Clinical Overview of Leukocyte Adhesion Deficiency Type I (LAD-I) for ICD-10-CM Committee

ICD-10 Coordination and Maintenance Meeting

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Susan Prockop, MD
Director of Clinical and Translational Research, Stem Cell Transplant Program
Dana-Farber/Boston Children's Cancer and Blood Disorders Center

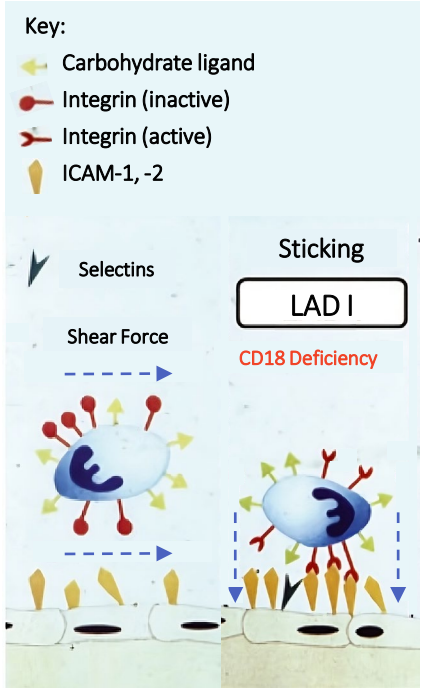
Dana-Farber/Boston Children's Cancer and Blood Disorders Center

What Is Leukocyte Adhesion Deficiency Type I (LAD-I)?

Definition	A rare genetic disorder caused by mutations in the ITGB2 gene resulting in decreased amounts of CD18 protein on the cell surface and **impaired migration of white blood cells to sites of infection** or inflammation in tissues[1]
Patient Population	• LAD-I symptoms often begin **in the neonatal period** • This disease **affects both males and females equally** • **Disease severity can be moderate** if there is partial function of the CD18 protein • **Severely affected individuals have a very high mortality** without curative therapy early in life
Diagnosis	• Should be suspected with **delayed separation of the umbilical cord,** or if patient presents with a wound which does not produce pus • **Positive diagnosis made via flow cytometry** for CD18
Prevalence	**Estimated to be under 10 in 1,000,000 live births,** though it may be underdiagnosed[2,3]

1. Parvaneh, N., Mamishi, S., Rezaei, A., Rezaei, N., Tamizifar, B., Parvaneh, L., Sherkat, R., Ghalehbaghi, B., Kashef, S., Chavoshzadeh, Z., Isaeian, A., Ashrafi, F., & Aghamohammadi, A. (2010). Characterization of 11 new cases of leukocyte adhesion deficiency type 1 with seven novel mutations in the ITGB2 gene. Journal of Clinical Immunology, 30(5), 756–760. https://doi.org/10.1007/s10875-010-9433-2
2. Cox, D. P., & Weathers, D. R. (2008). Leukocyte Adhesion Deficiency Type 1: An important consideration in the clinical differential diagnosis of prepubertal periodontitis. A case report and review of the literature. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, 105(1), 86–90. https://doi.org/10.1016/j.tripleo.2007.02.026
3. Leukocyte adhesion deficiency type I: Orphanet. (2023, October 17). https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=2968

What is the Pathophysiology of LAD-I?



LAD-I is due to mutations in CD18, which is essential for firm adhesion of leukocytes to the endothelium

This creates an inability for leukocytes to migrate to infections to neutralize offending microbes

Without leukocytes present at the site of infections, the patient is not able to properly eradicate infections and doesn't form "pus"

Source: Wolach, B., Gavrieli, R., Wolach, O., Stauber, T., Abuzaitoun, O., Kuperman, A., Amir, Y., Stepensky, P., Somech, R., & Etzioni, A. (2019). Leucocyte adhesion deficiency—a multicentre national experience. *European Journal of Clinical Investigation*, *49*(2). https://doi.org/10.1111/eci.13047

What Are Key Symptoms of LAD-I?

3 Key Characteristics of LAD-I

Frequent Infections

- Common infections include soft tissue infections and abscesses, pneumonia, gingivitis, and peritonitis
- These infections are more severe and occur at higher a frequency than in the general population

Poor Wound Healing

- Since white blood cells cannot move to wounds, wounds are unable to heal properly
- Non-healing wounds frequently become infected

Hyperinflammatory Response

- Separate from inability of white blood cells to migrate, patients have unregulated hyperinflammation
- This inflammation further compounds challenges of treating infections

Implications for Patients

- The frequent, poorly controlled infections and poorly healing wounds require **ongoing clinical care**
- Many of these infections have potential to become **life threatening**, leading to early mortality in patients with LAD-I
  - Only 39% of patients with severe LAD-I* survive to an age of 2 years or older[1]
  - Less than 50% of patients with moderate LAD-I** survive past age of 40 years old[1]

1. Almarza Novoa, E., Kasbekar, S., Thrasher, A. J., Kohn, D. B., Sevilla, J., Nguyen, T., Schwartz, J. D., & Bueren, J. A. (2018). Leukocyte adhesion deficiency-I: A comprehensive review of all published cases. The Journal of Allergy and Clinical Immunology: In Practice, 6(4). https://doi.org/10.1016/j.jaip.2017.12.008

*Severe LAD-I: Less than 2% expression of CD18
**Moderate LAD-I: 2 – 30% expression of CD18

How Is LAD-I Managed or Treated?

	Treatment	Implications
Infection Management	• Infections require **prolonged treatment with antimicrobial medications and careful monitoring for recurrence** • Wound care often requires special dressings, debridement, and **extended courses of antimicrobial medications**	• Some infections can be **life-threatening at presentation** • Other infections can **become life-threatening over time** • Many patients with severe disease **cannot leave the hospital** unless they receive curative therapy (a hematopoietic stem cell transplant)
Avoidance of Wounds and Infections	Patients, caregivers, and physicians must be **diligent to avoid any wound**, as the slow healing may lead to significant infections	• **Patients may require isolation** or limited interaction to minimize risk of further infection • **Procedures such as biopsies and incisions leading to wounds should be carefully considered by practitioners with specific expertise** as they could lead to permanent, non-healing wounds (e.g., due to surgeries, biopsies, circumcisions, drainage of abscesses)
Hematopoietic Stem Cell Transplant (HSCT)	Allogeneic **HSCT is currently the only curative treatment** for LAD-I	• Despite being the only option, **patients face high treatment-related complications of HSCT** including graft rejection and risk of acute graft vs host disease (aGVHD) • **8% of patients experience lethal aGVHD** following transplant[1]

1. Bakhtiar, S., Salzmann-Manrique, E., Blok, H. J., Eikema, D. J., Hazelaar, S., Ayas, M., Toren, A., Goldstein, G., Moshous, D., Locatelli, F., Merli, P., Michel, G., Öztürk, G., Schulz, A., Heilmann, C., Ifversen, M., Wynn, R. F., Aleinikova, O., Bertrand, Y., Tbakhi, A., … Lankester, A. (2021). Allogeneic hematopoietic stem cell transplantation in leukocyte adhesion deficiency type I and III. Blood advances, 5(1), 262–273. https://doi.org/10.1182/bloodadvances.2020002185

LAD-I Summary

- LAD-I is a **rare, genetic disorder** that impairs the ability of patients' white blood cells to **migrate to sites of infection** or inflammation in tissues
- Because white blood cells can't get to site of infections, patients with LAD-I experience **frequent, potentially life-threatening infections**
- LAD-I patients require **significant, ongoing, and highly unique care** to manage the risks and effects of chronic infections and non-healing wounds
- The creation of an ICD-10-CM code will **facilitate the use of appropriate monitoring and treatment** and **limit potential for management that could be generally appropriate (e.g., a biopsy) but is potentially life-threatening** for patients with severe LAD-I

Thank You

Questions?