RESEARCH PAPER

# Newborn Screening and Clinical Profile of Children With Sickle Cell Disease in a Tribal Area of Gujarat

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**Objectives**: To present the result of newborn sickle cell disease (SCD) screening and clinical profile of SCD newborns in a tribal area of Gujarat. **Methods:** We screened all newborns of sickle cell trait (SCT) and SCD mothers for SCD using high-performance liquid chromatography (HPLC) within two days of birth at a secondary care hospital in a tribal area in Gujarat from 2014 to 2019. Newborns with SCD were registered under an information technology based platform for hospital-based comprehensive care. Neonates were followed prospectively every 3 months. If they missed the clinic visit, a medical counsellor visited them at home to collect the required information. **Results:** Out of 2492 newborns screened, 87 (3.5%) were diagnosed with SCD. Among the 67 newborns screened for alpha-thalassemia deletion, 64 (95.4%) of babies had alpha-thalassemia deletion. We recorded total 554 clinic visits over the period of 221.5 person-years. The rates of acute febrile illness, painful crisis, hospitalization and severe anemia were 42.9, 14.9, 14.9 and 4.5 per 100 person-year, respectively. Two deaths were recorded, and 5 babies (5.7%) had severe SCD. **Conclusion:** We found a high prevalence of alpha thalassemia deletion among newborn SCD cohort in tribal area of Gujarat, and 70% babies had atleast one clinical complication on follow-up.

**Keywords:** *α-Thalassemia deletion, Follow-up, Mortality, Outcome*.

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Sickle cell disease (SCD) is most prevalent among indigenous ethnic groups in India. The prevalence of SCD carriers among different tribal groups varies from 1-40% [1-3], with a prevalence of 1-2% among tribal groups in Gujarat [1,4]. Early diagnosis by newborn screening (NBS) followed by comprehensive care, including regular clinical and laboratory check-up and prophylaxis for pneumococcal infection, can reduce the mortality and morbidity among children with SCD [5,6].

Most newborn babies are not screened for SCD in India [7], but the available data suggests that presentation of SCD is varied across regions in India [8-10]. There was a significant loss to follow-up in previous studies, making it difficult to determine the natural history of SCD. The present study was undertaken by systematically following-up a cohort of newborn babies suffering from SCD and receiving comprehensive care.

## METHODS

This is a descriptive study of a newborn cohort registered under the comprehensive SCD program in a secondary care hospital managed by SEWA Rural, a non-governmental organization (NGO), in a tribal area in Gujarat. The hospital works as the first referral unit and serves the catchment area of about 1500 villages including 1.5 million population from Narmada and Bharuch districts in southern Gujarat. About 65% of patients are from scheduled tribe population. Inpatient and outpatient care is provided on a highly subsidized basis, or free of cost to the patients [11,12].

A comprehensive care program for SCD was started by SEWA rural in February, 2014 [13,11]. All women visiting the hospital for antenatal care (ANC) were screened for SCD by solubility test and subsequently confirmed by high-performance liquid chromatography (HPLC). The newborn babies born to women with SCD and sickle cell trait (SCT) at the hospital were further screened by HPLC within two days of birth. We used dried spot Guthrie card method or heel prick method to collect the blood sample from the study participants. Hemogloblin analysis was done using automated HPLC on Variant Hb Testing System (Bio-Rad Labs) and Variant NBS (Bio-Rad Labs). Provisional diagnosis of SCD was given by a trained medical doctor based on the HPLC reports. In HPLC reports, if the peak of HbS was higher than HbA,

the baby was marked as SS-phenotype. For all newborns diagnosed with SS-phenotype, the HPLC test was repeated after nine months, and sickle cell status confirmed by DNA analysis.

All the newborns that were diagnosed with homozygous SCD were registered in an electronic registry by a trained counsellor/social worker after informed consent from parents. Parents of each newborn were counselled to visit the clinic once every three months for follow-up care. We followed evidence-based standard protocols for the inpatient and outpatient care of these patients [13]. A trained nurse-counselor collected data and tracked the newborns with SCD. We developed a mobile device application for registration and follow-up. At every visit, the counselor entered the laboratory and clinical data in the application under the guidance of a medical officer.

If any newborn failed to visit the clinic, the device sent an automatic reminder to the counselor, who then telephonically contacted parents of the newborn to remind them to visit the clinic. If the newborn did not visit the clinic for six months, then a trained medical counselor did a home visit of the newborn to collect information. Medical counselors filled the field visit form (which consisted of information about the medical condition of the newborn), collected blood samples and counseled parents to visit the clinic to ensure continuity of care. All information regarding follow-up of field visits (including home visits) were entered in the device by the counselor. The medical officer was responsible for quality assurance. A monthly monitoring meeting of all project staff was scheduled to review the processes.

The information collected at the time of registration and during follow-up included details of hospitalization, painful events, blood transfusion, acute febrile illness, sepsis, severe anemia (hemoglobin <7g/dL), dactylitis, acute chest syndrome, stroke, sequestration crisis, splenomegaly, hepatomegaly, acute respiratory infection, cough and cold, asthma, foot ulcer, and death. Information about interventions including prescription of required medicines and pneumococcal vaccine status was also recorded during each follow-up visit. We defined severe sickle cell disease when a patient had at least three vaso-occlusive crisis or three hospitalization or three blood transfusions [14].

*Statistical analysis*: The rate of incidence was calculated in 100 person-years (PY). Descriptive statistics was done using Microsoft Excel 2013.

## RESULTS

A total of 2492 newborns born between April, 2014 and June, 2019 were screened for SCD. A total of 87 newborns were diagnosed with SCD and registered in the hospital-based sickle cell registry. Among the 67 newborns screened for alpha-thalassemia deletion, 59 (88%) were homozygous (-α3.7/-α3.7) deletions, 5 (7.4%) were heterozygous (-α3.7/5αα) deletions, and 3 subjects (4.4%) were normal (αα/αα) for alpha gene deletion. Only one baby had HbS-β thalassemia. By October, 2019, none of the 87 newborns were lost to follow-up. A total of 544 follow-up outpatient visits occurred; follow-up period was 221.5 person-years. The number of visits ranged from 1-16 based on age of newborn, which ranged from 51 day to five year.

All newborn babies were from scheduled tribe population and parents of 9.2% of the babies were illiterate and 65.5% had received primary education. Most families were either laborers (41.4%) or doing a formal job (21.8%). 64% of the enrolled babies received amoxicillin prophylaxis and 82 (94.3%) received at least one dose of the 13-valent pneumococcal vaccine. Out of 50 children who completed their second birthday during the study period, 30 (60%) received the 23-valent pneumococcal vaccines. All newborn babies received folic acid treatment during follow-up.

**Table I** shows the incidence of various complications of SCD – 70 (80.5%) newborn babies had at least one clinical complication during the follow-up period. There was no incidence of acute splenic sequestration crisis or stroke. Splenomegaly (*n*=11) varied from 1 cm to 13 cm from the lower costal margin along the axis of spleen. Hemoglobin levels varied between 6.0-14.5 g/dL (average 9.3 g/dL).

**Table I Clinical Events During Follow-up in Newborns With Sickle Cell Disease Enrolled in the Study**

| *Clinical event* | *Number of events* | *Event per 100 person-years (95% CI)* |
|---|---|---|
| Hospitalization | 33 | 14.9 (9.8-20) |
| Painful events | 33 | 14.9 (9.8-20) |
| Blood transfusion | 7 | 3.2 |
| Acute febrile illness | 95 | 42.9 (34.3-51.5) |
| Sepsis | 10 | 4.5 (1.7-7.3) |
| Severe anemia | 10 | 4.5 (1.7-7.3) |
| Dactilytis | 1 | 0.5 |
| Death | 2 | 0.9 |
| Splenomegaly | 11 | 5.0 (2-7.9) |
| Hepatomegaly | 1 | 0.5 |
| Acute respiratory infection | 13 | 5.9 (2.7-9.1) |
| Cough and cold | 150 | 67.7 (56.9-78.6) |
| Foot ulcer | 11 | 5.0 (2-7.9) |

*Total follow-ups 544; total follow-up period 221.5 person-years. There were no episodes of acute chest syndrome, stroke, sequestration crisis and asthma.*

**WHAT THIS STUDY ADDS?**

- Among newborns with sickle cell disease, 95% of babies had alpha-thalassemia deletion and 70% of babies presented with at least one clinical complication during the follow-up period.

Five babies were diagnosed with severe SCD. Four of these had alpha-thalassemia in homozygous condition. All five children were put on hydroxyurea treatment, with no side effects reported. Two children died during the follow-up; a 2-year-old baby was hospitalized with fever, convulsion/unconsciousness, severe pallor, splenomegaly and died within few hours of hospitalization, and another 5-month-old baby died at home after fever, cough, and shortness of breath for two days.

## DISCUSSION

In India, very few reports are available on the health-seeking behavior, follow-up visits and coverage of proven interventions among children with SCD. In our targeted screening, 3.5% of the newborns were diagnosed with HbS and started on preventive treatment. Another study from Central India with a similar methodology had 4.5% newborns diagnosed with SCD [10], and the prevalence of HbS-α thalassemia was found 28% among newborn SCD babies in a previous study from Gujarat [9].

Uyoga, et al. [15] reported that in Kenya, the mortality rate for children under five years with SCD was 5.8 per 100 PY. While in a Jamaican sickle cell cohort, 14% of SCD children died before the age of two years when effective intervention strategies were not implemented. We found mortality of <1% in SCD children, when effective intervention strategies were implemented. A study from Gujarat reported that 21.8% children with SCD aged <5 years presented with severe clinical complications [9]. Another study from central India showed that 85% of children with SCD had some clinical symptoms by the age of 5 years and the mortality rate was 3.65 per 100 PY [10]. In our cohort, the mortality was similar to results of the Cooperative Study of Sickle Cell Disease (CSSCD) (1.1 per 100 PY) [22] and Dallas cohorts (0.6 per 100 PY) [16], both studies from developed countries. The lower death rate in Dallas cohort might be due to longer period of follow-up. In the Dallas cohort, if we consider only first six years of life, the mortality rate was 0.81per 100 PY, which is comparable to our cohort.

Infection was a leading cause of death among SCD children and acute febrile event (42.6 per 100 PY) was one of the vital features in our cohort. The similarity between painful events (14.8 per 100 PY) and hospitalization (14.8 per 100 PY) shows the improved care seeking behavior among the parents of the children with SCD. In the Jamaican study, a total of 8% of the children (age range 15 months-14 years) were diagnosed with a stroke. In the Nagpur study, the incidence of stroke was 3.0 per 100 PY [10] while in our cohort, none of the SCD babies had stroke. This lower stroke incidence could be due to the lower age-range of our cohort.

Our study is the first to systematically evaluate a newborn cohort of SCD patients for 3-4 years without any loss to follow-up. It has certain limitations. Firstly, we developed the IT-based technology in December, 2015, which ensured high-quality data entry. Chances of missing data may have been higher and the quality of data may have been affected during manual registrations. Second, as newborn babies were followed up in outpatient clinics and through home visits every three months, this may have increased chances of recall bias.

Our study presents a different genotypic picture of SCD compared to other parts of India. Although, a high prevalence of alpha-thalassemia deletion was seen, majority of SCD newborns presented with at least one clinical complication of SCD.

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*Contributors*: KD: performed experiment, analysis of data and drafted the manuscript; GD, SD: conceptualized the study, finalized the study design, performed experiement and critically reviewed and revised the manuscript; YI, MBM, PM: involved in data collection, interpretation of findings, critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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