

Paroxysmal Cold Hemoglobinuria: Not an “Uncommon” Disease Anymore

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Short Communication

In children, hemolytic anemia is usually caused by intrinsic defects in red blood cells as seen in membrane defects, enzyme deficiencies and/or hemoglobin abnormalities. Most of these anomalies are hereditary in nature. Hemolytic anemia can also be due to factors extrinsic to red blood cells with most of the causes being acquired. Autoimmune hemolytic anemia (AIHA) is one such group of acquired hemolytic anemia which results from the development of auto antibody directed against antigens on the surface of the patient's own red blood cells. Many reports describe paroxysmal cold hemoglobinuria (PCH) as an uncommon or rare disease. In recent years PCH has now become recognized as a relatively frequent cause of acute transient AIHA particularly in children. The disease was historically associated with complication of late-stage congenital syphilis with symptoms of jaundice and hemoglobinuria precipitated by exposure to cold temperatures [1].

However, this complication is rarely seen today because syphilis is easily treated with antibiotics. In children however, the symptoms are not induced by cold exposure but rather an upper respiratory tract infection.

Now the typical presentation is that of a child who, during the preceding 1-2 weeks, had suffered from an upper respiratory tract infection, and then presents with clinical manifestations of hemoglobinuria, jaundice and pallor [2-5].

I have now encountered 2 cases of PCH in less than a year with identical presentations. The first case was a 3 year old male who presented with severe anemia, jaundice and hemoglobinuria in the presence of a cold antibody consistent with AIHA after a recent upper respiratory infection. The second case was a five year old male who presented with severe anemia and jaundice and a prior history of respiratory tract infection diagnosed with a cold AIHA. Both cases had identical serologic findings with confirmation of Donath Landsteiner (DL) antibody in serum. The indirect antiglobulin test was negative and the direct antiglobulin test (DAT) was positive with complement C3b, C3d and negative with IgG.

Reference laboratory testing confirmed a positive DL antibody with autoanti-P specificity in both cases. In cold agglutinin disease the DAT is positive with anti-C3d but negative with anti-IgG. Cold agglutinin disease should be distinguished from PCH since both will have a positive test with mono-specific anti-C3d. In PCH, the DAT is usually positive due to sensitization of red blood cells; however, other causes of complement positive DAT such as clinically insignificant low thermal amplitude cold agglutinins such as anti-I should also be considered. True DL antibodies should be distinguished from typical cold autoantibody of unusually broad thermal amplitude to make a diagnosis of PCH. In pathologic cold agglutinin syndrome the typical

antibody class is IgM with the specificity of anti-I or anti-i. The thermal reactivity range is greater than 30°C and a titer of greater than 500 [6].

PCH should be suspected and testing for DL antibody performed in the child with acute hemolysis, prominent hemoglobinuria, and red cell complement sensitization. Most DL antibodies have specificity for the P antigen with only rare examples of other specificities such as I antigen [7]. Red cell phagocytosis by neutrophils called “erythrophagocytosis” is a prominent feature in acute transient PCH and is rarely seen in other forms of AIHA. The significance of finding “erythrophagocytosis”, especially by neutrophils, in a young child should trigger further investigation for DL autoantibody. Acute attacks are frequently severe but the acute illness usually resolves spontaneously within a few days to several weeks after onset and rarely recurs.

However, cases of recurrent PCH have been reported [8,9]. Corticosteroids are often given for treatment of PCH and may limit persistent hemolysis however, the effectiveness of steroid therapy may be difficult to evaluate because of the transient nature of the hemolysis.

PCH has now become a recognized cause of cold AIHA in children particularly with presentation of dramatic hemoglobinuria and jaundice associated with a prior infection. A positive DL test is essential in confirming PCH diagnosis to distinguish between a cold agglutinin and a true DL IgG biphasic hemolysin. Pathologists, hematologists and pediatricians should be aware of this “uncommon” disease which appears to be common.

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