Leukocyte Adhesion Deficiency: Report of Two Family Related Newborn Infants

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Abstract- Leukocyte adhesion deficiency type 1 (LAD 1) is an autosomal recessive hereditary disorder resulting from deficiency of CD18, characterized by recurrent bacterial infections. We report two consanguineous patients with Leukocyte adhesion deficiency type 1(LAD1). These two infant boy patients were referred to us, within a short period of time, with the complaints of recurrent infections at the age of 38 and 75 days -old, respectively. Parents of two patients were first cousins and their grandmothers also were first cousins. The history of delayed umbilical cord separation was shown in both patients. Patient 1 had history of omphalitis, conjunctivitis, skin lesion of groin area and abscess formation of vaccination site, and had infective wound of eye-lid at the last admission. Patient 2 had history of omphalitis and soft tissue infection of right wrist at the last admission. Laboratory findings showed marked leukocytosis and low CD18 levels (6.6% in Patient 1 and 2.4 % in Patient 2). In Patient 1 recurrent infections were treated with antibiotic regimens and received bone marrow transplantation but Patient 2 died because of septicemia, generalized edema, ascites and progression to acute renal failure at 4 months of age. Due to considerable rate of consanguineous marriages in parents of Leukocyte adhesion deficiency patients, sequence analysis especially for prenatal diagnosis in subsequent pregnancies and genetic counseling is recommended.

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Key words: Leukocyte- adhesion deficiency syndrome; consanguinity; signs and symptoms

Introduction

Leukocyte adhesion deficiency (LAD) represents one of the several genetic diseases of childhood that involve leukocyte functional defects. These disorders have in common the propensity to develop life-threatening bacterial infections. The syndrome that came to be known as LAD was first described in 1980 in patients with delayed separation of the umbilical cord, neutrophilia, neutrophil defects, and systemic bacterial infections (1–3).

Leukocyte adhesion deficiency type 1 (LAD-1) is a rare autosomal recessive disorder of neutrophil function and has a prevalence of 1 in 100,000 live births. The disease is caused by mutations in the β_2 integrin gene (*ITGB2*) at chromosome 21q22.3 (4, 5).

Early studies (6) found that leukocytes from patients with LAD I were deficient in the expression of the three integrins containing beta 2 or CD18 (Mac-1, LFA-1, p150, 95). In vitro studies demonstrated a marked defect in random migration and chemotaxis. Adhesion and transmigration through endothelial cells were also severely impaired (7). In LAD-1, leukocytes fail to adhere and migrate to extravascular sites of inflammations; a delay in the natural detachment of the umbilical cord is often the first symptom of the disorder (4, 8). This report describes two consanguineous patients with LAD1 who were referred to pediatric ward of Baqiyatallah Hospital, Tehran, Iran.

Case Report

Patient 1(P1)

A 38 days -old infant boy, whose parents were first cousins, was referred to pediatric ward of our hospital because an infected wound of eye-lid. He was the second offspring of his parents and his older sibling was a normal healthy girl. The patient had omphalitis 5 days after birth and his umbilical cord had been separated 24 days after birth.

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Table 1. The comparison of laboratory findings of two patients

Laboratory findings	Patient 1	Patient 2
Hemoglobin	8.7 g/dl ↓	7.6 g/dl ↓
White blood cell	53000/mm^3 ↑	46000/mm^3 ↑
Platelet	647000/mm^3 ↑	585000/mm^3 ↑
ESR	>120 ↑	>120 ↑
CRP	3+	1+
IgM	75(45-230) mg/dl N	59(45-230)mg/dl N
IgG	512(700-1600)) mg/dl ↓	917 (700-1600)) mg/dl N
IgA	210(70-400)) mg/dl N	10 (70-400)) mg/dl ↓
IgE	18(<11) IU/ml ↑	20 (<11)IU/ml ↑
C4	6(10-40)) mg/dl ↓	–
CD18	6.6%(100%) ↓	2.4% (100%) ↓
CD11a	3%(25%-35%) ↓	3.9% (25%-35%) ↓
CD11b	3%(25%-35%) ↓	2%(25%-35%) ↓
CD11c	30% (25%-35%) N	4.8% (25%-35%) ↓

↑= High, ↓= Low, N= Normal

Normal ranges are given in parenthesis

He had also history of conjunctivitis, skin lesion of groin area and abscess formation of vaccination site. There were relative good response to aggressive antimicrobial treatment, and the infection was controlled with difficulty. Laboratory data showed marked leukocytosis (leukemoid reaction), anemia, thrombocytosis, and a very high sedimentation rate (ESR). Immunologic studies showed slightly increased serum IgE and low serum IgG, with normal other immunoglobulins. Serum complements were normal except for C4. Flow cytometric study detected normal CD3, CD4, CD8, and CD4/CD8 but low CD18, CD11a, CD11b, CD19 and CD20. The patient has now received for bone marrow transplantation. He had several additional infective disorders such as osteomyelitis since then, but has been controlled although with relative difficulties.

Patient 2(P2)

This second 75 days infant boy was a third cousin of the first patient. Their grandmothers were first cousins. Parents of the second patient were also first cousins. Parents felt he must have had the same illness and brought him to our pediatric ward because of the right wrist erythema and swelling two months later than the first patient admission. The patients had history of neonatal intensive care unit admission because of meconium aspiration. He had also history of omphalitis 12 days after birth and his umbilical cord had been separated 27 days after birth. Appropriate antibiotics were prescribed with probable diagnosis of soft tissue infection. Arthritis and Osteomyelities were ruled out. Laboratory findings showed marked leukocytosis, anemia, thrombocytosis, high ESR, high serum IgE, low serum IgA. Serum IgG and IgM were normal. Flow cytometeric studies revealed normal CD2 and CD4, but CD18.CD11a, CD11b and CD11c were low. Response to aggressive antimicrobial treatment was not successful. The patient died because of septicemia, generalized edema, ascites and progression to acute renal failure at 4 months of age. The comparison of laboratory findings of two patients is presented in table 1.

Discussion

Characteristic clinical features of LAD include the elevation of neutrophil counts in the blood during infection (five to 20 times normal values or up to 100,000/mL), retarded wound healing, chronic ulcers with polymicrobial infection, dystrophic scars from skin injuries, infection of umbilical cord (omphalitis), severe gingivitis, and susceptibility to recurrent bacterial and fungal infections (9). Movahedi et al have described the clinical and laboratory findings of 15 patients with LAD I in Iran.

The most commonly occurred manifestations were: recurrent infections (93.3%), poor wound healing (86%), oral ulcers (86%), and skin abscesses (80%) (10). These two patients (P1, P2) were referred to us with the recurrent infections at the very early ages of life. The history of delayed umbilical cord separation was shown in both patients. P1 had history of omphalitis, conjunctivitis, skin lesion of groin area and abscess formation of vaccination site, and had infective wound of eye-lid at the last admission before the diagnosis. P2

had history of omphalitis and soft tissue infection of right wrist at the last admission. Laboratory findings of marked leukocytosis, anemia, thrombocytosis, high ESR, high serum IgE were detected in both patients. These two patients were third cousins (their grandmothers were first cousins). These two patients were referred to our hospital during a period of two months. Both patients had consanguineous parents. Movahedi et al also described 93.3% of consanguineous marriages among their patient's parents (10). Due to considerable rate of consanguineous marriages in parents of LAD patients, sequence analysis to define the exact molecular defect in the beta 2-subunit is recommended, especially for prenatal diagnosis in subsequent pregnancies and genetic counseling. Sequence analysis is available in many laboratories working in genetic molecular testing (11). In literature review we found only two reports of relative patients (12, 13). The first study reported two adolescent siblings (12), and second report was two patients who were cousins (13). Although LAD1 is a rare autosomal recessive hereditary disorder, but diagnosis of two related newborn infants within a short period of time is surprising.

The severity of infectious complications among patients with LAD I appear to be directly related to the degree of CD18 deficiency. Two phenotypes, designated severe deficiency and moderate deficiency, have been defined: Patients with less than 2 percent of the normal surface expression exhibit a severe form of the disease. It is characterized by earlier, more frequent, and more serious episodes of infection, often leading to death in infancy. Patients with some surface expression of CD18 (variably characterized as 2 to 30 percent of normal) manifest a mild to moderate phenotype with fewer serious infectious episodes and survival into adulthood (14).

Regarding very low level of CD18 in P2, the clinical progression to septicemia, generalized edema, renal failure and death appears inevitable. This very low level of CD18 shows severe adhesion deficiency that resulted the severe infective process. P1 whose CD18 was slightly decreased showed better prognosis.

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