ASGCT Annual Meeting
May 16-19, 2018
Chicago, IL

Abstract 832

Leukocyte Adhesion Deficiency-I : A Comprehensive Review of All Published Cases

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Abstract:

Introduction & Methods: LAD-I is a rare disorder of leukocyte adhesion, resulting from *ITGB2* gene mutations encoding for the Beta-2 Integrin component CD18. CD18 deficiencies prevent integrin dimerization and endothelial leukocyte adhesion, essential for extravasation and antimicrobial activity. Severe LAD-I (<2% of normal neutrophil [PMN] CD18 levels) is characterized by recurrent serious infections and early mortality unless treated by allogeneic hematopoietic stem cell transplant (HSCT). Mortality for severe LAD-I was reported as 75% by age 2 in an initial 1988 multicenter retrospective study. Moderate LAD-I (2-30% of PMN CD18 levels) is more indolent; although most patients (pts) survive childhood with recurrent skin and mucosal surface infections; mortality by age 40 can exceed 50%. LAD-I is characterized by umbilical cord complications (delayed separation and omphalitis), poor wound healing and leukocytosis.

Reports regarding LAD-I have been published in recent decades but no recent comprehensive prognostic assessments are available. We sought an updated understanding of severe LAD-I with emphasis on prognosis in the absence of HSCT, HSCT outcomes and association of CD18 expression with clinical features. We created a database of all published LAD-I cases via Pubmed searches and review of available references.

Results: Three hundred twenty-three LAD-I cases were reported between 1975-2017 in 107 publications (68 case-reports; largest series n=36). The nations reporting the most cases were Iran (n=65), USA (n=50), and India (n=45); the highest number of publications were from US centers (25). 113 pts were considered to have severe LAD-I, 63 moderate and 147 were not classified. PMN CD18 expression levels was reported for 265 cases and was <2% in 135 patients (51%) and ≥2% in 130 pts. Four pts with CD18 >2% were considered to have severe LAD-I (CD18% range 2.4 – 17.3). Gender was noted for 282 pts; 148 (52%) were male. Age at presentation was reported for 146 cases. For 63 pts with CD18<2%, median presentation was age 1 m (range 0.03-18m); for 62 pts with CD18 ≥2%, median presentation was age 6m (range 0.03-192m).

Infection details and CD18% were available for 154 (48%) cases. The most frequent infections in pts with CD18 <2% were respiratory tract (39%), sepsis (29%) and otitis media (27%) and for pts with CD18 ≥2% they were periodontal (52%), otitis media (365%) and sepsis (25%). Perianal skin infections and necrotic skin ulcers were noted in >10%. Umbilical complications were more frequent in severe LAD-I (92 of 110 pts with CD18<2% [84%] and 47 of 81 with CD18 ≥2% [58%; p = 0.0002]). For severe LAD-I pts with ≥2 years of follow-up (or death prior to 2y), there was correlation between absence of umbilical complications and survival to 24 m (p < 0.001). WBCs were reported in 143 cases (median 45 x 10^9/L; range 10 – 150 x 10^9/L). There were limited correlations between CD18 expression and WBC (r < 0.1) and between CD18 and CD11 expression (r < 0.5). Mutation analyses were reported in 139 cases with >20 gene locations noted and mutations on Exons 5, 6 and 7 accounting for 44% of specified cases. In 18 cases, CD18 expression was >30%; in 8 of 12 cases where CD11 expression was noted, at least one CD11 moiety was reported as <2%.

We sought to understand whether prognosis for severe LAD-I in the absence of HSCT is similar to the initially-reported 25% survival to age 2. There were 66 severe LAD-I cases (per investigator assessment or CD18 <2%) for whom survival to 2 years was reported, 40 of whom died prior to age 2 (61% mortality). Mortality was similar for the subset of 43 cases reported since 2000 (56%, 24 deaths). Early mortality was substantially lower in patients with CD18 ≥2% and the majority of pts with CD18 >4% survived to adulthood. Outcomes for 101 pts who received HSCT were consistent with recent series; phenotypic correction was reported in 83% of pts with HLA-matched sibling donors. Mortality was 19% overall (11% for HLA-matched sibling recipients). For 22 pts receiving haploidentical HSCT there was 32% mortality and 55% received ≥1 subsequent HSCT.

Conclusion: Severe LAD-I remains a life-threatening condition with limited 2-year survival in the absence of allogeneic HSCT. Umbilical complications and granulocytosis are frequent early manifestations; respiratory tract, ear, sepsis, oral and skin infections are common. HSCT is potentially curative; transplant-mortality and other complications are frequent, especially in haploidentical recipients. Diverse *ITGB2* mutations result in LAD-I, and genetic evaluation may be valuable for diagnosis and prognosis. Rapid identification of pts with potential LAD-I (unusual or severe infections in infancy, granulocytosis and umbilical complications) is essential to enable referral to centers with disease expertise.

Introduction:

LAD-I:

- Rare disorder of leukocyte adhesion, migration & chemotaxis
- Results from *ITGB2* gene mutations causing defective CD18 (β2 integrin)
- Intact β2 integrin complexes (CD11/CD18 dimers) are essential for WBC adhesion to endothelial surfaces; adhesion enables extravasation to sites of infection/injury
- LAD-I is characterized by infections, granulocytosis, absence of pus formation & umbilical cord complications.

Multiple reports have been published in recent decades, but there has been no comprehensive assessment since an initial 1988 retrospective summary (n=66; Fischer et al.). The Fischer 1988 paper has been the source of frequently quoted prognostic summaries:

Severe LAD-I (CD18 <2%): 25% survival to age 2 (n=22)
Moderate LAD-I (CD18 2-30%): 25% survival to age 40 (n=24)

Purpose of Updated Natural History:

- Updated understanding of severe (& moderate) LAD-I with emphasis on prognosis in absence of HSCT
- Up-to-date assessment of HSCT outcomes in LAD-I
- Updated assessment of CD18 expression & correlation with phenotype
- Comprehensive characterization of infections and other disease-related features including umbilical complications & granulocytosis.

Methods:

We created a database of all published LAD-I cases via PubMed searches and review of references in all identified publications.

Results:

323 LAD-I cases were identified between 1975-2017 in 107 publications (including 68 single-case reports; largest series was n=36).

Figure 1. Overview of cases:

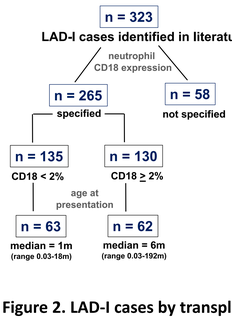


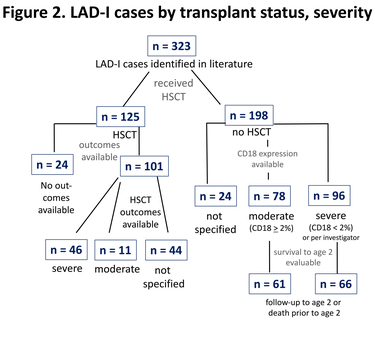
Table 1. Patient numbers by country:

Country	# publ.	# pts
Iran	12	65
USA	25	50
India	10	45
US/EU*	1	36
UK	8	16
Germany/ France	1	14
Saudi Arabia	2	13
Israel	2	12
EU*	2	10

* Publications w/ multiple contributing countries.

- Nations from which at least 10 pts were reported are listed in table.
- LAD-I cases were reported from 20 additional countries in East Asia, South Asia, Africa, Middle East, Europe, North & South America.

Figure 2. LAD-I cases by transplant status, severity & duration of follow-up:



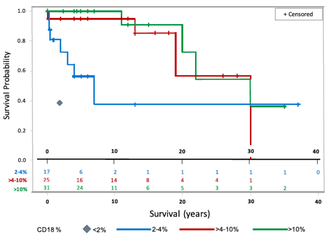
Results (ctd.)

Table 2. Survival to age 2 in absence of HSCT based on parameters of severity:

LAD-I severity	n	Survival to age 2 years: Alive at ≥ 2 years	F/U to age 2*	% alive to age 2
Severe: investigator assessment of CD18 <2% **	96	26	66	**39%**
Severe: CD18 <2%	73	21	48	**44%**
Severe: CD18 <2% (2000-2017 only)	67	19	43	**44%**
CD18 2-4%	17	9	13	**69%**
CD18 >4%-10%	25	18	19	**95%**
CD18 >10%	36	29	29	**100%**

* Or death prior to age 2 years
** Several patients were considered to have severe LAD-I despite CD18 expression on >2% neutrophils or unspecified CD18 expression; these cases are included in the top row in addition to those with CD18 expression on <2% neutrophils.

Figure 3. Overall survival in absence of HSCT based on CD18 expression:



- Because many reports did not provide precise survival (stating only that mortality occurred before the age of 2 years), it was not possible to generate plots incorporating most of the severe LAD-I cases.
- The grey diamond indicates the 39% survival to age 2 years for 66 evaluable patients with severe LAD-I not receiving HSCT.

Kaplan-Meier survival estimates for patients with moderate LAD-I not receiving allogeneic HSCT, by neutrophil CD18 expression.

Table 3. Infections & umbilical complications based on severity:

Infection	CD18 <2% (n=85) n	%	CD18 ≥2% (n=69) n	%
Otitis media	23	(27)	25	(36)
Respiratory tract (incl. pneumonia)	33	(39)	16	(23)
Sepsis	25	(29)	17	(25)
Periodontal incl. gingivitis, oral ulcer	20	(24)	36	(52)
Perianal skin infection	17	(20)	10	(14)
Necrotic skin ulcer	11	(13)	8	(12)
Umbilical cord complications	92/110	(84)	47/81	(58)

Includes conditions reported as >10% of specified infections

Umbilical cord complications:
- delayed separation
- omphalitis

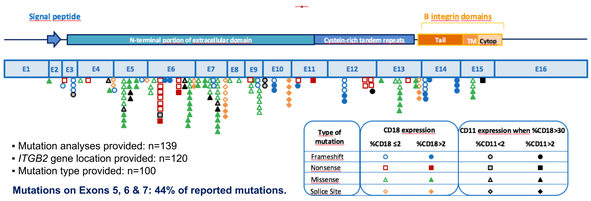
Table 4. Allogeneic stem cell transplant (HSCT) outcomes (n = 101):

HSCT Type	n	Phenotypic correction n	%	Engraftment failure n	%	Subsequent HSCT n	%	HSCT-rel. mortality n	%
MSD	36	30	(83)	2	(6)	2	(6)	4	(11)
MFD	10	8	(80)	0	--	0	--	2	(20)
MMFD	2	2	(100)	0	--	0	--	0	--
MUD	25	19	(76)	0	--	2	(8)	6	(24)
Haploidentical	22	11	(50)	4	(18)	12	(55)	7	(32)
Cord Blood	6	4	(67)	2	(33)	3	(50)	0	--

MSD: matched sibling donor; MFD: matched family donor; MMFD: mismatched family donor; MUD: matched unrelated donor.
Note: Outcomes were available for 101 of 125 patients reported to have received HSCT, for which LAD-I severity was as follows: severe n=46; moderate n=11; not specified n=44. Phenotypic correction is defined as a reversal of the underlying immunodeficiency.

Overall: ▪ Phenotypic correction was achieved in 73%; ▪ HSCT-related mortality was 19%.

Figure 4. Gene and protein map of reported *ITGB2* mutations (n = 100):



- Mutation analyses provided: n=139
- *ITGB2* gene location provided: n=120
- Mutation type provided: n=100

Mutations on Exons 5, 6 & 7: 44% of reported mutations.

Figure 5. Neutrophil CD18 expression : Limited correlation with β2-integrin heterodimer expression:

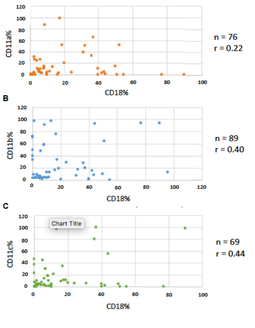


Fig 5. CD18 expression by **(A)** CD11a, **(B)** CD11b, and **(C)** CD11c. Most institutions did not provide the precise mechanisms by which β2-integrin expression was assessed; the percentage of neutrophils expressing CD18 (or CD11) via flow cytometry (relative to normal) is the most frequent modality for determination of CD18 expression.

Figure 6. Neutrophil CD18 expression : Limited correlation with granulocyte counts:

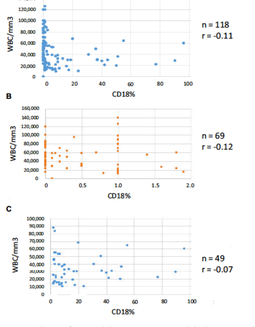


Fig 6. Correlation of neutrophil CD18 expression with highest reported WBC for **(A)** all patients for whom information was reported, **(B)** patients with CD18 <2%, and **(C)** patients with CD18 >2%. Upper limits of normal for WBC vary between clinical laboratories but are generally in the range of 9,800/mm^3

Conclusions:

- Severe LAD-I remains highly fatal during first years of life in the absence of HSCT
- Neutrophil CD18 expression is a major determinant of survival
- HSCT is curative in approximately 75% of cases, however engraftment failure, need for subsequent HSCT, and HSCT-related mortality are frequent (as are HSCT-related side effects including GVHD & infections)
- Although granulocytosis is nearly universal in LAD-I, there is no direct correlation between WBC and CD18 expression
- Triad of *umbilical complications*, *granulocytosis* and unusual/severe infection early in life are hallmarks of severe LAD-I and should prompt diagnostic evaluation and referral to centers of expertise.
- These observations provide additional rationale for the initiation of an LAD-I clinical trial evaluating LV-based gene therapy of autologous CD34+ cells: to commence 2018-2019.

For additional results including correlation of umbilical complications with survival, and severe cases with CD18>2% (CD11<2%), see Almarza 2018.

References:

Almarza E, Kasbekar S, Thrasher AJ et al. Leukocyte adhesion deficiency-I: A comprehensive review of all published cases. **J Allergy Clin Immunol Pract 2018**; Jan 20. pii:S2213-2196(17)31026-7. Epub ahead of print.

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