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CLINICAL VIGNETTE

A Rare Hemoglobinopathy: Hemoglobin Titusville

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Introduction

Hemoglobin (H_g) is responsible for the delivery of oxygen to the tissues throughout our body. It consists of alpha-like and non-alpha like chains. Together, these pairs of chains form a tetramer. One of hemoglobin's variable factors is its affinity for oxygen. This is affected by several factors, namely pH, 2-3 DPG, temperature, CO₂ and exercise. Additionally, hemoglobin can undergo mutations in the form of insertion, deletion, or base changes, which change the alpha-like and non-alpha like chains. These mutations can also greatly impact hemoglobin's oxygen carrying affinity. When the affinity increases, patients have decreased oxygen delivery to the tissue resulting in symptoms of dyspnea, cyanosis and polycythemia. Alternatively, a lower oxygen affinity may present asymptotically but can objectively have low oxygen saturations (S_aO₂) in the setting of normal partial pressure of oxygen (P_aO₂). The following is a case of diagnosing a patient with Hemoglobin Titusville, a rare hemoglobinopathy resulting in decreased oxygen affinity.

Case Report

A 51-year-old female with history of presumable asthma presented to the hospital with one week of dyspnea. The dyspnea began after she ran out of her inhalers; the patient stated her symptoms felt similar to her previous admissions for asthma exacerbation. She had no smoking history and no occupational exposures. After symptomatically improving in the ER with steroids, magnesium, and nebulizer treatments, she was prepared for discharge. At that point, however, her oxygen saturation was noted to be in the mid-80s despite her improved symptoms and was admitted to the hospital.

On physical exam, she was not anxious and was well appearing. Her lung sounds were clear without wheezing, rales or rhonchi. Heart sounds were regular and JVP was flat.

During her admission, different pulse oximetry devices were used to measure her oxygen saturation and all were consistent with hypoxia. Her labs revealed a H_g of 14.3. Her ABG showed a pH of 7.41, P_aCO₂ of 37, P_aO₂ of 76 and S_aO₂ of 82% on room air. In comparison to her prior admissions, this was similar to her O₂ saturation on discharge following her hospitalizations. Her S_aO₂ was consistently low despite a normal P_aO₂ on prior ABGs.

Studies included a CT chest negative for acute processes; a transthoracic echocardiogram with bubble study was normal and showed no evidence of intra-atrial shunt. Methemoglobin

and carboxyhemoglobin levels were normal. Given her improvement in symptoms, the patient was discharged on room air by the primary team with follow-up in Hematology clinic. Hemoglobin electrophoresis revealed the patient had Hemoglobin Titusville.

Discussion

Human hemoglobin has been found to have over 1,000 different mutations of the globin chain. As a result, there are over 270 million carriers worldwide of hemoglobinopathies. These mutations can lead to either an increased or decreased affinity of hemoglobin for oxygen.¹ Hemoglobin Titusville was first discovered in a healthy 3-year old girl in an Alabama population survey in 1975. It results from an amino acid substitution (asparagine for aspartic acid) of the α -globin chain from a single nucleotide change (G to A). The result is a conformational change in the $\alpha_1\beta_2$ contact region where hemoglobin dissociates into its dimers leading to a lower oxygen affinity and shifting the oxyhemoglobin dissociation curve to the right, as seen in the Figure 1.

The resultant oxygen dissociation may explain the lack of symptoms experienced by patients as there is greater tissue oxygenation. Furthermore, in addition to Hg Titusville, Hg Hammersmith, Rothschild and Cheverly are also associated with low S_aO₂ measurements.^{3,4,5} Patients with these hemoglobinopathies also do not have cardiopulmonary diseases or cyanosis as their otherwise low pulse oximetry would suggest.

In one study, mice were mutated with Hg Titusville such that the new Hg could react to physiological changes. First, the mice were found to consume more O₂ and produce more CO₂ in hypoxic conditions when compared to their wild types. Secondly, the Hg Titusville mutated mice had a higher percentage of type IIA (sustained activity) muscle fibers than type IIB (high intensity, short duration) fibers compared with the wild mice. Hg Titusville mice had 51.4% type IIA fibers and 48.6% type IIB fibers while wild type mice had 39.5% type IIA fibers and 60.5% type IIB fibers. The increased ratio of type IIA to type IIB muscle fibers suggests skeletal muscles rely more on oxidative energy metabolism.

This was confirmed by measuring succinate dehydrogenase (SDH) activity in the type IIA and IIB fibers of the tibialis anterior muscle. SDH is a critical mitochondrial enzyme involved in mitochondrial cell respiration and energy

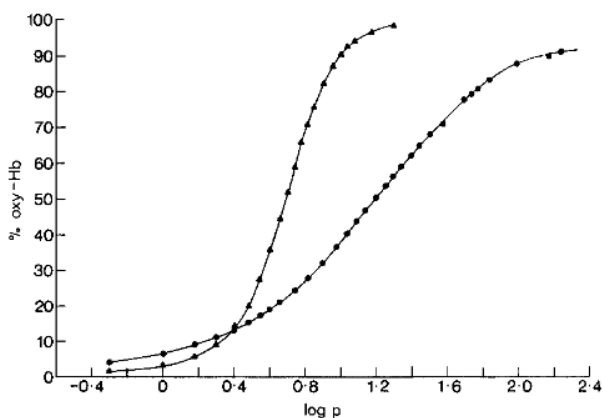
generation. The SDH activity in both was greater in mice with Hg Titusville than in wild type mice. The skeletal muscle in mice with Hg Titusville may be compensating for the increased O₂ delivery by increasing its SDH activity. The increased ATP produced by skeletal muscle from increased SDH activity is reflected when comparing physical activity among mice with Hg Titusville with their wild type. As seen in Figure 2, over a 28-day period, the average Hg Titusville mice ran 9539 meters compared to 4613 meters by their wild type. This phenomenon may be explained by two theories. Firstly, that higher concentrations of oxygen in peripheral tissue stimulates more activity. The second is that the mutation may trigger behavioral patterns resulting in the increased activity.

The change noted in activity raises interesting clinical perspectives. Patients who suffer from chronic hypoxic respiratory failure, such as those with COPD, pulmonary fibrosis, or other interstitial lung diseases, may benefit from this hemoglobin mutation. The increased oxygen delivery to peripheral tissue could significantly improve their quality of life. Additionally, in the sports arena, this could provide further controversy in multiple ways. If an athlete is born with the mutation, he or she may be predisposed to an increased exercise capacity. Alternatively, athletes with the knowledge of this increased exercise tolerance may begin transfusing with Hg Titusville blood or attempting to have gene therapy.

This case highlights the importance of recognizing a hemoglobinopathy in a patient with low oxygen saturation with a normal PaO₂. An asymptomatic patient with mild anemia, normal P_aO₂ in the setting of low oxygen saturation should prompt the clinician to consider hemoglobinopathies. This may prevent recurrent hospitalizations and a prolonged, lengthy, and expensive workup. Moreover, the genetic mutation could potentially benefit patients who suffer from chronic respiratory diseases and provide new therapies for the future.

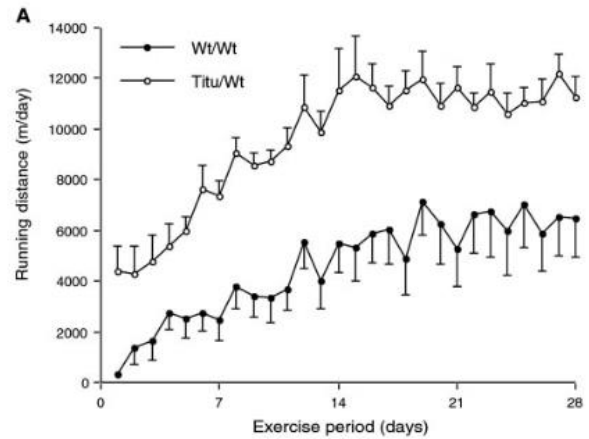
Figures

Figure 1. Oxyhemoglobin Dissociation Curve in Patients with Hg Titusville²



●-● Hg Titusville
 Δ-Δ Hg A

Figure 2. Average Running Distance in Mice with Hg Titusville Mutation when Compared to Wild Type⁶



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