

Distribution of Abnormal Hemoglobin around the Coast of the Seto Inland Sea in Comparison with Those of Surrounding Countries

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Abstract

About 760 sorts of abnormal hemoglobins (abn Hbs) have been reported in the world (1994). We continued to screen the blood specimens of inhabitants around the Seto Inland Sea for the past 15 years. The detection rate of abn Hb of our laboratory was different from area to area with an average of one per 1,800 which are slightly higher than one per 3,000 to 4,000 in Japan. More than 30 different abn Hbs as the summation of the reports of five Institute have been registered in these areas. However, neither Racial abn Hbs like Hb S nor specific variants common to all over Japan were detected.

Introduction

Since the first abn Hb (Hb M-Iwate) was reported^{1),2)} in 1960, the screening of abn Hb has been conducted^{3),4),5)} on about a million people by the laboratories or hospitals located at Fukuoka, Ube, Hiroshima, Kurashiki, Matsuyama, Osaka, Gifu and Tokyo (in order from west to east). Detection of abn Hb by electrophoretic screening has been carried out actively especially in the area on the coast of the Seto Inland Sea. Recently some abn Hbs happened to be detected by HPLC for quantitation of Hb A_{1c}, however, the electrophoretic screening provided a most efficient method of studying epidemiologic characters of abn Hbs. Since 1974, we have continued to screen the blood specimens of inhabitants around the Seto Inland Sea. The present paper aims to describe a brief review of our result of the screening survey on the bases of those of the aforescribed institutes.

Materials and Methods

Ice cold blood specimens used for the examination were shipped to us every once a week from Kagawa Prefectural Central Hospital in Kagawa prefecture, Fukuyama National Hospital in Hiroshima prefecture, Kobe Central Hospital in Hyogo prefecture and Kawasaki Hospital in Okayama prefecture during the period from 1974 to 1989. All of them were located in close proximity from our laboratory. Each specimens were registered into computer with items of living place, name, age and sex to avoid double testing of the same individuals. Venous blood was collected in Heparin solution. The anticoagulated blood was mixed with 0.3% KCN solution which was previously put in

a hollow of a 150 well plate and then the mixture was placed to freeze at -70°C overnight. When melting them using the so called "freeze and thaw method", 150 hemolysates were prepared at once. One μl of hemolysate was applied on acrylamide IEF plate (5%T, 2.6%C, pH 5-9, $10 \times 17\text{cm}$) and IEF were carried out at 4°C , 500V for 2-3 hr. About 80 hemolysate on an IEF plate were possible application.

The preparation of globin and its α and β chain, enzymatic digestion of the chain and amino acid sequencing for primary structural analysis were performed by the most conventional way of methodology at on time.

Result

The result of the survey which was carried out in our laboratory for the past 20 years is shown in the Table. In Takamatsu area, 73,536 people had been screened and 51

Table The Incidence of Abnormal Hbs Found around the Seto Inland Sea

		Takamatsu	Fukuyama	Kobe
No. of Examined*		1974. 1 - 1988. 12 73,536	1985. 4 - 1988. 6 31,419	1981. 7 - 1983 47,458
No. of abn. Hb Incidence		51 1/1442	33 1/952	15 1/3164
Variants	α chain	16 Ube-2 11 Mizushi 1 N.I. 4	17 Ube-2 9 St. Lukes 1 N.I. 7	10 Ube-2 3 Nunobiki 1 Albany-Suma 1 Handa 1 J Habana 1 Umi 1 N.I. 2
	β chain	27 Takamatsu 19 Yusa 3 J Bangkok 1 G Szuhu 1 N.I. 3	1 Fukuyama 1	5 Syracuse 1 G Coughatta 1 Ankara 1 Riyadh 1 N.I. 1
	γ chain	0	5 F-Fukuyama 1 F-Forest Park 1 N.I. 3	0
	N.I.	8	10	0

N.I.: not identified

*: The number is refer to computer registered individuals with items of living place, name, age and sex to avoid overlapped examination.

abn Hbs were detected. Detection rate was therefore 1 over 1,442 which is somewhat higher than an average in Japan (1/3,000-1/4,000). It is noteworthy that Hb Ube-2 (α 68 Asn \rightarrow Asp) and Hb Takamatsu (β 120 Lys \rightarrow Gln) was sporadically distributed in slightly high frequency, which are α and β chain variant, respectively. In Fukuyama district, 31,419 people had been screened and 33 abn Hbs were detected. Detection rate was 1/952 which is significantly higher than the average in Japan. Hb Ube-2 was a relatively high frequency indicating therefore that is more widely distributive than Hb Takamatsu. In Kobe area, 47,458 people had been screened and there were 15 abn Hbs. Detection rate was 1/3,164. There was not any commonly abundant abn Hbs in view of frequency, but many kinds of variants were detected. In Okayama area, 12,678 people had been screened and 4 abn Hbs were detected (data is not shown). Detection rate was 1/3,170. The three abn Hbs were Hb Ube-2, Hb Hoshida (β 43 Glu \rightarrow Gln) and Hb Fukutomi (α 126 Asp \rightarrow Val). One remaining abn Hb was not identified yet for the sake of a very limited amount of sample.

Discussion

According to the list of the International Hemoglobin Information Center (IHIC) in 1994¹⁾, about 760 kinds of abn Hbs have been registered. Since 1948, the number of papers for the new abn Hbs and the screening survey have been increased year to year in the world reaching a plateau.

In China, a fairly large number of people (About 800,000 people in total) in the provinces were reported to be screened^{7),8),9)}, lately. Detection rate of abn Hb in each province ranged from 0.05 to 1.09%, which were higher than that of Japan (0.03%). The kinds of abn Hb were reported to be rather few, 24 in total, in spite of such high frequency and large scale screened people. Hb E and Hb New York were distributed in pretty high frequency (Hb E was 66% and Hb New York was 10% of total abn Hb)⁷⁾. HbE is the major abn Hb especially in the south part of China.

Korea, the nearest neighboring country to Japan, has rare screening reports of abn Hb.

In Southeast Asian countries, the frequency was expressed only in term of Hb E, and in each country, except for Singapore, the screening was conducted on a small number of people¹⁰⁾, therefore it is not proper to compare with the data of Japan. But it is sure that Hb E exists in very high frequency in these countries (0.2-34.9%). This racial abn Hb is not distributed uniformly in each country, that is, the highest occurrence are seen in Laos and Cambodia (34.9% in both countries).

In Japan, about 160 kinds of abn Hbs were found. Seventeen of them were seriously unstable Hb variants which cause hemolytic or cyanotic disorder even in heterozygous condition. About 50 of them demonstrated abnormal oxygen affinity. More than 60% of them were detected in people around the Seto Inland Sea. About 14 million people have been estimated to live around the Seto Inland Sea and 460 thousand people in total had been screened by six laboratories located this area. They performed quite a large scale and exact survey which was never reported, since about 3% of the total population was subjected to the screening and provided a more efficient and

reliable epidemiological study. Twenty years ago, we started the screening test with use of the blood specimen of inhabitants around the Seto Inland Sea (Table). Detection rates of Hb variants in the Takamatus and the Fukuyama area (1/1,442 and 1/952, respectively) were higher than the average of Japan (1/3,000-4,000). There were locally specific and common abn Hbs in these areas, that was Hb Ube-2 and Hb Takamatsu. On the other hand, there was not sporadic abn Hb in the Kobe area in view of frequency but varieties of abn Hb were abundant. These three areas are located on the coast of the Inland Sea, therefore the presence of common variants in one location may denote that there has been a very minute gene flow up to the late era in Takamatsu and Fukuyama, therefore, assumption of the location origin of abn Hb may permit us to speculate that it is the same location as when we verified its endemicity even if they are port towns.

In the case of Hb Takamatsu, we did family study by careful inquiry. They had no blood relationship in at least 4 to 5 generations. The presumption that all carriers have descended from a single common ancestry seems a probable speculation. It was also noteworthy that this rarely occurring Hb variants possess one homozygous carrier without clinical manifestations.

In conclusion, many kinds of rare abn Hbs were reported but "Racial abn Hbs" like Hb S in Negroes and Hb E in Southeast Asians have not been detected in Japan. However, some variants, for example Hb Köln¹¹⁾, Hb M-Iwate, Hb Ube, Hb M-Saskatoon, were originated independently in Japan by natural mutation. It is germane to think some others are immigrated and dwelled from the mainland of Asia. For instance, in the case of Hb Hofu, it is a rare Hb variant in Japan, but it is not rare in India, that is, the abn Hb might have come to Japan by way of both sea and road from the South Asian country in old times. If this assumption is true, such a variant may exist in another country in Asia, too. In fact, Hb E is the main Hb variant in Southeast Asia¹⁰⁾ and it is often seen with a declivity in the south part of China, then minimum to Japan. It might be suggestion that abn Hb can be transported by road through the political boundary.

In future, it will be interesting to reinvestigate the distribution of abn Hb around the coast of the Seto Inland Sea after determination of the haplotype of common abn Hb gene^{12),13)} or other genetic markers such as HLA and blood group to know the exact origin of our race.

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