Journal of Advanced Zoology

ISSN: 0253-7214
Volume 44 Issue S3 Year 2023 Pages 341: 345

A Study on The Awareness of Consanguinity & Various Genetic Aspects Among the Parents of Children with Beta Thalassemia and To Understand the Usefulness of Various Indices in Identifying Beta Thalassemia Carriers in A Cohort of South Indian Patients

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Article History

Received: 10 June 2023
Revised: 12 Sept 2023
Accepted: 05 Oct 2023

Abstract

Background: Beta thalassemia is one of the common single gene disorders in India. Screening relies on High performance Liquid Chromatography (HPLC) / Hemoglobin electrophoresis. But this being an expensive test, we looked at the usefulness of red blood cell indices in the identification of beta thalassemia carriers. We have also looked at the proportion of consanguinity and the awareness of genetic aspects of Beta thalassemia in this cohort. Methods: This is an observational study among parents of children with Beta thalassemia major attending hematology out-patient Department in a tertiary care centre in Chennai, South India. Their complete hemograms were analysed using Mentzer Index, Srivastava Index and Green & King Index. They were also asked to fill in a questionnaire to understand their level of awareness of Beta thalassemia, consanguinity and other demographic parameters. Results: Though the three indices were able to identify majority of the carriers, they missed 10-20% of carriers underscoring the fact that Complete Blood counts and HPLC together would remain the best modality.53% of this cohort were graduates and 26.7% were consanguineous. None of the parents had heard of thalassemia before their child's diagnosis.53.3% understood the genetic nature of this disorder. Conclusion: Evaluating complete hemogram and HPLC would be the ideal screening method to identify Beta thalassemia carriers. More awareness needs to be initiated in the community about Beta thalassemia and universal screening for Beta thalassemia in all adults >18 years or at least for antenatal mothers should be initiated at the earliest.

Keywords: *Complete hemogram, HPLC, Beta thalassemia, consanguinity, Mentzer index, Srivastava index and Green & King indices*

1. Introduction

Beta thalassemia is one of the most common single gene disorders in India and the carrier status is estimated to be around 3-4% and in some communities it is around 5-15%[1]. Creating awareness, carrier screening and prenatal diagnosis are important cornerstones in the disease prevention. Identifying carriers with beta thalassemia trait (BTT) is very important to prevent the birth of children with beta thalassemia major. Carrier screening by hematological indices-Low MCV <80fl, low MCH <28 pg raises the suspicion of Beta thalassemia trait. This has to be confirmed by Hemoglobin electrophoresis or HPLC (High Performance liquid chromatography). HbA2 Value of >3.5 in HPLC is considered as the diagnostic criteria of Beta thalassemia trait. However, HPLC is expensive and is not available in remote areas. In such scenarios various screening tests using Red cell indices have been used to differentiate between Iron deficiency Anemia (IDA) and Beta thalassemia trait (BTT). Several indices

like Mentzer Index, Red cell distribution index, Shine and Lal index have been used as screening tools[2,3,4]. In this pilot study, we evaluated a small cohort of parents of children with beta thalassemia major. We looked at the Complete hemogram profile of 30 parents with Beta thalassemia trait to understand the performance of Mentzer index, Srivastava Index and Green and King Index(G&K)[4,5]. Raising awareness about thalassemia is a very important aspect for successful screening and as a part of this study we undertook a questionnaire to understand the general awareness about thalassemia and awareness about its genetic aspects in the same group.

Aims and Objectives

The aim of the study was to understand if Mentzer index, Srivastava index and Green & King indices could be considered accurate enough for screening of beta thalassemia carriers.

2. Materials and Methods

This prospective study was conducted from March 2023 to June 2023.Thirty parents of children with thalassemia major were interviewed and asked to complete a structured questionnaire on name, educational status, consanguinity, knowledge about genetic aspects of thalassemia major, their awareness about prenatal diagnosis and their willingness to spread awareness. Their Complete Blood counts, RBC indices and HbA2 levels were noted and Mentzer index, Srivastava index and Green & King indices(G&K) were calculated. Mentzer Index uses the formula MCV/RBC Count and cutoff of <13 was indicative of BTT. Srivastava Index uses the formula MCV/RBC Count and a cut off value of <4.4 is suggestive of BTT and Green and King Index uses the formula MCV*RDW/(Hb*100) and used a cut off of <72 indicate BTT.

3. Results and Discussion

The Complete blood counts of thirty parents of children with Beta thalassemia major were analyzed. HPLC was also done confirming that all were carriers (Beta thalassemia trait) and there were no silent carriers. There were 15 males and 15 females in the group. The average Hemoglobin was 10g/dl among the females and 12.19 g/dl among the males. The average RBC count was 6.27 million/cc in males and 5.04 million/cc in females. Average MCV was 62.62 fl among males and 63.1fl among females. Mean MCH in males was 19.4 in males and 19.5 in females. Mean MCHC was noted to be 30.3 g/dl among males and 31.2 g/dl in females. Mean HBA2 levels were 4.9 and 4.8 in males and females respectively.

Table 1: RBC indices and the various indices in 30 people with BTT

RBC count (m/cc)	Hb g/dl	MCV fl	MCH pg	MCHC g/dl	RDW %	HbA2	Mentzer Index	Srivastava	G&K
6.64	11.9	59.9	18	18	16.8	5.1	9.021084337	2.710843	50.65426
6.78	10.7	57.1	15.8	27.6	21.2	5.4	8.421828909	2.330383	64.59878
5.44	9.3	61.8	17.1	27.7	22.3	5.2	11.36029412	3.143382	91.57963
5.83	11.3	63.8	19.4	30.4	16.9	5.5	10.94339623	3.327616	60.87649
6.18	12.4	66.7	20.1	30.1	16	4.6	10.79288026	3.252427	57.40503
4.78	8.3	58.4	17.4	29.7	24.3	4.1	12.21757322	3.640167	99.85133
5.2	8.4	54.4	16.2	29.7	19.9	3.8	10.46153846	3.115385	70.10865
6.96	11.8	56.3	17	30.1	19.5	4.7	8.08908046	2.442529	52.38047
5.33	10.6	65.3	19.9	30.5	16.4	5.4	12.25140713	3.733583	65.97271
6	12.2	62	20.3	32.8	16.9	5.2	10.33333333	3.383333	53.24885
5	10.5	64.8	20.9	32.3	19.6	4.5	12.96	4.18	78.38208
5.2	10.7	72.7	20.6	28.3	15.7	5.8	13.98076923	3.961538	77.55052
5.97	11	66.5	18.4	27.7	15.5	5	11.13902848	3.082077	62.31352
5.11	10.1	62.4	19.8	31.7	15.1	4.7	12.21135029	3.874755	58.21364
6.65	13	60.2	19.5	32.5	17.7	5.2	9.052631579	2.932331	49.3427
5.75	10.6	58.6	18.4	31.5	17.1	4.9	10.19130435	3.2	55.3969
5.89	12.9	66.2	21.9	33.1	15.5	4.8	11.23938879	3.718166	52.65722
5.2	10.9	68.6	21	32.5	17.4	5.4	13.19230769	4.038462	75.12266
5.91	12.2	68.4	20.7	31.5	17.3	5.4	11.57360406	3.502538	66.34351

5.59	11.2	55.1	19.6	35.6	18.5	4.9	9.856887299	3.506261	50.14838
4.5	9	60.4	20	33.2	15.3	5.3	13.42222222	4.444444	62.01872
5.52	10.1	58	18.3	31.6	17	4.2	10.50724638	3.315217	56.62178
5.9	13	69.4	21.9	31.6	15.3	4.1	11.76271186	3.711864	56.68485
4.54	9.9	65.4	21.81	33.3	15	4.4	14.40528634	4.803965	64.80545
6.69	12.5	60.1	18.7	31.1	16.6	4.7	8.983557549	2.795217	47.96749
4.84	11.7	72.3	24.2	33.4	13.1	4.5	14.93801653	5	58.52778
6.67	14.3	64.6	21.4	33.2	15	3.8	9.685157421	3.208396	43.77441
4.24	11.1	61.5	21.1	34.3	14.5	4.7	14.50471698	4.976415	49.40777
4.95	8.9	63	18	28.4	18.4	5.2	12.72727273	3.636364	82.05573
6.46	12.5	63.1	19.3	30.6	16.4	6.4	9.767801858	2.987616	52.23872

Using Mentzer index 6 individuals who had beta thalassemia trait could not be identified which was 20% of the study population. The mean Mentzer index was 11.33. The mean Srivastava index was 3.53 and this index was able to identify 27 carriers correctly but missed 3 carriers which was 10% of the sampled population. The mean Green and King index was 62.2 and it missed six carriers which was 20% of this population. Overall, on applying the three indices, it was noted that all three indices were able to identify majority of the carriers but a few carriers were missed. Srivastava index missed 10% of carriers while Mentzer and Green & King index missed 20% of carriers. (Table 1). Though the sample size is small, we found that Srivastava Index performed better than Mentzer and Green and King index. Among the parents of the children with Beta thalassemia included in this study 53.3% were graduates and 46.7% were educated between class 5-12 class (Figure 1).

Figure 1: Educational Status of parents

We noted that majority (73.3%) of couples who had a child with beta thalassemia major were nonconsanguineous while 26.7% were only consanguineous (Figure 2).

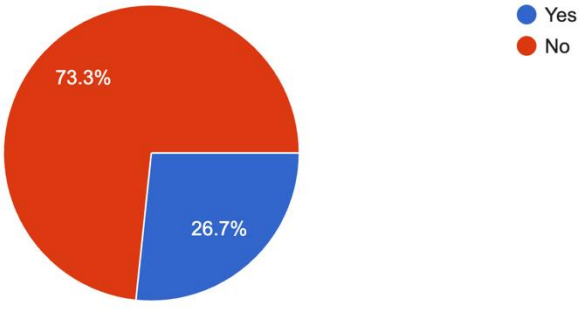

Figure 2: Consanguineous marriages

All of them were now aware that thalassemia was a genetic disorder(100%).But none of the parents were aware of this disorder before their child was diagnosed indicating the poor general awareness about this disorder. 6.7% of the parents thought that thalassemia occurred only in consanguineous couples. 53.3% answered that they had a 25% risk of having another baby with thalassemia major, while 40% thought it was 75% and 6.7% thought it would be 100%. 86.7% were aware that thalassemia can be identified prenatally and all of them were willing to spread awareness among their relatives and friends. Thus, this questionnaire helped us to understand the need for spreading more awareness about Beta thalassemia in our population and the availability of prenatal diagnosis by genetic counseling. Awareness about avoiding consanguineous marriages also needs to be reinforced.

Beta thalassemia is one of the most common hemoglobinopathies in India. The expenses incurred towards the diagnosis and the long-term management of children with Beta thalassemia places a huge burden on India's economy. Hence prevention of Beta thalassemia is the need of the hour. The prevention of beta thalassemia major can be done by identifying the carriers and planning prenatal diagnosis when both the partners are carriers[1,6,7].An important step in this is screening the population at risk and identifying the potential carriers. HbA2 >3.5 is considered as a gold standard in identifying carriers of Beta thalassemia. However, HPLC used to measure HBA2 levels is not easily available and is expensive. Hence screening methods using various formulae involving the red cell indices have been devised for inexpensive screening of large populations. Hypochromic microcytic anemia is common to both beta thalassemia carriers and Iron deficiency anemia. Using these indices one can differentiate

These two subgroups leading to effective identification of Beta thalassemia carriers. Our study showed that though the Mentzer Index, Srivastava Index and Green and King Index were able to pick up majority of the carriers, they still missed 10-20% of the carriers. Hence HPLC would be a more robust screening option rather than using these indices alone. Comprehensive screening and prenatal diagnosis are an effective way to prevent thalassemia. The genetic mutation varies according to the geography and ethnic groups even in different parts of India. When the mutation prevalent in a specific geographical area is known, carrier screening and prenatal testing becomes easy[7,8,9]. Consanguinity specially in India plays an important role in increasing the gene pool of disease-causing mutations. Consanguinity is more prevalent in South than Northern parts of India. According to Kumar et al consanguinity was observed in 7.5% of couples in Uttarpradesh who had a child with beta thalassemia major[7].According to the National Health and family survey 92-93 as reported by Brittles et al, the consanguinity in South India was found to be 30.8% in Andrapradesh and 29.7% in Karnataka and >20% in Tamil Nadu [10]. Our study too corroborates the rate of consansanguinity to be 26.7% which is much higher than the national average of 11.9%. It is unfortunate that the percentage of consanguinity remains almost the same even after around 30 years.

4. Conclusion

India is unique in view its cultural, geographical and ethnic diversity across the country and even across a region. With significant progress in controlling nutritional and infective disorders, the priority now lies in reducing the burden of genetic disorders. Among this beta thalassemia is a very important disorder causing a huge burden. Hence increasing awareness, identifying carriers and prenatal diagnosis is very important. Increasing awareness will make more people to take up the screening and avoid consanguineous marriages. Relying solely on various indices does not prove to be effective according to our study. Hence HPLC and RBC indices would be a better screening tool and ways to make this a universal screening program should be implemented.

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