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RESEARCH ARTICLE

Concerns of thalassemia inheritance amongst carrier parents within Kirkuk province, Iraq

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Abstract: Thalassemia is a widely spread disease within Mediterranean and some North African countries; particularly among the intra-marriage couples with scanty data in Iraq. ***Materials and Methods:*** An investigation of thalassemia in 1,267 carrier patients and their offspring was carried out within Kerkuk province, Iraq. ***Results:*** The proportion of hemoglobin (Hb%) was significantly ($p \leq 0.001$) dropped in thalassemia patients (8.0%±1.22) in comparison with healthy counterparts (11.87%±1.77) with an insignificant difference between the genders (46%) female and (54%) male. The frequency of infection was significantly different ($p \leq 0.05$) in rural (76%) compared to urban (24%) regions of Kirkuk. The proportion of sickle disease was 0.55% out of all patients, splenomegaly (0.47%) diabetics and 0.5% heart disorders; meanwhile 4% with delay in growth and 2% with bone malformation and bone britlitis. Blood transfusion cases involved 38.5% with disfral treatment and 30.6% without treatment. Almost 77.3% patients with a single; 21.6% twice and 1.03% received 3-4 times blood transfusion. Children between 2-5 years old made 39% of the whole patients, and dropped to 29% amongst youngsters aged 6-15 years old and further dropped to 19% in patients aged 16-25; less than 10.6% was recorded for patients aged 26-50 year old; meanwhile only 1.4% of thalassemia patients survived above 50 years old. ***Conclusion:*** In Iraq, thalassemia deems a common disease that may impact a considerable range of people if either or both parents carry deformed hemoglobin. Both couples, prior marriage, are highly recommended to check for autosomal recessive forms of disease genes to avoid any affected babies.

Keywords: Anemia, blood disorder, genetic factor, heredity, parents, thalassemia.

INTRODUCTION

The term thalassemia, or "Mediterranean anemia" was originally described in people of Mediterranean ethnicities which then was re-named thalassemia major in 1932 following genetics exploration [1][2]. Other specific names e.g. Constant Spring, Cooley's anemia (ß-thalassemia major) have also been used [3]. Geographically, thalassemias are widely spread among people over the world i.e. in Europe, the highest concentrations of the disease are found in Greece, Mediterranean coastal regions of Turkey, Southern Spain, and Southern Italy [4]. Others regions e.g. North Africa and West Asia as well as far Southeast Asians are also affected, with the world's highest rate of thalassemia carriers (16-18%) in the Maldives [5]. In year 2015, thalassemia occurred in about 280 million people worldwide, where about 439,000 had severe disease with an equal rate between the two genders [6]. Meanwhile, thalassemia resulted in 16,800 deaths in 2015, down from 36,000 deaths in 1990 [7]. This inherited blood disorder, results in abnormal hemoglobin as the body fails to produce adequate hemoglobin and normal healthy protein and bone marrow produces fewer healthy red blood corpuscles (RBC) that enable transport of enough oxygen (O2) to nourish body's leading to anemia-like symptoms that range between mild to severe [8]. At an inadequate hemoglobin, the body's RBC wouldn't function properly and may survive shorter periods leaving a fewer healthy RBC migrating in the bloodstream. The normal human hemoglobins are tetrameric (carry 4 protein molecules) as 2 pairs of globin chains, each of which contains one alpha-like (α-like) chain another beta-like (β-like) chain in balance and relatively constant ratio; meanwhile no excess of either type with each globin chain is associated with an iron-containing heme-moiety [9]. Accordingly, thalassemias are classified pending to which chain of the hemoglobin molecule is affected e.g. in α-thalassemias, production of the α-globin chain is affected, while in β-thalassemia, production of the β-globin chain is affected [10][11]. Symptoms-wise, anemia involve tiredness, pale skin, bone problems, splenomegaly, pulmonary hypertension, and dark urine [12] while the symptoms may change overtime, depending on the type of thalassemia and can vary from none to severe with slow growth may occur in children [8]. Therefore, the severity of α and ß-thalassemia depends on how many of the 4 genes for α-globin or two genes for β-globin are missing [13]. Those with minor degrees of thalassemia, in common with sickle-cell trait, have some protection against malaria, explaining why sickle-cell trait and thalassemia are more common in regions of the world where the risk of malaria is higher [14]. Further complication may accompany infection with thalassemia i.e. destruction of a large number of RBC meanwhile the task of removing destructed cells causes the spleen to enlarge and turn splenomegaly [15]. Simultaneously, thalassemia patients may have increased risk of infection, particularly, if the spleen has been removed [16]. Thalassemias are also considered inherited and genetic disorder which is classified under a medical term "hemoglobinopathy" [17]. They are single-gene

disorders and, in most cases, inherited as autosomal co-dominant traits [18-21]. Diagnosis is typically by blood tests including a complete blood count (CBC), special hemoglobin tests, and genetic tests or, it could also be diagnosed before birth through prenatal testing [22].

Justification: Similar studies over thalassemia yet are scanty for prevalence purposes and relevant to genetic factor amongst Iraqis where intra-marriage is a common phenomenon in the society.

MATERIAL AND METHODS

A total 1,267 patient from both genders involved in this research being are admitted hospital and examined where 76% were from rural and 24% from urban areas of Kirkuk Province. Ages ranged from a few months to a few years by their parents being diagnosed thalassemia in different stages. Apart from thalassemia, other diseases have also been diagnosed amongst these patients i.e. sickle. Personal data were collected and treated confidentially according to ethical code of conduct. Blood samples were collected by professional stuffs for full blood analysis using automated blood analyzer. Medical reports were prepared by hematologist experts. Thalassemia cases were diagnosed via a complete blood count (CBC), hemoglobin electrophoresis or high-performance liquid chromatography, and DNA testing [23].

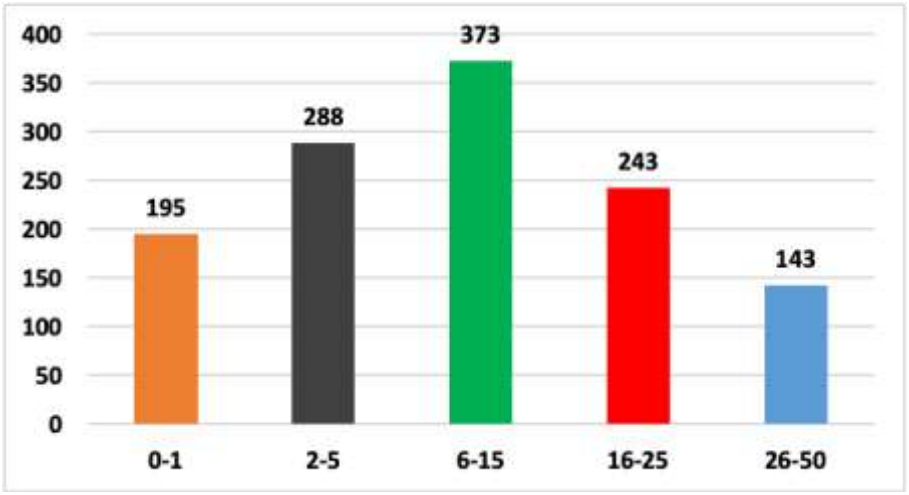
RESULTS

Out of 1267 patients being admitted hospital and examined an almost 76% were from rural and 24% from urban areas of Kerkuk province. Almost 75% of the patients encountered in this research were found to be first degree cousins, 14.7% second cousin and only 10.3% were non related couples. An insignificant difference was found between male thalassemia patients (46%) and (54%) female. An evenly distributed proportion of the three different stages of thalassemia (minor, intermediate and severe) were detectable amongst the patients. Only 6% of other diseases were detected among the total patients e.g. only Sickle disease (0.55%) while less than 4% was in common with thalassemia out of total patients. Other common diseases coincided thalassemia i.e. 22.5% had suffered from splenomegaly, with only 0.47% diabetics, 0.5% heart disorders, 4% delay in growth and 2% with bone malformation and bone britlitis. Amongst the total patients only 6.8% were detected to be hepatitis-C virus (HCV) victims where majority of them (20.2%) were in common with thalassemia major, 1.8% with intermediate and nil with minor (Table-1).

(Table-1): Distribution frequency of three types of thalassemia and others e.g. Sickle and sickle and thalassemia amongst the two genders of patients.

Type of thalassemia	General (%)	Male (%)	Female (%)	HCV (%)
Minor	420 (33)	194 (35.59)	226 (34.82)	0%
Intermediate (Mild)	379 (30)	161 (29.54)	218 (33.59)	7 (1.84%)
Major (Severe)	395 (31)	190 (34.86)	205 (31.58)	80 (20.2%)
Total thalassemia	1,194 (94.2)	545 (45.65)	649 (54.35)	87 7.2%
Total other diseases	91 (7.2%)	37 (2.92)	36 (2.84)	4 (0.31%)

The age of patients admitted the hospital ranged between (<1 to >50) years old. Children with a few months old (<1 year old) up to 5 years old made 39%, while the highest proportion of patients were teenagers at ages ranged between 6-15 years old (48%). Then it dropped down to 19% for patients aged 16-25, meanwhile fewer patients (10.5%) had survived above 26 years old of the whole thalassemia patient populations. Those over 50 years old have made around 1.5% of the total patients admitted the hospital (Fig.1).



(Fig. 1): Distribution of thalassemia amongst the age groups in patients ranged less than 1 year up to 50 years old. Only 17 patients had survived which is not shown as a column.

The proportion of hemoglobin (Hb%) was significantly ($p \leq 0.001$) dropped in thalassemia patients (8.0%±1.22) in comparison with healthy counterparts (11.87%±1.77) with an insignificant difference in between the genders. Blood transfusion cases involved 38.5% with *disfral* treatment and 30.6% without treatment. Almost 77.3% of those transfused patients had only a single blood transfused, 21.6% twice and 1.03% received 3-4 times blood transfusion.

DISCUSSION

The total patients of 1,267 subject of this survey have represented are being diagnosed thalassemia within Kerkuk province for last five years 2018-2023 and documented in the national data base within the hospital. Such a number of thalassemia patients represent samples out of 2 million commuters of Kerkuk province. The proportion of the thalassemia, therefore, may represent almost 0.06% of the total Kerkuk community or almost 600/million citizens. The gender variance in thalassemia patients showed an insignificantly higher proportion in females in comparison with males may denote an equal rate of infection in genders, which is in concomitant with most recent published research in France [6]. Our research involved all the diagnosed thalassemia cases, in general, included both α and β-protein molecule chains types of thalassemia. The intra-marriage in Iraq, as a part of Mediterranean country, is a common phenomenon between families and more tradition in rural regions than in urban. Should this phenomenon, be continued, it would then escalate the rate of inherited diseases in the society. This is evident in the higher percentage of thalassemia detected in rural couple than in urban. Unfortunately, most couples wouldn't bother to carry out some essential medical pre-marriage health checkup to ensure the quality of genetic outcome of their offspring. Such parental ignorance will have a strong impact on chances of inheriting thalassemia to their offspring. Almost all the children encountered in this research had a thalassemia parents who were carrier of the autosomal gene encoding thalassemia. While the health checkup deems mandatory prior marriage, the genetic impact seems so strong factor in inheriting thalassemia offspring from thalassemia parents.

The present study involved both parents and their offspring diagnosed positive, at various stages of thalassemia and treatment. Our results refers to equal proportion of patients (33%) at all three stage of diagnosis and that are subject to current treatment meanwhile the proportion was equal between the two genders in mild infection. Our results may confirm the earlier finding that thalassemia develops as single-gene disorders and inherited as autosomal co-dominant traits [18]. For the autosomal recessive forms, both parents must be carriers for a child to be affected. Simultaneously, if both parents carry a hemoglobinopathy trait, the risk is 25% for each pregnancy for an affected child [24]. Our results included diagnosis of 87 hepatitis-C patients 1,267 thalassemia patients where the majority encountered as major thalassemia. This finding could be interpreted as infection with other disease, i.e. sickle, splenomegaly or diabetes is not uncommon for thalassemia patients where health states may further deteriorate towards sever cases leading to death. No data are available, at this stage, to confirm the link between thalassemia and these diseases i.e. which one began first; however, health history of patients deems necessary to clarify this issue which, unfortunately, is an ignored challenge in Iraq.

The patients with <1-5 year old age have made 39%, while the highest proportion of patients were at ages ranged 6-15 years old (48%). Such a range represents the childhood-teenager ages where the infection has already been diagnosed at peak and likely on treatment, meanwhile it had dropped down to 19% for patients

aged 16-25. The latter might denote impact of treated period in ameliorating the health or patient have no longer alive, particularly only (10.5%) had survived above 26 years old of the whole thalassemia patient populations. Those >50 years old have made around 1.5% of the total patients admitted the hospital which represents either recovered patients or the survivals. Diagnosis of other common diseases might have, to certain extend, biased our data due to intermingled causes.

The main risk of thalassemia generate from the amount of Oxygen (O2), carried by RBC to all cells of the body, that cells use to function properly. Less oxygen denotes a fewer healthy hemoglobin proteins, and/or the bone marrow produces fewer healthy RBC causing anemia that kicks off pending upon 2 factors i.e. not enough oxygen delivered to all other cells or inadequate healthy RBCs. In the present research, hemoglobin percentages had significantly ($p \leq 0.001$) dropped down in thalassemia patients from 11.8%±1.77 to 8.0%±1.22 and were associated with some or all other symptoms e.g. tiredness, weakness, feeling cold, fatigue, trouble breathing, and dizziness with a pale skin which all were apparent in our patients leading to deprival of the body's cells of the oxygen they need to make energy and thrive [25]. The consequent would cause, if ignored, a mild or severe anemia and other complications over time i.e. iron overload [26] as a severe (major) anemia would cause a gradual damage to body organs and may therefore is the most serious form and usually requires regular treatment [27]; otherwise it may end up fatal. Hence, it becomes so necessary to have regular health checkup made to avoid further complications.

Thalassemia affects people who have ancestral links to parts of the world where malaria is prevalent i.e. Africa, Southern Europe and West, South and East Asia [8]. Such a phenomenon may indicate that Mediterranean peoples are more genetically susceptible to infection with thalassemia than other races. Whether or not this susceptibility is linked to Mediterranean environmental factors needs further researches.

Treatment of thalassemia varies pending on two factors, the severity of disease and the availability of valid techniques to be adopted. The more severe disease often includes regular blood transfusions, iron chelation, and folic acid and occasionally, a bone marrow transplant may be an option [28]. In worst cases the complications may involve iron overload from the transfusions, resulting heart or liver disease, infections, osteoporosis, and occasionally splenomegaly where surgical removal may be required [22]. Treatment could also follow gradual strategy as thalassemia patients who do not respond well to blood transfusions can take hydroxyurea or hemoglobin inducer, the thalidomide [27]. Hemoglobin electrophoresis is not widely available in developing countries, but the Mentzer index that can be calculated from a CBC report is recommended instead which can diagnose the possible thalassemia [29]. Further debate of medical treatment becomes out of scope of this research where details are mentioned in elsewhere [30][31].

International records suggest that approximately 1.5% of the global populations are β-thalassemia carriers [32]; however, exact data on carrier rates in many populations yet are lacking, particularly in developing areas of the world and prevalence of the disease in countries with little knowledge of thalassemia, access to proper treatment and diagnosis yet can be difficult [33]. Nevertheless, some diagnostic and treatment facilities are still available in developing countries, merely by private sectors and particularly, for patients who can afford [34][35]. Both blood transfusion and chelation therapy techniques are still affordable and treatable techniques, even in poorly developed countries, the retroviral vector–mediated gene transfer into hematopoietic stem cells provides a potentially curative therapy for severe β-thalassemia but deems not a straight forward technique that can be well-managed [36]. Due to consequent health risk of thalassemia the American Ministry of health recommends those women planning to get pregnant be tested for thalassemia meanwhile the genetic counseling and genetic testing are recommended for families who carry a thalassemia trait [37]. Similar tests in the UK [38]; Cyprus [39], Iran [40] and India [41] are carried out for the same purposes. Such screening tests should become a mandatory action in Iraq to stop or/and avoid spread of the thalassemia.

CONCLUSION

Thalassemia disorder deems a real social concern for marrying couples due to its inheriting impacts on their offspring that needs to be handled before planning for children meanwhile it could also lead to other diseases.

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