IJBPAS, December, 2022, 11(12): 4595-4610

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

GLOBAL SCENARIO OF SICKLE CELL ANAEMIA AND COMPARISON OF SCA AMONG TRIBAL AND NON-TRIBAL POPULATION OF UTTARAKHAND

MELKANI DC[*1], MIGLANI R[1], BORA S[1], KUMAR A[2], SHARMA N[1], RANA M[2], AND BISHT SS[1]

1: Department of Zoology, D.S.B Campus, Kumaun University, Nainital-263002

2: Department of Pharmaceutical Sciences Sir J.C. Bose Technical Campus Bhimtal-263136

***Corresponding Author: Dr. Deepak Chandra Melkani: E Mail: deepakmelkanintl@gmail.com**

Received 20th Dec. 2021; Revised 25th Jan. 2022; Accepted 23rd March 2022; Available online 1st Oct. 2022

https://doi.org/10.31032/IJBPAS/2021/11.10.6471

ABSTRACT

Sickle cell disease (SCD) is one of the most prevalent monogenic diseases worldwide; inherits in an autosomal recessive manner. Globally, SCD has been reported in a many countries worldwide. This manuscript focuses on various aspects of SCD that affect people's lifestyles and passes to the next generation due to poor understanding and awareness. The distribution of SCD in tribal and non-tribal populations in several Indian states is discussed. Tharu tribe is the most numerous schedule tribes in the state Uttarakhand, and many cases of SCD have been documented from this region in recent years. During the course of the research, socio-demographic data from Uttarakhand was gathered. The review revealed a significant lack of understanding of SCD among healthcare providers and the general public. When compared to planned care, the emergency setting provided a poor experience of care, with the absence of prompt provision of pain medication being a major worry. When compared to children and adults, adolescents and young people reported significantly worse care experiences in various domains.

Keywords: Sickle Cell Disease, Uttarakhand, Tribal and Non-tribal, Socio-demographic

INTRODUCTION

Sickle Cell Disease (SCD) is a group of inherited single-gene autosomal recessive disorder caused by the 'sickle' gene, which affects hemoglobin structure **[1]**. The molecular basis for sickle cell disease is an A to T transversion in the 6th codon of the human β-globin gene **[2]**. This simple transversion changes polar glutamic acid residues to a non-polar valine in β-globin polypeptide that results in a reduction of solubility of this sickle haemoglobin **[3]**. The clinical manifestations of SCD arise from the tendency of sickle hemoglobin (known as HbS or $\alpha_2\beta^S{}_2$) to polymerize at reduced oxygen tensions and deform red cells into the characteristic rigid sickle cell shape. Such inflexible red cells cannot pass through the microcirculation efficiently and this result in anemia (due to destruction of the red cells) and intermittent vaso-occlusion causing tissue damage and pain **[4-5]**.

These rigid sickle-shaped red blood cells (RBC) can occlude the microvasculature leading to the sudden onset of painful vasoocclusive episodes (VOC) **[6-7]**. Any cause that reduces microvascular blood flow will increase transit time, facilitating sickled RBC entrapment and resulting in vaso-occlusion. This condition causes stress, cold and pain **[8-9]**. SCD amid tribal populations and newly born children screening programs for SCD have recently been initiated in Maharashtra, Gujarat, Odisha and Chattisgarh. Monitoring these birth cohorts will help to know the actual status of SCD in India. The prenatal analysis is satisfactory by tribal families in India. The Indian Council of Medical Research and the National Rural Health Mission in different states are undertaking outreach programs for better management and control of the disease **[10]**.

SCD is one of the most common monogenetic diseases worldwide and is attributes significant morbidity and mortality. Mutations causing abnormal hemoglobin formation in this disease result in structural abnormalities and cumulative damage to the cellular membrane of sickled erythrocytes **[11]**. The sickle cells clog the blood vessel; they can block blood flow to various parts of the body causing painful episodes (known as sickle cell crises) and raises the risk of infection. Besides, sickle cells die earlier than healthy cells causing a content shortage of red blood cells also known as anemia **[12]**.

According to the American Society for Hematology Report **[13]** on Sickle Cell Disease, the SCD is a chronic disease that has been neglected so far. Those affected by this disease are among the most

vulnerable and underserved therefore the disease has a profound impact on their lives. Currently, the only approved drug for adults with SCD is hydroxyl urea reduce the severity and frequency of painful episodes and is used for stroke prevention, but may not prevent acute complications or reverse organ damage that can result in early death or other health problems.

SICKLE CELL ANAEMIA IN WORLD

Worldwide the most common monogenetic diseases is the sickle cell disease which trait significant mortality and morbidity. The morbidity forms due to SCD were abdominal pain (24%) and joint pain (56%) **[14]**. It is estimated that Mutations causing abnormal haemoglobin formation in this disease result in structural abnormalities and cumulative damage to the cellular membrane of sickled erythrocytes **[11]**.

People of Caucasian, Hispanic, Indian, Mediterranean, Middle Eastern, Native American and other ancestries may be influenced by migration patterns. Sickle cell disease is affecting various parts of the world as people travel or relocates from their home countries, such as North and South America and Europe. Between 2010 and 2050, the number of children born with sickle cell disease is projected to increase by 30% globally **[15]**.

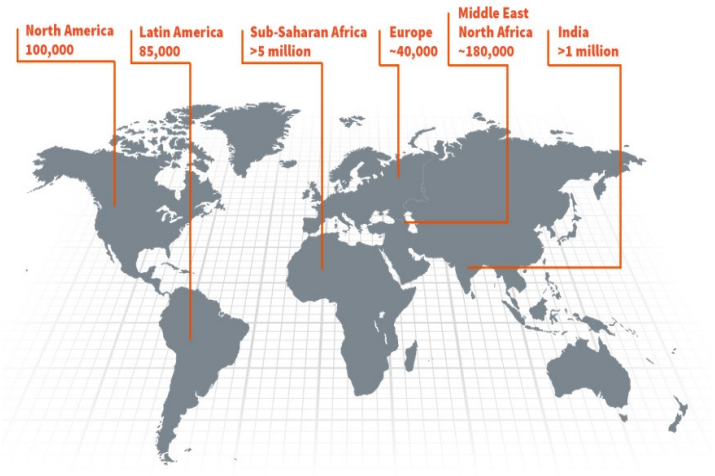

Figure 1: Number of SCD cases worldwide [15]

In Sub-Saharan Africa, which accounts for roughly 80% of the global disease burden, sickle cell disease is a public health priority and an underestimated health issue. Every day, an estimated 1000 children in Africa are born with sickle cell disease, with more than half dying before reaching the age of five **[15]**.

SICKLE CELL ANAEMIA IN INDIA WITH SPECIAL REFERENCE TO UTTARAKHAND

Sickle cell anaemia was not reported in India till the year 1951. Cases of sickle cell

anaemia were reported first by Dunlop and Majumdar **[16]** among laborers in the tea gardens of Assam and the same year Lehmann and Cutbushin **[17]** reported sickle cell disease (SCD) in Nilgiri Hills too. Hockham *et al* **[18]** highlighted some complexity and heterogeneities towards the population of India.

Hockham *et al* **[18]** stated that the data of SCA were scanty in the states like Haryana, Uttarakhand and in parts of southern India and North eastern India. In Uttarakhand the Tharu tribe is the largest of the five schedule tribes and also one of India's most populated tribes with the majority of its members (roughly 80%) live in the Khatima and Sitarganj tehsils **(Figure 1)** of the Udham Singh Nagar district **[19-20]**. The Frequency of HbS trait in Uttarakhand was found 0.15% of total cases **[21]**. SCD is a major public health problem in Uttarakhand as the state inhabits a sizeable number and types of tribes in both i.e. Mountains and plains of Uttarakhand. SCD is one of the most common monogenic disorders globally with an autosomal recessive inheritance **[22-23]**.

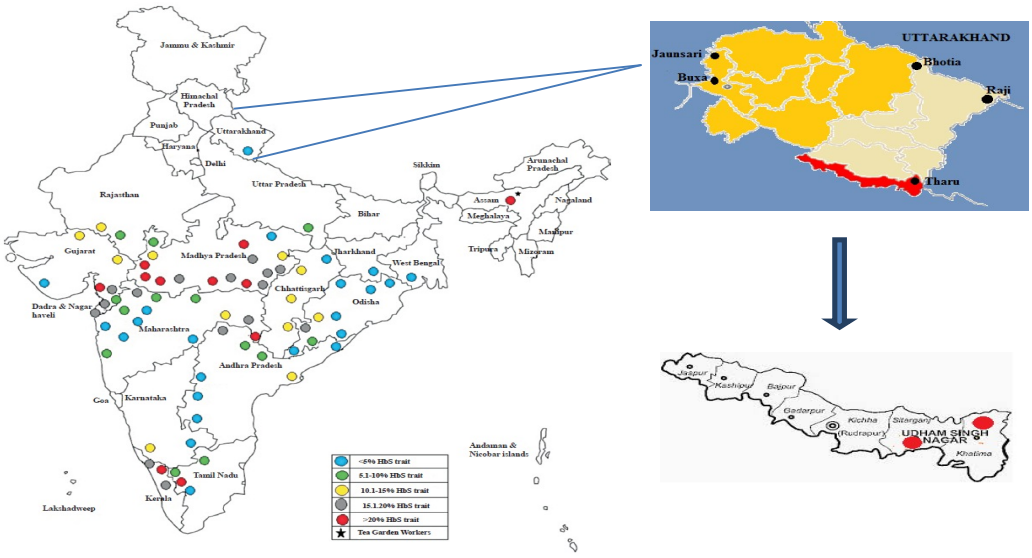

Figure 2: Map highlighting Tribes of Uttarakhand and Sitarganj and Khatima in U.S Nagar District have maximum population of tribal people

DISTRIBUTION OF SICKLE CELL ANAEMIA IN TRIBAL AND NON-TRIBAL POPULATION

India has the main attentiveness of tribal populations internationally. Tribal populations are believed to be the early settlers in the country and are considered to be the original population. According to the Census of India **[24]** they contribute approximately 8.6 % of the total Indian

population, which are about 67.8 million people. About 83% of the total scheduled tribal population in the country lives in rural areas of Madhya Pradesh, Maharashtra, Odisha, Gujarat, Rajasthan, Jharkhand, Chhattisgarh, Andhra Pradesh, West Bengal and Karnataka **[10]**.

Table 1: Caste based distribution in various states of India

State	Caste based Distribution	Percentage
Gujarat	SC ST GC	1-11% 6-31% 1-15%
Rajasthan	ST	1-31%
Uttar Pradesh	ST	1-18%
Madhya Pradesh	SC ST	15-33% 4-32%
Jharkhand	ST	1%
Chhattisgarh	SC ST GC OBC	7.7% 9.3% 5.6% 5.6%
Dadra and Nagar Haveli	ST	4-22%
West Bengal	ST	1-2%
Assam	TGW	15-29%
Maharashtra	SC ST OBC	4-24% 1-35% 5-12%
Orissa	SC ST GC	1-9% 1-13% 3-21%
Andhra Pradesh	ST	11-34%
Karnataka	ST	1-23%
Kerala	ST	18-34%
Tamil Nadu	ST	1-31%

***SC: Schedule Class *ST: Schedule Tribes *TGW: Tea Garden workers *GC: General Caste *OBC: Other backward class. Source [25]**

Dunlop and Mazumder **[16]** also reported the presence of sickle hemoglobin in the workers of tea garden from Assam who migrated from tribal groups of Bihar and Odisha. Since then, many inhabitant's groups have been screened and the sickle cell gene is prevalent among three socio-economically deprived ethnic groups, the scheduled tribes, scheduled castes, and other backward classes in India. The prevalence of sickle cell carriers among different tribal groups varies from 1-40% **[26]**.

SICKLE CELL ANAEMIA CASES IN DIFFERENT AGE AND HEALTH GROUPS

More than 500 children with sickle cell anemia (SCA) die worldwide every single day due to lack of timely access and early diagnosis associated with the treatment, therefore SCA remains an invisible global health problem **[26].** Wastnedge *et al* **[28]** highlighted the Global burden of sickle cell disease in children under five years of age through meta-analysis which clear the global birth prevalence of homozygous SCD to be 0.11%. SCD cases were present

in different regions of India i.e., North Eastern (0-18%), Western (0-33.5%), Central (22.5-44.4%), Southern (1-40%) **[29]**.

SOCIOLOGICAL GAP AWARENESS

Recent findings have focused on biomedical and epidemiological characteristics but there has been scarce research on social determinant and health systems. Progress in clinical understanding of SCD, as well as community awareness campaigns, have encouraged patients to gain access to therapeutic techniques but there are currently less national or state-led programs or mechanisms outlining a health-systems response to SCD **[30-31]**. In India, many population groups have been screened and the sickle cell gene has been shown to be prevalent among three socioeconomically disadvantaged ethnic groups, the scheduled tribes (ST), scheduled castes and other backward classes (OBC). Melkani *et al* **[20]** designed a questionnaire to collect the information on sickle cell disease from Kumaun region of Uttarakhand. The socio-demographic findings with special reference to age, caste, gender, Marital status, tribes, education occupation and income were highlighted. This study attempted to understand the level of awareness public concerns on sickle cell disease. It is also reported that sickle cell disease is not only limited to tribal population but it is prevalent in other religions e.g. Muslim families where congenial marriage or close relationship marriage are a common phenomenon.

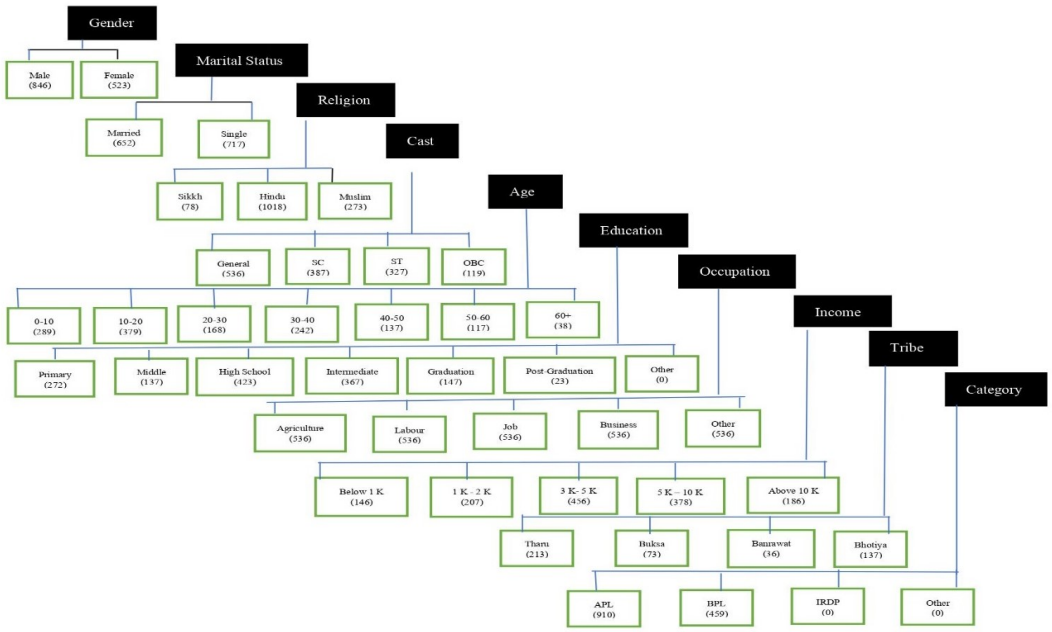

Figure 3: Socio demographic status of respondents [20]

It is concluded that there is an urgent need of health educational programs regarding sickle cell anemia in these tribal pockets of Uttarakhand as very less number of respondents or participants have heard about Sickle Cell Anemia. It was observed that people are interested and positive in attitude towards creating awareness among the tribal population through this survey, a positive response was received on educating them about Sickle Cell Disease, importance of pre-marital, new born screening and counselling and ready to adopt certain lifestyle modifications after proper counselling.

STATUS OF NATIONAL AND INTERNATIONAL REGISTRY OF SCA

The most common hereditary hemoglobinopathy in the world is sickle cell disease (SCD). SCD affects over 100,000 Americans and occurs in approximately one in every 500 people. This disease causes higher morbidity and mortality including India. Similar rates have been recorded in European and Caribbean countries; for example, the number of cases in France is estimated to be about 12 000. SCD has a mean incidence of 1 per 1000 births in Brazil, with 3000 new cases reported each year. There are about 25, 000,000 carriers of sickle cell disease. A gene (Hemoglobin AS) and about 1, 25,000 sickle cell disease patients. It is estimated that there are approximately 3.6 to 3.9 crore carriers of -thalassemia in India, and approximately every year 10 to 15 thousand babies are born with -thalassemia major **[32-34].**

SCD primarily affects immigrants and their descendants from endemic areas in Germany, especially those from Africa and the Middle East.SCD and its complications are becoming more common in Germany, according to admission diagnosis data. More comprehensive epidemiological data are needed to document the disease burden, identify gaps in patient management, and enhance patient care.

Many clinical questions about SCD have already been addressed by several patient registries around the world. The German Society of Pediatric Oncology and Hematology developed a registry for patients with SCD for these purposes (GPOH) **[35].**

Canadian government takes some steps towards the better approach to tackle SCD. So, the Sickle Cell Disease Association of Canada/Associationd' Anémie Falciforme du Canada (SCDAC/AAFC) were enforced to acknowledges its responsibility to work closely with the World Health Organization and the World Sickle Cell Network to achieve comprehensive care for all Sickle Cell Disease patients on the other hand

Sickle Cell Disease Association of America (SCDAA) recently launched Get Connected the first patient-driven registry for SCD **[36]**.

On June 19, World Sickle Cell Day, the SCDAA launched a national registry for children and adults with sickle cell disease, their families and healthcare providers, as well as advocacy organisations, researchers, and individuals with sickle cell trait.It also gives patients access to disease-specific healthcare resources as well as high-quality knowledge about clinical treatment, science, activism, and policy concerns related to sickle cell anaemia. Get Connected is also intended to support clinical research projects on sickle cell disease by bringing scientists together with the aim of conducting clinical trials focused on sickle cell patients' needs. The SCDAA describes the website as a way to link people with sickle cell disease to healthcare, mental health, clinical trials, and other services **[36].**

By 1982, Cuba was producing an average of 100 SCD infants per year. As a result, the Cuban health system developed a SCD preventive programme that operated in a network that included primary care settings, clinics, research facilities, and medical genetics laboratories. The Sickle Cell Anemia Prevention Program was created to screen pregnant women and couples for carriers and, if found, to perform antenatal SCD genotype testing in the foetus.From 1982 to 2006, laboratory work at the National Medical Genetics Center in Cuba used haemoglobin electrophoresis on equipment developed and patented by Cuban researchers (CNGM) **[37].**

The Sickle Cell Disease Clinical Trials Network was launched by ASH in 2019, and it offers a mechanism for finding and categorising patient cohorts for clinical trials, matching trial sponsors with sites, and recruiting qualified patients. It gathers data from the RC Data Hub to help identify areas of study and care that could benefit from more data **[38].**

Three approaches to collecting and reviewing data on people with SCD and SCT

- Screening is the process of determining whether an individual has a disease or is a carrier of a disease. In the United States, screening of SCD is usually done at birth (NBS) of during the prenatal period.
- A disease registry is a method for collecting data and communicating with people who are afflicted with a certain disease. Such systems may be funded by the government, disease advocacy groups,

pharmaceutical or device firms, or other entities.

- Public health surveillance: ongoing, systematic collection, review and interpretation of health-related data required for public health planning, implementation and evaluation **[39].**

In India to bridge the gap between patients and health care facilities in tribal areas, the Ministry of Tribal Affairs (MoTA) has launched the Sickle Cell Disease Support Corner. The Portal is a web-based patient-powered registry system that will collect all information about SCD among India's tribal people, including providing them with a website to register themselves if they have the disease or trait **[40].** The help corner is imagined as a one-stop hub for information on SCD in India's tribal regions. The portal will provide visitors with real-time data through a dashboard, an online self-registration service, which will serve as a knowledge repository with information about the disease and various government initiatives. A National Council on Sickle Cell Disease has also been established, comprised of senior officials from the Government of India as well as private and public health care organisations, to ensure prompt and efficient action **[40].**

STRESS DUE TO SICKLE CELL DISEASE

Health care is a must and a fundamental human need. The Alma Ata Declaration of 1978 recognizes the necessity to make social guarantees in the various Governments to guarantee the health and other fundamental requirements of the inhabitants of their country **[41].** SCD patients experience a great deal of stress, not just as a result of external factors, but also as a result of the illness itself, which includes painful episodes and recurrent medical treatments. Stress increases the sympathetic nervous system while suppressing the parasympathetic nervous system in SCD patients compared to non-SCD patients, causing ANS hyper reactivity **[42-43].** Stress is strongly related to higher pain severity, less social and physical activity and increased use of health care **[44-46].** SCD has an emotional and physical impact on individuals who live with it for the rest of their lives **[47].** Men and women with SCD reported relatively similar pain experiences, contrary to many studies on pain, particularly chronic pain [48]. In individuals with SCD, depression and anxiety predicted higher and lower physical and mental quality-of-life, accounting for more variation in all quality-of-life categories than hemoglobin type**[49].** Shah *et al* **[50]** highlights the effect of mental stress on autonomic nervous system and microvascular blood

flow and concluded that that the mental stress causes vasoconstriction and autonomic nervous system reactivity in all subjects.

GUIDELINES OF CDC, WHO, UNICEF AND ICMR FOR SCA

The Indian Council of Medical Research and the National Rural Health Mission in different states has undertaken outreach programs for better management and control of the disease **[10].** The ICMR report**[51]** says that in India about 70 million patients suffer from rare genetic diseases including SCD. ICMR has released National guidelines for the treatment of patients suffering from these rare genetic diseases which are assisting medical experts to get genetic therapy product development and carry out clinical trials in most of the states where prevalence of SCD is high. The diagnosis facilities including HPLC, molecular diagnosis and established the programs like population screening, antenatal screening, newborn screening and prenatal diagnosis. UNICEF, CDC, ICMR and WHO organised number of awareness programmes on Sickle Cell Anaemia and describes a series of public health strategies to minimize the burden of the illness through national creation or improvement of policy; early detection, management and community awareness.

THERAPEUTIC AWARENESS/COUNSELLING MEASURES USED IN SCA

Sickle cell studies require some national programme for control and care of Haemoglobinopatheis to generate data that will lend itself to improved precision in current estimates. Children's suffering with sickle cell anaemia should be given prophylactic penicillin from birth until they are at least five years old, and all people with sickle cell illness should be vaccinated against invasive pneumococcal disease. For all children with sickle cell disease beginning at the age of two and going through adolescence, annual screening with transcranial doppler ultrasound is suggested for stroke risk assessment and transfusion treatment in high-risk patients (For patients with acute chest syndrome, antibiotics, hospitalization and incentive spirometry are needed. The promotion and administration of hydroxyurea treatment in patients who have a sickle cell anaemia is well documented for nine months and older because it can reduce the incidence of vasoocclusive crisis and a limited-effect acutes in the chest syndrome **[52].**

Allele frequency differences between population groups are high, due to the custom of within-group marriages, thus there is likely an excess of recessive diseases in India that can be screened and

mapped genetically. In order to address this burden, there is a need for national comprehensive newborn screening to identify patients, and the development of holistic SCD care programmes to provide therapeutics and education for families and children with SCD.

FUTURE PLANNING AND PROSPECTS FOR THE MANAGEMENT OF SCA

SCA morbidity and mortality are reduced by newborn screening, early prevention procedures, education about risks and screening services. Going forward, diagnosis and treatment of youth and adults with SCA must be prioritized by adopting genetic test, with an emphasis on quality of life as well as medical risks. More strategies are needed to minimize the prevalence of SCD and the burden of healthcare costs must be focused. Mass consciousness campaign and education on Sickle cell is needed.

ACKNOWLEDGEMENT

Authors would like to thank Department of Zoology, D.S.B Nainital for their infrastructure support during the course of study.

CONFLICT OF INTEREST

The author declares no conflict of interest.

REFERENCES

[1] Pauling L, Itano H A, Singer S J. *et al.* Sickle cell anemia: a molecular disease. Science 1849; 110(2865): 543–548.

[2] Steinberg M H. Sickle cell anemia, the firstmolecular disease: overview of molecular etiology,pathophysiology, and therapeutic approaches. Scientific World Journal 2008; 8: 1295-324.

[3] Mehanna A S. Sickle cell anemia and anti sickling agents then and now. Curr MedChem. 2008; 8(2): 79-88. PMID: 11172667

[4] Bunn H F. Pathogenesis and treatment of sickle cell disease. N Engl J Med 1997; 337: 762–769.

[5] Neville K A, Panepinto J A. Pharmacotherapy of Sickle Cell Disease. 18th Expert Committee on the Selection and Use of Essential Medicines. 2011; 1-15.

[6] Rees D C, Williams T M, Gladwin M T. Sickle cell disease. Lancet 2010; 376(9757): 2018-31.

[7] Kassim A A, DeBaun M R. Sickle cell disease, vasculopathy, and therapeutics. Annu Rev Med 2013; 64(1): 451–466.

[8] Murray N, May A. Painful crises in sickle cell disease--patients' perspectives. BMJ. 1988; 297 (6646): 452–454.

[9] Christoph G W, Hofrichter J, Eaton W A. Understanding the shape of

sickled red cells. Biophys J. 2005; 88(2): 1371–1376

[10] Colah R B, Mukherjee M B, Martin S, Ghosh K. Sickle cell disease in tribal populations in India. Indian Journal of Medical Research 2015; 141(5): 509-515.

[11] Inusa B P D, Hsu L L, Kohli N. *et al.* Sickle Cell Disease Genetics, Pathophysiology, Clinical Presentation and Treatment. International Journal of Neonatal Screen 2019; 5: 20.

[12] Hodge J. Sickle Cell Trait vs. Sickle Cell Disease. Sickle cell disease. 2020. https://www.gethealthystayhealthy.com/articles/sickle-cell-trait-vs-sickle-cell-disease.

[13] American Society of Hematology report. State of Sickle disease. Research and Clinical Trials. 2016; 1-27.

[14] Sahas B, Goyal R C G, Yogesh R. Sickle cell anemia and morbidity in tribal population of pombhurna, district chandrapur, maharashtra, India. Innovative Journal of Medical and Health Science 2014; 4(6): 169 – 171.

[15] Novartis. Global impact of SCD. 2019. https://www.notaloneinsicklecell.com/untold-SCD-stories/

[16] Dunlop K J, Mazumber U K. The occurrence of sickle cell anemia among a group of tea garden labourers in Upper Assam. Indian Med Gaz 1952; 87: 387-91.

[17] Lehman H, Cutbush M. Sickle cell trait in southern India. British Medical Journal 1952; 1: 404-405.

[18] Hockham C, Bhatt S, Colah R. *et al.* The spatial epidemiology of sickle cell anaemia in India. Scientific Report 2018; 8: 176-85.

[19] Rajpoot A, Kumar V P, Sharma J. Current health status of Uttarakhand, Tharu TRIBE on the basis of blood clinical parameters: A biocultural perspective. International Clinical Pathology Journal. 2016; 3(3): 219–223. DOI: 10.15406/icpjl.2016.03.00077.

[20] Melkani D C, Sharma N P, Panda A K, Kumar K, Bisht S P S. Study of Proteomic Diversity for Sickle Cell Disease in Tribe and Non-Tribe Population of Kumaun Region of Uttarakhand. Bulletin of Environment, Pharmacology and Life Sciences. 2020; 9(12): 7.13.

[21] Nayar S, Acharya S, Acharya R, Kishore S, Thakur, B. Spectrum of Haemoglobinopathies: A Hospital

Based Study in Uttarakhand Pathology Section. Journal of Clinical and Diagnostic Research. 2017; 11(12): 18-21.

[22] Serjeant G R, Serjeant B E. Editors, Sickle cell disease, 3rd ed. Oxford: *Oxford Univ Press*. 2001.

[23] Xu J Z; Thein S L. The carrier state for sickle cell disease is not completely harmless. Haematologica 2019; 104(6): 1106-1111.

[24] Census of India. Office of the Registrar General and Census Commissioner. Ministry of Home Affairs, Govt of India. 2011. https://censusindia.gov.in/2011-common/censusdata2011

[25] Bhatia H M, Rao V. R. Genetic atlas of Indian Tribes. *Bombay: Institute of Immunohaematology Indian Council of Medical Research (ICMR)*. Bombay India.

[26] Colah, R., Mukherjee, M. & Ghosh, K. (2014). Sickle cell disease in India. Curr. Opin. Hematol; 1987; 21: 215-23.

[27] McGann P T. Time to Invest in Sickle Cell Anemia as a Global Health Priority. Pediatrics (2016) 137(6): e20160348.

[28] Wastnedge E, Waters D, Patel S, Morrison K, Goh M Y, Adeloye D, Rudan I. The global burden of sickle cell disease in children under five years of age: a systematic review and meta-analysis. Journal of global health (2018); *8*(2): 021103. https://doi.org/10.7189/jogh.08.021103.

[29] Gorakshakar A C. Epidemiology of Sickle Hemoglobin in India. Proceeding of National Symposium on Tribal Health. 2006; 103-108.

[30] Patil S S, Thikare A A, Wadhva S K, Narlawar U W, Shukla S. Knowledge, attitude and practice regarding sickle cell disease in adult sufferers and carriers in a rural area. International Journal of Community Medicine and Public Health. 2017, 4(4): 1075-1080.

[31] Raman V, Seshadri T, Joice S V, Srinivas P N. Sickle cell disease in India: a scoping review from a health systems perspective to identify an agenda for research and action. BMJ Global Health 2021; 6:e004322. doi: 10.1136/bmjgh-2020-004322.

[32] Policy For Prevention and Control of Hemoglobinopathies – Thalassemia, Sickle Cell Disease and variant Hemoglobins In India by Ministry of Health and Family

Welfare Government of India New Delhi 2018. https://www.cdc.gov/ncbddd/sicklecell/data.html

[33] Shukla R N, Solanki B R, Parande A S. Sickel Cell Disease in India. ASH Publication; 1958. http://ashpublications.org/blood/article-pdf/13/6/552/552506/552.pdf

[34] CDC. Centers for Disease Control and Protectionwhat is sickle cell disease? 2015. Available at: https://www.nhlbi.nih.gov/health-topics/sickle-cell-disease

[35] Kunz J B, Lobitz S, Grosse R, Oevermann L. *et al.* Sickle cell disease in Germany: Results from a national registry. Pediatric Blood & Cancer. 2019. https://onlinelibrary.wiley.com/doi/epdf/10.1002/pbc.28168.

[36] Pena A. Sickle Cell Disease Association Launches First Patient-powered Registry. Sickel Cell Disease News. 2016. https://sicklecellanemianews.com/2018/06/21/sickle-cell-disease-association-launches-first-patient-powered-registry/.

[37] Marcheco-Terue B. Sickle Cell Anemia in Cuba: Prevention and Management, 1982–2018. MEDICC Review. 2019. 21(4): 34-38.

[38] Ash R C. (American Society of Hematology Research Collaboration). Sickle Cell DiseaseClinical Trials Network. 2018. https://www.ashresearchcollaborative.org/sites/default/files/2018-12/ASH_Research_Collaborative_CTN_Handout.pdf.

[39] Mary H. Screening, Registries, and Surveillance. Addressing Sickle Cell Disease: A Strategic Plan and Blueprint for Action. The national Academies Press. Washington DC. 2001; 81-83. https://www.ncbi.nlm.nih.gov/books/NBK566461/.

[40] Ministry of Tribal affair (MoTA). Annual Report. 2020. https://tribal.nic.in/downloads/Statistics/AnnualReport/AREnglish2021.pdf

[41] Declaration of Alma-Ata September 12, 1978. [Accessed March 14, 2015]. Available from: http://www.who.int.

[42] Pearson S R, Alkon A, Treadwell M, Wolff B, Quirolo K, Boyce W T. Autonomic reactivity and clinical severity in children with sickle cell disease. Clin Auton Res. 2005; 15(6):400-407.

PubMed|https://doi.org/10.1007/s10286-005-0300-9.

[43] Treadwell M J, Alkon A, Styles L & Boyce W T. Autonomic nervous system reactivity: children with and without sickle cell disease. Nurs Res. 2011; 60(3): 197-207. PubMed|https://doi.org/10.1097/NNR.0b013e3182186a21.

[44] Porter L S, Gil K M, Sedway J A, Ready J, Workman E, Thompson R J. Pain and stress in sickle cell disease: an analysis of daily pain records. Int J Behav Med. 1998; 5(3): 185-203. PubMed|https://doi.org/10.1207/s15327558ijbm0503_1

[45] Porter L S, Gil K M, Carson J W, Anthony K K, Ready J. The role of stress and mood in sickle cell disease pain: an analysis of daily diary data. J Health Psychol. 2000; 5(1): 53-63. PubMed|https://doi.org/10.1177/135910530000500109

[46] Gil K M, Carson J W, Porter L S. Daily stress and mood and their association with pain, health-care use, and school activity in adolescents with sickle cell disease. J Pediatr Psychol. 2003; 28(5): 363-373. PubMed|https://doi.org/10.1093/jpepsy/jsg026

[47] Jenerette C, Funk M, Murdaugh C. Sickle cell disease: A stigmatizing condition that may lead to depression. Issues in Mental Health Nursing. 2005, 26(10): 1081–1101.

[48] McClish D K, Levenson J L, Penberthy L, Roseff S D, Bovbjerg V E, Roberts J D, Aisiku I P, Smith W R. Gender differences in pain and healthcare utilization for adult sickle cell patients: The PiSCES Project. J Womens Health (Larchmt) 2006; 15(2): 146-54. doi: 10.1089/jwh.2006.15.146.

[49] Levenson J L, McClish D K, Dahman B A, Bovbjerg V E, Citero V D A,. Penberthy L T. *et al.* Smith. "Depression and anxiety in adults with sickle cell disease: the PiSCES project." Psychosomatic medicine 2008; 70 (2): 192-196.

[50] Shah P, Khaleel M, Thuptimdang W, Sunwoo J, Veluswamy S, Chalacheva P, Kato R M. *et al* . Mental stress causes vasoconstriction in subjects with sickle cell disease and in normal controls. Haematologica 2020; 105(1): 83-90.

https://doi.org/10.3324/haematol.2018.211391

[51] ICMR. Media report "National Guidelines for Gene Therapy Product Development and Clinical Trials". Department of Health Research – Ministry of Health & Family Welfare Government of India. Department of Biotechnology Ministry of Science & Technology Government of India. 2020; 1-126. https://www.nhp.gov.in/NHPfiles/guidelines_GTP.pdf.

[52] Yawn B P, John-Sowah J. Management of Sickle Cell Disease: Recommendations from the 2014 Expert Panel Report. Am Fam Physician. 2015; 92(12): 1069-1076.