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□ Case Report □

Pyridoxine responsive sideroblastic anemia in a boy with mitral valve prolapse

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Sideroblastic anemia is a rare, heterogeneous group of disorders characterized by hyperferremia, microcytic hypochromic anemia, and bone marrow erythroid hyperplasia with the presence of numerous ringed sideroblasts. We describe herewith the case of a rare coincidence of sideroblastic anemia and mitral valve prolapse with resultant regurgitation in a 2-year-old boy. In addition to the inherent propensity for the development of cardiac dysfunction in sideroblastic anemia due to transfusion-associated myocardial iron overload and chronic anemia, a coincidence of MVP will further increase the likelihood of the morbidity or mortality of th patient. in this patient. After response to pyridoxine, the patient remains in good condition with stable hemoglobin levels. **(Korean J Pediatr 2006;49:1223-1226)**

Key Words : Sideroblastic anemia, Pyridoxine, Mitral valve prolapse

Introduction

Sideroblastic anemia is a rare, heterogeneous group of disorders characterized by hyperferremia, microcytic hypochromic anemia, and bone marrow erythroid hyperplasia with the presence of numerous ringed sideroblasts. The condition can be divided into hereditary and acquired types, which are both relatively rare in children[1]. The cause of this disorder is not yet clear. However, a decrease in the activity of delta-aminolevulinic acid synthase (ALAS), the rate-limiting enzyme in heme biosynthesis, has been implicated by some investigators. As both pyridoxine-responsive and non-responsive patients with this disorder have been reported, a complicated system for the activation and inactivation of ALA-S should exist, thus suggesting that the decrease of ALA-S activity may not always be attributable to a single cause[2].

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Mitral valve prolapse (MVP) is a multifactorial valvular abnormality that can be caused by histological abnormalities of valvular tissue, geometric disparities between the left ventricle and mitral valve, or various connective tissue disorders[3]. The reported incidence of mitral valve prolapse (MVP) of 5% in the pediatric population probably should be an overestimate. This condition occurs in older children and adolescents (it is more common in adults) and has a female preponderance (male-female ratio of 1:2)[4].

We describe herewith a boy with severe pyridoxine-responsive sideroblastic anemia with MVP. As these combination has not been reported in the literature, we might suggest that this case represents an extremely rare coincidence of both diseases. The association of MVP in a patient who has a chronic anemia and requires transfusions will further increase the risk of developing cardiac dysfunction in the future.

Case Report

A 25-month-old boy was referred to our hospital in September, 2003 for the evaluation of severe anemia. He

was pale and weak. Physical examination showed severe pallor, chest retractions, and hepatosplenomegaly. The late systolic murmur without midsystolic click was audible at the apex. The family history was negative for anemia and consanguinity. The hemogram showed hemoglobin 1.5 g/dL; hematocrit 5.5%; mean corpuscular volume (MCV) 55.5 fL; mean cell hemoglobin (MCH) 15.2 pg; and reticulocytes 0.7%. Serum iron was 308.5 μg/dL and the total iron binding capacity was 312 μg/dL. Serum ferritin, bilirubin, lead levels were all within the normal ranges. Direct and indirect Coombs′ test were negative. Hemoglobin electrophoresis was normal. Examination of the peripheral blood smear revealed microcytic hypochromic anemia with marked poikilocytosis, elliptocytosis and moderate anisocytosis (Fig. 1). A bone marrow aspiration smear revealed relatively erythroid hyperplasia, and iron staining showed distinct ringed sideroblasts in 30% of erythroids (Fig. 2). After slow and fractionated red cell transfusions, his symptoms relieved.

Administration of oral pyridoxine hydrochloride (100 mg/day) resulted in the stable hemoglobin level over 8.0 g/dL, with the hematocrit over 25 %. He remains well on continued pyridoxine medication for 32 months. The hemogram showed hemoglobin 8.3 g/dL; hematocrit 28.8%; MCV 65.4 fL; MCH 18.9 pg; and reticulocytes 0.47%. There was no evidence of family history, or secondary causes, such as underlying diseases or drug therapy that might be associated with sideroblastic anemia. Molecular diagnosis was not warranted.

Electrocardiogram (ECG) showed a normal sinus rhythm. Two-dimensional echocardiography showed the prolapse of the mitral valve leaflet superior to the plane of the mitral valve. Moderate degree of mitral regurgitation (MR) was demonstrated by color flow mapping (Fig. 3). After 30 months, he continues to have a MVP with moderate MR. Regular evaluation of his cardiac status by ECG and echocardiography has been done every six months. The antibiotic prophylaxis against bacterial endocarditis was recommended.

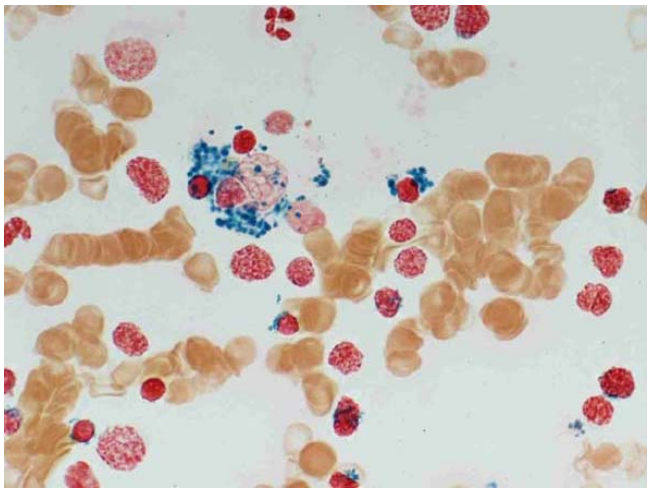

Fig. 2. Perls Prussian blue staining of a bone marrow aspirates shows many ringed sideroblasts having numerous positive granules (Wright′s Giemsa×1000).

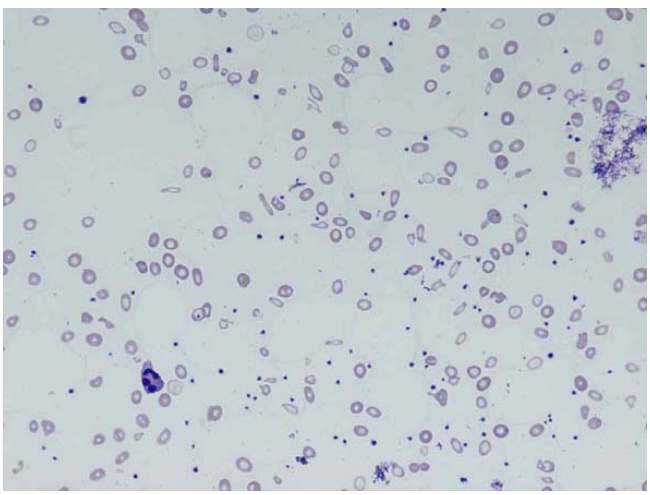

Fig. 1. Peripheral blood smear shows a microcytic hypochromic anemia with marked poikilocytosis, and moderate anisocytosis (Wright′s Giemsa×400).

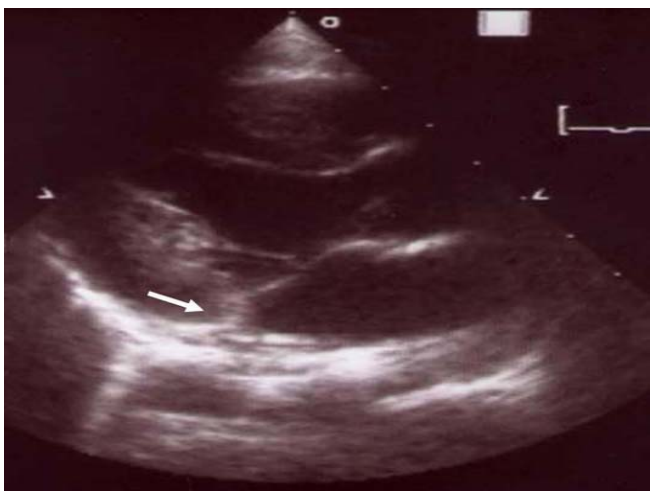

Fig. 3. Echocardiographic image of parasternal long-axis view shows a posterior mitral leaflet bowing backward and prolapsing into left atrium during systole (arrow).

Discussion

The sideroblastic anemias are a heterogeneous group of disorders whose two distinctive features are ringed sideroblasts in the bone marrow (abnormal erythroblasts with excessive iron accumulation in the mitochondria) and impaired hembiosynthesis[5, 6]. Most commonly, the sideroblastic anemias are classified as hereditary or acquired conditions. The acquired sideroblastic anemias are far more common than the hereditary varieties. The second common subgroup, refractory anemia with ringed sideroblasts, is an extremely rare subset of the myelodysplastic syndromes (MDS) in children[7].

The exact mechanism by which disturbed heme metabolism produces sideroblastic anemias remains elusive. However, some investigators have revealed a decrease in the activity of delta-aminolevulinic acid synthase (ALAS), the rate-limiting enzyme in heme biosynthesis[8].

Sideroblastic anemias tend to have hemoglobin levels usually ranging from 4 to 10 g/dL. Patients have the usual symptoms of anemia including fatigue, dizziness and decreased tolerance to physical activity. The history should include detailed questions concerning possible toxin or drug exposures, as these conditions are reversible[9]. A thorough family history looking for anemia, particularly in male relatives, is important as there are X-linked or autosomal recessive forms of sideroblastic anemia.

Clinical manifestation from iron overload is hepatosplenomegaly, elevated liver function test, skin pigmentation, diabetes, and cardiac arrhythmia, an important cause of morbidity and mortality[10]. No pathognomonic physical finding exists for sideroblastic anemia.

The blood smear sometimes reveals basophilic stippling, hypochromia and microcytosis, although normocytosis and macrocytosis are possible, particularly in myelodysplastic syndromes. Red cell distribution width may be elevated.

Treatment of sideroblastic anemia begins with ruling out reversible problems including alcohol or other drug toxicity, as well as exposure to toxins. Treatments are largely supportive, consisting primarily of blood transfusions to maintain an acceptable hemoglobin level. A trial of pyridoxine (100 mg/day orally) is reasonable as the drug has few drawbacks and is an enormous benefit in responsive cases[11]. A reticulocytosis occurs within 2 weeks in responsive cases, followed by a progressive increase in the hemoglobin level over the next several months. The maintenance dose of pyridoxine is that which holds the hemoglobin level at a steady state. More recently, combination of erythropoietin and granulocyte colony-stimulating factor (G-CSF) has been effective in the treatment of acquired sideroblastic anemia. Successful allogeneic stem cell transplantation has been reported in cases of inherited forms of sideroblastic anemia[12].

MVP is encountered in association with congenital (eg. atrial septal defect, Ebstein anomaly) or acquired heart diseases, such as, papillary muscle dysfunction (eg, ischemia, myocarditis), cardiac trauma, or rheumatic endocarditis. MVP has a well-recognized association with heritable connective tissue disorders including Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum[5]. The increased prevalence of MVP has been recognized in patients with autoimmune disorders (eg, systemic lupus erythematous, Grave's disease, Behçet's disease)[13], muscle disorders (eg, Duchenne muscular dystrophy, mucopolysaccharidoses, myotonic dystrophy, fragile X syndrome)[14, 15], or miscellaneous disorders (eg, Wolff-Parkinson-White syndrome, von Willebrand disease, sickle cell anemia, β-thalassemia)[16, 17].

In Korea, three cases of pyridoxine-nonresponsive hereditary sideroblastic anemia have been described[10, 18, 19]. Koh et al.[9] described a case of pyridoxine responsive acquired sideroblastic anemia in a 19-year old boy. There has been no report of pyridoxine responsive sideroblastic anemia in Korean children. Moreover, we describe the case of rare coincidence of sideroblastic anemia and mitral valve prolapse with resultant regurgitation.

Heart failure would be the main cause of morbidity and mortality for this patient. In addition to mitral regurgitation due to MVP, myocardial iron overload resulting from multiple transfusions and high output state caused by chronic anemia would further contribute to cardiac dysfunction in this patient[17]. Regular evaluation of cardiac function, and close observation of developing acute leukemia[20] is warranted in this patient.

한 글 요 약

승모판 탈출증을 가진 소아에서 Pyridoxine 반응성 철적모구성 빈혈 1례

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철적모구성 빈혈은 heme 대사의 이상으로 혈청철의 증가와 소구성 저색소성 빈혈을 보이며, 골수 소견에서 적혈구계 과다형성과 함께 환상 철적모구가 많이 나타나는 것이 특징이다. 저자들은 2세 남아에서 드문 질환인 철적모구성 빈혈과 승모판 탈출증에 의한 승모판 역류가 동시에 있는 증례를 경험하였다. 환아는 철적모구성 빈혈에 의해 수혈에 따른 철분의 과잉 침착과 만성 빈혈에 의한 심계 항진에 의한 심근 기능 장애가 발생할 가능성이 있는데다, 동반된 승모판 탈출증으로 심기능의 장애의 위험이 증가할 것으로 사료된다. 현재 환아는 pyridoxine 투약 후 전신 상태와 혈색소 수치가 안정적으로 유지되고 있다.

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