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Editorial

A century after discovery of sickle cell disease: keeping hope alive!

The discovery of hemoglobin 'S' by Linus Pauling and Colleague in 1949 was the first demonstration that the production of an abnormal protein could be the cause of a genetic disorder[1]. So was born the notion of molecular basis of the disease and sickle cell disease (SCD) was the first one to be described. In 1956, Vernon Ingram identified the abnormality in the amino acid sequence of the β-globin chain (β_6 Glu→val)[2]. Sickle cell disease is the most common genetic disorder in the world. Much has been written in recent years about large global burden of haemoglobinopathies and the neglect by all sectors in the global, national and local health systems to respond appropriately to the needs and rights of people affected by haemoglobinopathies like sickle cell disease and thalassaemia[3].

Current estimation of SCD and global burden

Approximately 5 per cent of the world's population carries trait genes for haemoglobinopathies disorders, mainly sickle cell disease and thalassaemias. It is estimated that each year about 300,000 babies are born with severe forms (homozygous) worldwide, the majority in low and middle income countries[3]. SCD is more common in Africa (Subsaharan areas), middle East and in India. It is interesting to note that due to recent population movement there is a gene flow from high allele frequency areas to Europe and USA[4].

It is predicted that the number of newborns with sickle cell anaemia (SCA) globally will increase from 305,800 in 2010 to 404,200 in 2050. It is likely that Nigeria and Democratic Republic of Congo will remain the countries most in need of policies for the prevention and management of SCA[4]. Thus with increasing global burden of SCA, there is a need to develop specific national policies for appropriate public health planning particularly in low and middle-income countries. However, timely estimates of the cost of care data are largely missing. One study conducted in USA suggests that interventions designed to prevent SCD complications and avoid hospitalizations may reduce the significant economic burden of the disease[5].

Indian scenario: India is a vast country with diverse culture and with many castes, tribes, languages and religions. Lehman and Cutbush[6] were the first to report the presence of β^S gene in the tribal groups of the Nilgiri Hills in southern India in 1952. It is common in Vidarbha, Chhatisgarh, Madhya Pradesh, Orissa, Gujarat, Nilgiri Hills of Tamil Nadu and Andhra Pradesh in India[7]. Contrary to the common earlier belief, it is also seen in non tribal population in central India, Orissa and Andhra Pradesh. The incidence of β^S gene varies from 0 to 40 per cent and the relatively high frequency of β-thalassaemia in the same population groups often leads to the clinically important condition, sickle haemoglobin β thalassaemia. In S-β-thalassaemia, the clinical manifestations were mild in majority of patients unlike β-thalassaemia major[8]. Thus the clinical and haematologic features in Hb S-β-thalassaemia are quite variable. The clinical severity largely depends upon the nature of the β-thalassaemia mutations. β^s gene haplotype was found to be strongly associated with the Arab-Indian haplotype[7]. Also β^s chromosome linked to Cameroon haplotype has been observed, occasionally in the non tribal groups of Maharashtra[8]. It has been reported that SCD in association with higher haemoglobin F (>10%) levels tends to have less anaemia and milder clinical manifestations[7].

Clinical manifestations: Common morbid events during infancy include hand-foot syndrome, febrile

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illness, acute painful events and acute febrile illness being most common[9]. SCD children are more prone to infection. *Staphylococcus aureus* and Gram-negative bacteria accounted for all cases of bacteraemia[9]. The pattern of bacteraemia in SCD children from India may be different from that of Africa[10] and western countries[11] where *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common causes of bacteraemia. Multicentric in depth studies need to be done to reach to a logical conclusion so that the antibiotic policy can be made for sickle cell anaemia affected children. Also, it will help in developing vaccination policy for SCA children.

In adults, the main clinical presentation is vaso-occlusive crisis (VOC), which seems to be universal throughout the country. Patients complain mostly of periodic pain all over the body or in joints and limbs. This has greater incidence in rainy season followed by winter. Our study has suggested that the phenotypic expression of sickle cell anaemia is not uniformly mild and α-thalassaemia is a powerful epistatic factor in the Arab Indian haplotype in alleviating the disease severity. Priapism and leg ulcers seem very uncommon in Indian patients. About 66 per cent had splenomegaly and 10 per cent had gallstones. Jaundice is not uncommon. About 52 per cent of the patients had hemolytic jaundice. In all these cases Hb F level was significantly low[7].

Hydroxyurea therapy in sickle cell anaemia: A large double-blind trial in adults has demonstrated the efficacy of hydroxyurea therapy in SCA[12]. Clinical benefits include significant reduction in the frequency of hospitalization, pain episodes, acute chest syndrome and blood transfusions. The use of hydroxyurea is an example of an intervention which could yield substantial cost offsets from reduced hospitalizations[5]. This can be given safely to children also[13].

Need of the hour

Despite the fact that the WHO has recognized the importance of the inherited disorders of haemoglobin, very little international action has been taken towards the development of services for the control and management of these disorders. The situation can only be improved when we have true calculated data about the natural history, frequency of mortality and morbidity pattern in each country affected. So, it is a call to all the hematologists to join hands to raise these data. The second important point is the paucity of budget allocations in national health budgets and input from the major international health agencies and funding organizations. Again, to advise governments about the health burden that will be posed by the SCD in the future it is vital that better health, economic data are collected. It is needless to mention that political will is equally important in successful execution of the programme. There is a move by several African countries in the last few years for separate allocation of resources for comprehensive care approach to SCA on a priority basis. Though therapeutic intervention like hydroxyurea administration to both adults and children has brought down the VOC rate and acute chest syndrome; bone marrow allogenic transplantation is the only cure available to a very limited number of patients.

Tasks ahead

Taking cognizance of Indian scenario it can be suggested that simple straight forward measures in a strategic manner will be helpful in the intervention programme of SCD. These include *(i)* early detection of the disorder by neonatal screening, *(ii)* counselling of the patients and their parents about the medical complications, *(iii)* genetic counselling, *(iv)* preventive measures in children like penicillin administration upto the age of five, vaccination with pneumococcal and meningococcal vaccines, *(v)* therapeutic intervention with hydroxyurea, *(vi)* development of some comprehensive care centres in the areas wherever the disorder is common, and *(vii)* public awareness and education of the medical fraternity about the disorder.

Premarital screening and counselling is always not accepted by the majority of people but prenatal diagnosis is welcomed. There are only a few centres in the country offering prenatal diagnosis for haemoglobinopathies. The effectiveness of awareness programme through school going children shown in Maharashtra, Gujarat and Chhatisgarh is encouraging[14].

Prenatal diagnosis for SCD may not be absolutely indicated since the severity of disease is less but neonatal screening is absolutely essential to improve the QOL (quality of life). It is possible even in the remote areas in tribal communities to do neonatal screening but the success depends upon the careful genetic counselling[15].

Hope & goal

A coalition involving both professionals in the health care sector and people affected by SCD and their

family members and extending to policy makers and general health care providers and concerned members of the community, is needed to spur collective action for change. Such a coalition should vociferously, and with a united voice, demand for greater visibility of genetic disease in the national policy and programmes, so that the rights of people with SCD to access care and live a life with dignity is fulfilled. Community-based primary healthcare schemes should be linked to specialized levels to optimize the quality of care, depending upon the requirements of the patient and the availability of resources.

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