Paroxysmal Cold Hemoglobinuria in a 4-year-old Child

Paroxysmal Cold Hemoglobinuria is a rare cause of intravascular hemolysis presenting in children following an acute viral illness. It is usually self-limiting in nature. We present the details of a 4-year-old boy who presented with rapid onset intravascular hemolysis. Donath Landsteiner antibody test was positive and hemolysis resolved within two weeks of onset.

Keywords: *Anemia, Hemolysis*.

A 4-year-old boy presented with fever and chills for 3 days, and history of passing red urine. On examination, the child was pale, but had no icterus or lymphadenopathy. Liver and spleen were enlarged 3 cm and 2 cm, respectively below the costal margin. Initial investigations showed hemoglobin of 8 g/dL, total leukocyte count of 20.4×10^9/L and platelet count of 160×10^9/L. He was empirically treated with ceftriaxone and artesunate. Peripheral smear for malarial parasite, and cultures of blood and urine were sterile. On day 2 of admission, his hemoglobin dropped to 5 g/dL and creatinine increased from 0.5 mg/dL to 1.3 mg/dL. There was no evidence of bleeding from any site. Serum bilirubin was 2.7 mg/dL with an indirect component of 1.7 mg/dL. Aspartate transaminase (AST) was 187 U/L and alanine transaminase (ALT), 27 U/L. Peripheral smear demonstrated nucleated RBCs and micro-spherocytes with a reticulocyte count of 4.3%. Lactate dehydrogenase (LDH) was 3474 IU/L and urine for hemoglobin was positive. Direct Coombs test, glucose-6-phosphate dehydrogenase, high pressure liquid chromatography and anti-nuclear antibodies were negative. Hemoglobin continued to drop despite blood transfusions. He was treated with oral prednisolone (2 mg/kg/day) considering possibility of Coombs negative autoimmune hemolytic anemia. Child had normal serum ceruloplasmin and negative flow cytometric analysis for paroxysmal nocturnal hemoglobinuria. Complement C3 was normal and C4 was low (<5 mg/dL). Further evaluation for hemolysis revealed a positive Donath Landsteiner antibody. Child was diagnosed as having paroxysmal cold hemoglobinuria (PCH), and prednisolone was stopped. We could not perform tests for Ebstein-Barr virus (EBV) or mycoplasma in this child. Hemoglobin improved spontaneously with improvement in LDH (2690 U/L to1842 U/L) and creatinine (1.3 mg/dL to 0.3 mg/dL). He was discharged 10 days after admission with stable hemoglobin.

Paroxysmal cold hemoglobinuria (PCH) is a rare acquired cause of intravascular hemolysis in children. Incidence rate is 0.04 cases per year per 100,000 people [1]. Sporadic reports of PCH have been published from India [2,3]. Microorganisms implicated in PCH include measles, mumps, chickenpox, cytomegalovirus, cox-sackie, parvovirus, adenovirus, EBV, RSV, *Hemophilus influenzae* and *Mycoplasma pneumoniae*. However, in most cases the precipitating factor is not usually found [4].

PCH is mediated by biphasic IgG antibody that bind to P antigen on RBC membrane at cold temperatures and causes complement-mediated intravascular hemolysis on rewarming. P antigen is the cellular receptor for parvovirus on red cell membrane. Possible pathophysiological mechanisms include stimulation of abnormal clones of B cells, alteration of cellular immunity and molecular structural alterations of RBC membrane by viruses that result in the formation of auto-reactive antibodies [5].

PCH presents acutely with dramatic and rapid intravascular hemolysis that is usually self-limiting, and typically presents following acute viral illness. The median age of presentation is 4 years (range 1- 82 years) [1]. Onset is marked by fever, jaundice, pallor and passage of dark urine. History of exposure to cold prior to hemolysis is present in only a few children [1]. Reactive leukocytosis with left shift and relative reticulocytopenia [1] can be seen. Peripheral smear examination can reveal abnormalities like spherocytes, anisocytosis, polychromatophils, fragmented RBCs, and erythrophagocytosis by neutrophils [2,6]. Transient renal dysfunction can occur as a result of intravascular hemolysis.

Demonstration of anti-P antibody is important for diagnosis. It is recommended to collect 3 aliquots of patient's blood kept in pre-warmed tubes to prevent hemolysis. The test is considered as positive for Donath Landsteiner antibodies if hemolysis occurs only in the aliquot that was incubated initially at 0-4°C for 30 min followed by incubation at 37°C for 60 min.

PCH resolves spontaneously with most patients improving within one month without any specific therapy. Patient should be kept warm; a blood warmer to be used during transfusion. P-negative blood has been used for transfusions in patients with PCH in whom hemolysis was severe and prolonged; however, its effectiveness is difficult to evaluate because of the unpredictable natural course of the disease. Corticosteroids are often administered to patients; however, the efficacy is not known [6]. Timely recognition of PCH will prevent initiation of unnecessary therapy and help in rapid resolution of hemolysis.

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A Rare Cause of Swelling and Pain in Extremities in Children: Complex Regional Pain Syndrome

Complex regional pain syndrome is a condition of uncertain etiology characterized by spontaneous or stimulus-induced pain that is out of proportion to the inciting event. We report a 14-year-7-month-old girl with swelling of the left hand and wrist, was diagnosed as complex regional pain syndrome. The patient was treated successfully with physical therapy and non-steroidal anti-inflammatory drugs. This condition should be kept in mind in the differential diagnosis of musculoskeletal non-inflammatory and inflammatory pains.

Key words: *Diagnosis, Management, Recurrent pain*.

Musculoskeletal pain and swelling are common reasons of admission for pediatricians. The causes include a variety of inflammatory and non-inflammatory diseases such as arthritis, myositis, fibromyalgia, hypermotility, growing pains [1]. Complex regional pain syndrome (CRPS), previously known as reflex sympathetic dystrophy, is a chronic pain condition usually affecting distal extremities characterized by spontaneous or stimuli-induced pain [2]. Herein we report an adolescent patient diagnosed with CRPS and treated successfully.

A 14-year-7-month-old girl was admitted to our hospital with swelling of the left hand and wrist, pain and redness on the whole arm, and difficulty in moving the arm for 2 days. There was a feeling of numbness and tingling on the left hand and in the left upper extremity with an itching and burning sensation in her left arm described as hyperalgesia. The pain had flammable character and was exacerbated with movement or light touch suggesting allodynia. The decrease of the pain was reliable when the contact was stopped. The patient reported no preceding trauma prior to admission. No prior infection or fever was reported. Her past medical and family history was unremarkable.

On physical examination, the patient was afebrile. Hyperemia and swelling was prominent on the distal part of the left upper extremity and on the palms of the left hand, plantar skin and the fingers. There was edema of the entire left upper limb. She had difficulty in moving the left and the fingers. Hyperalgesia, hyperesthesia and allodynia were prominent in the left hand and upper extremity. Pain sensitivity was prominent. In the laboratory evaluation, all of the results were in normal ranges for the complete blood count, erythrocyte sedimentation rate, C- reactive protein, coagulation tests, vitamin B_{12}, antistreptolysin O (ASO), and routine blood chemistry. Serologic evaluation for infections and rheumatologic evaluation were negative. Superficial tissue and Doppler ultrasonography, Echocardiography, direct radiographs were all normal. The magnetic resonance imaging of spine was did not show any abnormality. These findings, in conjunction with the history, were suggestive of CRPS type I.

The patient received physiotherapy that was performed intermittently in the therapy pool; as well as using passive therapy as the massage of the left arm. Beside the physical therapy, non-steroid anti-inflammatory drug treatment with naproxen sodium was initiated with a dose of 10 mg/kg/day. On the third day of therapy, the pain of the patient improved. Medical treatment lasted for 15 days, but the course of the disease lasted for approximately one month. She has been followed out-patiently by physical therapy for has 3 months without any symptoms.