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Sickle Hemoglobinopathy in West Bengal, India: Review of Literature and Future Direction

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Sickle cell disease (SCD) was the first example of a 'molecular disease'. SCD patients experience considerable morbidity from both acute and chronic sequelae; most severe cases can be fatal within the first few years of life without effective treatment or with sub-optimal treatment. In India, reported sickle-cell allele frequency is 10% spanned central India. West Bengal is the first state in India which had launched the State Thalassaemia Control Programme (STCP) for prevention of thalassemia since 2008. The present systematic review was made to know the community load of sickle hemoglobinopathy in West Bengal, an eastern state in India. Among all, as per the recently published, largest study screened for hemoglobinopathies over a period of 10 years, the estimated community load of sickle hemoglobinopathy in West Bengal would be sickle cell trait/carrier (703,010 cases; 0.77%), HbS beta thalassemia (45,650 cases; 0.05%) and SCD (36,520 cases; 0.04%). The National Health Mission, Government of India in 2016 have published the guidelines for 'prevention and control of hemoglobinopathies in India'. Data from many functioning thalassemia control units (TCUs) in West Bengal are not yet published; therefore not available for the current review. All the TCUs in West Bengal should publish their data to help the Government in planning comprehensive management of SCD including other thalassemia cases.

Keywords: Sickle hemoglobinopathy; West Bengal; iiterature review; burden; future direction.

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1. INTRODUCTION

Sickle cell disease (SCD) was the first example of a 'molecular disease'. Hemoglobin S (HbS) was discovered by Linus Pauling and colleagues in 1949 and that was the first demonstration that a genetic disorder could be caused by production of an abnormal protein [1]. Vernon Ingram in 1956 identified the molecular abnormality in HbS in terms of single nucleotide substitution where glutamic acid in 6th position of beta globin chain having been replaced by valine (β6Glu→Val) [2]. Abnormal polymerization of the resulting sickle hemoglobin triggers a cascade of erythrocyte alterations leading to the basic mechanisms of the vaso-occlusive events and the fragility of red blood cells is responsible for hemolytic anemia [3]. SCD patients experience considerable morbidity from both acute and chronic sequelae; without effective treatment or with sub-optimal treatment most severe cases can be fatal within the first few years of life [4]. Depending on the prevalence of other hemoglobin variants in the locality, the combination of the sickle gene mutation and other thalassemia mutations (such as beta thalassemia, Hb E, Hb D, Hb C) gives rise to a compound heterozygous state with varied clinical manifestations [5]. Overall, the compound heterozygous state of HbS beta thalassemia, first described in 1944 by Silvestroni and Bianco, is prevalent in the world [6]. HbS beta thalassemia may present with mild to severe anemia depending on the defect in beta thalassemia gene. In HbS β^0 thalassemia, the thalassemic globin gene produces no protein so that the only β globin comes from the HbS gene; similar to SCD in terms of severity of anemia, disease onset, course and prognosis. In $S\beta^+$ thalassemia, the thalassemic β globin (β^+) produces variable (low to near normal) amounts of protein, so that there is some HbA present; thus have minimal to moderate anemia [5]. The present systematic review was made to know the sickle gene frequency either in its purest forms (heterozygous and homozygous states) or in co-inheritance with other hemoglobinopathies (compound heterozygous states) in West Bengal, an eastern state in India.

2. METHODS

The method employed to search articles was Internet based. A PubMed and Google search using the following search terms, i.e., 'hemoglobinopathies', 'sickle cell disease', 'diagnosis', 'screening', 'neonatal diagnosis', 'Eastern India' 'West Bengal', was done. All the titles and abstracts with full article available till October, 2020 in 'English' were screened for published literature on 'sickle cell disease' from West Bengal. The reference section of the selected papers was also searched in order to identify additional articles. There were many publications on both small and large population screening from rural and urban areas from different districts of West Bengal. To study the burden of sickle cell disease in West Bengal, I had reviewed the articles with large number of cases of population screening from published literature especially from rural areas that may actually reflect the heterogenous population from different socio-economic status. Few others not included in the study were either with very small sample size or from tertiary care centers in urban areas.

3. GLOBAL PERSPECTIVE

Sickle cell disease is a significant public health problem in sub-Saharan Africa, parts of the Middle East, the Caribbean, Brazil and some areas of the Indian subcontinent; the highest reported incidence of SCD in sub-Saharan Africa ranges between 1% and 2% [7]. Annually, over 300,000 infants are born with the homozygous form of the disease, about two-thirds of them in Africa; Nigeria, India and the Democratic Republic of Congo shoulder half of the global burden [8]. Progress in the management of SCD has been slow in many of these regions. In low-income countries, basic facilities for management are lacking, systematic screening is not a common practice and diagnosis is made late [9]. Low income country like Brazil with a very high prevalence of SCD have implemented National Neonatal Screening Program (NNSP) aiming to reach 100% of live births in the country have achieved considerable gains including the implementation of neonatal screening at the national level together with scientific and technological progress with respect to treatment [10]. In a pilot study in Nigeria has shown that the integration of newborn screening into existing primary health-care immunization programmes is feasible and can rapidly be implemented with limited resources [11].

4. INDIAN SCENARIO

First described in 1952 in India from the Nilgiri Hills of Tamil Nadu, the sickle cell gene is now known to be widespread among people of the Deccan plateau of central India [12]. Some of the highest sickle gene frequencies have been reported in Indian populations and India has been ranked the second worst affected country in

terms of predicted SCD births [13]. The first India-specific model-based map of sickle-cell allele frequency revealed highest predicted frequencies of up to 10% spanned central India, whilst a hotspot of ~12% was observed in Jammu and Kashmir [14]. In India, HbS is predominantly found amongst scheduled tribe (ST) and scheduled caste (SC), the most socioeconomically disadvantaged population subgroups in the country [15]. The coincidence of large tribal populations and the 'sickle cell belt' of Central India, Tamil Nadu and northern Kerala has given rise to the assumption that tribal people are more prone to the *HbS* gene although this seems widely distributed among tribal and non-tribal people [16]. In India, SCD is largely undocumented and there is an urgent need to document the features of clinical phenotypes of SCD in Indian patients so that locally appropriate models of care may be evolved [17]. Although considerable work has been done on SCD in India, the bulk has occurred in a few centres with limited impact at the national level. The need for collaboration and networking between centres has been realized; multicentre studies have started the process of systematic documentation of the disease [18].

5. THE BURDEN OF SICKLE HEMO-GLOBINOPATHY IN WEST BENGAL

Way back in 1967, studying on blood groups and hemoglobin variants among the Santal tribe in Midnapore District of West Bengal, Chaudhuri S et al. [19] reported presence of HbS among them. Many years later, in 1981, Bhattacharyya PK et al [20] noticed the presence of sickle cell trait in the Santhals of Ajodhya hills of Purulia district of West Bengal. The first systematic study for screening of large number of patients from Kolkata, the capital city of West Bengal started as part of 'A national multi-centric Task Force Study of the Indian Council of Medical Research' from 2000 to 2005 under 'Jay Vigyan S and T mission project on community control of thalassaemia syndromes–Awareness, screening, genetic counseling and prevention for thalassemia' and the results were published in 2008 showed the frequency of HbS trait/heterozygous and HbSS homozygous in 0.14% and 0.01% respectively [21]. In another multicentric study by Mohanty D et al. [22] published their data in 2013 from six different cities in India including Kolkata showed significant regional variations. West Bengal is the first state in India which had launched the State Thalassaemia Control Programme (STCP) for prevention of thalassemia since 2008 [23]. This STCP involves two nodal centers in Kolkata with 34 thalassemia care units (TCUs) in different districts and sub-divisional hospitals; several reports have been published from these centers on the prevalence of different hemoglobin-pathies including HbS in both urban and rural areas (Table 1).

HbS trait: As per available published literature (Table 1), Jain BB et al. [24] in 2012 reported prevalence of HbS trait of 0.63% from the district of Burdwan. Dolai TK et al. [25], Mandal PK et al. [26] and Chattopadhyay P et al. [27] and Maji SK et al. [28] at different timelines reported the prevalence of HbS trait of 1.12%, 0.56%, 2.22% and 0.77% respectively from Paschim Medinipore district. Ghosh N et al. [29] and Goswami BK et al. [30] in the years 2013 and 2014 from Darjeeling district and the northern districts of West Bengal reported the prevalence of HbS trait of 1.06% and 0.42% respectively. Two independent publications from Kolkata by Choudhuri S et al. [23] and Mukhopadhyay D et al. [31] reported Hb S trait prevalence of 0.23% and 0% respectively. Study from Bankura district by Mondal SK et al. [32] during 2005-2015 in a large population (n=119,336) revealed the prevalence of HbS trait in 0.38%, whereas the study by Chakrabarti S et al. [33] from the same district in a focused group of antenatal mothers (n=3,500) revealed similar (0.31%) results. Naskar S et al. [34] from Malda district and Bhattacharyya KK et al. [35] from Hooghly district reported high prevalence of abnormal hemoglobins in both the districts and HbS trait of 0.35% was reported from Malda and no cases from the study in Hooghly district. Chatterjee T et al. [36] analyzed samples (n=18,166) from 12 districts (Kolkata, North 24 Parganas, South 24 Parganas, Howrah, Hooghly, undivided Medinipur, Birbhum, Burdwan, Nadia, Malda, Darjeeling and Murshidabad) of West Bengal and showed an overall prevalence of HbS trait in 0.03% cases. Thus it is evident from the different studies that the prevalence of HbS trait varies (range, 0.03%-2.22%) with change in geographic location with higher prevalence shown in the districts of Paschim Midnapore, Jhargram, Bankura and Darjeeling and lower in Kolkata and Hooghly districts. There was significant difference in the results among different studies in the same geographic region/district (Table 1).

HbS beta thalassemia: There was wide variation in the prevalence of HbS beta thalassemia revealed among different studies which ranged from 0.05% by Maji SK et al. [28]

from Midnapore district (n=114,606) to 1.41% by Goswami BK et al. [30] in a small population (n=1,872) studied from six districts of north Bengal. But, majority of the other community based studies in large population from different districts showed much lower incidence as compared to Goswami BK et al. [30].

Sickle cell disease: the prevalence of sickle cell disease as revealed in different studies ranged from 0.006% to 0.33% with reported very high incidence (0.94%) in the study by Goswami BK et al. [30] from the districts of north Bengal.

Thus far, among all these, the study by Maji SK et al. [28] included the largest number of subjects (287,258) screened for hemoglobinopathies over a long period (year 2010-2020) was most representative of all in a sense that it was mostly a rural community based study and included the heterogeneous population of West Bengal that may reflect the prevalence of sickle cell disease at large. This particular study included the data from the newly formed Jhargram distrct that is the inhabitant of large number of people from ST and SC category, the socially disadvantaged population with high disease burden for different hemoglobinopathies including SCD. As per 2011 census in India, population of West Bengal was 9.13 crore [37]; thus the estimated community load of sickle hemoglobinopathy in West Bengal as a whole would be sickle cell trait/carrier (703,010 cases; 0.77%), Hb S beta thalassemia (45,650 cases; 0.05%) and SCD (36,520 cases; 0.04%). But, it may probably be much less than that because many of the studies (Table 1) revealed much lower prevalence of HbS trait and not a single case of HbS beta thalassemia and SCD was reported in their studies. This may be further supported by the recent study by Ray R et al. [38] from Kolkata in school going children (n=17,369) from tribal populations of almost all districts of West Bengal reported HbS in only 0.4% of the study population. They postulated that the widely varying prevalence of alpha deletion (83%) and exceptionally low prevalence of HbS (0.4%) may be a consequence of epistasis. As evident from Table 1, studies over years have shown a gradual and sustained downtrend in detection of sickle hemoglobin-pathy over years from different regions of the state that may be the reflection of successful implementation of carrier detection programmes in the locality.

6. STANDARD OF CARE

Sickle cell disease causes significant disease-related morbidity including debilitating pain crises, chronic anemia and multiorgan damage. Until recently, Hydroxyurea, a known HbF modifier is used in SCD with proven efficacy to decrease complications such as vaso-occlusive crisis, acute chest syndrome, frequency of transfusions and is a feasible option in under-resourced countries [39]. Findings from the TWiTCH (TCD With Transfusions Changing to Hydroxyurea) have enabled switching from regular blood transfusions to oral hydroxyurea therapy as a key strategy for maintaining reduced TCD (transcranial Doppler) velocities in a large majority of at-risk children [40]. And, the Stroke Prevention Trial in Nigeria (SPIN) has demonstrated that hydroxyurea is effective in reducing strokes, providing further support for widespread TCD screening [41]. Few centres in India have implemented TCD screening and patients with abnormal velocities are offered chronic transfusion therapy and/or hydroxyurea therapy [42]. The REACH (Realizing Effective-ness across Continents with Hydroxyurea) trial conducted in four African countries established strong evidence of the safety and efficacy of hydroxyurea therapy in African children with sickle cell anaemia [43]. Advances have contributed to the FDA approval of three new medications in 2017 (L-glutamine) and 2019 (Voxelotor and Crizanlizumab) for management of SCD, with several other drugs currently under development [44]. Bone marrow transplantation is one of the newer methods of treatments available and is the only current cure for SCD. Gene therapy in sickle cell disease is showing promising results and seems to offer a possible cure.

Comprehensive care in SCD incorporates provision of proper and accurate diagnosis, standard therapies, preventive care and rehabilitative therapy by a team of specialists with maximum accessibility for all patients. It has been shown to provide better outcomes in SCD evidenced by significant reduction in mortality, hospitalizations, and blood transfusion rates and disease related morbidities. Carrier detection and genetic counseling have been proven to be successful in curbing the spread of SCD and other hemoglobinopathies like thalassaemia [45]. Genetic counseling by trained personnel helps individuals at risk to take informed decisions about their reproductive life choices. Unfortunately, comprehensive care is not easily available to most of the affected populations because of lack of infrastructures, funds and many other related factors. Many patients in remote rural areas are not adequately managed and are often unable to reach a hospital.

Table 1. Distribution of sickle hemoglobinopathy from different areas (districts) of West Bengal as reported by the previous studies

Name of the study (group)	Year of publication (Study period)	Name of the district (s) under study	Total number of screening, n	Abnormal Hb, n(%)	Hb S trait, n(%)	HbS Beta thalassemia, n(%)	Sickle cell disease, n(%)
Mohanty D et al. [21]	2008 (2000-2005)	Kolkata	9,990	841 (8.42%)	14 (0.14%)	N.A.	1 (0.01%)
Jain BB et al. [24]	2012 (2006-2009)	Burdwan	3,823	29.3%	0.63%	0.30%	0.15%
		Paschim	35,413	16.23%	*1.12%*		
	2012 (2007-2011)	Medinipore					
Dolai TK et al. [25]						NA	NA
Ghosh N et al. [29]	2013 (2011)	Darjeeling	188 (PNW)	26.6%	1.06%	NA	NA
Goswami BK et al. [30]	2014 (2010)	Six districts of North Bengal	1,872	47.5%	0.42%	1.41%	0.94%
Choudhuri S et al. [23]	2014 (2009-2012)	Kolkata	20,883 (PNW)	10.5%	0.23%	NA	NA
		Paschim	50,487	11.62%	0.56%	0.15%	NA
Mandal PK et al. [26]	2014(2010- 2013)	Medinipore					
Chatterjee T et al. [36]			18,166	2,092	23	N.A.	N.A.
	2015 (1999 – 2011)	12 districts in west Bengal		(11.52%)	(0.03%)		
Naskar S et al. [34]	2015 (2012-2013)	Malda	5,156	12.88%	0.35%	NA	NA
Mukhopadhyay D et al. [31]	2015(2010-2013)	Kolkata	10,407	14.5%	NA	NA	NA
Mondal SK et al. [32]	2016 (2005- 2015)	Bankura	119,336	12.17%	0.38%	0.26%	0.32%
Chakrabarti S et al. [33]	2016(2011-2012)	Bankura	3500 (ANM)	275 (7.86%)	11 (0.31%)	N.A.	N.A.
Bhattacharyya KK et al. [35]	2016(2012-2015)	Hooghly	21,137	13.1%	NA	NA	NA
Chattopadhyay P et al. [27]	2019 (2017 -2019)	Paschim Medinipore	899 (ANM & PMS)	133 (14.79%)	20 (2.22%)	1 (0.11%)	3 (0.33%)
Maji SK et al. [28]	2020 (2010-2020)	Paschim Medinipore & Jhargram	287,258	32,921 (11.46%)	2,203 (0.77%)	155 (0.05%)	125 (0.04%)

Abbreviations:- n= number; NA= data not available; ANM= antenatal mother, PMS=premarital screening; PNW=prenatal women

7. FUTURE DIRECTIONS

A great deal remains to be learnt about SCD in this part of the country and assuming that models of care developed for African disease should be followed may be inappropriate and waste limited resources. There is a need for early diagnosis of SCD through the implementation of neonatal and early childhood screening [9]. Studies based on newborn screening will avoid symptomatic selection and provide the best clinical data [17].

Partnerships between health care professionals, funding agencies, governments, and industry are needed to help reduce the high disease burden in developing countries, through widespread SCD education, relevant research and implementation of evidence-based cost-effective interventions [46]. WHO recommends that in areas where hemoglobin disorders are common, special dedicated centers are required in appropriate numbers and locations with a high degree of autonomy [45]. The primary health centers and rural hospitals located in rural areas need additional strengthening for immediate management of acute crisis in SCD in the form of basic care like adequate hydration, analgesia and blood transfusion services [47]. Public awareness raising and SCD education championed by government, non-governmental organizations and advocacy groups need enhancing to counter the stigma and myths associated with SCD. This is beginning to change, and effective groups have emerged in some countries; a global alliance of SCD advocacy groups has recently been formed [48]. The National Health Mission, Ministry of Health and Family Welfare, Govt. of India in 2016 have published the guidelines for 'prevention and control of hemoglobinopathies in India' [49]. It has emphasized on a comprehensive approach to hemoglobinopathies in reference to prevention and control that is expected to help both the administrators and clinicians in this endeavour. There is a need for more public-private partnerships to implement and sustain early diagnosis and interventions to reduce high mortality related to SCD. Point-of-care tests for the detection of SCD have been developed and should help provide rapid, accurate and timely diagnosis. TCU is a state Government endeavor which aids in case and carrier detection through screening programs and comprehensive management of SCD including other thalassemia cases. All the TCUs in West Bengal should come forward and publish their data and this prevalence data will be helpful in convincing Governments and other health policymakers of the need to develop SCD programs and services.

There are some limitations in the present review. First, the estimates are determined based on the available published data, which is non-randomly distributed. Moreover, data from many functioning TCUs in West Bengal are not published; therefore not available for the current review.

8. CONCLUSION

In conclusions, there is a need for early diagnosis of SCD through the implementation of neonatal and early childhood screening. Public awareness and education on SCD is a collective responsibility of the government, non-governmental organizations and different advocacy groups. All the TCUs in West Bengal should publish their data and this prevalence data will be helpful to develop SCD programs, services and their proper implementation. Integration of newborn screening for SCD into existing primary health-care programmes is feasible and can be implemented.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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