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Review

Current Trends in the Management of Sickle Cell Anaemia

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Abstract

Background: Sickle cell anaemia (SCA) is the most frequent monogenic disorder affecting more than 50 million persons worlwide with the largest health and socio-economic burden felt in the sub-saharan Africa particularly Nigeria.

Methods: Standard textbooks of haematology were consulted while online searches for relevant materials using specific keywords were conducted on PubMed and Google Scholar databases.

Results: Despite the current indepth understanding of the pathophysiology of SCA, majority of patients living with this disease are yet to have a sigh of relief. In developing countries where most patients with SCA abound, there is dearth of health care resources and the political will to tackle the menace of the disease. While most of the treatment modalities available address the downward sequelae of SCA, stem cell transplantation and gene therapy that offer cure for the disease are not yet affordable and accessible for most patients needing them. Additionally, the advent of COVID-19 pandemic has further exposed the challenges and the inequities encountered by SCA patients especially in the sub saharan Africa. During the pandemic, SCA patients could not access routine care due to lockdown, fear of contagion and redeployment of medical specialists involved in such care to the COVID-19 response. Furthermore, shortage of blood donors led to lack of optimal blood transfusion services for this patients and added to the increased morbidity and mortality of SCA patients during the pandemic.

Conclusion: While researches on antisickling agents, gene therapy and stem cell transplantation are on-going, there is the urgent need to put more emphasis on provision of basic management modalities for SCA such as health education, premarital counselling and screening, newborn screening and early intervention, routine folic acid supplementation, antimalarial and penicilline prophylaxis, use of hydroxyurea and availability of safe blood for transfusion.

Keywords: sickle cell anaemia, hydroxyurea, stem cell transplantation, gene therapy

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Introduction

Sickle cell anaemia (SCA) is the most frequent monogenic disorder affecting more than 50 million persons worlwide with the largest health and socio-economic burden felt in the sub-saharan Africa particularly Nigeria (1). SCA is an autosomal recessive inherited genetic disorder of the haemoglobin with protean manifestation and of public health concern (1,2). An indepth understanding of the pathogenesis of SCA has continued to pave way for varying treatment modalities employed or which are currently being evaluated for utilization in the management of the disease (3). The use of blood transfusion and recently, introduction of Hydroxyurea and Crizanluzimab in the management of SCA had remarkably improved the lives of people living with SCA (4,5). However, stem cell transplantation and gene therapy which are considered to offer cure for SCA are still not available for majority of patients living with this disease (6). The advent of COVID-19 pandemic has further exposed the challenges and the inequities encountered by SCA patients particularly in the sub saharan Africa where most reside (7,8,9). During the pandemic, SCA patients became more vulnerable by virtue of their immunosuppression, poor access to health care services for both routine and acute SCD care due to lockdowns, diagnostic challenges posed by the syndromic similarities between SCA-related complications (e.g. respiratory tract infection, acute chest syndrome) leading to misdiagnosis and treatment delays (7, 8, 9). The dearth of blood donors during the pandemic also mitigated against provision of safe blood for SCA patients and added up to the observed increase in morbidity and mortality of SCA during the pandemic (7,8,9). It is our hope that with the increased availability of blood transfusion services, widespread acceptance of the use of hydroxyurea, recent commencement of stem cell transplantation and on-going active search for a promising antisickling agent, our SCA patients in Nigeria will have better care in the near future.

Epidemiology

SCA affects >50 million people globally and >300, 000 babies are born annually with the disease (10). It is more prevalent in malaria endemic regions such as sub-Saharan Africa, Middle East and India where it has been observed that people with the sickle cell trait (HbAS) develop some resistance to the develoment of severe form of malaria (the

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concept of balanced polymorphism) (11). Though due to inter-racial marriages and easier travels, SCA patients are found all over the globe. Nigeria has the highest world burden with prevalence of 24% and 2-3% for the sickle cell trait and SCA respectively; >100,000 annual birth rate for SCA and contribute 8% of Infant Mortality Rate (1). In sub-Saharan Africa most SCA patients die before five years of age (1). Despite advances in the understanding of the pathophysiology of SCA., life expectancy is decreased by about 25 to 30 years (1,10).

Pathophysiology

A point mutation (G**A**G→G**T**G) in the sixth codon of the gene coding for the β-chain of the globin underlies the pathogenesis of SCA which is inherited in an autosomal recessive pattern (12, 13). The result of this mutation is the replacement of glutamic acid with valine as the sixth amino acid in the β-globin chain and subsequent production of HbS instead of the normal HbA. In conditions of low oxygen concentration, deoxy-HbS is less soluble when compared with deoxy-HbA and thus crystallizes out of solution within the red cells (13, 14, 15). The cross-linking of the monomeric HbS molecules via the valine amino acids leads to polymer formation which elongates to form bundles and precipitate inside the red cells giving it various abnormal shapes including the classical sickle cell morphology (13). Repeated sickling if unabated may lead to permanent damage to the red cell membrane and formation of irreversible sickled cells that worsen the vaso-occlusion or lead to premature destruction of the red cells (13). The major mechanisms that underlie the clinical manifestation of SCD are red cell sickling, vaso-occlusion, haemolysis and proneness to infection. The red cell sickling and other red cell membrane abnormalities lead to increased haemolysis with consequent anaemia. The blood vessel occlusion underlies the widespread tissue infarction which leads to multiple organ affectation and explains the protean clinical manifestation typical of SCA. The vaso-occlusion emanate from mechanical blockade of vascular lumen by the sickled cells and the active adhesion of both sickled and unsickled red cells, white blood cells and platelets to other blood cells and the vascular endothelium (14). The roles of cell-to-cell, cell-to-vascular endothelium and plasma proteins interactions will continue to pave way in our understanding of the pathophysiology of SCA and possibly help in identifying potential targets for treatment of this disease (14).

Clinical features and complications

SCA has myriad clinical manifestations due to the multi-organ affectation characteristic of the disease. It runs a variable clinical course ranging from mild disease to a severe crippling or life threatening one. Typically, SCA patients may be in a relative good health period referred to as 'steady state' which may have variable length (14,15). This steady state is periodically punctuated by periods of acute exacerbation or worsening of clinical features referred to as 'crises states'. The forms of crises recognised include; vaso-occlusive (such as bone pain, acute chest syndrome, priapism, mesenteric infarction and stroke), aplastic and hyperhaemolytic crises (1,14, 16,17). SCA crises may be triggered by exposure to any one of these; extreme of weather conditions, physical exertion, infections, dehydration, injury, psychological stress, idiosyncratic, idiopathic or the use of some drugs (1,14). Complications arising from SCA could be quite incapacitative with attendant socio-economic burden. Complications commonly encountered include avascular necrosis of head of the femuri/humeri, chronic leg ulcers, gall bladder stones, infertility, recurrent miscarriages, stunted growth, increased susceptibility to infections, renal and liver function impairment as well as loss of vision. SCA patients may face societal stigmatization, loss of means of livelihood and may suffer neglect, depression and drug addiction.

Laboratory evaluation

There are guidelines for the screening and diagnosis of SCD and their recommendations reflect availability of appropriate human and material resources in a given locality for evaluating patients suspected to have SCD (18). Presently, screening and testing can be performed prenatally (using chorionic villi sampling, amniotic fluid or maternal blood), at birth (heel prick or cord blood) or any red cell containing scrapings/fluids there after. In Nigeria for instance, the definitive diagnosis of SCD, in the appropriate clinical setting, requires a screening method (usually haemoglobin electrophoresis) and a positive result followed up with an unrelated second method (such as peripheral blood film review, sickling or solubility testing) for confirmation. Further testing such high-performance liquid chromatography (HPLC), isoelectric focusing (IEF), and DNA analysis, if available, may be performed to differentiate between haemoglobinopathies (1,19). Other supportive investigations that may disclose organ impairment include renal and liver function tests, neuro-cognitive assessment, radiologic evaluation of internal organs, viral screening all form an integral component of the laboratory assessment of SCA..

Treatment

For quite sometimes now, the treatment modalities for SCA have been largely restricted to infection control (health education, vaccination, penicilline prophylaxis, and antibiotics) and use of blood transfusion for prevention of stroke and silent cerebral infarctions (14, 15). Currently, a number of guidelines exist for management of SCA and such guidelines

factor availabilty of transfusion facilities and drugs in use for the treatment of SCA (1,18). Treatment is now viewed as either primary that addresses the root causes of the disease (HbS mutation and polymerisation) or secondary that addresses the downstream sequelae of the disease such as adhesion, inflammation, thrombophilia and oxidant stress. Modalities employed for addressing the root causes of SCA include stem cell transplantation, gene therapy and the use of HbF inducers and a variety of antisickling agents (4). There are quite a number of antisickling agents at different stages of develoment (3) but yet a promising antisickling agent has not been discovered. While the secondary treatment modalities include use of anti-adhesion drugs (intravenous Immunoglobulins, Propranolol, Rivipansel, Crizanluzimab), anti-inflammatory agents (Simvastatin, Zileuton, Rigadenoson), anti-thrombophilic agents (antiplatelet agents, Rivaroxaban, Apixaban) and antioxidants (Glutamine, N-acetylcysteine, Omega-3 FA) (20).

Traditionally, treatment of SCA patients could be seen as either during the steady state or crises state of the patient. In both of the stages, multidisciplinary approach is strongly advocated with periodic assessment of organ functions in order to address the attendant multiple organ impairment characteristic of the disease. During the steady state of the disease, patients are maintained on routine drugs (folic acid and paludrine/proguanil) in addition to penicilline prophylaxis, avoidance of factors that could trigger crises such as mosquito bites, extreme of weather conditions, infections, physical and emotional stress (14,15,16). With the onset of crises, patientss' management may require hydration, analgesia, antibiotic therapy and transfusion support in a hospital setting.

Day care wards and home care in the treatment of SCA

Considering the chronic course of SCA disease often punctuated by the crises periods, the utilization of day care wards or centres has enabled patients to access prompt care in a hospital setting for some part of the day before going home on the same day to continue medications (21). Such centres provide medical specialists including haematologists who provide expert laboratory evaluation, blood transfusion, pain management, other resuscitative and supportive care for SCA patients. The concept of home care has enabled uninterrupted care for SCA patients at home while reducing the challenges of hospitalization. Home care givers (parents, guardians, siblings, other relatives or individuals employed solely for that purpose) are usually encouraged to acquire additional information on how best to look after these patients (22). The utilization of both the day care services and home care givers could improve the health status of these patients as SCD-related complications could be averted on time (21, 22).

Future outlook

Availability of blood components for safe and optimal blood transfusion services as well as provision of supportive care in the form of sickle cell comprehensive centres will go a long way in improving the survival of patients with SCA (23). Similarly, efforts should be geared towards making stem cell transplantation and gene therapy more affordable and accessible to eligible SCA patients (6, 24). Other aspects requiring attention include monitoring the safety profile of Hydroxyurea and anticoagulation therapy, provision of Crizanluzimab and the development of drugs with antisickling effects beyond the animal model (3,5).

Conclusion

The existing in-depth understanding of the pathophysiology of SCA will continue to pave way for more revolutionary therapeutic advances in the management of this disease. While more funded researches targeting cure (stem cell transplantation and gene therapy) are encouraged, there is however the urgent need to put emphasis on the more readily available and affordable management modalities (health education, timely counseling and screening, routine folic acid and paludrine therapy, penicilline prophylaxis, safe blood transfusion services, comprehensive care, use of Hydroxyurea, Crizanluzimab and other antisickling agents) so as to bring succor to people living with SCA.

Conflict of interest

None declared

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