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PNH –What Is It and How Does It Affect Patients?

Announcer:
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Dr. Broome:
Hi, my name is Dr. Catherine Broome from MedStar Georgetown University Hospital. This presentation is entitled "PNH: What Is It and How Does It Affect Patients?" PNH was first reported in the medical literature in 1866 by Gull. In 1925, Enneking coined the name paroxysmal nocturnal hemoglobinuria based on the mistaken belief that hemolysis, or red blood cell breakdown and subsequent hemoglobinuria, free hemoglobin in the urine; occurred intermittently, hence the paroxysmal and with the greater frequency at night, hence nocturnal. We now know and understand that PNH is neither paroxysmal or nocturnal. In 1930, Ham identified the role of complement and developed the serum test, which can still be used for diagnosis known as the Ham Test. In the 1990's, the somatic mutation responsible for the formation of PNH was identified as the PIG-A gene.

The genesis of PNH includes a somatic mutation in the PIG-A gene in one hematopoietic stem cell. This results in GPI-linked protein deficiency on a clone of blood cells, including red blood cells as well as white blood cells. There is an immunologic mechanism believed to select for the defective hematopoietic stem cell allowing for expansion of the defective PNH clone. So in the bone marrow niche there are normal hematopoietic stem cells. However, in one of these hematopoietic stem cells there is a mutation of the gene, including for PIG-A. This results in a decreased amount of CD55 and CD59 attached to the surface of the red blood cells. And this results in the formation of a PNH clone of not only red blood cells, but also of white blood cells. And this can lead to bone marrow failure, thrombosis, and intravascular hemolysis.

So how does this affect patients? This is not a very common disease. There's estimated to be between four and 6,000 patients in the United States. Five-year mortality of this disease untreated is approximately 35%. It can be diagnosed at any age, but the median age at diagnosis is in the early 30's. There is a decreased quality of life and it does seem to be a progressive disease especially with regards to thrombosis risk. If you look at the graphic, you can see that compared to an age- and sex- matched control patient population, patients with PNH definitely have an increased mortality and a decreased survival.

What are the symptoms of anemia? These patients almost always are going to present with some degree of anemia. And depending on the degree of anemia they may experience shortness of breath. They may experience fatigue. They may experience syncope, if the anemia has developed relatively suddenly. They may experience angina type chest pains. They may experience jaundice. They may experience muscle pain related to decreased oxygenation. And they may also experience a change in the color of their stool related to bilirubin.

With regards to PNH the chronic hemolysis and the release of free hemoglobin are related to a whole variety of short and long-term complications. So normal red blood cells are protected from complement attack by a shield of terminal complement inhibitors, including CD55 and CD59. Without this protective complement inhibitor linked to the surface of the red blood cells by the GPI anchor, PNH red blood cells are susceptible to hemolysis, which is mediated by complement. This intravascular hemolysis releases free hemoglobin

which of course causes anemia. Free hemoglobin is a nitric oxide scavenger which is going to result in decreased nitric oxide levels. In addition, the unique abnormalities and the ongoing complement activation are related to increased risks of thrombosis, increased risk of renal insufficiency and renal failure, pulmonary hypertension, abdominal pain, and dyspnea, as well as dysphagia, fatigue, erectile dysfunction, and hemoglobinuria. Most common symptoms in patients with PNH include dysphagia at 41%; pulmonary hypertension, 47%; dyspnea, 66%; over 50% of patients are going to have abdominal pain; chronic renal insufficiency is noted in about 64% of patients; thrombosis in approximately 39%; the overwhelming majority, 88% are going to be anemic; and 96% of these patients are going to report fatigue and impaired quality of life. You will notice that although the disease is called paroxysmal nocturnal hemoglobinuria, only about a quarter of patients will actually experience hemoglobinuria.

What are some of the laboratory findings? Well, there's anemia. It is possible to have hemolysis without anemia, if the bone marrow is able to compensate. These patients will almost always have an increased reticulocyte count, an increased lactate dehydrogenase and indirect bilirubin, a decreased haptoglobin. They will have free serum hemoglobin with either pink or red serum. They'll have hemoglobinuria with pink or red urine which will have a positive dipstick for heme, but a negative sediment for red blood cells. And this is a Coombs negative or direct antiglobulin test negative hemolytic anemia. All of this information is vitally important in our understanding of how to recognize and also signs and symptoms of how to manage our patients with paroxysmal nocturnal hemoglobinuria. Thank you very much for your attention.

Announcer:
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