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Thalassaemia - The Need of the Day to Address the Issue; Awareness and Prevalence of Carrier Rate in a Cohort of University Students in Sri Lanka

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Abstract

Objective: The α and β Thalassaemias, a disorder of globin chain production, is an increasing global health problem. We performed a cross-sectional study of 384 undergraduates of the University of Sri Jayewardenepura to determine the prevalence and awareness of thalassaemia-minor among the students.

Method: A questionnaire assessed the awareness of thalassaemia followed by analyzing the Complete Blood Count. The initial carrier detection was done by red cell indices combined with the blood picture, which was confirmed by quantifying HbA2 by High-Performance Liquid Chromatography.

Results: Of the 384 blood samples tested, 53 (13.8 %) had hypochromic microcytic red cell indices where eleven students (2.9 %) were carriers of β thalassaemia and twenty-seven students (7%) had Iron Deficiency Anaemia (IDA). Fifteen students (3.9 %) were possible α thalassaemia carriers with normal iron studies and HPLC. Thalassaemia being a major health issue in the country, only two hundred and twenty-two (77.6 %) had awareness.

Conclusion: The β thalassaemia minor rate was 5.5%, which is higher than the previous studies. Out of the 5.5%, 2.6% had a coexisting IDA, which accounts for a 7% having IDA. These findings should alert the authorities to take serious preventive measures to address the issue.

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Introduction

Thalassaemia group of disorders are a major health problem worldwide. About 30,000 conceptions are affected by β Thalassaemia Major (TM) worldwide where the majority are found in developing and low-income countries [1]. Thalassaemia occurs at a high frequency throughout parts of Africa and the Mediterranean region, the Middle East, Southeast Asia, and the Indian subcontinent (India, Pakistan, Sri Lanka) [2]. It is important for individuals to be aware of their Thalassaemia Minor (Tm) status, particularly those in the reproductive age. The correct message has to be delivered to the community of the Tm status so that it will not give stigma to the diagnosed healthy individual in society, if not, this could lead to a failure in thalassaemia control programs. The objective of this study was to determine the awareness of thalassaemia and prevalence of thalassaemia state in a group of university students who should be somewhat aware of this problem learned from different awareness programs. Since most of the university students are in the reproductive and pre-marital stage representing the entire island, this is an ideal group to be diagnosed and this will contribute positively to improving the knowledge and awareness of thalassaemia in the country. Sri Lanka is a small island with a population of nearly over 20 million and preventive programs could be effectively carried out if organized systematically, which will prevent marriages between carriers and reduce future births of TM babies in Sri Lanka. The university, draining students from almost all the districts of the county with a population of 11,000 at any given time, provides an ideal ground for screening where the intellectually higher and younger fraction of society will help to increase the awareness of thalassaemia in the country.

One of the studies that were done in Sri Lanka in the year 2000 surveyed gene frequencies in school children and estimated the burden (5% of the total health budget) of the disease and the need for its control. This study revealed that most patients were homozygotes or compound heterozygotes (HbE/β-40%) for β thalassaemia. The prevalence of both the β Tm and HbE trait was variable among school children and on average, it was 2.2% for β Tm and 0.5% for HbE trait. This research urged the health sector to plan for disease control programs for screening and counseling [3]. The carrier state varies from country to country which can be related to the ethnicity of people. The average β thalassaemia carrier rate is 3.4 % in Hong Kong, 5.0 % in Pakistan, 3.3 % in India, and 3.1 % in Tunisia (WHO, 1994). In countries where thalassaemia is prevalent, many national premarital screening programs have been made mandatory to limit carrier marriages.1 Premarital screening programs interfere with ethical, cultural, religious, and social believes which can be aggravated by a lack of resources to do appropriate testing.

Moreover, some of these areas have low literacy rates and low priority for counseling programs [4]. Unfortunately approximately 80% of the annual births of babies with these conditions occur in low-or middle-income countries. Despite the increment of population size and this becoming a global health issue, it has been largely ignored by the global health forum [5]. Prevalence of Thalassaemia is significant in Sri Lanka even though the studies done to identify the depth of the problem are less. Therefore, this study will also help in identifying the gaps of data related to Thalassaemia awareness and the burden of Thalassaemia in Sri Lanka.

Methodology

An analytical prospective cross-sectional survey was done in randomly selected 384 consented university students of faculties, Arts and Commerce, Management Studies, Applied sciences and Medical Sciences in University of Sri Jayewardenepura (USJP), Sri Lanka. The study was conducted after obtaining ethical clearance by the ethical review committee at the University of Sri Jayewardenapura. Students who had a chronic illness or did not consent were excluded from the study. A self-administered questionnaire was given in all three languages to the study participants after explaining the details of the research, which included the demographic data and questions to check for awareness of thalassaemia. The results were then analyzed to investigate the participants' answers of the demographic details, the awareness, and knowledge about Thalassaemia.

After submitting the questionnaire, Venous blood (2 ml) was drawn and anticoagulated with K2EDTA and tested for Complete Blood Count (CBC)which was analyzed from a fully automated hematology analyzer Sysmex SX 500i. The initial diagnosis of thalassaemia carrier was done by using red cell indices of the analyzer report, combined with the blood picture reported by the consultant hematologist. Weatherall et al concluded that a well calibrated analyzer would pick up >95% of the heterozygous thalassaemics with cut-off values of MCV and MCH of 80fl and 27pg respectively with greater sensitivity [2]. The positive predictive value of patients who are likely to be missed are these two groups of patients: MCH <27pg and HbA2 3.5–3.9% and MCH >27pg and HbA2 4–4.3% which make up to very small proportions [6]. A blood picture of hypochromic microcytic red cells with basophilic stippling, target cells, and irregularly contracted cells would complement the diagnosis [7]. Final confirmation was done by quantifying the HbA2 levels by High-Performance Liquid Chromatography (HPLC). Those who had hypochromic microcytic indices were also subjected to ferritin studies, which were done by immunoassay. Data were analyzed with SPSS version 18.

Results

This study included a total of 384 participants with a Male: female ratio of 1.1:1. Their ages ranged from 20-26 with a mean of 23yrs.

Awareness of thalassaemia

About half of the participants (58.2%) were aware of Tm and the source of knowledge was mainly from the television and newspapers.

Out of the percentage who knew about thalassaemia, the following aspects of knowledge were reviewed (Figure 1) Over 60% had a misconception that Tm is a symptomatic disease.

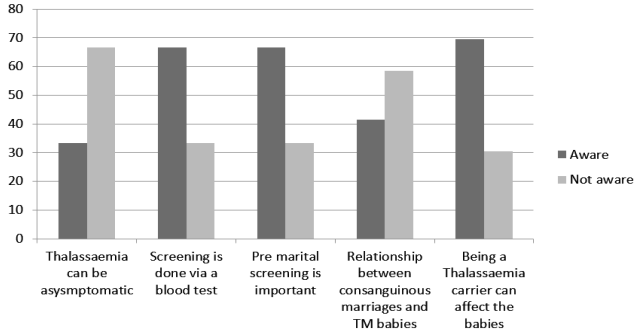

Figure 1: Summary of the percentages of indices of Awareness of Thalassaemia.

Sixty-six (66.6%) were aware that Tm can be recognized by a blood test and the same percentage knew the importance of pre-marital screening in preventing TM births. However, 58.5 % didn't know about the pattern of inheritance of TM and they did not know the relationship between consanguineous marriage and the incidence of TM. Most of them (69.5 %) thought that being a carrier could affect their marriage. About half (53.9 %) were not aware that marriage between two Tm can produce a TM baby (Figure 2).

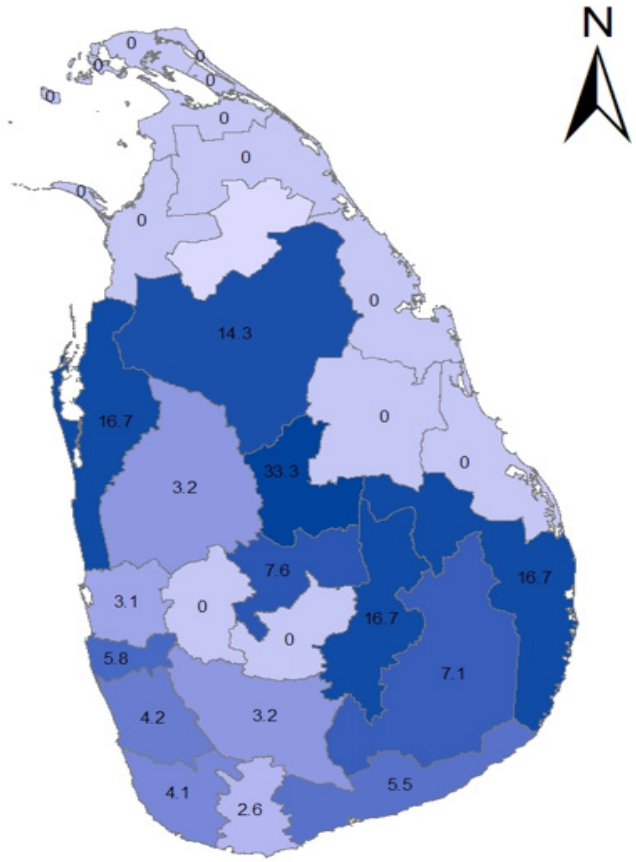

Figure 2: Percentage of presentation of Thalassaemia carriers, district wise in Sri Lanka.

Prevalence of Thalassaemia carrier state (Table 1)

The Tm state was diagnosed by identifying indices of low MCV, MCH, high RCC, and normal RDW and performing HPLC, and quantifying the HbA2 [7,8]. The group who had thalassaemia indices was 2.9 % (CI 1.2-4.6) and out of them, 3.9% (95% CI 1.9-5.8) were positive for β thalassaemia with high HbA2 (>3.5%) levels. Another 10 (2.6%) students had IDA coinciding β Tm. This brings the total β Tm rate to 5.5%. The rest who had thalassaemia indices with normal Hb and iron studies and normal HPLC were considered as possible α-thalassaemia, given a report, and advised for further screening with genetic studies.

Students who had low Hb (Female <11.5g/dL, male<13.5g/dL) but had no typical thalassaemia indices were considered anaemic and were investigated separately with serum iron studies, blood film, to rule out IDA. As per Table 1, the majority of participants (331, 86.2%) had normal parameters while the minority had hypochromic microcytic red cell indices such as possible α thalassaemia (15/ 3.9 %), β Tm (21/5.5 %), and IDA. (27/ 7.0 %) (Table 2).

Table 1: Prevalence of Thalassaemia carrier state.

State	Frequency	Percentage
Normal	321	83.6
Anaemia(IDA)	27	7.0
Possible α thalassaemia	15	3.9
β thalassaemia	11	2.9
β thalassaemia + IDA	10	2.6
Total	384	100

Table 2: Percentages of students of the cohort from each district nationwide.

District	No of students	No of Tm	%
Colombo	17	01	5.8
Kalutara	24	01	4.2
Gampaha	32	01	3.1
Matara	38	01	2.6
Kurunegala	31	01	3.2
Kegalle	17	00	00
Kandy	13	01	7.6
Galle	49	02	4.1
Badulla	12	02	16.7
Anuradhapura	14	02	14.3
Ampara	6	01	16.7
Ratnapura	63	02	3.2
Polonnaruwa	12	00	00
Putalam	12	02	16.7
Nuwara Eliya	4	00	00
Monaragale	14	01	7.1
Matale	3	01	33.3
Hambantota	18	01	5.5
Trincomalee	2	00	00
Mannar	1	00	00
Jaffna	2	00	00
Total	**384**	**21**	**5.5**

Discussion

Thalassaemia causes an enormous burden on health care resources throughout the developing world. The types and frequencies of thalassaemia are heterogeneous in this vast region even within a country. The α and β thalassaemias and Hemoglobin E (HbE) are commonly noted as the hallmark of southeast Asia, Sri Lanka, Bangladesh, Maldives, and the eastern region of India [9] (Fucharoes, et al., 1987). Thalassaemia was first identified in Sri Lanka in 1951 [10]. Since then there have been few reports of further cases and the occurrence of HbE and HbE/thalassaemia in the population. In the initial studies done in Sri Lanka, the rates were described as α thalassaemia carriers (+), β thalassaemia (2.2 %), and HbE (0.5 %) [9]. During the past few years, an increased number of patients with the clinical features of severe thalassaemia are being found. In 2000, de Silva et al, in a Sri Lankan study, estimated that there is an unevenness of the distribution of thalassaemia within the island and found the occurrence of many different mutations, out of which, only 2

account for about 80% of them that give rise to severe disease, which is also widespread throughout India and South East Asia. The same study investigated for α thalassaemia, where 472 individuals attending the transfusion clinics (or their parents) were assessed to know the number of α globin genes and the presence of the common forms of α + thalassaemia. Two common deletions of α + thalassaemia were found involving 3·7 kb (-α 3·7), and 4·2 kb (α 4·2). It was found that 13·6% of the population were heterozygous for the 3·7 deletion and 1·9% were heterozygous for 4·2 deletion while about 3% of the population were heterozygous for the triplicated α -globin gene arrangement (ααα) [3].

Another study done later in 2003 in Sri Lanka, it was found that the allele frequency of α + thalassaemia was 6.5% and 1.1% for -α 3·7, and α 4·2deletions respectively. Non-deletion α -thalassaemia was not observed. Triplicate or quadruplicate α globin genes were unusually common [11]. In 2013, α globin gene studies were done in nine families who had unexplained hypochromic microcytic anaemia, and in three families from an ethnic minority, a novel form of previously unreported αo deletion was found [12]. Although the deletion forms of α + thalassaemia are clinically silent, if it is co-inherited with the common HbE β thalassaemia, it can ameliorate the effects of β thalassaemia. Since the population genetics of thalassaemia is markedly diverse and the gene frequencies even within small geographical regions can greatly vary, it is important to micro map the populations to get accurate information of their gene frequencies [5].

A study done in Thailand has concluded that the total cost of treatment for four major thalassaemic diseases namely Hb Bart's hydrops fetalis, homozygous β-thalassaemia, HbE β thalassaemia and HbH diseases is about USD 220 million per year and elsewhere the cost of a total prevention program has been demonstrated to be $1/5^{th}$ to $1/10^{th}$ of the cost of treating the existing affected patients highlighting the importance of prevention programs especially in low economy countries. It has been shown that there was an abrupt reduction of new cases of severe thalassaemic disorders following the introduction of annual pre-natal screening in Thailand [13]. However, selecting the most suitable section of the population is vital in a successful screening program where, ethical and cultural implications in abortion and marriage could have a bearing. This could very well be applied to Sri Lanka where strong religious beliefs and cultural taboos could affect policy decisions.

It is a common problem that the thalassaemia carrier states can coincide with Iron Deficiency Anemia (IDA), which is also often prevalent in the areas where thalassaemia is prevalent. However, large-scale studies have proven that correction of IDA is not required to diagnose thalassaemia carriers by HPLC or Hb electrophoresis, as HBA2 levels are not affected when thalassaemia coexists with (IDA) [8]. In our study also, IDA did not interfere with the diagnosis of β Tm state. According to the annual birth rates assessed by the Ministry of Health Sri Lanka[14], between 60 and 80 new cases of severe forms of β thalassaemia are expected to be born each year out of which about 40% will have HbE/ β thalassaemia. This indicated that more than 2000 patients will need regular treatment [3]. This shows the magnitude of the problem which has not been addressed as a priority health issue in Sri Lanka.

In our study, participants' age ranged between 20-26 and the majority were from second and third academic years. Most of them (89.1 %) lived in their ancestral areas since birth. The majority of participants (95.6%) had siblings. Identification of this factor is vital in the prevention program, as family screening of a diagnosed carrier will contribute to the population screening for carriers in a county. The highest number of participants in this study (16.4 %) was from Ratnapura district.

Our study revealed that out of the 384 students who participated in this study, 53 students had hypochromic microcytic red cell indices with low MCV and MCH. Out of 53 students, 26 students had typical red cell indices of Tm (MCV & MCH were very low but RBC count was usually more than 5.5 million per cubic mm with normal RDW [15] and high RCC. Of these 26 students, 11(2.9 %) were diagnosed as β Tm carriers following a positive HPLC with high A2 levels. This brings the total population of β Tm to a total of 5.5% which is increased compared to the previous studies [3]. Ten students (2.6%) had β Tm coinciding with IDA which is a common finding in this part of the world. In the rest of the group with thalassaemia indices, 15 (3.9 %) were possible α thalassaemia carriers. The remaining 27 (7.0 %) students out of 53 who had hypochromic microcytic indices were anaemic and they showed a Hb between 7-11.5g/dL with no obvious thalassaemia indices. Compared to the previous studies done in Sri Lanka where some districts such as Colombo had low prevalence, our study shows that it is emerging in such capital cities probably due to population migration.

Awareness thalassaemia minor

About half of the participants (58.2 %) have heard about Tm. The rest of the facts were checked from that percentage (58.2 %) who knew about the disease. The fact that 60% thought that this is a symptomatic disease is a negative finding for population screening as this could bring about stigma to the diagnosed carrier preventing further screening. Most of them (69.5 %) thought that being a carrier could affect their marriage considering the social and ethical values practiced by the community. However, most of the participants (53.9 %) were not aware that marriage between two traits can produce a TM baby. Most (66.6 %) knew that it can be recognized by blood tests and also majority (70.8 %) knew that it was important to screen for Tm at pre-marital stage. This highlights the importance of taking measures to improve public awareness about this condition, and this study highlights the importance of using modern technologies such as social media, given the high usage of these technologies, in addition to newspapers and television as a method of creating awareness about the disease in the general public who represent many parts of the country.

The diagnosed Tm were given pink cards and were further followed up by screening the partner and family where possible. The group, who had thalassaemia indices but negative HPLC, were directed for genetic screening to exclude α thalassaemia.

The students who had hypochromic microcytic indices with anaemia showed an Hb between 7-11.5g/dL with no obvious thalassaemia indices and they had signs of anemia. Their iron profile was compatible with IDA. These students were referred to the haematology clinic for treatment and follow-up.

Conclusion

Based on the study findings, the carrier rate for β thalassaemia among university students was 5.5% which is higher than the estimated figures of previous studies in Sri Lanka. Out of them, 2.6% coincided with IDA. The incidence of IDA was 9.6%. The possibility of having α thalassaemia was 3.9%, which needs genetic studies for confirmation. The carriers were found in 15

districts out of 21 studied, which showed an emerging trend in some districts compared to the previous study. Considering that this is a significant problem in the country and that the study population is an educated fraction of the community, the knowledge of thalassaemia is unsatisfactory. The most effective way of eliminating the problem is creating public awareness through effective methods of education, emphasizing that it is a preventable disease by introducing screening programs for carrier detection at a national level.

Limitations

1. These results cannot be generalized to the whole population in Sri Lanka as only a cohort of students in a single unit was studied. However, they represented the entire island except for the north and east. This study will be followed up by further studies involving a bigger sample size.

2. We were unable to do genetic studies for individuals diagnosed with possible alpha thalassaemia at this moment due to financial constraints. These students were directed to centers for it to be done when possible.

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