

A Review on Leukocyte Adhesion Deficiency

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Abstract: *Leukocyte Adhesion Deficiency (LAD) is a group of rare autosomal recessive (<1 in 1000000 births) inherited disorders belonging to an immune deficiency and peripheral neutrophilia. Naturally, in the human body, a series of several definite steps results in the movement of leucocytes from the bloodstream to the site of infection, which also involves some adhesion of leucocytes to the foreign molecules/antigens due to mutations in CD18 glycoprotein. A failure in adhesion of leukocytes to vascular endothelium affecting their movement to extravascular space gives rise to a group of rare immunodeficiency known as Leukocyte Adhesion Deficiency. The paper aims to review the available relevant literature and overall study LAD and present a concise quality overview and analysis of the same.*

Keywords: Immunodeficiency, Integrin, Stem cell transplant, CD18, Neutrophilia

1. Introduction

Immunodeficiency is a condition in which an individual's immune system cannot fight diseases and infections, leading to immunodeficiency disorders. Immunodeficiency is broadly classified into primary immunodeficiency and secondary immunodeficiency. Secondary immunodeficiency is called acquired immunodeficiency, which is caused by many extrinsic factors. Whereas primary immunodeficiency is inherent and is autosomal recessive or X - linked. There are more than 250 primary immunodeficiency disorders and many more being studied by scientists and researchers. [1] In this review paper, we are pitching in to leukocyte adhesion deficiency (LAD) as primary immunodeficiency affects both B cells and cellular T cells. These combined immunodeficiency disorders bring about leukocyte adhesion deficiency (LAD). Leukocyte adhesion deficiency is a defect in the expression of leukocyte adhesion molecules of the integrin family. This rare disorder is caused by innate molecular defects in genes, in which white blood cells (WBCs) or leukocytes lack a protein on their surface, making them susceptible to recurring bacterial and fungal infections. It has an autosomal recessive pattern of inheritance. Primarily, Leukocyte adhesion deficiency (LAD) be categorized into three types as LAD1, LAD2, and LAD3. LAD1 is caused by a mutation in the ITGB2 gene, encoding CD18 of the beta - 2 integrin subunit. In this, the production of β two subunits cannot bind with other subunits to form β two integrins. Defects in the SLC35C1 gene, absent fucosylated carbohydrates ligands for selection, are caused in LAD2. LAD3 is caused by alterations in FERMT3 or KINDLIN3, which creates beta - integrin 1, 2, and 3 in hematopoietic cells. The types of leukocyte adhesion deficiency can be ingrained through molecular genetic testing. LAD has been rumoured since 1970. It is first suspected in newborns by a delayed detachment of the umbilical cord with repeated bacterial and fungal infections, poor wound healing capacity, and absence of pus formation, which can be fatal. The malignant case of an infant with LAD type 1 was diagnosed in Santiago, Chile. [2] The severity in LAD1 is based on the total absence of CD18 in leukocytes; higher severity can result in early death, whereas moderate severity patients have better survival rates. LAD1 is most prevalent, affecting 1 per million people yearly. The

mortality rate is 75% till two years and exceeds 50% by the age of 40 years of the patient's life. [3] On the contrary, LAD2 is less common, and research on oral fucose as a different alternative exists, but not every patient responds to it. It was first reported in 1992 in two unrelated boys exhibiting the rare Bombay phenotype showing symptoms of severe mental retardation and delayed growth. [4] Cases with LAD3 are sporadic, and hematopoietic stem cell transplantation (HSCT) is used in treatment. The mortality rate is reported to be 22% in transplanted patients, whereas the survival rate of non - transplanted patients is as low as 55%. LAD3 can prove to be lethal for patients with severe complications. [5] Stem cell transplantation is the only curative therapy used for leukocyte adhesion deficiency disorder, in which allogeneic hematopoietic stem cell transplantation can be done. Researchers have currently opted for gene therapy by implanting copies of the ITGB2 gene into hematopoietic stem cells as a potential alternative treatment for an individual with leukocyte adhesion deficiency (LAD) disorder.

2. Epidemiology

Leukocyte adhesion deficiency type 1 is a recessive primary immunodeficiency that links to heterogeneous germ - line mutations of the integrin β 2 gene represented as ITGB2, located on chromosome 21 (21q22.3). The genetic defects usually lead to the absence or reduced expression of the β 2 integrin proteins, low natural killer and low cytotoxic T lymphocyte activity might be observed. [6] According to a literature review, some common symptoms are recurrent infections (93.3%), poor wound healing (86%), oral ulcers (86%), and skin abscesses (80%). The most specific laboratory findings were a defect in CD18 in all of 15 patients. [7]. Umbilical cord complications that often include delayed separation or omphalitis are more frequent in patients with severe LAD - I. For the subset of patients with severe LAD - I with at least two years of follow - up (or death before the age of 2 years), there was a significant correlation between the absence of umbilical cord complications and survival to 24 months. [8]

3. Pathophysiology

Integrins are crucially important because they are the primary receptor proteins that cells bind and respond to the extracellular matrix. An integrin molecule is structurally composed of two noncovalently associated trans membrane glycoprotein sub - units. These sub - units are called α and β . Integrins are heterodimers of α and β subunits, each of which is a type I trans membrane protein with large multidomain extracellular portions, a single - pass trans membrane region and a generally short cytoplasmic tail. [9] The molecular basis of this Leukocyte adhesion deficiency was demonstrated to be due to the absence or deficiency of the three different types of heterodimeric β_2 integrins, namely LFA - 1, Mac - 1, and p150/95, which are adhesion molecules on the surface of leukocytes. The β subunit (CD18) is common to all three of these β_2 - integrins. Mutations are found in the CD18 gene in patients affected by this syndrome. [10]

Defective biosynthesis of the beta chain shared by each molecule that comprises alpha 1 beta 1 complexes represents the fundamental molecular basis of this disease. [11] LAD - 1 consists of failure to express the mentioned integrins, $\alpha M\beta 2$ and $\alpha L\beta 2$. These integrins serve as the receptor for C3b in myeloid and lymphoid cells. They are encoded by the CD18 gene, which is mapped to the long arm of chromosome 21. LAD - 1 has a variable phenotype that may be classified as severe, moderate or unstable, depending on the leukocytes' level of CD18 expression. In the severe form, there is a total absence of CD18 in leukocytes, and such conditions usually result in early death. In the moderate form, the CD18 expression level is 2% to 5%, with mild persistent leukocytosis, which results in less frequent infections and a better survival rate. In the variable form of LAD, normal levels of CD18 are expressed, but they are non - functional. [12] LAD - 2 is a relatively less common disease. It was described for the first time in 1992 in Palestinian children who were born from unrelated parents. Its symptoms are similar to LAD - 1, but children affected with LAD - 2 are usually mentally disabled and present failure to thrive and survive, delayed growth, dysmorphic phenotype characteristics and a Bombay blood phenotype. [13]

4. Screening

Detection of a LAD syndrome is suspected based upon a thorough clinical evaluation, a detailed patient history, identification of characteristic findings and a variety of inspections such as a complete blood count (CBC). A CBC test can determine elevated levels of a type of white blood cell known as a neutrophil (neutrophilia) and lymphocytes. A diagnosis of LAD I should be prohibited in any infant with recurrent soft tissue infections and a very high white blood cell count (leukocytosis). [14] Testing for adhesive glycoprotein's on the surface of WBCs can also be used as a screening mechanism. Leukocyte adhesion deficiency is determined by detecting the absence or severe lack of adhesive glycoproteins on the surface of WBCs using monoclonal antibodies (e. g. anti - CD11, anti - CD18) and flow cytometry. Eukocytosis is examined by complete blood count is common but nonspecific. [15]. A diagnosis of LAD I or LAD II or III can be verified through molecular genetic

testing, which can reveal the characteristic mutations of the ITGB2, the SLC35C1 or the FERMT3 genes responsible for these disorders. Diagnosis before birth (prenatal diagnosis) is attainable in families where the exact molecular defect has already been discovered. A laboratory test called chorionic villi biopsy is executed. Chorionic villi are thin, hair - like structures that exist on the placenta. Chorionic villi cells possess the same genetic material found in the cells of the fetus. A sample of tissue is extracted from the placenta and studied to detect the presence of the specific genetic mutation that has caused LAD I, LAD II or LAD III in that family. LAD II can also be detected before birth by recognizing the characteristic blood type (Bombay blood phenotype) associated with the disorder.

5. Effects of leukocyte adhesion deficiency type 1 (LAD1)

LAD TYPE1

- Delayed separation of the umbilical cord
- Recurrent pyogenic infections, with onset in the first weeks of life
- Infections caused mainly by *Staphylococcus aureus* and *Pseudomonas aeruginosa*
- Absent pus formation
- Periodontitis [16]

Delayed umbilical cord separation

The patients (typically neonate or infants) have delayed separation of the umbilical cord. The umbilical cord is usually found to separate within three days of birth and it takes a maximum of 45 days after birth. If there is no separation of the umbilical cord by the end 45 days, it points towards delayed separation of the umbilical cord, which is a common finding in LAD Type1.

Recurrent Infection

In LAD1, there is the presence of recurrent infections like bacterial and fungal infections, primarily of the skin and mucous. But characteristically, there is no pus formation because of absence of neutrophil invasion. The infection is mainly caused by bacterial entities like *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

Impaired wound healing

The wound healing is delayed in patients affected with LAD. Another characteristic effect observed is impaired wound healing. Cigarette paper appearance of the skin is also observed because of scars that tend to acquire a dystrophic.

Periodontitis

Mainly in the later stages of life, periodontitis is seen.

Blood Neutrophilia

A persistent marked neutrophilia that is increased neutrophil count in the blood is associated with recurrent infections, mainly in the newborn period or early infancy. In the persistent marked neutrophilia in the newborn period, the neutrophil count is very high because the tissues hardly get any neutrophils. There is no migration or movement of neutrophils to the injured site, this results in Neutropenia i.e lack of neutrophils in the tissues.

Deficiency

Severe deficiency of CD18+ve neutrophil is always less than 1% in earlier cases. In the early stage of infection, more frequent and more serious infection occurs. The patient dies in infancy without Hematopoietic stem cell transplantation (HSCT). In mild to moderate deficiency, the CD18+ve is upto 18%, but severe fever and severe infections are found in patients. But they usually survive into adulthood unlike infants. [17]

6. Management

- The existing therapeutic recommendations are based mostly on case reports and small controlled PG management trials since the disease is rare. As mainstream therapy, the treatment usually combines local wound care and systemic immunosuppression. [18]
- To heal EG in severely immune - compromised patients of LAD - 1 Granulocytes pockets transfusion is carried out. [19]
- The optimal or accurate treatment for LAD - 1 is still unclear, and only allogeneic Hematopoietic Stem Cell Transplantation or Umbilical, cord Blood Transplantation can lead to a cure.
- Commonly used Immunosuppressive agents are Corticosteroids and cyclosporine. For some cases, even other immune suppressants are given, such as Cytostatic, or immune modulators such as Azathioprine, Mycophenolate mofetil, Methotrexate, Thalidomide, Interferon - alpha IVIg or biologically predominantly antitumor necrosis factor inhibitors are prescribed.
- Alternate therapeutic options include Antibiotic prophylaxis and prophylactic IVIg therapy.
- Infiximab treatment in colitis and also in cases of arthritis related to LAD1 can be thought of.
- Ustekinumab treatment in patients with sacral ulcer and severe periodontitis was successful. [6]

7. Current Research

Clinical researches pave the way for every cure to find its place for humanity. Various studies are going on to cure the leukocyte adhesion deficiency, out of which some are completed, and some are being recruited.

Allogeneic stem cell transplantation

In allogeneic stem cell transplantation, healthy blood - forming stem cells are collected from the donor to replace collected the damaged stem cells of the patients that are being destroyed during chemotherapy and radiation. This treatment is also called transplant as allogeneic bone marrow. [20]

Treatment

For the treatment by allogeneic stem cell transplant, the patient should weigh at least 12 kgs with no infections and have a blood - related donor, except pregnant, breastfeeding women. Full - body medical examination, healthy lifestyle, and an active mind are some pre - requisites for the treatment. The hormone named. G - CSF is infused for a few days so that it can be transferred from the stem cells of the bone marrow to the blood vessels for the stocking of stem

cells from the donor and the patient by the process of apheresis. For the entire treatment period, the central venous line is placed in a primary vein to transplant the donated stem cells, extract blood samples, transfuse blood & for medication purposes. [21] Ahead of transplantation, patients are made ready for the process of low - dose chemotherapy with cyclophosphamide, fludarabine, and Campath 1H initiating the treatment [22]. Cyclosporine is given one month prior to prevent donor cells rejection. There is a significant death risk in this procedure, notably for patients with active infections. To minimize these risks, the donor's T - cells have to be removed from the remaining stem cells before transplantation. The success rate of allogeneic stem cell transplants for treating LAD is 75%. [22]

Interferon - gamma

Interferon - gamma is an injectable drug that is used for treating LAD type I as it boosts the no. of adhesion molecules on white blood cells, improving their functions. [23] Patients getting treated by interferon - gamma should at least weigh 13 kgs with the full - body examination. This drug is infused into the patient suffering from LAD type 1 three times a week for three months. [24] As patients suffering from leukocyte adhesion deficiency type 1 often get infected in soft tissues like gums, skin, etc. and have a low healing capacity, patients are made to check the WBC count during the treatment, which can be done either by collecting samples from salt - water mouth specimen or blood. [25]

Orl 1 - f

the treatment with ORL 1 - F is given for the patients suffering from leukocyte adhesion deficiency type 2 [26], in which the person has an insufficient amount of fucosylated glycoconjugate [27]. Fucose is a form of sugar which, when given orally activates the fucosylated selectin ligands or neutrophils and core fucosylation of serum glycoprotein. [28]

Ustekinumab

Ustekinumab is a monoclonal antibody that binds the p - 40 subunit of interleukin - 12 and interleukin - 23 and arrests the action of cytokines which stops the interleukin - 23 - dependent production of interleukin - 17. This antibody is used for treating fatal bacterial infections caused by leukocyte adhesion deficiency type 1. [29] [30]

Gene Therapy

LAD emanates from heterogeneous molecular defects in the leukocyte integrin CD18, which counters the CD11/CD18 heterodimer formation and surface expression by the process of gene therapy, transfer of the CD18 subunit repairs the structural and functional defect in LAD leukocytes. [31]

8. Conclusion

LAD is a deficiency of various glycoproteins, including LFA - 1/Mac - 1, glycoprotein 150/95. All the factors mentioned above result in abnormal inflammatory responses in the human body, eventually leading to recurrent bacterial infections and losing its ability to form pus. Until now, four distinct LADs have been discovered, out of which LAD type 1 is the most common type, which is caused by a mutation in the integrin B2 gene that codes the ITGB subunit (CD18 antigen). LAD type 2 is caused due to a general defect in

fructose metabolism. Abnormal integrin activation leads to the disease LAD type 3. LAD type 4 is the most recently discovered type which is caused due to defects in B2. Patients with this particular disorder are treated with various treatments like antibiotics, gene therapy, and leukocyte transfusion. Since it is a rare disease the treatments for this disease are very limited. Research and technology might pave a way to cure immune deficiencies without causing immune suppression.

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