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Research Article

Sickle Cell Disease (SCD) A Hidden Genetic Disorder can be treated by Comprehensive Therapy: Research Based Approaches - 8

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ABSTRACT

Sickle cell disease is caused by a mutation of hemoglobin-beta gene on chromosome 11. It is due to abnormal hemoglobin molecules - hemoglobin S which is attached to each other and form long, rod-like structures. These structures cause red blood cells to become stiff and form a sickle shape. The shape of red blood cells leading to blockage and progressive damage of vital organs and tissues and representing acute chest syndrome, stroke and priapism [painful, prolonged erection]. Pre-marital, post marital counseling, combined or comprehensive therapy are mandatory to reduce the prevalence and consequences of SCD. Early diagnosis and treatment can prevent the drastic effect of SCD. To increase awareness with information, education and communication system is the cost-effective method of SCD prevention.

INTRODUCTION

Sickle cell disease is caused by a mutation of hemoglobin-beta gene on chromosome 11 [1]. Hemoglobin transports oxygen from the lungs to other parts of the body. Red blood cells with normal hemoglobin [hemoglobin-A] are smooth, round and glide through blood vessels. It is due to abnormal hemoglobin molecules - hemoglobin S which is attached to each other and form long, rod-like structures [2]. These structures cause red blood cells to become stiff and form a sickle shape. The shape of red blood cells leading to blockage and progressive damage of vital organs and tissues and representing acute chest syndrome, stroke and priapism [painful, prolonged erection] [3]. It may also debilitate the spleen, kidneys and liver. A baby born with sickle cell disease inherits a gene for the disorder from both parents. If the both parents are having the genetic defect, there will be 25 percent chance to born their babies with sickle cell disease. If a child inherits only one copy of the defective gene [from either parent], there is a 50 percent chance that the child will carry the sickle cell trait. Those people who are only carrier of the sickle cell trait, typically they didn't get the disease, but can transmit the defective gene to their children. Aside from Africa and countries in the border of the Mediterranean [e.g., Italy, Greece, Spain, and Turkey] that have high incidence of SCD, significant prevalence has been reported especially in Saudi Arabia, Yemen, India, Pakistan, Bangladesh, and China. It can also be detected in an unborn baby. Amniocentesis, a procedure in which a needle is used to take fluid from around the baby for testing, can show whether the fetus has sickle cell disease or carries the sickle cell gene. It is better to discontinue the pregnancy, if the aminocentesis test is positive for the disease. Genetic counselors can help parents to make the difficult decision. Morbidity, frequency of crisis, degree of anemia, and the organ systems involved vary considerably from individual to individual. Treatments for sickle cell disease include antibiotics, pain management and blood transfusions. Hydroxyurea is an antitumor drug, which is stimulated to produce fetal hemoglobin in newborns. Fetal hemoglobin helps to prevent the "sickling" of red blood cells. Patients treated with hydroxyurea have chance to attack acute chest syndrome, potential adverse and toxic side effects include bone marrow toxicity, liver toxicity, nausea, vomiting, diarrhea, constipation, mucositis, hair loss, problems with blood urea and creatinine among others. Currently the only cure for sickle cell disease is bone marrow transplantation though it is a risky procedure with many complications. In this procedure, a sick patient bone marrow is transplanted from bone marrow from healthy, genetically compatible sibling donors. Only 18 percent of children with sickle cell disease are having healthy and matched sibling donor. So, comprehensive approaches are needed to combat the disease.

RESEARCH BASED APPROACHES

One hundred patients with steady-state SCA were randomized into treatment and placebo arms. The extract/placebo [*Cajanus*

cajan] were administered twice daily to the subjects. Weight, hepatosplenomegaly, blood levels of biliurubin, urea, creatinine, and Packed Cell Volume [PCV] were monitored over a 6-month period. Recall episodes of pain 6 months before enrolment were compared with episodes of pains recorded during the treatment period. Twenty-six cases [55.3 per cent] had hepatomegaly on enrolment. This significantly reduced to 33.3 per cent at 6 months [$p = 0.03$]; but increased in the placebo arm ($p > 0.05$). The total number of recall painful episodes in cases was 207 [mean 4.4 +/- 10.3 [SD], range 0-60] and fell to 191 (mean 4.2 +/- 4.4 [SD], range 0-16); $p = 0.03$. Episodes of pain increased from 109 in controls [mean 2.6 +/- 5.0 [SD], range 0-26] to 164 [mean 3.9 +/- 4.3 [SD], range 0-22]; $p = 0.01$. Mean PCV in the cases showed no appreciable changes [$p = 0.1$] but there was a significant increase in the controls [$p = 0.02$]. In conclusion, the extract may cause a reduction of painful crises and may ameliorate the adverse effects of sickle cell anemia on the liver [6].

It was found that 38 asymptomatic children with SCD develop hypertension and abnormal blood pressure. The investigators suggested that measuring of 24-hour Ambulatory BP Monitoring [ABPM] are needed to young patients. In the study, 17 patients [43.6%] had ambulatory hypertension, whereas 4 [10.3%] had hypertension on the basis of their clinic blood pressure. Twenty-three patients [59%] had impaired systolic blood pressure dipping, 7 [18%] had impaired diastolic blood pressure dipping, and 5 [13%] had reversed dipping [7].

It has proved that induction of defective human gene to mice produce sickle cell disease in mice. Bone marrow containing the defective hemoglobin gene was removed from the mice and genetically "corrected" by the addition of the anti-sickling human beta-hemoglobin gene. The corrected marrow was then transplanted into other mice with sickle cell disease. The genetically corrected mice started to produce high levels of normal red blood cells and showed a dramatic result. Scientists are very enthusiastic for applying the human gene transplant to combat the disease.

A new technique used in conjunction with *in vitro* fertilization, called Pre-Implantation Genetic Diagnosis (PGD), enables parents who carry the sickle cell trait to test embryos for the defective gene before implantation, and to choose to implant only those embryos free of the sickle cell gene [8].

Signs and symptoms

Sickle Cell Disease (SCD) usually manifests early in childhood. Sign and symptoms of the SCD are as following:

- Complain acute and chronic pain in any part of the body part due to vaso-occlusive crisis. Vaso-occlusion leads to infarction, hemolysis, and inflammation. Inflammation enhances the expression of adhesion molecules in endothelium, increasing

the tendency of sickled erythrocytes to adhere to the vascular endothelium. In worsen vaso-occlusion condition [9], reperfusion of the ischemic tissue generates free radicals and oxidative damage. The ruptured erythrocytes may release free hemoglobin which binds with nitric oxide and leads to develop functional nitric oxide deficiency and vasculopathy [10].

- Pain in the long bones of the extremities are mostly affected due to bone marrow infarction.
- Chronic hemolytic anemia.
- Aplastic crisis due to infection with B19V.
- Splenic sequestration which is characterized by the onset of life-threatening anemia with rapid enlargement of the spleen and high reticulocyte count.
- *Streptococcus pneumonia* infection more common in adult.
- Delayed sexual maturation with underweight.
- Dactylitis may present in hands or feet in children.
- Chest pain, fever, cough, tachypnea, leukocytosis, and pulmonary infiltration are most common in children than adult. Adults may develop afebrile and dyspneic with severe chest pain.
- Pulmonary hypertension.
- Avascular necrosis of the femoral or humeral head due to vascular occlusion.
- Stroke.
- Ptosis, retinal vascular changes and proliferative retinitis.
- Hypertrophy of both ventricles and the left atrium.
- Cholelithiasis is common in children.
- Priapism is a well-recognized complication of SCD.
- Leg ulcers are a chronic painful problem.

Triggering factors related to vaso-occlusive crisis are as following:

- Hypoxemia due to acute chest syndrome or respiratory complications
- Acidosis results in a shift of the oxygen dissociation curve
- Changes in body temperature

Diagnosis

Laboratory tests are usually advised to the patients of SCD-

- Screening for HbS at birth. It can be obtained via chorionic villus sampling.
- Hemoglobin electrophoresis.
- Total Count of WBC and RBC.
- Serum electrolytes.
- Hemoglobin solubility testing.
- Peripheral blood smears.
- Pulmonary function tests [transcutaneous O₂ saturation].

- Renal function [creatinine, BUN and urinalysis].
- Hepatobiliary function tests, [ALT and fractionated bilirubin].
- CSF examination: Lumber Puncture in febrile children who appear toxic and in those with neurologic finding may consider CT scanning before performing LP.
- Blood cultures.
- ABGs
- Secretory phospholipase A2 [sPLA2]

Imaging studies

- Radiography: Chest x-rays should be performed in patients with respiratory symptoms.
- MRI: Useful for early detection of bone marrow due to acute and chronic bone marrow infarction, marrow hyperplasia, osteomyelitis, and osteonecrosis.
- CT scanning: May demonstrate subtle regions of osteonecrosis not apparent on plain radiographs in patients who are unable to have an MRI and to exclude renal medullary carcinoma in patients presenting with hematuria
- ^{99m}Tc bone scanning showed that early stages of osteonecrosis;
- Transcranial Doppler ultrasonography: Can identify children with SCD at high risk for stroke
- Cholecystitis, cholelithiasis, or ectopic pregnancy can be excluded by abdominal ultrasonography.
- Echocardiography: Identifies patients with pulmonary hypertension
- Transcranial near-infrared spectroscopy or cerebral oximetry: Can be used as a screening tool for low cerebral venous oxygen saturation in children with SCD

Management

The goals of treatment of SCD are symptomatic relief and minimize disease complications. Treatment strategies are as following:

- Management of vaso-occlusive crisis
- Management of chronic pain syndromes
- Management of chronic hemolytic anemia
- Prevention and treatment of infections
- Management of the complications and the various organ damage syndromes associated with the disease
- Prevention of stroke
- Detection and treatment of pulmonary hypertension

Phytotherapy

Cajanus Cajan [Fabaceae] is an important legume plant used as nutrient and rich source of vitamin and protein containing free amino acids [phenylalanine most active], phenolic compounds [p hydroxybenzoic acid], tannins, globulins and saponins [4]. Crude alcoholic extracts of *C. cajan* were reported to inhibit sickling and also quickly revert normal morphology of already sickled erythrocytes [5] while aqueous extract of the dried seeds of an *C. Cajan* which contain

p-hydroxybenzoic in high amount has shown reversal of pre-sickled erythrocytes [HbSS] [6].

It has been proved that *Boerhaavia diffusa*, *Zingiber officinale*, *Piper longum*, *Piper nigrum*, *Embllica officinalis*, *Terminalia chebula*, *Piper chaba*, *Curcuma longa*, *Embelia ribes*, *Plumbago zeylanica*, *Boswellia serrata*, *Curcumin longa* and *Phyllanthus niruri* are very useful to manage the symptoms of sickle cell anemia in a natural way without causing any adverse effects on health [11].

An herbal combination extract called Niprisan (*Piper guineense seed*, *Eugenia caryophyllus*, *Pterocarpus osum stem*) – has shown significant success among the research. In a Phase IIb clinical trial, among the 30 sickle cell patients given the herbal formula, 73% had no sickle cell crisis during the twelve month testing period, while the remainder of the group – 27% – had fewer and less severe sickle cell crises [12].

In vitro and in vivo studies in various herbs revealed that anthraquinones, anthocaynin, amino acids, caricapinoside, p-hydroxy benzoic acid etc. are the potent herbal constituents responsible for antisickling activity in sickle cell anemia patients and these herbal constituents can be further researched for development of a much safer and affordable medicine [13].

A study with *Adansonia digitata* bark during crises showed that the plant can reverse sickling [14]. M piana reported that antisickling activity of *Adansonia digitata* aqueous extract is dose dependent while chemical screening on the aqueous extract of this plant revealed presence of anthocyanins and tannins. After that *A. digitata* anthocynin extract was tested for antisickling activity which has shown a good effect in the stabilization of sickle cell membranes and on Fe^{3+}/Fe^{2+} ratio that play major role on managing sickle cell disease [15].

Study showed that *Cacia xanthoploea Benth* (Stem Bark) is containing anthocyanins. The anthocyanin can reduce the polymerization of deoxy HbS molecules [16].

Allium sativum L [bulb] is containing an active alkaloid called allicin. The allicin has been shown to enhance LDL oxidation and to oxidize the iron of HGB in RBC with methemoglobin. It produces water-soluble S-allylcysteine that inhibits formation of dense cells [Heinz bodies] in blood samples from patients with SCD [17].

Aloe vera [Gel and leaf extracts] which is having active metabolite called aloverone. It has shown significant result to inhibit of sickle cell polymerization and improve Fe^{2+}/Fe^{3+} ratio of HbS [18].

Nigella sativa [seeds] is containing fixed oil which has an anti-sickling activity [*in vitro*]. It acts as an antioxidant. So in sickle cell, it inhibit oxidative reaction and the Ca^{+} channel antagonist activity [19].

Vitis vinifera [Fruit] contain an active metabolite called resveratrol. It acts as an HbF inducer which is mimicking with the biological activity of hydroxyurea [17].

Pharmacy therapy

Hydroxyurea [Hydroxycarbamide]: In sickle-cell disease it decreases the number of attacks. It is taken by mouth [20]. Common side effects include bone marrow suppression, fevers, loss of appetite, psychiatric problems, shortness of breath, and headaches [20, 21]. It also increases the risk of developing cancers. Use of the drug during pregnancy is typically harmful to the baby. It is believed that the drug is worked by blocking the DNA [20].

- Opioid analgesics [e.g., oxycodone/ASA, methadone, morphine sulfate, oxycodone/APAP, fentanyl, nalbuphine, codeine and APAP/codeine]
- Nonsteroidal analgesics [e.g., ketorolac, ASA, APAP and ibuprofen]
- Antibiotics [e.g., cefuroxime, amoxicillin/clavulanate, penicillin VK, ceftriaxone, azithromycin and cefaclor]
- Vaccines [e.g., PCV7, PPV23, meningococcal and influenza, recommended scheduled childhood/adult vaccinations]
- Vitamins [e.g., folic acid]

Non pharmaco therapy

- Stem cell transplantation
- Transfusions of blood is needed for sudden, severe anemia
- Physical therapy
- Heat and cold application.
- Acupuncture and acupressure.

Combination pharmacotherapy and non-pharmacotherapy

- Vigorous hydration [plus analgesics] for vaso-occlusive crisis
- Oxygen, antibiotics, analgesics, incentive spirometry, simple transfusion, and bronchodilators for treatment of acute chest syndrome

CONCLUSION

Sickle cell disease is caused by a mutation of hemoglobin-beta gene on chromosome 11. Pre-marital, post marital counseling, combined or comprehensive therapy are mandatory to reduce the prevalence and consequences of SCD. Early diagnosis and treatment can prevent the drastic effect of SCD. To increase awareness with information, education and communication system is the cost-effective method of SCD prevention.

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