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EDİTÖRE MEKTUP / LETTER TO THE EDITOR

HB UBE-2 variant hemoglobin case detected during HBA1C measurement

HBA1C ölçümü sırasında saptanan HB UBE-2 varyant hemoglobin olgusu

Evin Kocatürk[1], Zeynep Kuşku Kiraz[1], Şükrü Saygın Demir[1], Oğuz Çilingir[2], Hava Üsküdar Teke[3], Ibrahim Özkan Alataş[1]

[1]Eskisehir Osmangazi University Medical Faculty, Department of Medical Biochemistry, [2]Department of Medical Genetic, [3]Department of Hematology, Eskisehir, Turkey

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To the Editor,

Hemoglobin A1c (HbA1c), is widely used in the diagnosis of Diabetes Mellitus, follow-up of treatment and in assessing the risk of diabetes complications. HbA1c can be measured with separation of hemoglobin fractions or chemical reactions and the most common interferences of these methods are variant hemoglobins[1,2]. It has been demonstrated that hemoglobinopathies and their derivatives interfere the measurement positively or negatively[3] and this analytical interference is variable and method-specific[4]. Chemical methods do not detect variant hemoglobins, however, their measurements are rarely interfered by variant hemoglobins. In ion exchange chromatography (IEC) method, variant hemoglobins are seen and can interfere measurements however, it can be regarded to detection of carriers and genetic counselling[2]. Here, we report a Hb Ube-2 variant hemoglobin case whose variant hemoglobin and low HbA1c values were detected by high performance liquid chromatography (HPLC).

The patient is a 56-year-old female and followed-up with the diagnosis of type 2 diabetes. During HbA1c measurement, an abnormal peak suggesting variant hemoglobin was detected in the chromatogram by HPLC (UltiMate 3000 Thermo Fisher Scientific, MA USA) (Figure 1) and an inconsistency was determined between the serum glucose (138 mg/dl) and the HbA1c value (5.2%). HbA1c measurement was repeated with the turbidimetric inhibition immunological test method (TINIA, c501, Roche Diagnostics, Germany) and HbA1c value that support the variant hemoglobin thought was found 6.96%. Hemoglobin level of patient without clinical history of hematological disease was 13.5 g / dl, red blood cell 4.40x106 / µl, mean cell volume 89.8 fl, mean corpuscular hemoglobin 30.7 pg and the blood smear examination was evaluated as normal (Figure 2). To determine variant hemoglobin type, hemoglobin electrophoresis and genetic examinations were performed. Patient's hemoglobin A was 73.3%, hemoglobin A2 2%, hemoglobin F 0.3% and variant hemoglobin was detected as 24.4% in zone 12 in capillary electrophoresis (Minicap, Sebia, Evry Cedex France) (Figure 3) and heterozygote (αube-2α/αα) NM_000558.4 c.205A>G p.(Asn69Asp) variation was detected in HbA1 gene by whole exome sequencing and the protein synthesized by this variant is defined as hemoglobin Ube-2 in the ClinVar database[5].

HbA1c, a glycated hemoglobin describes a chemically stable conjugate of hemoglobin with glucose and is formed slowly, nonenzymatically, and irreversibly by glycation modification of the amino terminal valine residue of the β-globin chain[6]. HbA1c is used to reflect average plasma glucose level over the previous 3 months and has the advantage that can be measured

Yazışma Adresi/Address for Correspondence: Dr. Evin Kocatürk, Eskişehir Osmangazi University Medical Faculty, Department of Medical Biochemistry, Eskişehir, Turkey E-mail: evinadsiz@hotmail.com
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at any time of the day and the patient does not need to be hungry for blood sampling[7,8]. HbA1c had not been recommended to use for diagnosis of diabetes due to the problems in its standardization and uncertainty with its diagnostic threshold for many years, however, as a result of increased evidence with regards to its prognostic importance and the global standardization efforts[7], it was started to use in diagnosis of diabetes with a cut-off at 6.5%[8,9].

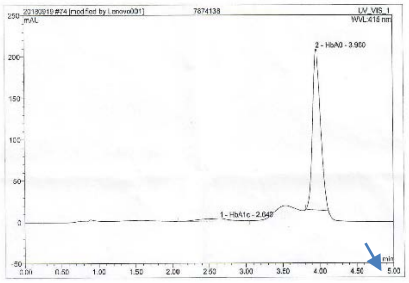

Figure 1. HbA1c measurement of case by HPLC (The abnormal peak detected is marked).

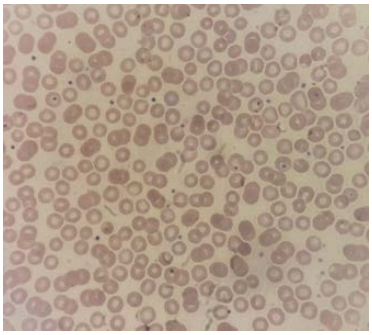

Figure 2. Image of blood smear preparation

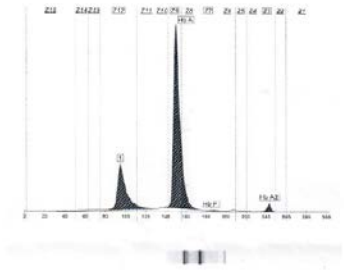

Figure 3. Hemoglobin electrophoresis result of case Patient's Hemoglobin A was 73.3%, Hemoglobin A2 %2, Hemoglobin F 0.3% and Variant Hemoglobin was detected as %24.4 in zone 12 in capillary electrophoresis (Minicap, Sebia, Evry Cedex France).

The accuracy of HbA1c measurements may be affected by various factors and the most common interferences are variant hemoglobins, elevated levels of hemoglobin F and derivatives[1,2]. National Glycohemoglobin Standardization Program (NGSP) systematically evaluates most methods and describes them on own website[10]. It was known that more than 1300 types of variant hemoglobins have been reported[11] and the majority of these variant hemoglobins do not have any clinical effect and are often found incidentally[12]. Especially when HbA1c results are incompatible with patient's clinical status, interference effect of variant hemoglobin should be considered.

In 1967, hemoglobin Ube-2 was established as a new variant hemoglobins expressed by the formula α268Aspβ2[13] and it was known that this variant is resulted from an AAC→GAC mutation at codon 68 of the α-globin gene and hemoglobin Ube-2 carriers do not have hematological changes and clinical symptoms and their oxygen affinity is normal[12]. Hemoglobin Ube-2 has been reported to cause falsely low HbA1c results in a limited number of studies[14-16].

The knowledge about the frequency of hemoglobin Ube-2 is limited. In 1984, hemoglobin Ube-2 was first reported in a Turkish family[17] and was detected in only 1 case of 1616 samples from 884 families in 1993 in Antalya[18]. As in this case, since hemoglobin Ube-2 carriers have no hematological changes and clinical symptoms, it is difficult to identify and can only be detected incidentally.

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