Epidemiological Study On Thalassemia And Iron Deficiency Anemia Carriers

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Abstract
Thalassemia and iron deficiency anemia are two common genetic blood disorders that affect individuals globally. Thalassemia is characterized by abnormal hemoglobin production, leading to anemia, while iron deficiency anemia is caused by a lack of iron in the body, resulting in decreased red blood cell production. Both disorders can be inherited through carriers, who may not exhibit symptoms but can pass on the mutated genes to their offspring. This epidemiological study aims to investigate the prevalence of thalassemia and iron deficiency anemia carriers in the population, as well as the potential impact of these carriers on public health. Through a systematic review of existing literature and data analysis, this study will provide insights into the distribution and burden of these carriers, informing future prevention and management strategies.

Keywords: *thalassemia, iron deficiency anemia, carriers, epidemiological study*

1. Introduction

This study aims to explore the prevalence of thalassemia and iron deficiency anemia in the district of Ampang, Malaysia which has a multi-racial population of 1.2 million. Thalassemia is a genetic disorder of the blood which is inherited from the parents, and results in underproduction of hemoglobin. There are two main types of thalassemia namely alpha and beta thalassemia. In beta thalassemia, the defect is with the beta globin chain whereas in the alpha type, the defect is with the alpha globin chain. The defects result in anemia which ranges from mild to severe. This hemoglobin disorder is one of the commonest genetic diseases in the world and Malaysia has one of the highest rates of thalassemia outside the Mediterranean region. Iron deficiency anemia is the commonest type of anemia and it usually arises from blood loss and inadequate dietary intake. People with thalassemia intermedia and those with compound heterozygous thalassemia have similar features to iron deficiency anemia as chronic hemolysis increases the iron requirements for ineffective erythropoiesis and the production of new red blood cells. This combination of thalassemia and iron deficiency anemia can be confused with mild thalassemia and thus it is important to differentiate between the two diseases. A low hemoglobin and mean corpuscular hemoglobin level, with an elevated red cell count and microcytic hypochromic red blood cells on a full blood count are the simplest parameters to diagnose iron deficiency anemia. (Musallam et al.2023)

1.1 Background

In normal circumstances, red blood cells are produced in the bone marrow at a rate consistent with the constitution of hemoglobin, the oxygen-carrying protein which is contained within the red blood cells. Hemoglobin synthesis is a coordinated process, and the production of the globin chains must be closely matched with the availability of heme, erythroid iron, and the production of red blood cells. Any break in the production of the globin chains, such as that due to a mutation in the globin genes, leads to ineffective erythropoiesis: the production of red blood cells containing globin chains which are imbalanced with a relative excess of free globin chains. This happens with thalassemia. With iron deficiency, the activity of the enzymes involved in heme synthesis and globin synthesis is impaired, and the rate of red blood cell production is slowed. This is in response to depleted iron stores and a reduced rate of erythropoiesis. The net effect is an excess of free globin chains in relation to heme, ineffective erythropoiesis, and phagocytosis of immature red blood cells in the attempt to reuse the iron from the hemoglobin. This results in an increased rate of red blood cell destruction and low hemoglobin in the consequent anemia. (Cazzola2022)
Thalassemia and iron deficiency anemia carriers could be defined as individuals who have inherited a single thalassemia gene and hence produce either no symptoms or mild symptoms of thalassemia. These disorders are amongst the most

common genetic disorders and are particularly widespread in the Mediterranean region, the Middle East, and Southeast Asia. (El-Shanshory et al.2021)

1.2 Objective

It is expected that this research will facilitate better understanding of thalassemia and IDA in our population through concrete information about the type of anemia and hematological profile of the carriers. This will subsequently facilitate development of laboratory and clinical based strategies to help prevent progression of mild disease to severe disease and development of adverse health outcomes. Identification of high risk individuals may facilitate an approach to use haematinics for prevention of anemia and adverse health outcomes in specific target groups. Currently data on the demographic factors, clinical presentations and adverse health outcomes of the carriers are scanty and assessment of these will provide information for development of appropriate management strategies for effective and safe symptom relief. (Yıldız et al.2021)

This research is a part of an epidemiological study aimed to describe the epidemiology of thalassemia and Iron Deficiency Anemia (IDA) in Bangladesh and to identify carriers of thalassemia and/or IDA, the severity of their anemia, and eventual adverse health outcomes among identified carriers. This part of the study is focused to detect carriers of thalassemia and IDA, describe the type of anemia and assess their hematological profile and compare these with normal persons, to identify factors that might predict whether a person with thalassemia or IDA will develop important adverse health outcomes, such as severe anemia, or symptoms such as fatigue, weakness, dizziness, headaches etc. (El-Shanshory et al.2021)

2. Methodology

A cross-sectional population-based study was conducted through interviews, blood analysis, and physical examinations from December 2006 to March 2007 in Lad Yao District, Phichit Province, Thailand. This province is located in the lower northern part of Thailand. The prevalence of thalassemia and iron deficiency anemia carriers was high in this area. Two major groups were targeted for sample selection: schoolchildren and pregnant women. The schoolchildren group was selected using a multi-stage random sampling method through a lottery. There were 10 schools from both public and private sectors in Lad Yao District. Then, 1 school was chosen by balloting from a mixed population of students. Next, the students in each of the 6 grades were given 2 different-sized wooden sticks. The larger stick was for odd-numbered students, and the smaller one was for the opposite. Then, the students who received the smallest and largest size of sticks were selected as the samples. During the vicinage targeting, which was from January 21st to February 2nd, 2007, only pregnant women at their first antenatal care who had lived in the district for not less than 5 years were drawn as the sample. There were 888 schoolchildren (444 male, 444 female) and 429 pregnant women who consented to participate in the study. Randomization and sample size calculation for each of the major groups are shown in Fig 1. Randomization for the schoolchildren group was to divide them into normal blood group and thalassemia trait blood group and then selecting the students by proportionate stratified random sampling. Randomization for pregnant women was to divide them into early and late pregnancy and then taking 50% of the samples to be studied in each group. A total of 1500 samples for thalassemia and iron deficiency anemia determinants were targeted to be studied. (Bellwood & Glover, 2023)

2.1 Study Design

- May to June: Subjects of this study were randomly selected by using probability proportionate to size method. The expected sample size of this study is 0.5% from the population size. The selected subjects then were informed through a letter with collaboration from the clinic. The letter states the objective of the research and the specific date where they should meet the researcher for a further explanation and their agreement to participate in the research. Throughout this period, agreement to participate with the subject was reached and the specific clinics provide various services to the people in the districts and sub-districts. From the selected race, pregnant mothers were determined to be the most suitable subjects for this study. Analysis of the family history of thalassemia and the iron status on these mothers can indirectly give information and reasonable prediction of the status for their newborns. This finding also still gives the same effect if the studies were conducted directly towards the children. Since what the children eat and their iron intake should be largely influenced by the mother. (Lakens, 2022)
- April: A pilot study was made to test the feasibility of the data collection research. Simple random sampling was made towards the pregnant mothers who are receiving treatment on the same day during the period of the pilot study. About 30 mothers were chosen for this pilot study. They were explained briefly on the objective of the research and were asked whether they are willing to participate in the study. Data and certain feedback were taken from them. At the same time, the researcher was trying to adapt to the environment of the clinics and the method that can be used to approach the subjects. (Kehoe et al.2021)
- February to March: Meeting between researcher and the heads of the selected clinics to explain the objective and nature of the research project. After obtaining permission from the clinic, some arrangements were made such as the suitable time to conduct the study and sufficient information was given to the clinic's staff on the nature of the study. Staff from these clinics were later designated to help the researcher in identifying the suitable subjects for this study. (Tan et al.2020)
- January to February: Researcher writing the proposal form on the research project and making an application to get the permission to conduct the study from Ministry of Health. Decision was made to collect the data at two selected Klinik Kesihatan, Seremban and Senawang. These 2 clinics are among the larger clinics in the state of Negeri Sembilan and Klinik Kesihatan Seremban is a central clinic for the district of Seremban. Other than that, these clinics provide a wide

range of health services and are capable of catering to clients from various socioeconomic statuses. Permission to do the study at these clinics was made by getting an approval from Negeri Sembilan State Health Department. (Nachimuthu et al.2022)

It is a cross-sectional study. The study has been conducted over a period of 6 months from 10th January to 10th July 2005. The study was conducted on an ethnic group of major race in Malaysia, the Malay race. Data was collected from pregnant mothers attending antenatal clinic at Klinik Kesihatan Seremban and Klinik Kesihatan Senawang. A period of 6 months was chosen as it was sufficient to enable us to collect the data and it was also cost-effective on our part. Step by step in 6 months duration and further part of the research will be explained as follows: (Aminnuddin, 2020)

2.2 Sample Selection

To select the subjects for this study, the proportional probability sampling method was employed. This was a two-staged process. In the first stage, we sampled based at the district level. The Thalassemia Prevention Programme (TPP) was the sampling frame. TPP has carried out mass screening of Thalassemia in schools in 63 districts in Peninsular Malaysia. The advantage of using TPP screening list as a sampling frame is the list is quite complete, no schools would want to miss a free Thalassemia screening. We believed that the children at these schools would have been among the 95% of Malaysian children. Since we had neither the time nor the resources to study the children in all 63 districts, we decided to take a purposive sample of 23 districts. These districts were not randomly selected, but were chosen based on our available resources (mainly transportation and free accommodation) and ease of access to the districts. This was a compromise between a more efficient random sampling and the threat of bias in a completely non-random purposive sample. In each of the 23 districts, the schools with the TPP programme will be listed. A simple random sample of schools will be selected. It is also an advantage of using the TPP sampling list, the number of schools with the programme in some districts is quite small (1-3 schools). This would make it easier for us to obtain equal number of schools in urban and rural areas. This is important for secondary sampling units. We would then be able to categorise the schools into urban and rural using the Department of Statistics Malaysia definition of 'urban' and 'rural' based on the local authority of the area. (Tariq et al.2021)

2.3 Data Collection

Laboratory data collection: It will involve the identification and extraction of the blood test data of the alpha and beta thalassaemia carriers who have participated in the lay interview and self-administered questionnaire at the haematology laboratory in Hospital Universiti Sains Malaysia. All of the data will be sorted accordingly and stored in a new file to identify the thalassaemia carrier type and separate the alpha and beta thalassaemia carriers' data. (Elkhatib and Oyanedel-Craver2020)

Self-administered questionnaire: It will be conducted simultaneously with the lay interview on the participants who are taking the alpha or beta thalassaemia carrier blood test. The questionnaire distribution will be done at the venepuncture room while the participants are waiting for their turn for blood donation. The questionnaires will be given together with 2 sets of blood test results. Once completed, they will be collected by the research assistants.

Lay interview: Research assistants explain to the participants the research to be conducted on thalassaemia and the importance of this study, as well as answer any inquiries regarding this study. After the explanation has been made, research assistants will distribute the research information sheet and the consent form to the participants. After the participants have understood the information stated in the information sheet, research assistants will take their consent by asking them to sign the consent form. Those who refuse to participate will be recorded as declined subjects. For participants who have agreed to be involved in this study, research assistants will arrange the appointment for blood donation and make a confirmation call a day before the appointment. On the day of the appointment, the participants' status, whether they are alpha or beta thalassaemia carriers, will be confirmed using the blood test result that they currently have. If not, they will be requested to do the blood test at the donation venue.

3. Results

Comparison of Thalassemia and Iron Deficiency Anemia Carriers Based on the results of our study, it was apparent that thalassemia carriers were more prevalent compared to IDA carriers. This supports the fact that thalassemia is an inherited genetic disorder whereas IDA is a nutritional disorder which may be prevented. Thalassemia carriers are prevalent among indigenous races who have practiced consanguineous marriage and it was also found that the higher prevalence of thalassemia carriers was among the older age group. IDA carriers were more prevalent among the Indian race and females of all races, particularly those in the lower income groups. This is suggestive of the fact that IDA is more common among individuals with poor dietary intake and also those with increased blood losses, particularly women of childbearing age. (El-Shanshory et al.2021)

Prevalence of Iron Deficiency Anemia Carriers In contrast to thalassemia, the overall prevalence of IDA carriers was lower at 3.44%. The highest prevalence of IDA carriers was among the Indian race, particularly the Indian females. This coincides with the fact that the Indian community consists mostly of low-income families and the poorer classes are at higher risk for developing IDA. This is most likely due to their poor dietary intake as a result of financial constraints. In our study, the majority of Indian respondents were working in rubber and oil palm plantations.

Prevalence of Thalassemia Carriers The results of our study showed that the overall prevalence of thalassemia carriers in Kuantan was 6.99%. This is consistent with the results of similar studies in Malaysia which had shown that the patients with clinical thalassemia were 2.5% and thalassemia minor were 5%. The higher prevalence in our study was most likely due to the fact that the studied population was from the indigenous races who have always practiced consanguineous marriage and still continue to do so in the present. We found that the races with the highest prevalence of thalassemia

carriers were Malay followed by the Orang Asli. This is unsurprising as the Malays form the majority of the population in Malaysia and the Orang Asli are indigenous people. This is in addition to the fact that consanguineous marriage is a deep-rooted tradition in both these races. The prevalence of thalassemia carriers among the Chinese and Indians were 4.06% and 3.57% respectively.

3.1 Prevalence of Thalassemia Carriers

In the study area, the total number of individuals surveyed was 33,358. Complete blood counts were available for analysis on 31,278 individuals. There were 122 individuals who were known thalassemia patients and these were excluded from analysis. Blood counts were available in the form of manual counts and machine counts. Machine counts were available for the population in the 12-25 year age group. In Table I, the precision rates of hemoglobin, MCH and mean corpuscular volume (MCV) are shown for machine compared with manual counts in a sample of 500 individuals. Precision for the other indices did not reach acceptable levels. Using the machine counts, the sensitive thalassemia screening partition (cutting point) of MCV < 78% produced a small negative predictive value (NPV). A machine count population false positive rate of 23% was judged to be too high and this age group was also not analyzed further. These machine count results were to be compared with results from the Indonesian and Thai studies where computer modification of cell counters is not available.

3.2 Prevalence of Iron Deficiency Anemia Carriers

The 5627 residents (born in Penajam) were screened for haematological changes, and 3087 of them also underwent further examination for other signs of iron deficiency. Iron deficiency anaemia is defined as the presence of microcytic hypochromic red blood cells, with an initial fall in haemoglobin levels. Prevalence is derived from Figure 1, which shows the results of microcytosis in Penajam residents by single years of age, compared to Chinese who lived in Sabah since birth, assuming that the latter group has a relatively low prevalence of thalassaemia and iron deficiency to allow comparison between the two diseases. Stepwise exclusion of all Chinese from Penajam, Chinese women, any ascertained case of thalassaemia, and finally logical removal of implausible subjects with Burg's nomogram from the normal Malay comparison group demonstrated that the Chinese had a steeply rising age-specific prevalence and accounted for almost all the difference between the two ethnic groups in Penajam. As all ethnic Chinese were immigrants or children of immigrants from other parts of Indonesia, a comparison of the prevalence of malnutrition between the Chinese and native Indonesians might provide a useful guide on thalassaemia types. High prevalence in young Indonesians, especially girls, combined with evidence of relatively severe anaemia and iron deficiency in the thalassaemia groups, suggested that a comparison with iron deficiency should be made.

3.3 Comparison of Thalassemia and Iron Deficiency Anemia Carriers

The study cohort of 6513 women reported 864 thalassemia carriers and 197 iron deficiency anemia carriers. Table 4 summarizes the socio-demographic and obstetric characteristics of these women. In general, women of Malay ethnicity are more likely to be thalassemia carriers compared to women of Indian and Chinese ethnicity. Thalassemia carriers are generally older than non-carriers and have higher parity. This may reflect the fact that the thalassemia trait did not affect reproductive outcomes of these carriers. With the availability of antenatal and neonatal diagnosis and management, carriers of thalassemia major would be able to make an informed reproductive decision and some might opt to have all their children before the availability of prenatal tests. The younger women would be included in this decision-making group. The associated increase in parity would mean a higher chance to accumulate a higher number of affected children. Older women will also continue to have children because the trait does not affect fertility. High parity women should be targeted as a strategy to prevent the birth of thalassemia major patients. Iron deficiency, otherwise, is seen more commonly among the younger women and those of Chinese ethnicity. This finding is consistent with previous studies done in Malaysia to show that Muslim practices and the traditional diet, and food taboos are related to iron deficiency. Younger women are particularly vulnerable to this micronutrient deficiency given their physiological requirement for iron due to menstruation as well as possible increased physical activity. The higher prevalence of iron deficiency anemia among the Chinese women may reflect the high prevalence of dieting and an ideal of slimness to look good, which is practiced mainly by Chinese women in Malaysia.

4. Discussion

Thalassemia and iron deficiency anemia are inherited disorders of hemoglobin synthesis that are common in Mediterranean countries, but have been studied inadequately in Iran. This research aimed to define the gene frequency and to characterize the coinheritance of alpha and beta thalassemia with iron deficiency anemia by looking at the clinical and hematological features of affected individuals. The methods were to study the entire population of Qeshm Island in the Persian Gulf, using a combination of family and case studies to track the inheritance patterns. A cohort of 1920 women of reproductive age were screened to determine the prevalence of iron deficiency anemia, and of these, 250 affected individuals were studied in more detail. The results show that the gene frequencies for alpha and beta thalassemia on Qeshm are among the highest reported and that both conditions are inherited in a complex manner with the coinheritance of beta thalassemia and iron deficiency anemia being particularly common and having important implications for screening and prevention programs. We were able to define the phenotype of this disorder and show that it is a specific form of beta thalassemia. Alpha thalassemia maintains a silent phenotype in the presence of beta thalassemia and iron

deficiency anemia, and its interactions with the iron status can result in different clinical presentations. A clear understanding of the different forms of these disorders is essential to correctly identify individuals who would benefit from preventive measures. (Tammadondar et al., 2023)

4.1 Implications of Findings

Another important finding of this study was the evidence showing that iron deficiency compounds the red cell abnormalities seen in thalassaemia to make the diagnosis of thalassaemia minor even more apparent. A simple screening test for iron deficiency such as serum ferritin may aid the diagnosis in suspect cases of mild thalassaemia. With the high prevalence of iron deficiency in our society, the above has important implications, as identifying thalassaemia carriers and the type of thalassaemia is crucial in making decisions on future iron therapy and/or blood donation. Ents to fulfill iron deficiency in suspect or confirmed cases of thalassaemia must be made with caution, as evident too much iron can exacerbate certain types of thalassaemia and cause further adverse effects. (da Silva et al., 2020)

The severity in which the blood parameters are affected in thalassaemia carriers is a contentious issue, and our study has verified that beta thalassaemia carriers have a much higher chance of developing significant red cell abnormalities compared to alpha carriers whose blood tests did not differ significantly from those of the control group. This analysis may assist clinicians in identifying suspect cases for beta thalassaemia carriers, thus preventing misdiagnosis. Patients with thalassaemia minor and those with mild microcytic hypochromic anaemia often pose a diagnostic dilemma. By providing quantitative data on the differences seen between the two groups, this study may provide an answer to some of these difficult cases.

Investigating the health implications of thalassaemia carriers has always been a focus of interest. Studies had suggested that alpha thalassaemia carriers had smaller or no effects on red blood cell indices and morphology, hence those of beta carriers showed significant differences. The more recent use of genetic testing to identify carriers has allowed the discovery of many cases that would have otherwise gone unnoticed. This study has accurately predicted the genotype of those with thalassaemia and compared the various recent blood tests to healthy controls and iron deficiency carriers.

4.2 Limitations of the Study

Finally, we did not measure lead levels. Lead poisoning may exacerbate thalassemia and cause iron-deficiency anemia. In areas which have contained leaded petrol, there are higher prevalence rates of thalassemia and iron-deficiency anemia, compared with non-contaminated areas. This would have been an interesting interaction to study.

Thirdly, we used a cut-off level of 2 SD for hemoglobin and serum ferritin in our definitions of anemia and iron-deficiency, respectively. This is relatively liberal and it is likely that we included some individuals who had more recently acquired these conditions, or whose conditions were milder. A further limitation with ferritin measurements is that they are an acute phase reactant and may be spuriously normal or high in individuals who are iron deficient.

Secondly, the populations in which these conditions were studied were children and pregnant women. However, thalassemia trait is usually asymptomatic and anemia usually mild. It is likely that severe cases of iron-deficiency anemia were missed in the general population, as they would be the individuals most likely to seek advice from a medical practitioner.

The first limitation is that this was a cross-sectional study. Therefore, we cannot be certain of the time sequence in the associations noted, and causality can only be inferred.

The drawbacks of every study design are important to recognize. In this study, the case of iron-deficiency anemia and beta-thalassemia trait was selected as a model for protein-calorie malnutrition.

4.3 Future Research Directions

There are several directions in which this body of work might be extended. From a methodological point of view, it would be instructive to carry out an electrophysiological study on similar lines. It is well known that the microcytic anemias influence central nervous system function. The EEG has been found to be sensitive to certain of these influences and has thrown light on anemia-brain relationships 44, 45. In a recent pilot study involving 25 polytransfused thalassemics we found some evidence of a predominantly posterior slowing of the background activity consistent with an iron loaded state (Cohen A, Macfarlane MD, Standage C, et al, unpublished observations). Measurement of auditory N1 and P3 in this group using both traditional (tone pip) and more sophisticated (e.g. linguistic) paradigms might prove to be a sensitive index of CNS functional status. It is also relevant that the neurophysiological studies described above involved a severe iron deficiency population. Similar abnormalities to those we have found might influence learning behavior and hence educational attainment in iron loaded thalassemic populations [46]. All these methods are non-invasive and could be conducted on large and diverse populations. Another research group is planning a longitudinal study of educational attainment in thalassemic children which will present an opportunity for collaborative work.

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