, women experienced high level of anxiety over pregnancy related crises. Thus, limited understanding and awareness exists among mental health practitioners on the need for genetic counseling and about the psychotherapeutic management of painful crises in persons affected by SCD. Hence, the need for this research that attempt to examine the differences in crises as well as proffer solutions for the genetic and mental health implications of these disorders.

Keywords: Sickle cell disorders; Genetics; Counselling; Psychotherapy

Introduction

Painless and painful crises are common phenomena in sickle cell disorder which is a genetic blood disorder caused by the presence of an abnormal form of hemoglobin. It is an inherited autosomal recessive genetic disorder of hemoglobin (Hb) structure caused by point mutation at the sixth position in beta globin chain, valine substituting glutamic acid [1]. The affected person inherits 2 mutant globin genes one is always the sickle mutation (abnormal haemoglobin structure). This leads to periodic episodes of pain and damages the vital organs. Sickle red cells die after only about 10 to 20 days, instead of the usual 120 days. Because they cannot be replaced fast enough, the blood is chronically short of red cells, thereby, causing anemia.

There are 4 important genotypes among patients of West African origin: SS, sickle cell-hemoglobin C (SC), sickle cell-beta thalassemia ($S\beta^0$ and $S\beta^+$). All of these disorders occur equally in males and females. The most severe form of SCD is homozygous sickle cell anemia (Hb SS). Individuals with sickle cell trait, i.e., heterozygote's for HbS, do not experience any adverse clinical consequences (except under acute hypoxic conditions, e.g., exposure to high altitude without time to accommodate) and have had a selective advantage against malaria. Those with the homozygous disease face a chronic disease, with onset in childhood leading to devastating consequences.

For most people, sickle cell disorder usually results in anemia, but the primary symptomatic manifestation is pain (Figure 1). Many affected persons do experience both chronic and acute pain throughout life. The painful crises are caused by recurrent acute vaso-occlusion in the short run and chronic pain and end-organ damage in the long run; potentially affecting all organ systems with particular harm to bones, kidneys, lungs, eyes, and brain. Essentially, SCD crises usually occur whenever partially or totally deoxygenated Hgb molecules distort their normal disk shape, producing stiff, sticky, sickle-shaped cells

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that obstruct small blood vessels and produce vaso-occlusion as well as the disruption of oxygen to body tissues. (i.e. cyclic polymerization of HbS, generation of dense, dehydrated red cells and the interaction between sickle red cells and abnormal activated vascular endothelial cells). Thus, SCD painful crises are unpleasant with wide variation in intensity, quality, duration and persistence; and accounts for over 60% of hospital admissions in any given year of persons affected with SCD. Complications include acute chest syndrome, avascular necrosis, priapism, ischemic leg ulcers, transient ischemic attacks and stroke, gallstones, renal insufficiency (Figure 2). Dehydration, temperature extremes, infection, changes in altitude, stress, and physical exertion sometimes precipitate crises, but most crises occur without an identifiable cause.

A sickle cell crisis can be life-threatening. The crises clinical features can affect every organ of the body. It can also occur at multiple foci, thus patients with SCD are at risk for other medical complications including, but not limited to, delayed growth and sexual maturation; acute and chronic pulmonary dysfunction; stroke; aseptic necrosis of the hip, shoulders, or both; sickle cell retinopathy; dermal ulcers; and severe chronic pain.

Global and national burden of SCD

SCD usually manifests early in childhood, affects millions throughout the world. It occurs more commonly in people (or their

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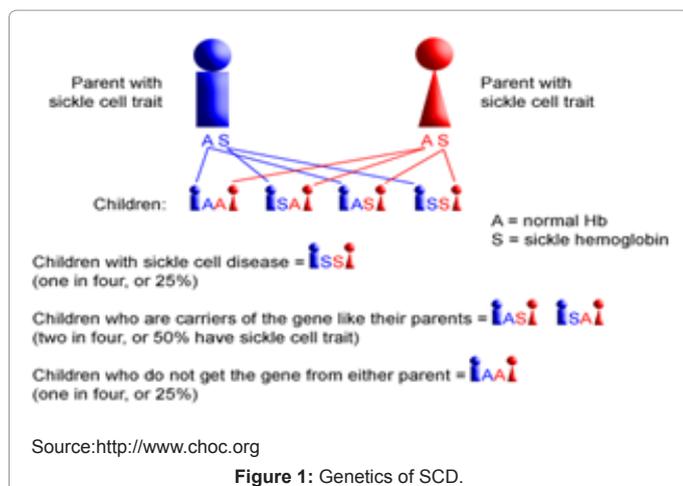


Figure 1: Genetics of SCD.

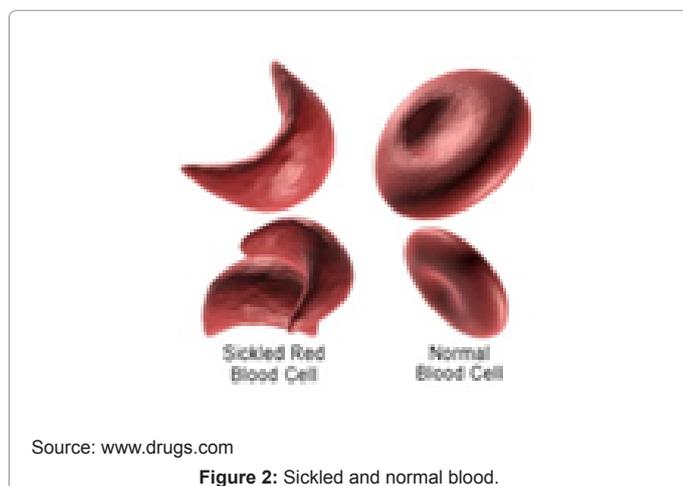


Figure 2: Sickled and normal blood.

descendants) from parts of tropical and sub-tropical regions where malaria is or was common. It occurs primarily in those of African descent, but it also afflicts people of Mediterranean, Middle Eastern, and Asian origins. One-third of all aboriginal inhabitants of Sub-Saharan Africa; Spanish-speaking regions (South America, Cuba, Central America); Saudi Arabia; India; and Mediterranean countries such as Turkey, Greece, and Italy carry the gene². This is because in areas where malaria is common, there is a survival value in carrying only a single sickle-cell gene (sickle cell trait)³ (Table 1).

Those with only one of the two alleles of the sickle-cell disorder are more resistant to malaria, since the infestation of the malaria plasmodium is halted by the sickling of the cells which it infests. In the US, it affects around 72,000 people, most of whose ancestors come from Africa Benjamin and Payne. The disorder occurs in about 1:500 African-American births and 1:1000-1400 Hispanic-American births. About 2 million Americans, or 1:12 African Americans, carry the sickle cell trait. SCD is considered the most common monogenic disease in Brazil.

The burden in Nigeria

Nigeria bears the highest burden of SCD in sub-Saharan Africa.

²Sicklecell.md

³Sicklecell.md FAQ: "Why is Sickle Cell Anaemia only found in Black people?"

The nation has the largest burden of sickle cell disorder (SCD) in the whole world. Carriers of the sickle cell gene (Hb AS) have, over the past centuries, flourished and multiplied in tropical sub-Saharan Africa because their carrier status protected them from succumbing to the deadly falciparum malaria prevalent in the Region. The nation has the largest population of carriers/SCT-Hb AS. About 2% of babies born to Nigerian women have Sickle Cell Anaemia. Nigeria has the largest number of people with HbAS or Sickle Cell Anaemia (SCA); about 100,000 babies are born annually with SCA. In other words, they enjoyed a survival advantage over their peers who had not inherited the gene (Hb AA) and those who had inherited it from both parents and therefore had sickle cell anaemia (Hb SS). Economically, most affected families are poor.

Gender and SCD crises

Sickle cell disorder is irreversible, untreatable health problem which affects males and females equally, and is responsible for increased morbidity and mortality in affected persons. Significant gender differences in morbidity and mortality have been reported in adults with sickle cell disease [2]. For instance Garvin [3] noted that morbidity appears to be increased in males; and further suggested that there may be gender-related differences in some of the acute and chronic complications of this disorder. In a cooperative study of Sickle Cell Disease, Platt et al. [4] found a median age of death of 42 years for men and 48 years for women, a greater difference than in black control subjects. For example, hyper-hemolytic crisis is associated with red cell G6PD deficiency, and therefore considerably more likely in boys than girls. Garvin [3] also stated that gender related differences in red blood cell production are noted in adolescence and persist throughout adult life. Baum et al. [5] also observed a striking increase in veno-occlusive crisis after age 15 years, with a greater rate of pain attacks in males than females. Gladwin et al. [6] also found that female patients have slightly greater fetal hemoglobin levels, which may be protective; and concluded that the basis for these differences could lie in the observation that nitric oxide bioavailability and responsiveness are reduced in males but not females with sickle cell disease. Nitric oxide is thought to be important in maintaining vasomotor tone, limiting platelet aggregation, inhibiting ischemia-reperfusion injury, and modulating endothelial adhesion molecule expression. Sickle cell-related vascular phenomena of increased shear stress and compensatory responses to chronic vascular injury normally promote increased endothelial nitric oxide production, but this system is impaired in males. Estrogens facilitate nitric oxide production and limit its consumption. Moreover, Ikuta et al. [7] have linked nitric oxide to transcriptional control of fetal hemoglobin and could therefore contribute to gender differences in fetal hemoglobin

Indigenous	Imported
<ul style="list-style-type: none"> Sub Saharan countries north of Zambesi River Eastern Saudi Arabia Some States in India 	<ul style="list-style-type: none"> Mediterranean Basin e.g. Greece, Sardinia USA & Canada Brazil, Belize Columbia etc Cuba, Jamaica, Haiti, Barbados, Trinidad etc. UK, France, Holland,
Distribution and Names of Indigenous Sickle Gene Haplotypes	
Region	Haplotype
• Western West Africa	• Senegal – 3
• *Cameroon (Ekona)	• Cameroon – 17
• Central West Africa	• Benin – 19
• Central & East Africa	• Bantu – 20
East Saudi Arabia & India	• Arab/India – 31

Note: *Most Cameroonians have the Benin haplotype. The Ekona haplotype is a recent discovery among the small population of the Ekona ethnic group

Table 1: Where SCD is found [45].

expression. Therapies that restore nitric oxide bioactivity or reduce its consumption (or enhance non-nitric oxide induced vasodilatation) could be particularly beneficial in male patients with sickle cell anemia.

The onset of puberty may be delayed by several years in both boys and girls with sickle cell disease. Various nutritional abnormalities have been reported. A study of adolescents and young adults in Nigeria found that, compared to controls, male patients had a significantly lower mean weight, body mass index, mid-arm circumference, and triceps and subscapular skinfold thickness, whereas these differences from controls were not noted in female patients. This was not due to any difference in intake of calories and micronutrients (when corrected for body weight), and suggested a gender-related difference in somatic growth.

In spite of these findings little attempt has been made to survey gender differences in frequency and intensity of pain as well as types of crises often experienced by individuals suffering SCD. Thus researches focusing on gender differences in SCD crises are rare despite the fact that women often report lower pain thresholds, higher pain ratings, and lower tolerance for pain. Men affected by SCD also experience low nitric oxide. Psychologically, women experienced high level of anxiety over pregnancy related crises. Thus, limited understanding and awareness exists among mental health practitioners on the need for genetic counseling and about the psychotherapeutic management of painful crises in persons affected by SCD. Hence, the need for this paper which attempts to examine the differences in crises as well as proffer solutions for the genetic and mental health implications of these disorders.

Purpose of Study

This cross-sectional quantitative survey study was undertaken to assess the gender differences in sickle cell episodic painful crises among affected persons in Nigeria in order to proffer solutions for the genetic and mental health implications of sickle cell disorder.

Research questions

1. What are the demographical variables of the study's respondents?
2. How many of the male respondents have ever had painful erection without desire for sex?
3. How many of the male respondents have experienced either a) stuttering or b) major priapism?
4. How many of the respondents have ever been hospitalized for painful erectile crises?
5. What are the physical changes experienced by the boys since age 12?
6. Is there any increase in SCD crises which may be associated with these developmental tasks?
7. How many of the female respondents menstruate?
8. What are the ages of onset of menarche for those who do?
9. Do the respondents ever experience severe SCD crises during menstruation?
10. If yes, how often do they experience severe SCD crises during menstruation?
11. How many of the respondents have ever been hospitalized for SCD crises during menstruation?
12. What is the attitude of adolescent girls with sickle cell disease towards pregnancy?

13. What are the reasons given for the negative feelings?

Methodology

The study adopted a cross-sectional quantitative survey research design.

Sample and sampling techniques

A total of 40 adolescents (Male=20, Female=20) who have sickle cell disorders {age 15-18; mean age=16.35, SD=1.11} from three randomly selected SCD clubs in three different Local Governments areas {through fish bowl method} out of a larger number of seven purposively selected LGAs which had SCD Clubs in Lagos States, Nigeria participated in the study. Initially, a total of the 50 participants (25 boys and 25 girls) indicated their willingness to participate in the study, but only 40 returned useable instruments. The face-to-face validated *SCD Pubertal and Priapism Questionnaire* was distributed to them during their SCD club meetings in the three different locations in Lagos States, Nigeria. Detailed information regarding socio-demographic profile was inquired.

Instrumentation

The SCD Pubertal and Priapism Questionnaire developed and validated through face to face validation for the purpose of this study was administered to 40 {Male=20, 50% and Female=20, 50%} respondents who were members of three SCD clubs in Lagos State. The instrument consisted of three sections. Section A sought respondents' demographical variables, Section B which is for Boys only sought information on priapism crises and onset of pubertal changes in adolescence, while Section C (-girls only) sought information on SCD crises in relation to Menstruation and general attitudes of respondents towards pregnancy.

Statistical analysis

Percentages were calculated for statistical analysis using SPSS version 17.

Results

A total of 40 {Male 20 (50%) and Female 20 (50%)} respondents who were members of SCD clubs in Lagos State participated in the study. Results of their responses are presented below.

What are the demographical variables of the study's respondents?

Tables 2 to 4 below present the demographic variables of the respondents. Table 2 presents the age and haemoglobin status of the respondents thus: a) male=20,50%; Hb SS=17,85%, Hb SC=3,15% and b) female=20,50%; Hb SS=15,75%, Hb SC=5,25%. The table also showed their educational status.

Results in table 3 indicated that 60% of the male respondents are Christians and 40% Muslims; 45% of the females are Christians and 55% are Muslims. It also showed that 17.5% are Hausa, 32.5% are Igbo and 50% are Yoruba.

Details of respondents' family background are as presented in table 4 below.

Sex	N	Hb Status	Educational Background	Age						
		SS	SC	Primary	Secondary	Tertiary	15	16	17	18
Male	20, 50%	17, 85%	3, 15%	3, 15%	10, 50%	7, 35 %	7, 35 %	4, 20%	6, 30%	3, 15%
Female	20, 50%	15,75%	5, 25%	5, 25%	11, 55%	4, 20%	5, 25%	6, 30%	4, 20%	5, 25%

Table 2: This table presents the Hb status, sex, age, religion and tribe of respondents.

Sex	N	Religion	Tribe			
		Christian	Muslims	Hausa =17.5%	Igbo =32.5%	Yoruba =50%
Male	20, 50%	12, 60%	8, 40%	3, 15%	6, 30%	11, 55%
Female	20, 50%	9, 45%	11, 55%	4,20%	7,35%	9, 45%

Table 3: Respondents' religious and ethnicity background.

Sex	N	Siblings	Parental Background					Parental Occupation				
		Other siblings	single parent (Mother only or Father only)	Living with Both parents	Divorced home	Orphan	Mother alive	Father alive	Artisan	Civil servant	self-employed	unemployed
Male	20	20, 100%	4, 20%	7, 35 %	4, 20%	1, 5%	3, 15%	1, 5%	7, 35 %	4, 20%	6, 30%	3, 15%
Female	20	20, 100%	5, 25%	6, 30%	3, 15%	2,10%	3, 15%	1, 5%	3, 15%	6, 30%	9, 45%	2,10%

Table 4: This table presents the respondents' Family background.

How many of the male respondents have ever had painful erection without desire for sex?

Results presented in Table 5 below indicated that 17(85%) adolescent boys experience priapism.

How many of the male respondents have experienced either a) stuttering or b) major priapism?

Out of the 17(85%) adolescent boys who experience priapism, table 6 below showed that 8(47%) of them have had stuttering and the remaining 9 (53%) have had major priapism.

How many of the respondents have ever been hospitalized for painful erectile crises?

Out of the 17(85%) adolescent boys who experience priapism, table 7 below indicated that 12(71%) of them have been admitted at one point in time in the hospital for the treatment of priapism.

What are the physical changes experienced by the boys since age 12?

Results are shown in below table 8.

Is there any increase in SCD crises which may be associated with these developmental tasks?

Results are shown in below table 9.

How many of the female respondents menstruate?

Results in table 10 below indicated the 80% of the respondents have attained menarche.

What are the ages of onset of menarche for those who do?

Results in table 11 below showed age variations in onset of menarche among the 16 (80%) respondents who indicated that they had started menstruation. The ages of onset of menarche as presented in table are: 14 years=3(18.75%); 15 years=7(43.75%); 16 years=4(25%); and 17 years=2(12.5%).

Do the respondents ever experience severe SCD crises during menstruation?

Results in table 12 below showed that 13 (81%) of the girls who had attained menarche have had severe painful crises during menstruation.

If yes, how often do they experience severe SCD crises during menstruation?

In table 13 below, 62% of the girls experience severe pains on monthly basis, 23% quite often and 15% once in a while.

How many of the respondents have ever been hospitalized for SCD crises during menstruation?

Table 14 showed that a total of 9(69%) of the girls had been hospitalized for SCD crises during menstrual flow in the past.

What is the attitude of adolescent girls with sickle cell disease towards pregnancy?

Table 15 showed that 11(55%) of the girls had negative attitude towards pregnancy.

What are the reasons given for the negative feelings about pregnancy?

Table 16 below presented the respondents fear that pregnancy may increase and worsen their episodic painful vaso-occlusion.

Discussions

Results obtained from this study indicated that 17(85%) adolescent boys had experienced priapism (stuttering=8, 47% and major priapism =9,53%); and that 12(71%) had been admitted at one point in time in the hospital for the treatment of priapism. The findings of this study also showed that 80% of the female respondents had attained menarche; with the following variations their age of onset: 14 years=3(18.75%); 15 years=7(43.75%); 16 years=4(25%); and 17 years=2(12.5%). The findings also showed that 13(81%) of the girls who had attained menarche have had severe painful crises during menstruation and that 62% have experienced severe pains on monthly basis, 23% quite often and 15% once in a while. It also showed that 9(69%) of the girls had been hospitalized for SCD crises during menstrual flow in the past; and that 11(55%) of the girls had negative attitude towards pregnancy.

The findings of this study on the gender differences in adolescents with SCD are similar to the observations of Gladwin et al. study [6]. In a study conducted in Dallas with 21 African-American patients (men=11 and women=10, ages 18 to 55) with sickle cell disease and 18 African Americans without sickle cell disease (controls); Gladwin

Sex	N	Yes	No
Male	20 (age = 15-18)	17(85%)	3 (15%)

Table 5: Showing percentage of male respondents with or without priapism experience.

Sex	N	Stuttering	Major Priapism
Male	17 (age = 15-18)	8 (47%)	9 (53%)

Table 6: Showing types of priapism ever experienced by respondents.

Sex	N	Yes	No
Male	17 (age = 15-18)	12 (71%)	5(29%)

Table 7: Showing number of respondents ever hospitalized for priapism.

Responses	Height (taller)
	Broadness of chest
	Change in voice

Table 8: Respondents' physical changes experienced since age 12.

Bone pains, knee pains, pain in the arms, severe pains on the hip, leg pain, and malaria
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Table 9: Types of crises.

Sex	N	Yes	No
Female	20 (age = 15-18)	16 (80%)	4 (20%)

Table 10: Percentage of menstruating girls.

Sex	N	Age of menarche onset			
		14	15	16	17
Female	16 (age = 15-18)	3(18.75%)	7 (43.75%)	4 (25%)	2(12.5%)

Table 11: Age of menarche onset.

Sex	N	Yes	No
Female	16 (age = 15-18)	13 (81%)	3 (19%)

Table 12: Percentage of girls who had experience severe SCD crises during menstruation.

Sex	N	Frequency of severe SCD crises during menstruation		
		Monthly	Quite often	once in a while
Female	13 (age = 15-18)	8 (62%)	3 (23%)	2 (15%)

Table 13: Frequency of severe SCD crises during menstruation.

Sex	N	Yes	No
Female	13 (age = 15-18)	9 (69%)	4(41%)

Table 14: Number of Respondents ever hospitalized for SCD crises during menstruation.

Sex	N	Positive	Negative
Female	20 (age = 15-18)	9 (45%)	11 (55%)

Table 15: Respondents' attitude towards pregnancy.

et al. [6] measured forearm blood flow before and after administering a series of drugs known to affect vessel dilation and blood flow. They observed that Nitric Oxide (NO) is up to two times more available in women than men with sickle cell anemia. The result showed that the men appear to have problems both in making nitric oxide and with increased destruction of nitric oxide. When the men were given a substance containing NO, their blood flow increased by 86 percent, while women's blood flow increased 171 percent. The NO result may help explain results from previous studies that found that men with sickle cell disease experience more sickle cell crises after puberty than

do women; and that the median age of death was 42 for men compared to 48 for women. Research has also shown that estrogen, which rises in women beginning at puberty, increases the production of NO.

Implications for genetic counselling and psychotherapy

The findings of this study on the differences in painful vaso-occlusion often experienced by individuals with SCD have serious implications for genetic counseling and psychotherapy. The disorder is an important public health problem in Nigeria which demands critical psychotherapeutic attention to the varying degrees of mental health issues often experienced by affected persons. Such issues include depression and anxiety that may result from living with such a chronic stigmatizing disorders; chronic pain; unpredictable painful crises; multiple serious complications; poor health-related quality of life (HRQOL); high mortality; problems of pain management; frequent under-treatment; and potential for substance abuse and addiction; coping styles; alcohol abuse; and central nervous system (CNS) injury; and resulting cognitive dysfunction from strokes primarily during childhood. As such, depression and other psychiatric disorders are common in SCD [8-10]. Rates of depression among SCD patients are similar to those found in other serious chronic medical disorders, ranging from 18% to 44%, [11-13] and are increased over rates in the general population even when one controls for illness-related physical symptoms. In a Nigerian study, subjects with SCD had a prevalence rate of depression greater than those with cancer or malaria (but less than those with HIV/AIDS) [14]. While studies of depression in children with SCD have shown mixed results, children experience high rates of fatigue and other somatic complaints, impaired self-esteem, feelings of hopelessness in the context of frequent hospitalizations, absences from school, and the inability to experience a normal childhood [15].

Sickle cell disease carries a huge psychosocial burden impacting on physical, psychological, social and occupational well-being as well as levels of independence [16-21]. Psychological complications in patients with SCD mainly result from the impact of pain and symptoms on their daily lives and society's attitudes towards them [22]. Both children and adults with sickle cell disease often suffer from depression [23]. The financial costs of medical treatments combined with lost work can be very burdensome. Any chronic illness places stress on the patient and family, but sickle cell patients and caregivers often face great obstacles in finding psychological support for the disease [24].

Responses:	
i.	Going through pregnancy and labour procedure might be like adding pain to pain;
ii.	I am indifferent though the idea of getting pregnant is scary;
iii.	I am not sure I can combine the stress to the SCD crises;
iv.	I am afraid; the pregnancy crises might be worse than what I am currently experiencing during menstruation;
v.	Pregnancy may worsen the frequency of crises and degree of excruciating pain that I experience monthly;
vi.	I am scared, because I know someone who died of pregnancy complications;
vii.	I do not want to imagine the painful crises it may cause, I just want to live one day at a time;
viii.	I do not want to talk about it because, already, I do not know which SCD crises I will survive;
ix.	If God enables me to get pregnant, he will deliver me, but the SCD painful crises may be worse as I am told that pregnant women go through all sorts of crises;
x.	I may refuse to get pregnant so as not to complicate things for myself;
xi.	I assume the crises will be dreadful

Table 16: Respondents' negative feelings about pregnancy.

Anie et al. [17] have shown that society's attitudes and perception not only have a psychological impact on patients with SCD, but that health beliefs can be influenced by their culture, family support and work responsibility. Studies have shown increased anxiety, depression, social withdrawal, aggression, poor relationships and poor school performance [25-26]. A few case reports also indicated high levels of parental anxiety, overprotection, excessive feelings of responsibility and guilt [20]. Some of the potential contributing causes of depression and anxiety in SCD include the chronicity of the illness; unpredictability of crises; chronic pain; overwhelming nature of medical complications, including anemia, fatigue, growth retardation, physical deformities, leg ulcers, renal failure, strokes, and substantially reduced life expectancy; and racial prejudice and stereotyping. SCD may result in social derision, disability, and financial stress [27], as well as stigmatization for pseudo-addiction to opioid analgesics [28]. One study found that adults with SCD had lower self-esteem than those with HIV/AIDS or cancer [14]. Chronically prescribed opioids may contribute a component of substance-induced mood disorder [10].

More so, children with SCD are often underweight, shorter than normal children, and have delayed puberty. With their small stature, adolescents with SCD encounter problems with self-esteem, dissatisfaction with body image, and social isolation, with participation in athletics also limited due to fear of initiating a vaso-occlusive crisis [15]. School performance suffers when hospitalizations lead to missing multiple school days. Accordingly, adolescents often experience hopelessness and social withdrawal [29].

In Nigeria, the consequences of SCD are aggravated by social, economic, and healthcare disparities. Many of the affected families are poor, they can barely afford to feed the babies, majority of them do not fall under the health insurance scheme available for civil servants in Nigeria. They have more limited access to healthcare services [30]. Medical advances, such as prophylactic penicillin for children, have transformed the disease from a pediatric illness with few surviving beyond adolescence into one chronically extending into adulthood. Life expectancy has increased from a mean of 14 years of age in the 1970s to close to 50 years of age at present [4]. By the 1980s, the United States federally funded Cooperative Study of Sickle Cell Disease (CSSCD) [31] found median survival was into the fourth decade for homozygous patients. Patients with doubly heterozygous forms of SCD, such as Hb SC, fared even better, and the presence of a higher percentage of persistent fetal hemoglobin (Hb F) was associated with less severe disease and greater longevity.

This improved survival has created the relatively new phenomenon of adults with chronic SCD. Consequently, much less is known about psychosocial factors in adults with SCD than in many other chronic medical disorders, with most studies to date addressing prevalence of depression (see below). The increase in longevity has also resulted in physicians for adults treating pain resulting from a disease for which they have limited training and experience.

Thus the impacts of its emotional strain from unpredictable bouts of pain, fear of death, and lost time and social isolation at school and work [32] are enormous. These are not just the physical pain which the patients endure, but emotional pain caused by psychological and social factors such as gender, age, education, and socioeconomic status. These thus set the imperatives for psychotherapists and genetic counselors to develop skills such as coping style, coping capacity, and social support that will assist affected persons deal with pain intensity, pain threshold, and pain tolerance, both clinically and in research settings.

In view of the above, a thorough understanding of the key gender

differences of vaso-occlusive crises among mental health practitioners will facilitate effective administration of genetic counseling and psychotherapy for the amelioration of psychosocial burden of these disorders. Thence, the need to provide answers to pertinent questions such as "what are the observable key genders differences in SCD crises? What are genetic counseling and psychotherapy? What types of genetic counseling and psychotherapy are needed for SCD patients and their care givers?".

Key gender differences in SCD crises

A thorough review of literature has indicated the following as some of the key gender difference in vaso-occlusive crises:

Inflammation in the arteries: Sickle cell disorders have been linked to inflammation in the arteries, probably due to the blocking of the blood vessel by the misshapen red blood cells.

The role of NO: The molecule nitric oxide (NO) is substance that helps blood vessels dilate (i.e. 'the WD-40' of the blood vessels) so blood can flow through them easily. NO helps the body to repair injured areas of the blood vessels—such as after blood flow is cut off in a heart attack or sickle cell crisis; prevents the inflammatory white cells of that repair process from sticking to the cells that line the arteries; reduces clotting by keeping the platelets in the blood from sticking together; and protects vessels by knocking out a substance called superoxide that generates highly destructive particles, "free radicals,"

Acute and chronic complications: There may also be gender-related differences in some of the acute and chronic complications of this disease. For example, hyper-hemolytic crisis is associated with red cell G6PD deficiency, and therefore considerably more likely in boys than girls.

Morbidity and mortality: Gender differences in morbidity and mortality have also been reported in adults with sickle cell disease. The Cooperative Study of Sickle Cell Disease reported a median age of death of 42 years for men and 48 years for women, a greater difference than in black control subjects [4]. There is a striking increase in veno-occlusive crisis after age 15 years, with a greater rate of pain attacks in males than females [5]. Female patients have slightly greater fetal hemoglobin levels, which may be protective. The basis for these differences could lie in the observation that nitric oxide bioavailability and responsiveness are reduced in males but not females with sickle cell disease [6]. Nitric oxide is thought to be important in maintaining vasomotor tone, limiting platelet aggregation, inhibiting ischemia-reperfusion injury, and modulating endothelial adhesion molecule expression. Sickle cell-related vascular phenomena of increased shear stress and compensatory responses to chronic vascular injury normally promote increased endothelial nitric oxide production, but this system is impaired in males. Estrogens facilitate nitric oxide production and limit its consumption. Moreover, nitric oxide has been linked to transcriptional control of fetal hemoglobin and could therefore contribute to gender differences in fetal hemoglobin expression [7]. Therapies that restore nitric oxide bioactivity or reduce its consumption (or enhance non-nitric oxide induced vasodilatation) could be particularly beneficial in male patients with sickle cell anemia.

The teenage years/puberty: The long-term effects of sickle cell disease often begin to emerge during the teenage years or pubescence. This is the period of physical developmental changes in a child's body thus making him/her become a young adult who is capable of reproduction (having babies). For persons with SCD, this may be a time of increased episodes of sickle cell crisis as hormonal changes of

pubertal development may contribute to increasing episodes of crisis and pain.

Onset of pubescence: This may be delayed by several years in both boys and girls with sickle cell disease. Various nutritional abnormalities have been reported. A study of adolescents and young adults in Nigeria found that, compared to controls, male patients had a significantly lower mean weight, body mass index, mid-arm circumference, and triceps and subscapular skinfold thickness, whereas these differences from controls were not noted in female patients. This was not due to any difference in intake of calories and micronutrients (when corrected for body weight), and suggested a gender-related difference in somatic growth.

Menstruation and PMS: These could be traumatizing for girls with HbSS, SC and SBeta⁺. Some girls have reported an increase in episodes of painful crisis during their menstrual periods because they are losing blood on top of their low hemoglobin count. Research has indicated that menstrual cycles can contribute to painful crises in some women with sickle cell disease. In the 2010 FWGBD annual meeting, O'Brien et al. noted that one of the most important concerns cited by women and girls with SCD and SCT was the pain they experienced during menstruation [33].

Gender specific episodic painful crisis (VOC): These refer to vaso-occlusive crises commonly seen in men or women. The two common VOC for male are priapism and low Nitric Oxide, while those that affect females are reproductive stage related crises such as acute menstrual pain and pregnancy related crises (Figure 3).

Priapism is an unwanted, prolonged erection of the penis in males with Hb SS, SC, S-βthal etc. It can last for hours and often causes pain. It often occurs during sleep. Priapism does not occur because of sexual feelings or desires. Rather it occurs when red blood cells sickle and change the chemistry of the blood, causing a blockage of normal blood flow draining from the penis. There are two major types of priapism a) Come and Go form which is also known as stuttering priapism and b) Stay for Long type which is also known as Acute or Major priapism. Major priapism erection often lasts over four hours and if untreated, it may cause permanent damage to the penis. Major priapism is often preceded by a long history of minor or stuttering episodes. In a prevalence study conducted by Adeyolu et al. [34] on a sample of 130 males with SCD in UK and Nigeria with Mean age 25y SD 11; range 4y-66y; 78% SS; 15% SC; 1.5% S-thal; 46 (35%) reported history of priapism; 72% stuttering and 52% major priapism; Mean age of onset was 15y; 75% first episode before age 20y; and of 46 (35%) with priapism 10 (21%) reported erectile dysfunction. Another 21% reported unsatisfactory sexual performance or fear of engaging in it. Thus, it is essential for mental health practitioners to gain a thorough understanding of the major causes of priapism, which include but not limited to drugs such as intra cavernosal, phenothiazines, benzodiazepines, prazosin, labetalol, hydralazine; sudden withdrawal of heparin, warfarin, cocaine, marijuana; spinal cord injuries; spinal stenosis; autonomic neuropathy; leukaemia, polycythaemia; multiple myeloma; cancer – prostate, urethral; and idiopathic i.e. unknown 30-50%.



Source: Nan, available <http://livingwithra-nan.blogspot.com/2011/07/10987-how-valid-are-pain-scales.html>

Figure 3: SCD Pain Scale.

Next on the gender specific VOC are pregnancy related complications. SCD Crises often becomes more severe—and pain episodes more frequent—during pregnancy, particularly in the third trimester. Women with SCD are known to have high-risk pregnancies mainly because of fetal risks. Pregnancy creates intense demands on a woman's body, and the normal physiologic changes of pregnancy—and common complications like anemia—can easily make the sickling of red blood cells worse. If blood vessels become blocked by sickled cells, body tissues may be deprived of oxygen and die. Even minor areas of damage in the placenta may reduce the amount of oxygen and nutrients available for the baby's growth in the womb.

Other pregnancy related complications which may arise for the mothers include:

Infections and thromboembolic events: SCD complicates 0.1% of pregnancies but accounts for 1% of all maternal deaths [35]. Not only women with SCD but also women with SCT are at risk of having a child with SCD if their partner also carries sickle cell or thalassemia trait. Infections by bacterial organisms, including urinary tract infection (UTI), pneumonia, and uterine infection, which can all lead to pain episodes. Women with SCT are known to be at higher risk of urinary tract infections during pregnancy and perhaps other infections; they have double the risk of blood clots, further increasing the risk of thromboembolic events associated with pregnancy itself.

Cesarean Deliveries: Women with SCD also have higher rates of cesarean deliveries.

Gallbladder problems, including gallstones: Acute chest syndrome such as heart enlargement and heart failure from anemia; Bone pain crisis - worse from the 2nd half of pregnancy to puerperium; Malaria; Increased number of blood transfusions; Transmission of clots to the lungs leading to sudden death (Pulmonary Embolus).

Acute Sequestration Crisis: Sudden massive blood cell destruction leading to acute anaemia; and Pseudotoxaemia (PET). The occurrence of PET during a crisis refers to raised blood pressure with feet and face swelling, which may lead to convulsions Pregnancy-related complications for the baby include preeclampsia, eclampsia, preterm labor/birth, placental abruption, fetal growth restriction, miscarriage (0-30%), a low-birth-weight baby i.e. <2.5 kg; Stillbirth or Intra-Uterine Growth Restriction (malnutrition) affecting baby.

VOC and treatment modalities: In line with Loeser's conceptualization of the phenomenon of pain [36], VOC can be categorized into four nested components: nociception, pain, suffering, and pain behaviors. This categorization justifies Bonica's biopsychosocial model of chronic pain which stipulates multidisciplinary evaluation and care for the complex, multidimensional nature of chronic episodic vaso-occlusive crises among SCD patients. This is to be provided by specialists such as psychologists, genetic counsellors, paediatricians, physicians, haematologists, obstetricians, orthopaedic surgeons, urologists and nurses (Figure 4). The training, dedication and experience of above members of the team can make a significant difference to quality of lives and survival.

The biopsychosocial model views VOC as chronic syndromes which extend over time due to the dynamic and reciprocal interplay of biological, psychological, and social factors that shapes the experience and responses of patients. Biological factors may initiate, maintain, and modulate physical perturbations; while psychological variables

influence appraisals and perception of internal physiological signs; and social factors shape patients' behavioral responses to the perceptions of their physical perturbations.

What are genetic counseling and psychotherapy?

With respect to SCD, genetic counseling is the delivery of professional advice concerning the magnitude of the implication of and the alternatives for dealing with risk of occurrence of the disorder within the family. Genetic counseling is one of the fundamental means of reducing the impact of or eliminating sickle cell disorder in Nigeria and Africa at large. It could help identify individuals who are suspected of a heritable disease such as sickle cell disorder, at risk because of their family history and concerned about the possibility of having an affected child based upon personal or family history or ethnicity. In developing Nations like Nigeria, genetic services are rare and are rarely consulted except when there are manifest problems.

The genetic counsellor is a trained specialist in medical genetics and counseling who works with medical personnel to give information, answer questions, and offer support to persons and families who have genetic disorders, are undergoing gene testing, or may be at risk for inheriting genetic disorders. The genetic counsellor conducts one-on-one counseling in helping people understand the disease, its implications for their lives and the lives of family members, and their testing and treatment options. Genetic counselling enables parents and affected individuals to make informed decisions in their own interest about future family planning; a woman with SCD or SCT to make an informed decision about a current or future pregnancy; and lead the individual concerned to self-determination. In spite of these, there is a dearth of qualified genetic professionals in Nigeria. The view available ones are seldom consulted except in cases of severe or chronic deliberating problems. It is therefore, imperative for genetic counseling to be encouraged in Nigeria for genotype testing before marriage; prenatal diagnosis and informed decision on whether to keep or terminate affected pregnancy when one or both parents are positive; before the adolescent becomes sexually active and should be reinforced periodically.

Psychotherapy refers to therapeutic interaction or treatment contracted between a trained professional and a client, patient, family, couple, or group [37]. The problems addressed are psychological in nature and can vary in terms of their causes, influences, triggers, and potential resolutions. The psycho-social and emotional burden of SCD and its gender specific VOC require psychotherapeutic management in order to increase the individual's sense of his/her own well-being. Psychosocial management of SCD painful crises consists of the application of a series of techniques based on experiential relationship building, dialogue, communication and behavior change which may be designed to improve the mental health of a affected persons and or their care-giver, or to improve group relationships (such as in a family).



Source: available <http://sites.tufts.edu/prep/page/2/>

Figure 4: Loeser's (1982) conceptualization of pain.

What types of genetic counseling and psychotherapy are needed for SCD patients and their care givers?

On the psychotherapeutic plane, the societal burden of SCD is genetically mediated and sometimes complicated by economic and environmental factors. Genetic effects refer to the influence genes have on the development of individual differences in behavior relative to the influences of learning, experience, and environmental conditions. In SCD, the impact of genetic and environmental effects can be estimated for psychological disorders such as major depression or for individual symptoms like sadness or insomnia. Furthermore, genetic predispositions are likely to impose limits on the degree to which change is possible and the goals of treatment are to help individuals adapt to their psychopathology and express it in useful (or at least neutral) ways. Just as Weinberg [38] put it: "Genes do not fix behavior. Rather, they establish a range of possible reactions to the range of possible experiences that environments can provide". Thus, a number of psychotherapeutic approaches focusing on psychosocial management of episodic painful vaso-occlusion and emphasizing the manipulation of the environmental conditions, behaviors, or cognitions to effect change in response to pain have been put forward. Some of these models of psychotherapy are based on the underlying notion that psychopathology is the result of a deficit or conflict. In the deficit model of psychopathology, disorder is characterized by deficits that occurred because the early environment failed to provide the necessary ingredients for the child to develop psychologically. Change is believed to arise from the provision of a supportive, empathic, and validating therapeutic environment. In the traditional psychoanalytic approaches or the conflict model of psychopathology, behavioural disorder results from defenses against conflicts. Thus, with respect to psychotherapeutic management of SCD crises, behavior geneticists offer a series of coherent therapeutic approaches using traditional strategies such as confrontation, clarification, interpretation, and working through conflicts and painful crises, especially in transference situation. The following are therefore some of the available genetic counseling services which could be offered persons with SCD and their care givers:

Preconception counseling (PC): Sickle cell pregnancies are almost always considered high risk; therefore, women with SCD should receive PC by a sickle specialist on how SCD affects pregnancy and how pregnancy affects sickle cell disease, and how to improve outcomes for mother and baby. This consultation should include optimization of management and screening for end organ damage. Primary care physicians have a key role in preconception screening, including the provision of contraceptive advice.

Pregnancy and abortion counseling: For SCD patients with high risk pregnancy to-increase contraceptive uptake; reduce repeat terminations; consider alternatives; improve medical follow-up rate; and reduce negative feelings relating to the abortion.

Genetic screening: Women and men with SCD should be encouraged to have the haemoglobinopathy status of their partner determined before they embark on pregnancy. If identified as an 'at risk couple', they should receive counseling and advice about reproductive options.

Antenatal haemoglobinopathy screening: If the woman has not been seen pre-conceptually, she should be offered partner testing. If the partner is a carrier, appropriate counselling should be offered as early as possible in pregnancy—ideally by 10 weeks of gestation—to allow the option of first-trimester diagnosis and termination if that is the woman's choice. Women and men with SCD should be encouraged to

have the haemoglobinopathy status of their partner determined before they embark on pregnancy.

Multiple pregnancies and safe delivery: Women with Sickle Cell Anaemia who have had two successful pregnancies should be encouraged to cease childbearing.

Spousal selection counseling: This will enable individuals to know their genotype status and its heritability implications on their offsprings. It will enable couples-to-be to make informed choices about whom to marry or not to marry.

With regards to psychotherapeutic interventions available for the psychosocial management of feelings of sadness and worry often associated with episodic vaso-occlusive painful crises in persons suffering SCD, the following are some of the available treatment mechanisms.

Psycho-education training: on health, nutrition, use of unapproved drugs, sex, contraception and pregnancy.

Cognitive-behavior therapy (CBT): Pain is a psychological state. VOC pain depends on consciousness, it has perceptual and emotional features, and the affected person's expression of it is a behavior that exerts a psychological impact on other persons. CBT may be useful for pain management in VOC as the model helps patients to understand the relationship between one's physiology (e.g., pain and muscle tension), thoughts, emotions, and behaviors. A main goal in treatment is cognitive restructuring to encourage helpful thought patterns, targeting a behavioral activation of healthy activities such as regular exercise and pacing. Lifestyle changes are also trained to improve sleep patterns and to develop better coping skills for pain and other stressors using various techniques (e.g., relaxation, diaphragmatic breathing, and even biofeedback) in individual or group short or brief therapy.

Addiction counseling: Because of the chronicity of SCD crises, affected persons have tendencies towards drug abuse and addiction.

Hypnosis: This therapy will enable affected persons to change their level of awareness of pain and think about something else other than the pain. It opens the affected persons to suggestions, like feeling happy and having more energy. Hypnosis can give long-lasting relief from depression without changing ones normal activities. For some people, hypnosis may help prevent a sickle cell crisis.

Relaxation therapy: This refers to the relaxation of the body, muscles and mind with of affected persons through good smells, favorite music, warm bath, and lying down on a bed. It can begin at the toes and feet, and then slowly move up to the rest of the body in order to relax body parts.

Distraction techniques: This is a way of focusing your attention on something other than your pain. Playing cards or games, watching TV or taking a walk are all ways to do this. Other ways are visiting with friends, painting, petting animals, and writing down your feelings.

Biofeedback: A biofeedback machine can help you learn when your body is tense and when it is relaxed. This can also slow down breathing, and decrease blood pressure.

What is the reality of implementing genetic counselling and psychotherapy in Nigeria?

The religious specificity and cultural sensitivity of the Nigerian society to marriage, singleness, and childlessness are likely to hinder

a lot of Nigerians from accessing genetic counseling services such as genotype diagnosis before marriage, pre-conception counselling and pre-natal diagnosis.

Social-economic factors: Socio-economic factors (e.g. poverty, work in the family) are closely related to health and negatively impact SCD affected persons in Nigeria. In terms of health care financing, the adverse effects of poverty on the health of SCD affected persons are well established in literature [39]. It is also reflected in their access to modern diagnostic equipment and health services [40]. Individually financed health services leave large groups of the affected population, especially those from the lower economic groups without coverage. There are high rate of poverty (50-60%) among affected families, particularly those in the rural areas [39]. Majority of them cannot afford maintenance of routine medication and drug compliance; neither could they afford genetic counseling and psychotherapeutic services. This therefore necessitates the need for a holistic integration of genetic counseling services and mental health care at PHC level across the nation.

Recommendation

For mental health specialist

Acknowledging the severity of menstrual pain and appropriately managing this pain in women and girls with sickle cell disease/trait is essential to improving the care of sickle cell patients.

Providing preventive care to the pregnant woman with sickle cell disease/trait is essential in warding off severe or life-threatening complications.

Healthcare professionals should be educated about the range of morbidity associated with this disease in menses and in pregnancy.

Also, a more specialized network of treatment centers is needed to reach reproductive-age women with sickle cell disease/trait, especially within the African population globally.

A stronger network of clinics providing comprehensive coordinated care can dramatically reduce complications, hospitalization rates and medical costs.

Education and research can help determine the most effective model for identifying and caring for women with this disease.

For affected persons

Drink enough liquid: Drink at least 3 to 4 liters (about 14 to 16 eight-ounce cups) of healthy liquids every day.

Get vaccinated: Vaccinations can help prevent the infections that may lead to a sickle cell crisis. You should get a flu shot every year. If you do not have hepatitis B (a type of liver infection), get vaccinated against this virus.

Balance rest and exercise: Rest during a sickle cell crisis. Over time, increase your activity to a moderate amount. Exercise regularly, such as every day. Avoid high-impact exercise or activities, such as playing football, which may cause injury. Avoid lifting heavy weights for exercise. Talk to you caregiver about the best exercise plan for you

Avoid a sudden change of air pressure or lack of oxygen: Travel in airplanes with normal cabin pressure when flying. Avoid going to high altitude places, such as the mountains.

Avoid cold places: Keep your body warm in the winter, and at a temperature that feels right for you in the summer. Avoid quickly going from a warm to a cold place. Do not go swimming in cold water.

Quit smoking and substance abuse

Healthy diet: With sickle cell disease, you may need to be sure that you get enough folic acid. This vitamin is found in vegetables and fruit. Eat at least five servings a day of leafy vegetables and fruit. Get to and stay at a healthy weight. Ask your caregiver about the best eating plan for you.

For creation of large scale awareness

In Nigeria, no genetic counseling clinic is known [41]. Large scale awareness of genetic understanding and screening is yet to be implemented in Nigeria [40]. Genetic counseling and the diagnoses are usually made in general practice when it is presented with a severe complication. Even when tragedies such as two or more miscarriages, still births, or children die in infancy, many at times doctors do not order a blood test to take a closer look at genetic make-up of parents or refer them to a genetic counselor. Therefore, the most important challenge is to raise the awareness on its causes and prevention through health education [41]. Hence the need for greater awareness about sickle cell disorders, especially in sub-Saharan African and Nigeria in particular.

For advocacy visits to policy makers and key stakeholders in the society

The economic, social and psychological impact of sickle cell disorders on patients are often neglected in rural communities in Nigeria. Therefore, Nigerian Government need to integrate genetic counseling and mental health into primary health care, provide mental health care in general hospitals and develop community-based mental health services. This is because primary Health Care (PHC) service is the first level of health care that most people encounter and feel comfortable with at the grassroots.

For training and curriculum review

In view of the urgent needs for these services in Nigeria, it is apt for key stakeholders in the education industry and curriculum developers to mainstreaming genetic counseling and psychotherapy training into core clinical psychology training in tertiary institutions across the nation. This will build capacities of trainees in becoming well-informed genetic counselors and psychotherapists. There is also the need for development of therapy manuals and practice guidelines in for effective implementation in biopsychosocial management of SCD which may include brief therapy, individual therapy and group therapy techniques. The key stakeholders are administrators responsible for developing and approving psychotherapy training programs which includes psychotherapists in universities and members of curriculum committees; teachers and supervisors who directly provide psychotherapy training; and the consumers; that is, those who receive psychotherapy training and provide psychotherapy to patients [42].

Public education

Bankowski and Capron [43] suggested that education about human reproduction and genetics should be part of the educational heritage of every person. The principle of respect for persons and the "ethics of care" suggest that individuals and families should participate in decision making [44]. Generally, users of genetic services are more likely to assess information accurately, more likely to reach informed decisions, and more likely to cooperate in treatment if they work together actively

with professionals. In order for individuals and families in Nigeria to be active participants, it is necessary that they receive some basic education about genetics. This can best be achieved for the public through education in schools, education of the media and education of health workers in contact with individuals at the primary health care level. Combining educational goals with community genetic services and prevention measures integrated into primary health care may prove very valuable in disseminating the correct genetic information to the population in general [45].

Conclusion

The societal burden of SCD is genetically mediated and sometimes complicated by economic and environmental factors. Genetic effects refer to the influence genes have on the development of individual differences in behavior relative to the influences of learning, experience, and environmental conditions. In SCD, the impact of genetic and environmental effects can be estimated for psychological disorders such as major depression or for individual symptoms like sadness or insomnia. Thus, observable gender differences in its episodic vaso-occlusion requires multi-disciplinary care, most especially the contributions of behavior geneticists and other mental health practitioners for the psychosocial management of any form of psychopathological condition traceable to behavior deficits and conflicts over repressed childhood traumas and SCD associated pains.

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