CASE REPORT

THE ASSOCIATION OF IMMUNE THROMBOCYTOPENIC PURPURA WITH HEREDITARY SPHEROCYTOSIS

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ABSTRACT

A five year-old girl, followed up as hereditary spherocytosis from birth, was admitted to the hospital for erythematous and violet-colored lesions. Physical examination revealed petechiae, purpura and ecchymoses on her body. She was evaluated and diagnosed as having immune thrombocytopenic purpura. In many diseases, heredity contributes to disease susceptibility and outcome. The molecular bases of hereditary spherocytosis have been unravelled, but this is not valid for immune thrombocytopenic purpura. Genetic contributors in complex diseases such as immune thrombocytopenic purpura give new dimensions to studies on immune thrombocytopenic purpura. This is the first case, reported in the literature associating immune thrombocytopenic purpura with hereditary spherocytosis.

Keywords: Association, Child, Comorbidity, Hereditary Spherocytosis, Immune thrombocytopenic purpura

HEREDİTER SFEROSİTOZ VE İMMÜN TROMBOSİTOPENİK PURPURA BİRLİKTELİĞİ OLAN BİR OLGU

ÖZET

Yenidoğan döneminde herediter sferositoz tanısı konarak beş yıldır bu tanıyla izlenen kız çocuğu birkaç gündür farkedilen, hafif travmayla oluşan morluk ve kırmızılıklar nedeniyle başvurdu. Fizik muayene tüm vücutta ekimozlar, purpura ve peteşiler saptanan hasta immün trombositopenik purpura tanısı aldı. Birçok hastalıkta genetik faktörler rol oynamaktadır. Herediter sferositozun moleküler temeli açığa çıkarılmıştır, ancak immün trombositopenik purpura gibi kompleks hastalıklar için bu konu henüz araştırma aşamasındadır. Literatürde immün trombositopenik purpura ile herediter sferositoz birlikteliği bu güne kadar hiç bildirilmediği için bu vakayı sunuyoruz.

Anahtar Kelimeler: Çocuk, Herediter sferositoz, Immün trombositopenik purpura, Komorbidite

INTRODUCTION

Hereditary spherocytosis (HS) is a common cause of hemolysis and hemolytic anemia that is transmitted as an autosomal dominant and, less frequently, as an autosomal recessive trait. The most common molecular defects are abnormalities of spectrin or ankyrin, which are major components of the cytoskeleton responsible for the red blood cell (RBC) shape. A deficiency in spectrin, protein 3, or

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ankyrin results in uncoupling in the "vertical"interactions of the lipid bilayer skeleton and the loss of membrane micro vesicles. The loss of the membrane surface area without a proportional loss of volume causes sphering of RBCs and an associated in cation permeability, cation transport, adenosine triphosphate utilization and glycolysis. The decreased deformability of the spherocytic RBCs impairs cell passage from the splenic cords to the splenic sinuses, and the spherocytic RBCs are destroyed prematurely in the spleen. Splenectomy markedly improves the RBC lifespan and cures the anemia[1-3].

Immune thrombocytopenic purpura (ITP) is the most common cause of the acute onset of thrombocytopenia in an otherwise healthy child. One to four weeks after exposure to a common viral infection, a small number of children develop auto antibodies against the platelet surface. The exact antigenic target for most such antibodies in acute ITP remains undetermined. After the binding of antibodies to the platelet surface, circulating antibody coated platelets are recognized by the Fc receptor on splenic macrophages, ingested and destroyed. A preceding viral illness is described in 50-65 % of cases of childhood ITP. The reason why some children respond to the common infection with an autoimmune disease remains unknown[4-5].

The molecular bases of HS have been unrevealed but this is not valid for ITP. HS is due to mutations at different chromosome loci. Two genetic loci for HS have been identified by the study of balanced chromosomal translocations or small deletion, and by linkage analysis. One of the loci, and interstitial deletion of chromosome 8p11.1-p21.2 eliminates the gene for ankyrin. The second locus is the gene for β-spectrin, which resides on chromosome 14q23-q24.2. Other loci involve the genes for band 3, protein 4.2, α- spectrin, and possibly β-adductin and dematin[6]. Although genetic basis of ITP have not been determined yet recent results provide preliminary evidence that variant genotypes of Fc gamma receptor and cytokines contribute to chronic ITP pathogenesis[7-8].

Here we present a case followed up by our outpatient hematology department with the diagnosis of HS for five years, admitted to our Hospital with acute onset isolated thrombocytopenia. History, physical examination and laboratory findings yielded a diagnosis of acute ITP. As far as we are considered, this is the first case of ITP and HS association reported in the literature. Although we could not determine, if the appearance of ITP was in the setting of HS, we think there may be a possible relationship between HS and ITP.

CASE REPORT

A five year-old girl was admitted to hospital with erythematous and violet-colored lesions noticed after a minor trauma. At history, she was evaluated as having prolonged jaundice in the newborn period and diagnosed as having HS. She was considered as a severe HS case because she depended on regular transfusions.

She has been followed in our pediatric hematology department for five years together with her mother, brother; two aunts and one uncle who were also diagnosed as having HS.

On examination, she had jaundice, fatigue and pallor. There were petechiae, purpura and ecchymoses on her body. Postnasal drip was present. Expansion of the diploe of the skull was found. There was a grade II/VI degree systolic ejection murmur at the left sternal border. The liver was palpable at 4 cm, and spleen at 5 cm on the midclavicular line. She was admitted to hospital for an evaluation of the etiology of petechia and ecchymoses. On laboratory examination her platelet count was $5x10^3/mm^3$, hemoglobin value was 6 gr/dl, and white blood count was $13.200/mm^3$. Blood smear examination showed hypochromia, polychromasia, poikilocytes, anisocytosis and spherocytes. Bone marrow aspiration revealed moderate increase at young megacaryocytes. The other findings at bone marrow examination were normal. Spleen scintigraphy was made in order to exclude sequestration and it was considered as normal. Due to the etiology of thrombocytopenia autoimmune markers,

except antithrombocyte, the antibodies were negative. According to these findings, this was an acute event, an isolated thrombocytopenia (her anemia was due to HS). Bone marrow examination revealed young megakaryocytes. Antithrombocyte antibodies were positive. Acute immune thrombocytopenic purpura (ITP) was diagnosed. Immunoglobulin therapy rapidly increased her thrombocyte count to normal range in five days. Splenectomy was performed after one month. Pre-splenectomy vaccination for pneumococcus, haemophilus and meningococcus were administered. After surgery, she was recommended folinic acid and penicillin prophylaxis for life. Her platelet values recovered after the splenectomy. Her platelet count at postoperative second month was $424.000x10^3/mm^3$, her hemoglobin value was 9.5 gr/dl, and white blood count was $8.300/mm^3$.

DISCUSSION

When the child followed up as HS was admitted to our hospital with acute onset petechiae and purpura; sequestration in the spleen should have been considered. But her spleen scintigraphy was normal, antithrombocyte antibodies were positive, and bone marrow examination revealed moderate increase at young megakaryocytes. Due to these findings, we thought this situation was an association of HS and ITP.Today, within our knowledge, referring to MEDLINE for stored documents, no association of HS and ITP has been reported. This first case of HS and ITP association is discussed in the view of literature, by reviewing the pathogenesis and genetic base of both diseases.

Hereditary spherocytosis is due to mutations at different chromosome loci[6]. Two genetic loci for HS have been identified: one of the loci, an interstitial deletion of chromosome 8p11.1-p21.2, eliminates the gene for ankyrin. The second locus is the gene for beta-spectrin, which resides on chromosome 14q23-q24.2. In about two thirds of patients, the disease is inherited in a dominant pattern and can be followed from generation to generation. In the remaining cases both parents are normal. About half of these cases are due to de novo mutations of the type associated with dominant inheritance; the others are assumed to be due to recessive genes.

Disturbance in immune function in ITP causes generation of auto antibodies through the loss of tolerance to self-antigens. Platelet associated antigens such as GP1b or GPIIb/IIIa and its assorted epitopes are a target for auto antibodies. Molecular similarity could be the mechanism by which tolerance to self-antigens is destroyed by pathogen-associated antigen. The common end point is that alteration in immune function results in the accelerated destruction of platelets. Other than megakaryocytes, key-circulating molecules of immune regulation implicated in the pathogenesis of ITP such as cytokines, interleukins, and thrombopoetin also influence hematopoiesis. Analysis of the cytokine profile at the time of diagnosis has yielded important observation in the pathogenesis of ITP. Alternations in the levels of interleukin (IL)-2 or IL-4 have been implicated in the models of autoimmunity partly because IL-4 is thought to shut off the proinflamatory response. Differences in the circulating levels of IL-2 have been reported to confer differences in antiplatelet T-cell reactivity, particularly in relation to platelet phenotype. It is plausible that the circulating cytokines alter the response of HLA class 2 presentations, but it is probable that the cytokines influence the interaction between T and B-lymphocytes and in the end induce resting B cells to proliferate and produce high affinity auto antibodies. For many diseases heredity contributes to disease susceptibility and outcome. Genetic contributors in complex diseases such as ITP present new dimensions to be studied. A single base chance in the regulatory region of a cytokine causes alternations in immune response. The variation in key genes in the host response might lead to loss of tolerance or the sustained production of auto antibodies in ITP[8].

Fc gamma receptor-mediated destruction of auto antibody-sensitized platelets is central to the immune pathophysiology of childhood

ITP. Allelic variants exist among the random population for some Fc gamma receptors[9]. In a study of Carcao et. al., the genotypic frequencies for two Fc gamma receptor single nucleotide polymorphisms, FcgammaRIIa-131 arginine versus histidine and FcgammaRIIIa-158 valine versus phenylalanine were examined in 98 children diagnosed with childhood ITP. The genotype frequencies were compared with those of 130 healthy control subjects. Both the FcgammaRIIa-131H and the FcgammaRIIIa-158V were significantly over-represented in children with ITP versus the control subjects (P-values 0.03)[9]. Further studies based on larger groups of patients will be necessary to identify genetic susceptibility factors for this disease.

In our present knowledge, we know that there are certain mutations causing HS, and studies on ITP reveal that there is a genetic base under this autoimmunity. Is the association of HS and ITP in our patient a random coexistence or a co morbidity? It is possible that common mechanisms may be responsible for the occurrence of HS and ITP together in this case. We think further research is necessary.

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