Hemoglobin Andrew-Minneapolis (β 144 (HCl) Lysine $\rightarrow$ Asparagine) in a Japanese Family

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Hemoglobin Andrew-Minneapolis, an abnormal hemoglobin with an asparagine residue substituted for a lysine at position 144 of the β -globulin chains, was identified in three members of two generations in a Japanese family. The carriers of hemoglobin Andrew-Minneapolis showed false high levels of hemoglobin A_{1c}, as measured by the standard cation exchange high performance liquid chromatography, and a moderate tendency for erythrocytosis. This family is the first report of this abnormal hemoglobin in Japan. (Internal Medicine 31: 659–661, 1992)

Key words: abnormal hemoglobin, hemoglobin A_{1c}, fructosamine

Introduction

In Japan, about 400 families with 113 variants of hemoglobin were reported up to 1985 (1). About half of these were not associated with any clinical abnormalities, including seven stable abnormal hemoglobins with erythrocytosis (1). This is the first case report of a Japanese family with hemoglobin Andrew-Minneapolis associated with mild erythrocytosis.

Case Report

The probanda, a 34-year-old woman, had been followed for 10 years because of nephropathy with proteinuria caused by pregnancy. Physical examination revealed an apparently healthy woman, 155 cm tall, 48 kg in weight. Spleen and liver were not enlarged. Urine was 1+ positive for protein, negative for sugar, and 2–3 of red blood cell per high power field in the sediment. Routine blood chemistry including electrolytes, cholesterol, serum glutamic oxaloacetic transaminase, glutamic-pyruvic transaminase, lactate dehydrogenase, and alkaline phosphatase gave normal results. Hematological data are shown in Table 1. Measurement of glycosylated hemoglobin by high performance liquid chromatography (HPLC) revealed 37.4% of hemoglobin A_{1c} (HbA_{1c}) (normal: 4.8–6.2%). Serum fructosamine level was 246 μ mol/l (normal; 200–280 μ mol/l); fasting blood sugar level, 88 mg/dl. The extremely high HbA_{1c} level despite normal fructosamine value and glucose level

suggested the presence of abnormal hemoglobin with identical chromatographic mobility with HbA_{1c} rather than diabetes mellitus.

Abnormal hemoglobin with a low isoelectric point was detected in the hemolysate of the probanda, her sister and her daughter (Fig. 1). It comprised 40–46% of the total hemoglobin.

Urea-dissociation cellulose acetate electrophoresis of the hemolysate revealed the β -chain anomaly (2). Deviation of 1 electron charge was conceivable on the basis of a comparison of the electrophoretic migration of the abnormal β chain with that of the normal chain. The abnormal β chain was aminoethylated and digested with TPCK-trypsin, and the digest was subjected to fingerprinting in a cellulose thin layer (3). The fingerprint showed the absence of β T-14 and β T-15 and the presence of a new abnormal spot between normal β T-14 and β T-8-9 spots (Fig. 2). The amino acid composition of the abnormal peptide was Asp 2.13 (theoretical value: 1), Gly 1.12 (1), Ala 4.21 (4), Val 1.91 (3), Leu 1.30 (1), Tyr 0.79 (1), Lys 0.14 (1), and His 2.10 (2). Because of the presence of a Val-Val sequence in β T-14, the estimated value of the Val residue might have been lower than the expected value in the abnormal peptide. This revealed that an Asp residue or Asn residue substituted for Lys in the 144 position of the β -chain. From the results of chromatography and electrophoresis, the substitution of Asp for Lys could be determined at position 144 of β -chain, just as is reported in Hemoglobin Andrew-Minneapolis (β 144 (HCl) lysine $\rightarrow$ asparagine).

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Table 1. Hematological Findings, Fasting Blood Sugar, Fructosamine, and Hemoglobin Composition in Family Members

	Proposita	Sister	Daughter	Son	Husband
Age (year old)	34	40	5	10	36
Hemoglobin (g/dl)	16.3	16.0	15.3	13.6	17.1
Red blood cell count ($\times 10^6/\text{mm}^3$)	492	510	546	506	536
Packed cell volume (%)	47.4	47.6	48.7	44.3	49.6
White blood cell count (mm^3)	8,000	7,600	6,400	8,300	5,900
Platelet count ($\times 10^4/\text{mm}^3$)	26.1	26.7	27.1	30.0	17.5
Fasting blood sugar (mg/dl)	88	124	—	—	—
Fructosamine ($\mu\text{mol/l}$)	246	—	—	—	—
Hemoglobin A _{1c} (%)	37.4*	37.2*	35.8*	5.5	5.7
Abnormal Hb (%)	46.0#	40.0#	42.9#	—	—
Hb F (%)	1.19	0.69	2.01	0.78	0.61
Hb A ₂ (%)	2.47	2.87	2.77	2.46	2.57

* Interference by the abnormal hemoglobin, # By isoelectric focusing

Fig. 1. Pedigree of two generations for Hb Andrew-Minneapolis. Proposita is indicated by an arrow.

● Heterozygous for Hb Andrew-Minneapolis, □ Examined normal, □ Not tested, ○ Female, □ Male

From measurement of oxygen equilibrium by method of Imai (4), the partial pressure of oxygen (P₅₀) of Hb Andrew-Minneapolis was 1.8 mmHg compared to 4.1 mmHg for normal Hb A hemolysate under the same condition in 0.1 M Cl-Tris buffer (pH 7.4) at 25°C.

Discussion

Hemoglobin Andrew-Minneapolis was originally reported by Zak et al (5, 6) in Minneapolis, MN, USA in 1973. This mutant hemoglobin is transmitted as an autosomal dominant and displays a profound increase in oxygen affinity. In the original report, the proband, a

Fig. 2. Fingerprint of the digest of the aminoethylated (AE) β -Andrew-Minneapolis on cellulose thin layer. Dotted circles indicate the missing peptide and the hatched circle indicates the new peptide.

37-year-old male, with 50% abnormal hemoglobin had asymptomatic erythrocytosis (hemoglobin 19.8 g/dl). The P₅₀ of this case was 3.5 mmHg (pH 6.8, 37°C) compared with 10 mmHg for Hg A. In contrast to this case, the present three carriers had a moderate tendency for erythrocytosis with a hemoglobin concentration which ranged from 15.3 to 16.3 g/dl with 40–45% abnormal hemoglobin and P₅₀ of our case was 1.8 mmHg compared to 4.1 mmHg of normal Hb A in hemolysate condition. The difference in the severity of erythrocytosis may be related to the relative concentration of the abnormal hemoglobin and to the degree of alteration in P₅₀ in each case.

Measurement of HbA_{1c} by HPLC is widely used in clinical laboratories for an index reflecting the long-term glycemic situation in diabetic patients. The abnormal hemoglobin with an increased net negative charge may be coeluted with HbA_{1c}. Recently, the number of case reports of abnormal hemoglobin which are discovered because of inappropriate HbA_{1c} levels is increasing. For instance, Hemoglobin Hope (7), Okayama (8), Long Island (9), and Mito (10) were found by the same reason as in present case. The present patient, the HbA_{1c} value was extremely high, while serum fructosamine and fasting blood sugar were within normal range. These results indicate that serum fructosamine should be measured when the HbA_{1c} value is inconsistent with clinical observations or with the fasting blood sugar level. If inappropriately high levels of HbA_{1c} are found by cation exchange, further screening tests for abnormal hemoglobin are indicated.

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