

Leukocyte adhesion defects



A White Blood Cell or Leukocyte
(along with some red blood cells)

What is Leukocyte Adhesion Deficiency?

Leukocyte Adhesion Deficiency or L.A.D. is a very rare genetic disorder that affects the body's immune system.

L.A.D. occurs when a patient's white blood cells or leukocytes are unable to produce a protein called CD18. In some cases, the leukocytes do not produce enough CD18. In other cases, normal or near-normal levels of the protein may be produced but might be defective and not function properly. CD18 is necessary for leukocytes to "travel to the site of an infection"... more on this later.

To date, only about 300 cases of L.A.D. have been identified worldwide. However, the actual number of cases may be significantly higher because many patients may be misdiagnosed or go undiagnosed due to the medical community's current lack of familiarity with L.A.D.

Since L.A.D. is a genetic disorder it is considered a Primary Immunodeficiency, (P.I.) and is **NOT** contagious.

What do we mean when we say "travel to the site of an infection"?

Even though leukocytes are constantly circulating through your bloodstream, they are not always in the right place at the right time... at least not in sufficient quantity. So, when you develop an infection, a signal or message is sent out from the affected area.

The message is passed to the blood vessels where it is "seen" by leukocytes that happen to be going by at the time. Leukocytes in a healthy person receive the message, activate and begin to move into the affected area by "sticking" or adhering to the blood vessel wall with tiny CD18-based, velcro-

like "hooks". The image at the top of the page may help you visualize these "hooks".

Then they slowly "crawl" through the blood vessel wall, migrate to the sight of the infection and get to work. This migration is also called chemotaxis. For a better understanding of how this process works, take a look at the following image.

How Leukocytes "Get to Work"...

Courtesy the Hospital Practice web site ...

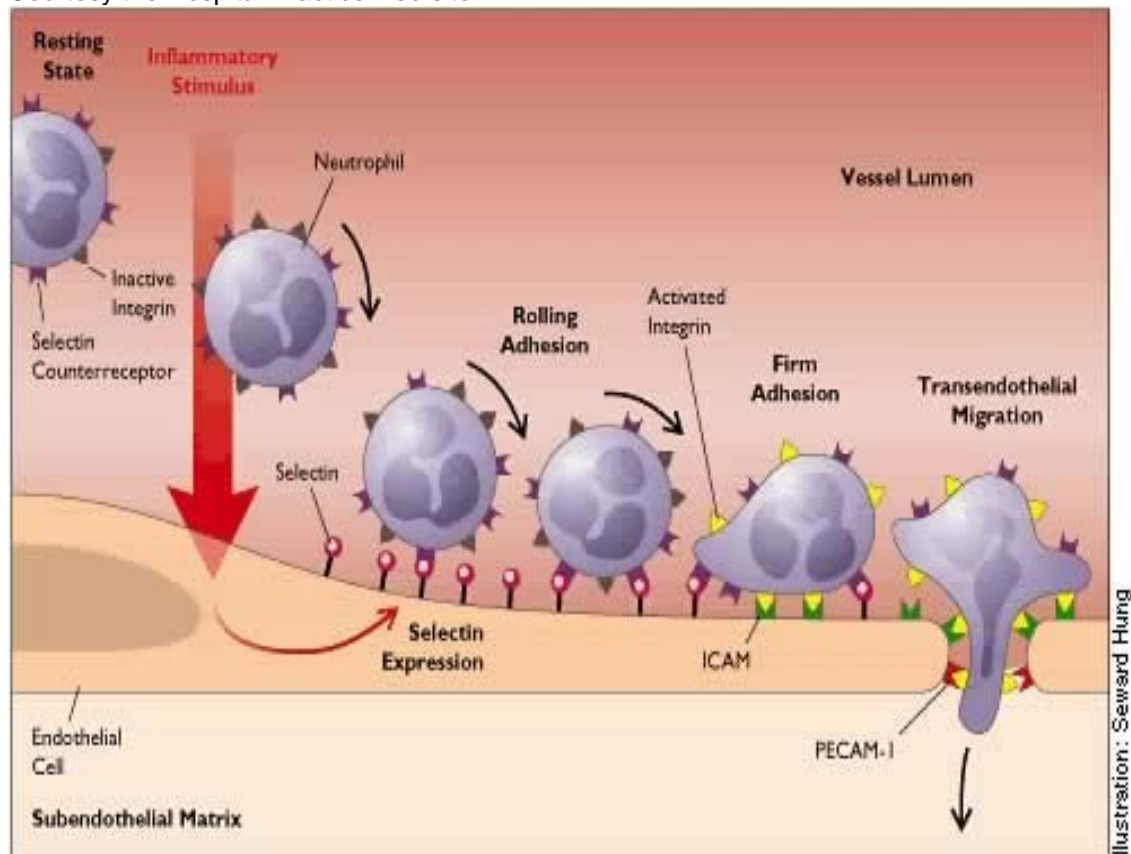


Figure 1. Cell-to-cell adhesions that enable a neutrophil to leave the circulation begin with both the neutrophil and the vascular endothelium in a resting, noninteractive state. Activated by an inflammatory stimulus, the endothelium expresses selectins, whose binding to their receptors on neutrophils initiates a rolling adhesion of neutrophils

to the vessel's luminal wall. The neutrophils activate their integrins, which bind to endothelial ICAMs, permitting a firmer, stationary adhesion. Transendothelial migration may be guided by further adhesive interactions, perhaps involving molecules such as PECAM-1, which endothelial cells express at intercellular junctions.

What happens in a person with L.A.D. is that the message goes out and is "seen" but the leukocytes are unable to successfully activate and "grab" or adhere to the blood vessel wall because they lack the necessary "hooks". Sometimes the "hooks" are present but may be defective and not work properly.

Since these leukocytes cannot adhere, because of missing or defective "hooks", they experience an "adhesion deficiency", which is where the disorder gets its name... **Leukocyte Adhesion Deficiency**. Without the ability

to adhere, leukocytes cannot make their way to the site of an infection to protect the body, which can lead to the symptoms described in the section entitled "What are the symptoms of L.A.D.?"

For more information about how the immune system protects the body from infection, click here to view "Anatomy of a Splinter". This link is provided courtesy of CellsAlive.com.

What are the different types of L.A.D.?

L.A.D. is broken down into what are called genotypes and phenotypes. Genotypes are genetically different types of L.A.D. This means that L.A.D. can be caused by a number of genetic errors. Within each genotype, there can be one or more phenotypes. Each phenotype describes how the genetic defect affects each patient.

There are currently two general genotypes of L.A.D. that have been identified. They are designated, L.A.D. Type 1 and L.A.D. Type 2. A third LAD type was recently described and more information may be provided when it becomes available. It has been tentatively designated L.A.D. Type 3.

••• L.A.D. Type 1 - "Classic"

Genotype - the genetics of this type of L.A.D.:

L.A.D. Type 1 is described in technical terms as the "deficiency of beta chain (CD18) of LFA- 1, Mac 1, p150,95". In other words, the protein mentioned earlier does not get produced in either the correct quantity or the correct form.

Phenotypes - how this defect can affect the patient:

L.A.D. Type 1 "Classic" currently has two known phenotypes: Severe and Moderate.

Severe - is probably best described by an almost to total lack of the CD18 protein on the leukocytes of the patient. This, in turn, causes the symptoms of this phenotype to be more severe or acute. The severe phenotype, is a very serious disease and should be considered potentially life-threatening.

Moderate - is probably best described as a decrease in the expression of the CD18 protein on the leukocytes of the patient. This, in general, may cause the symptoms of this phenotype to be less severe or acute. However, this phenotype can still be life-threatening, if not aggressively managed.

••• L.A.D. Type 1 - Novel or Variant

Genotype - the genetics of this type of L.A.D.:

This form of L.A.D. tends to be caused by unique, extremely rare, genetic defects that are classified as L.A.D. but can't necessarily be considered

"Classic" L.A.D. In some Novel or Variant patients, the CD18 protein may be produced at normal or near-normal levels but may not function correctly... in other words the CD18 is present but still cannot "stick" or adhere to the blood vessel wall thus resulting in an "adhesion deficiency". For specific genetic information on a Novel or Variant case, please visit this page.

Phenotype - how this defect can affect the patient:

The phenotype(s) for this disorder may take a different path for each patient which may be similar to the Severe or Moderate phenotypes of "Classic" L.A.D. depending on the specific nature of the genetic defect(s) but it might also manifest unique symptoms. This phenotype may be life-threatening, if not aggressively managed.

••• L.A.D. Type 2

Genotype - the genetics of this type of L.A.D.:

L.A.D. Type 2 is described in technical terms as a "genetic mutation in the specific transporter of fucose from the cytoplasm into the Golgi apparatus", which may lead to the "failure to convert GDP mannose to fucose".

Phenotype - how this defect can affect the patient:

Unfortunately, we are unfamiliar with the different phenotypes of L.A.D. Type 2. You might want to consider visiting the following link to the National Institutes of Health database for more information on L.A.D. Type 2.

••• L.A.D. Type 3

Genotype - the genetics of this type of L.A.D.:

At this time, we don't have any specific information on the L.A.D. Type 3 genotype.

Phenotype - how this defect can affect the patient:

Unfortunately, we are unfamiliar with the different phenotypes of L.A.D. Type 3. You might want to consider using some of the links to the different search engines listed below for more information.

Does L.A.D. only affect people?

No, actually there have been cases where both dogs and cattle have been diagnosed with the disease. The type that affects dogs is called Canine L.A.D. or C.L.A.D. and the type that affects cattle is called Bovine L.A.D. or B.L.A.D.

What are the symptoms of L.A.D.?

There are many symptoms of L.A.D. Some differ with the specific genotype and/or phenotype of L.A.D. The symptoms listed immediately below are generally common to human genotypes and phenotypes of L.A.D.

- Recurrent skin infections - may be more frequent and severe in younger patients.
- Sometimes significant internal infections - these may occur less frequently than skin infections mentioned above, depending on the Type of L.A.D. the patient has, their ability to manage it and their age.
- Severe Periodontal disease - up to and possibly including complete tooth loss.
- Delayed wound healing - this might initially present itself as delayed umbilical cord separation.
- Candidiasis
- Leukocytosis - an increased white blood cell count. This symptom may be more severe in younger patients and may decrease as the patient ages.

Additionally, the following symptoms have been observed and reported in a patient with L.A.D. Type 1 Variant but may not be present in other forms of L.A.D.

- Enlarged spleen or splenomegaly.
- Muscle, tendon and joint discomfort, pain and/or swelling. This is thought to be caused by either a significantly increased level of superoxides a.k.a. "free radicals" in white blood cells and the bloodstream or increased pro-inflammatory cytokine production. This symptom did not appear to be present when the patient was younger but has become evident as the patient aged and could be related to the patient's genetic variant. This "effect" seems to be similar to some autoimmune disorders where the immune system is in some way "over active" and may therefore adversely affect normal tissues. For specific case information visit this web page.

How do I know if I have L.A.D.?

Symptoms alone are not enough to tell you if you have L.A.D. since other diseases may have similar symptoms. The only way to know for sure if you or someone you know has L.A.D. is to be tested, usually by a research or hospital hematopathology laboratory.

The ***European Society for Immunodeficiencies (ESID)*** provides a diagnostic criteria web page that may be helpful. You can click here to view it.

PLEASE NOTE: If you have a laboratory perform tests to determine if you or a family member has L.A.D., please be aware that a widely used test, called "**Flow Cytometry**", while generally considered to be accurate, **can yield**

"false negative" results in patients with a certain type of L.A.D. In other words, you might have L.A.D. even though this test indicates that you don't. Additional, perhaps genetic, testing may be required to receive a definitive diagnosis.

What treatments are available for L.A.D.?

There are a number of treatments for L.A.D. and we emphasize the term "treatments". Currently, there is no cure for L.A.D., although L.A.D. is thought to be a good candidate for gene therapy, when that becomes available.

- **Oral Antibiotics** - usually used for maintaining the day-to-day health of the patient.
- **Intravenous Antibiotics** - usually used when the patient suffers from a severe infection.
- **White Blood Cell Transfusions** - again usually suggested when the patient suffers from a severe infection. Other treatments are usually used first since this treatment can have potentially significant adverse side effects.
- **Bone Marrow or Stem Cell Transplants** - this is usually the treatment of last resort because of life-threatening nature of the procedure. However, this is currently the best chance that some L.A.D. patients have at a normal quality of life because it comes closest to a cure for L.A.D. But we must emphasize that the potential benefits must be carefully weighed against the risks and costs.
- **Permanent Gene Therapy** - the best future hope for L.A.D. patients. The ability to actually replace the defective gene and provide normal quality of life. At last we heard, the ability to permanently replace a defective gene was 3-5 years away, but we're still hopeful that this is a conservative estimate.