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Homozygous sickle cell disease in Central India & Jamaica: A comparison of newborn cohorts

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***Background & objectives*: Homozygous sickle cell (SS) disease in Central India runs a more severe clinical course than reports from other areas of India. The current study was undertaken to compare the disease in Central India (Nagpur) with that in Jamaica, both populations defined by newborn screening.**

***Methods*: The Nagpur cohort included infants born to sickling-positive mothers from May 2008 to 2012, examined by high-pressure liquid chromatography and DNA analysis. The Jamaican cohort screened 100,000 consecutive non-operative deliveries between June 1973 and December 1981, analyzed by haemoglobin (Hb) electrophoresis and confirmed by family studies and compatible HbA_2 levels.**

***Results*: In Nagpur, 103 SS patients were detected, but only 78 (76%) were followed up. In Jamaica, 311 cases were followed from birth and compliance with follow up remained 100 per cent up to 45 years. In the Nagpur cohort all had the Asian haplotype, and 82 per cent of Jamaicans had at least one Benin chromosome; none had the Asian haplotype. Compared to Jamaica, Nagpur patients had higher foetal Hb, less alpha-thalassaemia, later development of splenomegaly and less dactylitis. There were also high admission rates for febrile illness and marked anaemia. Invasive pneumococcal disease occurred in 10 per cent of Jamaicans but was not seen in Nagpur.**

***Interpretation & conclusions*: There were many differences between the disease in Nagpur, Central India and the African form observed in Jamaica. The causes of severe anaemia in Nagpur require further study, and reticulocyte counts may be recommended as a routine parameter in the management of SS disease. The role of pneumococcal prophylaxis needs to be determined in Nagpur patients. Future studies in India must avoid high default rates.**

Key words Anaemia - Central India - foetal haemoglobin - Jamaica - newborn cohort - sickle cell disease - splenomegaly

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An early comparison of homozygous sickle cell (SS) disease in the State of Odisha, India, and Jamaica concluded that Odisha patients had more frequent alpha-thalassaemia, higher foetal haemoglobin (HbF) and lower HbA_2 levels, higher total haemoglobin (Hb), microcytic red cell indices and lower reticulocyte counts compared to Jamaicans[1]. Clinically, Odisha patients had greater persistence of splenomegaly, and possibly splenic function, frequent bone pain, but less chronic leg ulceration and priapism. Broadly, similar conclusions were later drawn from a population in Gujarat[2] but that study found more severe disease in Central India, an impression since amply confirmed[3-6]. This raises two issues, the mechanism of the difference between mild and severe disease in India and also how the more severe disease in Central India compares with those of African origin in Jamaica. The current study was undertaken to address the latter question and was based on populations diagnosed by newborn screening in Nagpur[7] and Jamaica[8] which avoided the symptomatic bias inherent in clinic-based populations.

Material & Methods

Patient ascertainment: The Nagpur cohort study[5,7] was based on newborn screening at the Government Medical College, Nagpur, between May 11, 2008 and May 15, 2012. The offspring of mothers with positive solubility tests had heel-prick samples taken into ethylenediaminetetraacetic acid (EDTA) 1-7 days after birth and analyzed by high-performance liquid chromatography (HPLC) (Bio-Rad Laboratories, USA). There were 103 infants with SS disease, of whom 25 defaulted at birth and the current study was confined to the 78 SS infants with follow up. Scheduled Castes (SCs) accounted for 69 (88%) among whom the Mahar dominated and only three were Scheduled Tribes (STs). The Jamaican cohort[8] recruited 311 infants with SS disease during screening of 100,000 consecutive non-operative deliveries at Victoria Jubilee Hospital in Kingston, Jamaica, between June 25, 1973 and December 28, 1981. The current study of Nagpur and Jamaican data involved reanalysis to make the group data comparable and was conducted between November 2017 and October 2018.

Genotype diagnostic criteria: In Nagpur, the diagnosis of SS disease was based on a single-dominant band in the position of HbS on HPLC, consistent HbA_2 levels and family studies. In the 78 newborns with some follow up, both parents had the SS gene in 59 (76%). Haematological indices were determined electronically (Sysmex K-1000, Sysmex Corporation, Kobe, Japan) and HbA_2 and HbF levels estimated by HPLC.

In Jamaica, umbilical cord samples were collected into EDTA and analyzed by electrophoresis on cellulose acetate followed by acid agar gel electrophoresis of all electrophoretically abnormal bands[9], and the diagnosis was confirmed by consistent HbA_2 levels, and family studies. Haematological indices were determined electronically[10] (Coulter Counters, Hialeah, Florida), HbA_2 by elution after alkaline Hb electrophoresis and HbF by alkali denaturation.

Comparison of Nagpur and Jamaican data: Molecular, clinical and haematological data of Nagpur cohort were compared with the Jamaican cohort[10]. The relatively small numbers and narrow age range of the Nagpur group implied that comparisons with Jamaican data were usually confined to the first three years of life for haematology and clinical indices. For Hb and red cell indices, Nagpur data were restricted to steady-state outpatient visits excluding values on hydroxyurea and for three months following transfusion. Reticulocyte counts in Nagpur were uncommon but routine in Jamaica. Where multiple observations were available in Nagpur, only that closest to the target age was used whereas Jamaican data were the mean of all steady state observations for each age group. Beta-globin haplotypes were determined in Jamaicans[11] and Nagpur[5] as specified. The presence of alpha-thalassaemia was determined by multiplex gap-polymerase chain reaction in Nagpur patients and by restriction endonuclease analysis of peripheral blood DNA in Jamaica[12].

Procedure for follow up: Nagpur patients were given regular appointments, and defaulters were pursued by phone calls, letters and social workers. The protocols required pneumococcal prophylaxis with oral penicillin and the 23-valent pneumococcal vaccine (costs covered by the study funders), and the conjugate vaccine was recommended (course cost ₹16,000/- charged to the patient). Hydroxyurea (10 mg/kg) was used in four patients. For Jamaican patients, the follow up schedule was monthly for the first six months, alternate months from 6 to 12 months and three monthly thereafter. From 1983, pneumococcal prophylaxis was provided by monthly injection of depot penicillin from four months to four years and pneumococcal vaccine (initially, the 14-valent vaccine, later the 23-valent vaccine at two years); all patients completed the first four year high-risk period

before the advent of conjugate vaccine. None received hydroxyurea. Patients were encouraged to follow this schedule when perfectly well and to attend at any time when sick; computerized reminders were sent followed by home visits, if necessary.

Statistical analysis: Normally distributed data were compared by means and standard deviations. HbF distributions were skewed and transformed using the formula $\log_e$ (HbF+4). The difference in alpha-thalassaemia frequency between populations was tested by Fisher's exact test, and any influence of alpha-thalassaemia on the prevalence of bone pain, fever, and anaemia in the Nagpur dataset was tested by the incidence rate ratio (IRR) after Poisson regression of event counts.

Results

Compliance with follow up: Of the 103 Nagpur infants, 25 defaulted at birth, 12 within one year and a further 10 within two years. This left 56 followed over two years, with an average follow up of 4.3 yr (median 4.3 yr, range 2.0-8.7 yr), of whom 25 were seen within the previous year. In Jamaica, 201 patients left the study (121 deaths and 80 emigrated) leaving 110 survivors resident in Jamaica, of whom there has been 100 per cent follow up for 37-45 years.

Attendances and admissions: Among the 78 Nagpur patients with some follow up, there were 770 clinic visits (mean 9.9, range 1-36). Forty one patients had no admissions, but the remaining 37 patients had 157 admissions (mean 4.2, range 1-17). The three most common clinical diagnoses at admission were fever (38), bone pain (28) and anaemia (25).

Interventions: Of the 78 Nagpur patients, 61 (84%) received oral penicillin from a mean age of 0.9 yr (range 0.2-2.7 yr) and conjugate vaccine was given in eight. Four were treated with hydroxyurea starting at a mean age of 4.6 yr. In Jamaica, the interventions changed with time as more data became apparent; pneumococcal prophylaxis became routine around 1984[13] and teaching parents splenic palpation from 1985[14]. Hydroxyurea was not used in the first 25 years of the study.

Molecular findings: Alpha-thalassaemia in Jamaica was entirely of the $\alpha^{-3.7}$ type whereas the $\alpha^{-4.2}$ mutation occurred on four occasions in Nagpur (Table I); alpha-thalassaemia was less frequent in Nagpur

Table I. Distribution of alpha- and beta-globin haplotypes in the two populations

Globin genotype	Jamaica (n=311)	Nagpur (n=103)
Alpha-globin genotype		
Analyzed	272 (87.5%)	73 (70.9%)
αα/αα	172	61
$\alpha^{-3.7}$/αα	91	7
$\alpha^{-3.7}/\alpha^{-3.7}$	9	0
$\alpha^{-4.2}$/αα	0	4
$\alpha^{-3.7}/\alpha^{-4.2}$	0	1
Beta-globin genotype		
Analyzed	213 (68.5%)	74 (71.8%)
Benin/Benin	123	0
Benin/Bantu	35	0
Benin/Senegal	17	0
Crossovers	36	0
Bantu/Bantu	1	0
Senegal/Senegal	1	0
Asian/Asian	0	73
Asian/Bantu A2	0	1

($P<0.01$) as compared to Jamaica. The presence of alpha-thalassaemia did not influence the prevalence of admissions in Nagpur for bone pain [IRR: 1.52; 95% confidence interval (CI): 0.43, 5.32; $P=0.52$], fever (IRR: 0.64; 95% CI: 0.24, 1.74; $P=0.38$) or anaemia (IRR: 1.58; 95% CI: 0.34, 7.29; $P=0.56$). All Nagpur patients had the Asian haplotype, which did not occur in the Jamaica sample.

Higher foetal haemoglobin (HbF) and HbA_2 levels: In Nagpur, HbF levels were consistently and significantly higher than Jamaicans at ages 1-3 yr (Table II). HbA_2 levels were consistently lower at ages one, two, and three years in Nagpur, but the differences did not reach significance.

Haematological indices: There were no significant differences in total Hb or mean cell Hb (MCH) at ages 1-3 yr (Table II). Conclusions on reticulocyte distributions were limited by a few observations in Nagpur, but the mean values of 4.3, 6.3 and 7.0 per cent at ages one, two and three years were consistently lower than 9.1, 11.9 and 12.7 per cent in the Jamaican cohort[10].

Table II. Comparison of some haematological features between the two cohorts

HbF (untransformed mean %)	Jamaica[15]		Nagpur (unpublished data)		Mean difference when transformed, 95% CI	*P*
One year	15.5		25.2		2.51, 2.35-2.68	<0.001
Two years	12.1		22.5		2.58, 2.42-2.73	<0.01
Three years	11.2		22.0		0.89, 0.18-1.60	<0.05
	Jamaica[15]		Nagpur (unpublished data)		Mean difference	*P*
	n	Mean±SD	n	Mean±SD		
Total Hb (g/dl)						
One year	140	7.9±1.6	44	8.37±1.22	0.47, −0.05-0.99	0.08
Two years	125	7.9±1.5	30	7.93±0.83	0.03, −0.53-0.59	0.92
Three years	97	8.0±1.4	16	8.27±0.58	0.27, −0.44-0.98	0.45
MCH (pg)						
One year	140	24.2±3.5	32	23.4±3.9	−0.80, −2.18-0.58	0.26
Two years	125	25.2±3.4	10	24.7±2.8	−0.50, −2.69-1.69	0.65
Three years	97	27.1±3.6	8	25.4±2.1	−1.70, −4.27-0.87	0.19

Hb, haemoglobin; HbF, foetal Hb; CI, confidence interval; MCH, mean cell Hb; SD, standard deviation

Anaemia and transfusions: In Nagpur, 26 (33%) patients received 74 transfusions (mean 2.8 episodes/patient; range 1-9 episodes). Pre-transfusion Hb levels, available in 57 episodes, varied from 1.6 to 8.2g/dl and were below 6 g/dl in 38 (67%) (unpublished data). Red cell indices were available in 35 patients in whom the pre-transfusion MCH was below 26 pg in 23 (66%) and below 24 pg in 14 (40%) consistent with iron deficiency. Anaemia was more common during the six months of the monsoon period (June-November) accounting for 17 of 25 (68%) admissions. In the Jamaican cohort, 197 (63%) patients were given transfusions, the major indications being parvovirus-induced aplastic crisis, acute chest syndrome and acute splenic sequestration[16].

Splenomegaly: In Nagpur patients, splenomegaly occurred in 5 of 28 (15%) at six months, 12 of 40 (30%) at one year and 11 of 29 (38%) at two years, lower than the corresponding figures for Jamaica 37, 65 and 77 per cent[17].

Other clinical features: In Nagpur, dactylitis occurred in seven (9%) patients before the age of five years (recurrent in 4) (unpublished data), compared to frequencies of 8 per cent by six months, 24 per cent by one year and 45 per cent by two years in the Jamaican cohort[18]. Acute chest syndrome occurred in nine, recurred in three and was usually associated with admission. In Nagpur, acute splenic sequestration occurred in two patients (one with three events at 1.2, 2.1 and 2.5 yr, the other at 1.3 yr) or 2 of 56 (4%) by the age of two years (unpublished data) compared with 23 per cent by this age in Jamaica[14]. One Nagpur patient developed a stroke at 14 months compared with seven before the age of five years and an incidence of 7.8 per cent by 14 yr in the Jamaican cohort[19]. One Nagpur patient was deemed to have chronic hypersplenism which occurred in approximately five per cent of the Jamaican cohort (unpublished data). In Nagpur, osteomyelitis was diagnosed in two patients.

Sepsis: Sepsis was clinically suspected in six patients but blood cultures performed in five showed no growth. Sepsis might also have contributed to 38 episodes of acute febrile illness, but of 28 blood cultures, only six yielded a potential pathogen (*Staphylococcus aureus* coagulase negative 3, *S. aureus* coagulase positive 1, *Klebsiella* 1, diphtheroid 1). By contrast, severe infections in the Jamaican cohort were overwhelmingly *Streptococcus pneumoniae, Haemophilus influenza B* and *Salmonella* spp.[13,20-22].

Deaths: In the Nagpur cohort, 9 of 78 (12%) patients died (Table III), of whom three and possibly five deaths occurred in the first month of life so were probably unrelated to SS disease. Of the other deaths, few details were available although one child was irritable and died on the way to hospital. In Jamaica, an early study of the causes of death found that acute splenic sequestration (ASS) accounted for 15, acute chest syndrome (ACS)

Table III. Details of deaths with presumed causes in Nagpur patients

Study	Date of birth	Date of death	Age (yr)	Clinical details	Presumed causes
18	June 11, 2008	August 12, 2015	7.2	Severe anaemia	Unknown
34	January 1, 2010	January 5, 2010*	Unknown	Unknown	Unknown - no FU
35	August 20, 2009	May 14, 2014	4.8	Unknown	Severe anaemia with sepsis
49	June 6, 2010	June 21, 2012	2.1	Unknown	Death on road, possible splenic sequestration
60	August 7, 2010	November 2, 2010*	Unknown	Unknown	Unknown
61	September 25, 2010	September 26, 2010	0.1	See presumed cause	Meconium aspiration
75	July 30, 2010	September 20, 2011	1.1	Drowsy	Unknown
90	June 3, 2011	June 23, 2011	0.1	See presumed cause	Asphyxia, possible sepsis
94	June 29, 2011	July 7, 2011	0.1	Very low BW	Unknown

*Date last seen alive as date of death unknown. BW, birth weight; FU, follow up

for 13 and meningitis/septicaemia for eight of the 41 deaths before the age of two years[23]. Interpretation of deaths become complicated by the changing management and interventions over long follow up, but it was clear that most mortality occurred within the first three years of life, reduced with improving care, and that acute chest syndrome was the dominant single cause[24].

Discussion

First reported among tribal people in southern India[25], there was an early misconception that the *SS* gene was linked to the tribal origin, but it was found to be widespread among the scheduled castes and other backward classes in Odisha[26] and only a small proportion was tribal in origin. The polymorphisms in DNA surrounding the beta-globin locus are different from those observed in African peoples, most readily explained as an independent occurrence of the HbS gene, known as the Asian haplotype. This haplotype occurs in 91-100 per cent Indian patients with SS disease[2,5,6,11] and is typical of the disease in the eastern province of Saudi Arabia.

The associated high HbF levels inhibit sickling and promote the persistence of splenomegaly[27]. In African disease, there is a dichotomy between splenomegaly and splenic function whereby, despite clinical enlargement, splenic function is often lost early in life[28,29] and early splenomegaly may predict an increased susceptibility to infection[17]. The age specificity of invasive pneumococcal disease falls sharply after three years[30], and the early loss of splenic function in patients of African origin results in an incidence of 10 per cent[31] before pneumococcal prophylaxis. Although there are no direct measures of splenic function currently available in Indian patients, the later appearance of splenomegaly is consistent with persisting function, which may explain why invasive pneumococcal disease has never been reported in Indian SS disease.

Dactylitis, which results from bone marrow necrosis, is a better indicator of pathology than bone pain crisis which is influenced by many other factors, and the lower frequency of dactylitis in the Nagpur cohort was consistent with more mild disease. Severe anaemia was a common cause of hospital admission, the lower MCH being consistent with iron-limited erythropoiesis but reticulocyte counts, ferritin and serum iron indices and a trial of iron supplementation may clarify the cause of anaemia. The lack of routine blood film examination for malarial parasites was a shortcoming of the present study especially in view of an increase during the monsoon period which might have been expected to be malaria-related. Jamaica is malaria-free, but acute anaemia from parvovirus-induced aplasia with seroconversion in 70 per cent by the age of 20 yr[32] would be missed in the absence of reticulocyte counts.

There were several limitations in comparing these studies. Inevitably, the diagnostic technology for the newborn detection of SS disease has evolved, but there has been ample confirmation of Hb genotype during follow up. Recruitment of Nagpur patients was confined to the offspring of sickle-positive mothers, and although this would have missed cases of S beta-thalassaemia and other double heterozygous forms of SS disease, but would not bias the selection of cases with SS disease. Of a major concern was the high

default rate in the Nagpur patients, noted in other Indian studies[4]; such default would have introduced bias, but the nature of this bias could not be addressed as details were not available on the reasons for default. A further deficiency was the limited information on the causes of death which, in Jamaica, were confirmed by formal autopsies in over 50 per cent cases (unpublished data), but for cultural and other reasons were not confirmed in Indian patients although the young age in three and possibly five of nine deaths made it unlikely that these deaths were related to SS disease.

Both the studies had different durations of follow up, but the observations were mostly confined to the first three years of life and this was unlikely to affect the molecular features and the presented haematology and clinical features. Compared to Jamaicans, the Nagpur patients demonstrated less alpha-thalassaemia, less dactylitis, a later appearance of splenomegaly, the apparent absence of pneumococcal septicaemia and a high prevalence of unexplained severe anaemia. Cohort studies from birth are vitally important in addressing these questions, but mechanisms must be found to avoid the high default rates in this and other attempted cohorts[4]. Furthermore, the lower prevalence of alpha-thalassaemia in central India might have contributed to the more severe disease compared to the milder disease in other areas of India.

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***Conflicts of Interest*:** None.

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