REVIEW

Epidemiology and current status of case management of thalassaemia in Myanmar - Country Report

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Country report was orally presented at the second Pan-Asian Conference on Haemoglobinopathies, at Hanoi, Vietnam in September 2015.

Abstract

Myanmar has high prevalence of important haemoglobinopathies: α-thalassaemia - 10% to 56.9%, HbE - 1 to 28.3%, β-thalassaemia - 0.54 to 4.07%, accounting for 1 to 4.9 births per 1000 infants with a major haemoglobinopathy. In Myanmar, - $\alpha^{3.7}$ type of alpha-thala-ssaemia mutation is the commonest mutation. The commonest genetic abnormalities in Hb H disease are ($--^{SEA}/-\alpha^{3.7}$) (53%) and ($--^{SEA}/-\alpha^{4.2}$) (30%). Eighteen different beta-thalassaemia mutations have been characterized. The commonest beta-thalassaemia mutations are CD 41/42 (-TCCT), IVS 1-1 (G › T), CD 17 (A › T) and IVS 1-5 (G › C).

There is no national thalassaemia registry but hospital registries exist. According to hospital-based records, HbE/β-thalassaemia accounts for 46% to 58% and HbH 6% to 37%. There is no reference expert center but four specialist haematology centers exist. Molecular diagnostic facilities are available only at National Health Laboratory but not at primary and regional levels. The diagnosis and management guideline at national level does not exist but Thalassaemia International Federation's (TIF) guidelines are used in specialist haematology centers. Thalassaemia patients are managed in government and private-owned hospitals by haematologists, physicians, paediatricians and general practitioners. Joint care with obstetricians, endocrinologists etc. is being practised.

Blood transfusion was a cost-sharing service in the past but recently became free-of-charge at public institutions. At National Blood Center, Nucleic acid amplification test (NAT) screening is used, and leuco-depleted blood units (by centrifugation) are available but are not irradiated. Red cell allo-immunisation is seen in 5% to 9.7%. Anti-E and anti-C rhesus antibodies are commonest. Hepatitis B and C serology positivity rate is around 3.88% and 12.6% respectively. Free-of-charge hepatitis B vaccinations for patients and blood donors are recently introduced by a local NGO.

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More than half of transfused thalassaemia (52% - 93.25%) with serum ferritin level at or above cut-off (> 1000 ng/ml) have to start iron chelation therapy. But only 20.4% to 33% of patients needing iron chelation are taking treatment. Desferrioxamine is unregistered in Myanmar. Deferiprone is available but not deferasirox.

Increased transfusion demand and symptomatic splenomegaly are the main indications for splenectomy, and sepsis is the most common complication of splenectomy.

Hydroxyurea for fetal haemoglobin modulation is being used only by specialists. Sixty percent of patients complied one year treatment without side effects, with reduction in transfusion requirement, modest increase in pre-transfusion Hb and elevation in HbF percentage.

Bone marrow transplantation for thalassaemia has not been started yet.

Growth stunting was observed in 70.5% of β-thalassaemia patients in Yangon Children Hospital. Among beta-thalassaemia intermedia patients, delayed puberty was observed in 25% of male and 85% of female. Osteopenia in 18%, osteoporosis in 21%, enlarged left ventricle in 17%, enlarged left atrium in 27%, enlarged right ventricle 77% and deranged glucose metabolism in 13% of beta-thalassaemia intermedia patients were also observed.

About 49.5% of thalassaemia families attending day care centre has financial burden having to use 10% to 40% of total monthly income for blood transfusion visit. National prevention program, structured population screening, genetic counseling, premarital counseling and prenatal diagnosis are not available yet.

Introduction

The inherited diseases of haemoglobin are the commonest single gene disorders: the World Health Organisation estimates that about 7% of world's populations are carriers[1]. Most of them live in the South-east Asian region, where the thalassaemias (β-thalassaemia, α-thalassaemia and haemoglobin E) predominate. There are 9.2 million pregnant carriers annually. Annual pregnancies at risk for haemoglobin disorders are about 1.47 million. It is estimated that 365,100 infants are born each year with major hemoglobin disorders[2]. Thalassaemia haemoglobin E disease is also the commonest of the thalassaemia syndromes presenting with clinical symptoms of anaemia in Myanmar[3].

Epidemiology of thalassaemia in Myanmar

In the thalassaemia survey made by Anaemia Research Project, the prevalence of thalassaemia trait among the Burmese (Bamar) is 4.3% and that of β-thalassaemia trait is 0.54%[4]. The prevalence of alpha thalassaemia trait was reported to be approximately 10%

among the Burmese (Myanmar) patients[5]. High prevalence of alpha thalassaemia (56.9%) was reported among Bamar population in some parts of Myanmar[6]. Recent report in 2011 reported that beta thalassaemia carrier among asymptomatic Myanmar aged between 16 to 45 years was 4.07%[7]. Haemoglobin E in Bamar was first reported in 1956[8] and the prevalence of haemoglobin E trait was reported as 1% to 28% among the various races of Myanmar[6, 9, 10]. In Myanmar, it was estimated that 1 to 4.9 births per 1000 infants had a major haemoglobinopathy[11].

The molecular situation of alpha thalassaemia occurring in thalassaemia major patients of Myanmar was first described in 2001[12]. In Myanmar, - $\alpha^{3.7}$ type of alpha-thalassaemia mutation is the commonest deletional type of mutation[13]. The commonest genetic abnormalities in Myanmar patients with Hb H disease are ($--^{SEA}/-\ \alpha^{3.7}$) (53%) and ($--^{SEA}/-\ \alpha^{4.2}$) (30%)[14].

Eighteen different β-thalassaemia mutations in Myanmar patients were characterized in 2002[15]. The commonest beta-thalassaemia mutations are CD 41/42 (-TCCT), IVS 1-1 (G → T), CD 17 (A → T) and IVS 1-5 (G → C) in both thalassaemia major and intermedia[16, 17, 18].

Current status of case management of thalassaemia in Myanmar

Complete patient registries are installed in tertiary care hospitals and day care centers[19]. There is no national thalassaemia registry per se.

According to hospital-based records, HbE / β-thalassaemia accounts for 46% to 58%, β-thalassaemia 5.4% to 22%, and HbH 6% to 37%[20, 21, 22]. There is no reference expert center[19] but four specialist haematology centers exist to cover the fifty million-population of the Union of Myanmar.

Cellulose acetate electrophoresis at alkaline pH is mainly used for detection of structural variants of haemoglobin. Isoelectric focusing and automated high-performance liquid chromatography facilities for haemoglobinopathies are available only at the national level laboratory.

Molecular diagnostic facilities are available only at National Health Laboratory but not at primary and regional level[19].

The diagnosis and management guideline at national level does not exist but TIF's guidelines are used in specialist haematology centers. Thalassaemia patients are managed in government and private-owned hospitals by haematologists, physicians, paediatricians and general practitioners. Joint care with obstetricians, orthopaedics and endocrinologists etc. is being practiced especially in tertiary centers.

Blood transfusion in Myanmar was a cost-sharing service in the past but recently became free-of-charge at public institutions. At National Blood Center, Nucleic acid amplification test (NAT) screening is used for every blood units. Leuco-depleted blood units (by centrifugation) are available at the National Blood Center but blood products are not irradiated.

Red cell allo-immunisation is seen in 5% and 9.7% of thalassaemia major and intermedia patients respectively. Anti-E and anti-c rhesus antibodies are commonest. Antibodies against Kidd blood group anti-Jk^a and anti-Jk^b, antibodies against Lewis blood group anti-Le^a and anti-M antibodies were also identified in thalassaemia patients[22, 23].

Although high prevalence of hepatitis virus infection was reported among thalassaemia patients in Myanmar in the year 2000[24], ten years later Hepatitis B and C serology positivity rate is reported as 3.88% and 12.6% respectively[22]. The National Blood Center has succeeded in reducing transfusion transmitted infection risk over the past decade simply by WHO-recommended ordinary interventions like formulating the donor group, donor deferral by questionnaire, introduction of computerized registration and preparation of component blood[25]. Free-of-charge hepatitis B vaccinations for patients and blood donors are recently introduced by a local NGO, Myanmar Liver Foundation.

More than half of transfused thalassaemia cases (52% - 93.25%) has crossed the serum ferritin cut-off (> 1000 ng/ml) to start iron chelation therapy. Only 20.4% to 33% of patients needing iron chelation are taking treatment[22, 26]. Desferrioxamine is unregistered in Myanmar. Oral deferiprone is available in the market but deferasirox is ordered from other countries on individual basis.

Increased transfusion demand (80.6%) and symptomatic splenomegaly (38.7%) are the main indications for splenectomy, while growth retardation (9.7%), thrombocytopenia (9.7%) and splenic abscess (3.23%) were other indications. Sepsis is the most common complication of splenectomy (16.12%) while primary haemorrhage (3.22%), poor wound healing (6.44%) and operative mortality (3.22%) were other complications[22].

Hydroxyurea for fetal haemoglobin modulation is being used only by specialists. A preliminary report in 2003 found that sixty percentage of patients complied one year treatment without side effects, with reduction in transfusion requirement, modest increase in pre-transfusion Hb and elevation in HbF percentage[27]. Another study in 2011 found that 26.21% of patients with beta-thalassaemia intermedia were taking hydroxyurea therapy[28].

Bone marrow transplantation for cure of thalassaemia has not been started yet but there are skilled transplant physicians for that purpose.

Growth stunting was observed in 70.5% of β-thalassaemia patients in Yangon Children Hospital[29]. Average height of Myanmar adult patients with Hb H disease is

comparable to normal height of people from neighbouring countries[21]. In adult beta-thalassaemia intermedia patients, one third has more than mid-parental height and two third has less than mid-parental height[22].

Among beta-thalassaemia intermedia patients, delayed puberty was observed in 25.53% of male and 85.71% of female. Mean age of puberty in male beta-thalassaemia intermedia patients was 15.53 years (range 13 - 20 year). Mean age of menarche in female beta-thalassaemia intermedia patients was 15.65 years (range 12 - 20 year). Primary amenorrhoea was observed in 12.5% and secondary amenorrhoea in 26.53%[22].

Among married female beta thalassaemia intermedia patients, 86.66% got pregnancy. Average number of pregnancies was 2.3. The outcome of pregnancies were full term babies in 91.43% including one twin, abortions in 5.71%, premature baby in 2.86%, and neonatal death in 2.86%. Average birth weight of babies of female beta thalassaemia intermedia patients was 5.95 lb (SD 2.02, range 5.3-9). Mean haemoglobin level during pregnancy was 7.7 g/dl (SD 1.48, range 6.1-10). Transfusion was needed in 46.15%, among them 30.77% was first transfused during pregnancy and 7.69% was first diagnosed as thalassaemia during pregnancy[22]. Genetic counseling, premarital counseling and pre-natal diagnosis are not available yet.

Bone mineral density measurement in beta-thalassaemia intermedia patients showed osteopenia in 18.42%, and osteoporosis in 21.05%. Past history of bone fracture was found in 26.21% (one fracture in 17.48%, two fractures in 4.85%, three fractures in 1.94% and four fractures in 1.94%)[22].

In Myanmar beta-thalassaemia intermedia patients, displaced cardiac apex was observed in 13.59%, left parasternal heave in 6.8%, loud second sound in 9.71%, cardiac murmur in 44.66%, and signs of congestive cardiac failure in 13.59%. On chest X-ray, cardiomegaly was found in 39.8%, prominent pulmonary artery in 15.53%, rib expansion in 10.68% and extramedullary intrathoracic masses in 3.88% of beta-thalassaemia intermedia patients. On electrocardiogram, electrocardiographic criteria of enlarged left ventricle, enlarged right ventricle and enlarged both ventricles were observed in 11.65%, 3.88% and 2.91% respectively. Right axis deviation was observed in 9.71%, right bundle branch block in 0.97% and atrial fibrillation in 0.97% of beta-thalassaemia intermedia patients[30].

During echocardiographic assessment of beta-thalassaemia intermedia patients, enlarged left ventricle, enlarged left atrium and enlarged right ventricle were observed in 16.66%, 27.38% and 77.38% respectively. Impaired LV contractility was observed in 7.14%, restrictive filling in 4.76% and impaired relaxation in 5.95%. Increased systolic pulmonary artery pressure was observed in 21.42% and cardiac haemosiderosis in 14.28%. No association was found between serum ferritin and size of left atrium, left ventricle, right atrium and right ventricle, and right ventricular systolic pressure[30]. In Myanmar patients

with HbH disease, left ventricular systolic dysfunction was found in 11% and diastolic dysfunction in 21%[21].

As hepatobiliary complications, gallstone was detected in 22.33%, gall bladder sludge in 7.77%, and thickened gall bladder in 3.88% of beta-thalassaemia intermedia patients. Diabetes mellitus was observed in 5.82%, fasting hyperglycaemia in 5.82%, and impaired glucose tolerance in 0.97%. So altogether 12.61% had deranged glucose metabolism in beta-thalassaemia intermedia patients[22].

Among Myanmar HbH disease patients, 52% were university graduates, 38% had attended high school, 8% had attended the primary school and 2% was illiterate[2]. Among beta-thalassaemia intermedia patients, 13.59% had attended primary school, 32.04% had attended secondary school, 30.1% had attended high school, 8.74% had attended colleges and universities, and 15.53% were graduates[22].

In a study attempting to identify financial burden to the families of thalassaemia patients who attend day care room service of Yangon Children Hospital, about 49.5% of thalassaemia families attending day care centre has financial burden having to use 10% to 40% of total monthly income for blood transfusion visits[3].

For psychosocial management of thalassaemia patients and their families, social workers and some volunteers can give support but there is no designated thalassaemia coordinator nurse or volunteer for this purpose. World Thalassaemia Day celebrations were done every year starting from 2009 on treatment center basis to give health education to patients and families by their attending doctors and to share the knowledge among each other. Although these celebrations were very successful and very much acknowledged by patients and their families, national level advocacy meeting has never been done.

Conclusion

Myanmar has high incidence of important haemoglobinopathies. Thalassaemia has significant impacts on the patients' lives as well as on their families. National prevention program, and structured population screening are not available yet. Current case management of thalassaemia in Myanmar has areas to be improved. The diagnosis and management guidelines at national level should be made urgently. Public awareness has to be extended and public participation in setting up a Thalassaemia Society in Myanmar is also needed.

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