Review Article

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Haemoglobinopathies in tribal populations of India

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Haemoglobinopathies particularly haemoglobin S and E (HbS, HbE) and β-thalassaemia are important challenges for tribal populations in India. The HbS, HbE and β-thalassaemia genes are variably distributed across various tribal populations of India. HbE is mainly restricted in tribals of North-East, West Bengal, Odisha and those in Andaman and Nicobar islands. HbS has more extensive distribution in the country (10-40% trait frequency) and the homozygotes and double heterozygotes present with a wide array of morbidities. The morbidity varies greatly in different areas of the country due to differential co-inheritance of α-thalassaemia gene and interaction of various epistatic and environmental factors. Though substantial data on prevalence of these disorders exist, there is an urgent need to develop integrated hierarchical core facilities to manage the disease. Such centres will generate more data and will also explore areas of management which need more local attention. Newborn screening, genetic counselling, carrier detection, prenatal diagnosis along with management of cases should form the basic infrastructure of haemoglobinopathy management. Research in this areas should continue focusing on various challenges in care delivery, prevention and basic sciences on interaction of haemoglobinopathies with various other infections.

Key words β-thalassaemia - haemoglobin E - HbS - thalassaemia - tribals

Tribal population of India constitutes approximately 8.5 per cent of the total population of India[1]. Tribal population in India is not a homogenous group. Further, because of their isolated existence and endogamy over centuries, different tribal populations have distinctive genetic identities. With industrialization and availability of jobs in different areas of India many of these tribal populations have migrated from their homelands to cities in search of jobs. Although these migrations are relatively in small proportions (5-10%) but the absolute number of tribal persons living in big cities and industrialized areas of the country is substantial[2].

Why is this information important when we discuss haemoglobinopathies in tribal populations of India? The answer lies in deciding whether to provide haemoglobinopathy care only in the tribal belts of India or whether it should be broad-based across the length and breadth of the country. These tribals can be broadly divided into several groups *(i)* Tribal populations in the North-East, *(ii)* Tea Garden tribal populations, *(iii)* Tribal populations in central India, *(iv)* Tribal populations in western India, *(v)* Tribal population in eastern parts of Odisha and Andhara Pradesh, and *(vi)* Tribal populations in south India. This distinction is important because there are some variations in the

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nature, composition and clinical severity of various haemoglobinopathies in different tribal areas of the country. Tribal populations of North-East predominantly show haemoglobin E (HbE) a structural haemoglobin disorder with variable combination of β-thalassaemia and α-thalassaemia genes[3-7]. Tribals working in tea gardens in the North-East show sickle cell haemoglobin (HbS) as the predominant haemoglobinopathy[8]. In the tribal populations of central India and eastern parts of Odisha and Jharkhand HbS emerges out as the predominant haemoglobinopathy[8]. Interacting α-and β-thalassaemia genes amongst tribals are more frequent in Odisha where haemoglobin E is also infrequent. Hence in Odisha one can see interaction of HbS, HbE, β-thalassaemia with varying combination of deletional α-thalassaemia and hereditary persistance of foetal haemoglobin (HPFH) genes[9,10]. Unusual α chain structural variants like HbJ Paris, HbJ Meerut have also been detected in these tribal populations. Unusual haemoglobin variants like structural α chain variants Hb Koya Dora[11] have also been described in certain tribes of Andhra Pradesh. In the western part of Rajasthan, Gujarat and Maharashtra haemoglobinopathies in tribal populations are largely restricted to HbS and interacting deletional α-thalassaemia is present in various proportions in these different States[12-14] *e.g.* 97 per cent of HbS carrying tribal population in south Gujarat carried the α-thalassaemia gene while this proportion falls drastically in tribals of Maharashtra and those from central India. Rare haemoglobin variants like Hb Fontainebleau[15], HbM Ratnagiri[16] have also been reported from Maharashtra. From south India, tribes in Nilgiri Hills area[17] and from Wayanad district of Kerala[18] have been shown to have largely sickle cell anaemia as the major haemoglobinopathy.

HbD has not been reported on a large scale in any of the tribal populations from India. Hence it can be argued that haemoglobinopathies with sickle cell haemoglobin is the major challenge in tribal populations. Small scale studies on haplotypic association of HbS in tribals of India suggest a unicentric origin of HbS in India[19] as majority of HbS across the country is linked to the Arab-India haplotype[14]. However, there could be an alternative explanation of this phenomenon as historically and geographically the tribal populations of India have been found to be highly heterogenous and the clinical severity of sickle homozygous or compound heterozygous cases is extremely heterogenous and the two important contributors of severity of the disease being the haplotype (Arab-Indian type) of the β-globin gene cluster and co-inheritance of α-thalassaemia. Foetal haemoglobin levels[20] modulate the severity of HbS disease and these levels are extremely variable across various tribal populations in India. Tribal populations in Wayanad district of Kerala show highest levels of foetal haemoglobin in association with homozygous HbS disease[20].

One of the arguments after describing this broad spectrum of haemoglobinopathies in India is that we still have a long way to go as we have not micro-mapped the prevalence of HbS across the country and this is needed to develop a clear picture of HbS prevalence in each of the >400 tribal populations of India. However, we have done these prevalence studies from late 1950s and a reasonable amount of data show that sickle haemoglobin is a major problem in the country and the recent migration of tribals across the metropolis to 1-and 2-tier cities in search of livelihood also suggests that geography of haemoglobinopathy in both tribal and non-tribal populations in this country is changing. Though α-thalassaemia gene is prevalent across the country and on the average 14 per cent of the Indian population carry this gene[21]. Deletional α-thalassaemia in India in general does not produce a large number of HbH disease cases[22] and this condition is largely asymptomatic or mild except for producing microcytosis. This microcytosis is important in the differential diagnosis of β-thalassaemia syndromes and sickle cell disease, hence directly α-thalassaemias are not really a clinical challenge.

One of the major deficits in the studies of haemoglobinopathies in India among tribal populations is *(i)* lack of integrated hierarchical management and diagnostic facilities for haemoglobinopathies in remote areas where majority of the tribal populations reside, and *(ii)* lack of a haemoglobinopathy registry for the country as this would be a major tool for the State and central governments to concentrate efforts to develop facilities for care and diagnosis where they are needed most.

The primary health centres, rural hospitals and *Taluka* hospitals located in tribal areas of the country need additional strengthening for immediate management of sickle cell related clinical conditions through intravenous fluid therapy, pain relief, regular supply of folic acid tablets and referring more complicated patients (chest syndrome, pregnancy,

strokes and other complications) to district hospitals, and finally to other tertiary care centres where facilities for management of such cases are available. These facilities need extra manpower, space, instruments which should be urgently provided.

Genetic counselling forms an important component in the management of such disorders[23]. Non-governmental organizations (NGOs) with patient groups can take over some of the burden of counselling.

Apart from adequate hydration, pain relief, folic acid supplementation, adequate nutrition, personal protection from extreme weather conditions, prompt treatment for infection and diarrhoeal disorders, low dose hydroxyurea therapy have been shown to be safe and significantly reduce pain and improve quality of life in sickle cell anaemia patients[24,25]. Hydroxyurea has also been shown to be effective in <30 per cent patients with β-thalassaemia major and >70 per cent of patients of thalassaemia intermedia[26].

Several centres in India are engaged in haemoglobinopathy research in tribal areas. Certain key areas are being looked at or need to be looked at in future with a view to better understand the disease in the Indian context. These areas are: *(i)* Newborn screening for haemoglobinopathies in tribal areas; *(ii)* Follow up of newborn cohorts in a multicentric fashion for atleast five years to understand the nature of early mortality and morbidity in these populations; *(iii)* Developing a registry on haemoglobinopathies for tribal populations; *(iv)* Study the interaction of gastrointestinal parasitism, iron deficiency, nutritional intake with haemoglobinopathies and finally deciding whether these components should be routinely assessed and what remedial measures should be undertaken; *(v)* Evaluation of various ethno- pharmacological products for management of the condition; *(vi)* Prevalence and cause of hypersplenism in sickle cell anaemia patients in tribals; *(vii)* Interaction of various genetic factors for epistatic interaction in modulation of the disease; *(viii)* Interaction of malarial infection with haemoglobinopathy; and *(ix)* Prenatal diagnosis for severe haemoglobinopathies.

As the centres managing haemoglobinopathies in tribals increase their experience, more and more families with this condition will come forward and cascade screening and counselling of these families will provide additional cases and carriers, and this will also provide newer area for research.

References

1. Census of India 2011, Office of the Registrar General and Census Commissioner. Ministry of Home Affairs, Govt. of India. Available from: *http;// www.censusindia.gov.in* , accessed on April 24, 2015.
2. Migration of tribal woman - Planning Commission. 2010. Available from: *http://www.planningcommission.nic.in*, accessed on April 24, 2015.
3. Das BM, Chakravartti MR, Delbruck H, Flatz G. High prevalence of haemoglobin E in two populations in Assam. *Humangenetik* 1971; *12* : 264-6.
4. Flatz G, Chakravartti MR, Das BM, Delbruck H. Genetic survey in the population of Assam. I. ABO blood groups, glucose-6-phosphate dehydrogenase and haemoglobin type. *Hum Hered* 1972; *22* : 323-30.
5. Das BM, Deka R, Flatz G. Predominance of the haemoglobin E gene in a Mongoloid population in Assam (India). *Humangenetik* 1975; *30* : 187-91.
6. Das BM, Deka R, Das R. Haemoglobin E in six populations of Assam. *J Indian Anthropol Soc* 1980; *15* : 153-6.
7. De M, Halder A, Podder S, Sen R, Chakrabarty S, Sengupta B, *et al*. Anemia and hemoglobinopathies in tribal population of Eastern and North eastern India. *Hematology* 2006; *11* : 371-3
8. Bhatia HM, Rao VR, editors. *Genetic atlas of the Indian tribes*. Mumbai: Institute of Immunohaematology, Indian Council of Medical Research; 1986.
9. Chottray GP, Dash BP, Ranjit M. Spectrum of hemoglobinopathies in Orissa, India. *Hemoglobin* 2004; *28* : 117-22.
10. Balgir RS. Spectrum of hemoglobinopathies in the state of Orissa, India: a ten years cohort study. *J Assoc Physicians India* 2005; *53* : 1021-6.
11. De Jong WW, Meera Khan P, Bernini LF. Hemoglobin Koya Dora: high frequency of a chain termination mutant. *Am J Hum Genet* 1975; *27* : 81-90.
12. Kar BC, Satapathy RK, Kulozik AE, Kulozik M, Sirrs S, Serjeant BE, *et al*. Sickle cell disease in Orissa state, India. *Lancet* 1986; *2* : 1198-201.
13. Kulozik AE, Kar BC, Serjeant GR, Serjeant BE, Weatherall DJ. The molecular basis of alpha thalassemia in India. Its interaction with the sickle cell gene. *Blood* 1988; *71* : 467-72.
14. Mukherjee MB, Lu CY, Ducrocq R, Gangakhedkar RR, Colah RB, Kadam MD, *et al*. Effect of alpha-thalassemia on sickle cell anemia linked to the Arab - Indian haplotype in India. *Am J Hematol* 1997; *55* : 104-9.
15. Upadhye DS, Jain D, Nair SB, Nadkarni AH, Ghosh K, Colah RB. First case of Hb Fontainebleau with sickle hemoglobin and other non-deletional α gene variants identified in neonates during newborn screening for sickle cell disorders. *J Clin Pathol* 2012; *65* : 654-9.
16. Kedar PS, Nadkarni AH, Phanasgoankar S, Madkaikar M, Ghosh K, Gorakshakar AC, *et al*. Congenital methemoglobinemia caused by Hb-M Ratnagiri (beta-63CAT-

->TAT, His-->Tyr) in an Indian family. *Am J Hematol* 2005; *79* : 168-70.

17. Ramasamy S, Balakrishnan K, Pitchappan RM. Prevalence of sickle cells in Irula, Kurumba, Paniya & Mullukurumba tribes of Nilgiris (Tamil Nadu, India). *Indian J Med Res* 1994; *100* : 242-5.
18. Feroze M, Aravindan KP. Sickle cell disease in Wayanad, Kerala: gene frequencies and disease characteristics. *Natl Med J India* 2001; *14* : 267-70.
19. Labie D, Srinivas R, Dunda O, Dode C, Lapoumeroulie C, Devi V, *et al*. Haplotypes in tribal Indians bearing the sickle gene: evidence for the unicentric origin of the beta S mutation and the unicentric origin of the tribal populations of India. *Hum Biol* 1989; *61* : 479-91.
20. Colah R, Mukherjee M, Ghosh K. Sickle cell disease in India. *Curr Opin Hematol* 2014; *21* : 215-23.
21. Nadkarni AH, Gorakshakar AC, Mohanty D, Colah RB. Alpha genotyping in a heterogeneous Indian population. *Am J Hematol* 1996; *53* : 149-50.
22. Nair SB, Nadkarni AH, Ghosh K, Colah RB. Variable presentation of Hb H disease due to homozygosity for the rare polyadenylation signal AT (Indian) (AATAAA → AATA--) mutation in four Indian families. *Hemoglobin* 2013; *37* : 277-84.
23. Mohanty D, Das K. Genetic counselling in tribals in India. *Indian J Med Res* 2011; *134* : 561-71.
24. Italia K, Jain D, Gattani S, Jijina F, Nadkarni A, Sawant P, *et al*. Hydroxyurea in sickle cell disease - a study of clinico - pharmacological efficacy in the Indian haplotype. *Blood Cells Mol Dis* 2009; *42* : 25-31.
25. Jain DL, Apte M, Colah R, Sarathi V, Desai S, Gokhale A, *et al*. Efficacy of fixed low dose hydroxyurea in Indian children with sickle cell anemia: a single centre experience. *Indian Pediatr* 2013; *50* : 929-33.
26. Italia KY, Jijina FJ, Merchant R, Panjwani S, Nadkarni AH, Sawant PM, *et al*. Response to hydroxyurea in beta-thalassemia major and intermedia: experience in western India. *Clin Chim Acta* 2009; *407* : 10-5.

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