

Leukocyte Adhesion Deficiency (LAD) Syndromes

Author: Amos Etzioni, MD *

* Amos Etzioni, Rambam Hospital, B. Rappaport Faculty of Medicine, Technion, Haifa 31096, Israel, etzioni@rambam.health.gov.il

Scientific editor: Prof. Alain Fischer

Creation date: July 2005

[Abstract](#)

[Key words](#)

[Disease name and included diseases](#)

[Definition](#)

[Epidemiology](#)

[Genetics](#)

[Diagnostic criteria](#)

[Differential diagnosis](#)

[Etiology](#)

[Clinical description](#)

[Diagnostic methods](#)

[Prenatal diagnosis](#)

[Management and treatment](#)

[References](#)

Abstract

The hallmarks of leukocyte adhesion deficiency (LAD) are defects in the leukocyte adhesion process, marked leukocytosis and recurrent infections. These molecular and clinical manifestations result from an impaired step in the inflammatory process, namely, the emigration of leukocytes from the blood vessels to sites of infection, which requires adhesion of leukocytes to the endothelium. In the last 20 years, three distinctive defects in the leukocyte adhesion cascade, involving several precise ordered steps such as rolling, integrin activation and firm adhesion of the leukocytes have been described. While LAD I and II are clearly autosomal recessive disorders, the mode of inheritance of LAD III is still not clear. LAD I is due to structural defects in the integrin molecule, preventing a firm adhesion to occur. In LAD II, the primary genetic defect is in a specific Golgi GDP-fucose transporter that leads to absence of the selectin ligand on the leukocyte and a defective rolling. LAD III or LADI/variant, which was last described, is due to defects in the integrin activation process. All three syndromes are very rare, LAD I being more frequent than LAD II and III, with LAD I being described in more than 300 patients worldwide and LAD II and III in less than 10 children each. The most important focus should be to control infections. Treatment includes antibiotics and in many cases bone marrow transplantation.

Key words

Leukocyte, Adhesion, Selectin, Integrin, Fucose, Leukocytosis.

Disease name and included diseases

Leucocyte adhesion deficiency syndromes

LAD I

LAD II

LAD III

congenital disorder of glycosylation type II (CDG II syndrome)

Definition

The hallmarks of leukocyte adhesion deficiency (LAD) are defects in the adhesion process, marked leukocytosis and recurrent infections.

Epidemiology

LAD I has been described in more than 300 patients worldwide and LAD II and III in less than 10 children each.

Genetics

In the last 20 years, three distinctive defects have been described in the leucocyte adhesion cascade, which involves several precise steps [1] and plays a major role in the recruitment of leukocytes to the site of inflammation. While LAD I and II are clearly autosomal recessive disorders, the mode of inheritance of LAD-I/variant or LAD III is still not clear. LAD I (OMIM 116920) is due to mutations in a gene (*ITGB2*) which is located on chromosome 21 and encodes the β_2 subunit of the integrin molecule. In LAD II (OMIM 266265), the genetic defect, located to chromosome 11 is mutations in the gene encoding the specific Golgi GDP-fucose transporter [2, 3]. The precise molecular defect in LAD III is still unknown and it may be the result of several different genes involved in the inside-out signalling for general integrin activation [4,5,6].

Diagnostic criteria

Leukocytosis is a constant feature in all LAD syndromes, but each of the three syndromes has unique clinical features, which should allow an accurate diagnosis.

- LAD I is characterized by delayed separation of the umbilical cord, omphalitis, severe recurrent infections with no pus formation [7].
- In LAD II, patients have the rare Bombay blood group and they suffer from severe psychological and growth retardation [8].
- LAD III is somewhat similar to LAD I but also includes a severe bleeding tendency starting at delivery or later [4,5,6]. Laboratory workup will show absence of CD18 or CD15s in LAD I and LAD II, respectively. Various defects in leukocyte chemotaxis and adhesion to endothelial cells will be found in the syndrome [9]. In order to characterise the exact defect in LAD I and II, genetic analysis of the corresponding genes should be done. In LAD III, the definitive diagnosis is established by the presence of defects in the integrin activation process while the CD18 molecule is structurally intact.

Differential diagnosis

In most cases, the clinical and laboratory findings are very suggestive of LAD syndrome. Other causes of leukocytosis should be ruled out, e.g. leukemoid reaction in early age or

severe infections. In LAD III, due to the bleeding tendency, other congenital coagulation disorders should be ruled out.

Etiology

- LAD I is the consequence of mutations in the gene coding CD18, the β_2 integrin subunit of the heterodimers LFA-1, Mac-1 (CR3) and p150,95 [10, 11]. The α subunit will not bind the defective β subunit and thus almost no CD18 will be expressed on the leukocyte surface membrane. This will eventually lead to severe defects in the firm adhesion of leukocytes on endothelial cells and thus to the defective inflammatory response leading to infections [12]. Rarely, CD18 may be present on the leukocyte surface but it will be non-functional, due to the mutation [13].
- In LAD II, mutations in the gene encoding the fucosyl transporter impede fucose entry in the Golgi apparatus and the fucosylation process normally taking place in the Golgi apparatus. As a consequence, all fucosylated glycoproteins including the H antigen on erythrocytes and CD15s (Sialyl-Lewis X) on leukocytes are markedly decreased. Since CD15s is the ligand for the endothelial selectin, the main defect will be in the rolling phase of the adhesion process. The precise mechanism leading to the severe psychological and growth retardation is still unknown.
- Finally, LAD III involves a general defect in integrin activation. Defects in the activation of β_1 , β_2 and β_3 integrin subunits have been observed and it seems that this rare syndrome may be due to several defects in molecules involved in integrin activation [14].

Clinical description

LAD I

The prominent clinical feature of these patients is recurrent bacterial infections, primarily localised to skin and mucosal surfaces. Infections are usually apparent from birth onward, and a common presenting infection is omphalitis with delayed separation of the umbilical cord. The absence of pus formation at the sites of infection is one of the hallmarks of LAD I. Severe gingivitis and periodontitis are major features among all patients who survive infancy. Impaired healing of traumatic or surgical wounds is also characteristic of this syndrome [15]. The severity of clinical infectious complications among patients with LAD I appears to be directly related to the degree of CD18 deficiency. Two phenotypes, designated as severe deficiency and moderate deficiency,

have been defined. Patients with less than 1% of the normal CD18 surface expression exhibit a severe form of disease with earlier, more frequent, and more serious episodes of infection, often leading to death in infancy. Patients with some surface expression of CD18 (2.5-10%) manifest a moderate to mild phenotype with fewer serious infectious episodes and with survival into adulthood [10]. *In vitro* studies demonstrated a marked defect in random migration as well as chemotaxis to various chemoattractant substances. Adhesion and transmigration through endothelial cells were found to be severely impaired [16].

LAD II

Affected children are born after uneventful pregnancies with normal height and weight. No delay in the separation of the umbilical cord is observed. Affected individuals have the rare Bombay (hh) blood phenotype. Later in life, they show severe mental retardation, short stature, and a distinctive facial appearance. Infections are generally not life-threatening and are usually treated in an out-patient clinic. There is no pus formation at the site of infection. After the age of 3 years, the frequency of infections decreases and children no longer need prophylactic antibiotics [17]. The hallmark of LAD II syndrome is the deficiency in the expression of the sLe^x antigen, the selectin ligand, on leukocytes. Neutrophilia (10,000-40,000/mm³) is a constant finding [18]. LAD II is also called congenital disorder of glycosylation type IIc (CDG IIc) syndrome.

LAD III

The clinical picture in the four patients described so far with this syndrome is very similar to LAD I but also includes defects in platelet activation [19] and a severe bleeding tendency [20].

Diagnostic methods

A simple complete blood count (CBC) test is the most important diagnostic test: it should reveal a profound neutrophilia. FACS (Fluorescence activated cell sorter) analysis using specific monoclonal antibodies is essential for the diagnosis of both LAD I and LAD II. Adhesion assays are not performed in most laboratories and should be carried out only in laboratories which are specialized in these assays [21]. Mutation analysis of patients DNA should be carried out to confirm the diagnosis and for genetic counselling.

Prenatal diagnosis

As leukocytes express CD18 on their surface from 20 weeks of gestation, cordocentesis can establish the diagnosis [22]. In families in whom the exact molecular defect has been previously

identified, an earlier prenatal diagnosis is possible by chorionic villi biopsy. In LAD II the Bombay blood phenotype can be checked at 20 weeks of gestation. Genetic analysis of the defective gene can be performed at 10-11 weeks of gestation. No prenatal diagnosis in LAD III has been reported so far, since the genetic defect(s) is/are not known yet.

Management and treatment

The most important focus should be to control infections. Prompt antibiotic therapy should be initiated as early as possible in case of acute infection. Granulocyte transfusion should be restricted to life-threatening situations when all other measures have failed. Blood transfusion should be given in bleeding episodes in LAD III. In the severe phenotype of LAD I, bone marrow transplantation should be performed and excellent results have been reported [23]. Gene therapy is still experimental in LAD I [24]. In two cases of LAD II, fucose supplementation showed encouraging results [18, 25].

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