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

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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 asparagine. 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 oximetry 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 PaO2.

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 O2 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>
<thead>
<tr>
<th>Condition</th>
<th>Room air</th>
<th>Hyperventilation</th>
<th>Oxygen supplementation by nasal prongs</th>
<th>100% oxygen supplementation by mask</th>
<th>Room air</th>
<th>After effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCO2</td>
<td>42.5</td>
<td>20.3</td>
<td>38.4</td>
<td>40</td>
<td>44</td>
<td>42</td>
</tr>
<tr>
<td>PaO2</td>
<td>78.4</td>
<td>124.2</td>
<td>160</td>
<td>669.8</td>
<td>80.9</td>
<td>89</td>
</tr>
<tr>
<td>O2 saturation</td>
<td>79%</td>
<td>85%</td>
<td>87%</td>
<td>95%</td>
<td>78%</td>
<td>80%</td>
</tr>
</tbody>
</table>

PCO2, PaO2 and O2 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 an extensive diagnostic workup in search of pulmonary and/or cardiac abnormalities, which were not found. Nevertheless, a normal PaO2 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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**References**


**Capsule**

**Resident memory T cells sound the alarm**

Immunological memory protects against reinfection. Resident memory T cells (TRM) are long-lived and remain in the tissues where they first encountered a pathogen. Schenkel et al. and Ariotti et al. (Science 2014; 346: 98, 101) found that CD8+ TRM cells act like first responders in the female reproductive tissue or the skin of mice upon antigen reencounter. By secreting inflammatory proteins, TRM cells rapidly activated local immune cells to respond, so much so that they protected against infection with an unrelated pathogen. Iijima and Iwasaki (Science 2014; 346: 93) found that CD4+ TRM cells protected mice against reinfection with intravaginal herpes simplex virus 2.

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**Capsule**

**Overcoming Staph infections is hardwired**

Several evolutionarily conserved components of anti-staphylococcal immunity have been identified, using Drosophila as a model organism. However, no vertebrate ortholog has been identified for the Toll ligand Spaetzle, which plays a key role in controlling gram-positive infection in flies. Hepburn and group have now identified NGF-β as a functional equivalent to Spaetzle in vertebrates. NGF-β acts as a paracrine “alarmin” orchestrating macrophage and neutrophil responses to S. aureus infection. People with deleterious mutations in genes encoding NGF-β or its high-affinity receptor TRKA are predisposed to recurrent and severe Staph infections. S. aureus proteins selectively trigger macrophage production of NGF-β, which enhances uptake and superoxide-dependent killing of S. aureus, stimulates pro-inflammatory cytokine production, and promotes neutrophil recruitment. Moreover, TrkA silencing in vivo increases susceptibility to S. aureus. Thus, the NGF-β-TRKA pathway is a critical, evolutionarily conserved component of vertebrate immunity to S. aureus infection.

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