Titusville Hemoglobinopathy Presenting as New-Onset Dyspnea in a Young Soldier

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KEY WORDS: Titusville hemogobinopathy, dyspnea, hypoxia, hypoxemia

IMAJ 2014; 16: 799–800

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Over 1000 different mutations of the globin chains of the human hemoglobin molecule have been discovered. The majority of these mutations are not associated with any clinical manifestations, and many were revealed during the course of large population surveys or accidentally due to different signs and symptoms. In 1975, during the course of a voluntary screening program in Alabama, USA, a new hemoglobin variant was discovered in a healthy 3 year old girl [1]. This mutant hemoglobin, called Titusville (TV) hemoglobin, was found to have low oxygen affinity due to single nucleotide change from G→A at codon 94 of the α-globin gene, resulting in an amino acid substitution from aspartic acid to aspargine. However, TV hemoglobinopathy has clinical significance only rarely.

We present here, to the best of our knowledge, the first description of this hemoglobinopathy in Israel, presenting a diagnostic challenge in young adults with late-onset dyspnea.

PATIENT DESCRIPTION

A 20 year old soldier was admitted to our internal medicine ward with recent-onset dyspnea that developed during the previous year. His past medical history was unremarkable except for heavy smoking over the previous 4 years. Physical examination demonstrated overweight but no other findings. Room air oxygen saturation determined by pulse oxymetry was 78%. Prior to his admission, he had been hospitalized several times in other medical centers with the same complaint and low oxygen saturation.

A comprehensive workup was performed, including high resolution computed tomography (HRCT), pulmonary CT-angiography, trans-thoracic echocardiography (TTE), trans-esophageal echocardiography (TEE), stress test and spirometry, with no evidence of any pathology that could result in low oxygen saturation including pulmonary embolism, right-to-left shunt, or any cardiac structural anomalies. Blood gases showed normal PaO_2.

Upon admission we reevaluated his arterial blood gases under different ventilation conditions with and without oxygen supplementations. As shown in Table 1, his oxygen saturation remained persistently below normal range even after partial correction with oxygen supplementation or following induced effort. This pattern indicated a right deviation of the hemoglobin dissociation curve, suggesting a low affinity of the hemoglobin to oxygen. In the absence of known physiological mediators of low hemoglobin oxygen affinity such as high temperature, low pH and in view of his recent extensive diagnostic workup, a hemoglobin electrophoresis was performed. Initial analysis revealed the presence of an unknown fraction which was later identified by molecular sequencing as hemoglobin Titusville, Asp94Asn. Repeated spirometry demonstrated a moderate obstructive dynamic pattern with good response to bronchodilators.

COMMENT

Under normal circumstances Titusville hemoglobinopathy results in a mild hypoxia with no clinical symptoms. In fact, studies in mutant mice expressing TV hemoglobinopathy revealed a higher effort capacity in these animals. It is therefore speculated that TV is a gain-of-function mutation, and its low oxygen affinity allows higher oxygen delivery in the peripheral tissues [2].

Based on limited case descriptions, the clinical presentation of patients with TV mutation is variable. The documented O_2 saturation in most of these patients is around 85%, indicating a mild hypoxia. Nevertheless, some are diagnosed in early infancy/childhood and others only in

Table 1. Arterial blood gases in various conditions

Condition	Room air	Hyperventilation	Oxygen supplementation by nasal prongs	100% oxygen supplementation by mask	Room air	After effort
PCO_2	42.5	20.3	38.4	40	44	42
PaO_2	78.4	124.2	160	669.8	80.9	89
O_2 saturation	78%	85%	87%	95%	78%	80%

PCO_2, PaO_2 and O_2 saturation were determined sequentially via an arterial line during complete rest at room air followed by hyperventilation, oxygen supplementation and effort (6 minutes walking)

adulthood; the reported age range of diagnosed patients is between newborn and 61 years [3-5].

Presenting symptoms may be either shortness of breath or peripheral cyanosis. Our patient presented at the age of 19 years with new-onset effort dyspnea. A few years earlier, at the start of his military service, he became a heavy smoker. Lung function test demonstrated a moderate obstructive pattern with good response to bronchodilators associated with significant hypoxemia at room air. Thus, the late-onset acquired hypoxemia due to the smoking-mediated lung disease served as the additional clinical trigger exacerbating his preexisting hypoxia and resulting in dyspnea. It is conceivable that in the absence of smoking this patient may have remained asymptomatic and undiagnosed. It should be emphasized that this patient underwent intensive and costly diagnostic imaging including CT scans, TTE, TEE, pulmonary CT-angiography, stress test and blood tests. Nevertheless, his diagnosis remained elusive for many months, suggesting non-organic causes for his complaints such as depression and secondary gain.

The diagnostic clue leading to the correct diagnosis in this case was rather a non-sophisticated determination of blood gases and oxygen saturation which remained low under various conditions. These findings strongly suggested a low oxygen affinity hemoglobinopathy as the leading cause of his complaints. Prior to his most recent admission to our ward this patient underwent an extensive diagnostic workup in search of pulmonary and/or cardiac abnormalities, which were not found. Nevertheless, a normal PaO_2 and low oxygen saturation were evident. This combination is highly suggestive of hemoglobinopathy. Thus, the delayed diagnosis in this case was most probably due to improper interpretation of these two simple key diagnostic clues and to the well-recognized tendency to perform complex diagnostic procedures.

In conclusion, we present here, to the best of our knowledge, the first case description in Israel of a young adult patient with TV hemoglobinopathy presenting as effort dyspnea. Clinical awareness and relatively simple diagnostic measures can provide accurate diagnosis in similar patients.

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