RESEARCH BRIEF

Clinical Profile of Leukocyte Adhesion Deficiency Type I

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Leukocyte adhesion deficiency type I (LAD-I) is a rare, inherited immunodeficiency with defect in the recruitment of leukocyte to the site of inflammation. Patients with severe LAD-I have absent or markedly reduced expression of CD18 and CD11. Here we report clinical profile of 7 cases of LAD-I diagnosed at our center over a period of 3 years. Recurrent skin and mucous membrane infections were the major presenting manifestations. All children had a history of delayed cord separation.

Key words: *Inherited immunodeficiency, Leukocyte adhesion deficiency (LAD-I), Neutrophilia.*

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Leukocyte adhesion deficiency (LAD) syndromes result from failure of leukocytes to defend the host because of missing or dysfunctional surface adhesion molecules [1]. LAD-I (OMIM 116920) results from mutations in the *ITGB2* gene encoding for the β2 subunit (CD18) of beta 2-integrin [2-5]. It is the commonest of the LAD syndromes with more than 300 cases reported worldwide. Patients usually present soon after birth with omphalitis and delayed separation of the cord (often beyond 21 days) [6,7]. The prominent clinical feature of these patients is recurrent bacterial infections, primarily localized to skin and mucosal surfaces [6,7]. Life threatening infections such as septicemia, bronchopneumonia, and aseptic meningitis can occur. The most frequent organisms involved are *S. aureus*, Gram negative enteric organisms, and fungi. The severity of infections and complications is related to the severity of CD18 deficiency; cases with < 1% expression are clinically severe, whereas those with 2.5–10% expression are moderate to mild [1].

The exact incidence of LAD-I is not known, but it is estimated to be one in one million. In India, as there is a very high rate of consanguineous marriages in certain communities, a relatively higher frequency of this recessive disorder is expected; however, except few case reports [8,9], no comprehensive study has been published from this subcontinent. Here we report clinical profile of 7 cases of LAD-I diagnosed over a period of 3 years.

METHODS

The study group included 7 patients from 6 unrelated families. These families were from different parts of India: 5 from western India and 1 from south India. 4 index cases along with their parents were investigated whereas in 2 cases parents were not available for study. The clinical details including birth weight, presenting complaints, time of separation of umbilical cord, number of infections, site of infections, treatment required, organisms causing the infection, were recorded at the time of diagnosis.

Complete hemogram with peripheral smear examination was performed on all the cases. The diagnosis was done by studying the expression of CD18, CD11a, CD11b and CD11c on neutrophils and lymphocytes using multi-parametric flowcytometry. Nitro Blue Tetrazolium test (NBT), lymphocyte subset analysis and immunoglobulin estimation was done in all the patients to rule out other immunodeficiency disorders.

RESULTS

All the patients presented below the age of 2 years. There was positive family history in the form of early death in the sibling due to infection was present in 3 cases. History of consanguineous marriage in the parents was present in 3 cases. History of early death in the sibling due to infections was present in 4 families. Recurrent skin and mucous membrane infections were the major presenting

complaints in these patients (***Table* I**). In one patient omphalitis required surgical intervention.

***Table* II** shows the hematological parameters and expression of CD18/CD11 in the patients. All patients had neutrophilia and ANC at the time of diagnosis ranged from 14100 to 63500/mm^3. The CD18/CD11 expression ranged from 0% - 2% in all the patients suggesting severe LAD-I. All the patients were deficient for CD11a, CD11b and CD11c along with CD18. The expression in parents ranged from 95-100%. The infectious agents cultured were *S. aureus*, streptococci and *Pseudomonas*. Fungal disease was documented only in one child who had persistent oral candidiasis. Repeated skin infections especially in perianal area were common. One patient has repeated episodes of bacterial meningitis, whereas two patients had repeated otitis media caused by pseudomonas infection. Splenomegaly and hepatomegaly was observed in one patient. None of the patients had any hematologic malignancy or solid tumors.

Follow up was available in all 7 of these children and 6 of them expired due to septicemia within 1 year after diagnosis. One patient is alive and is 4 month of age. He was diagnosed at birth as the previous child in the family had LAD-I. He is on antibacterial and antifungal prophylaxis, but requires frequent hospitalization due to infections.

DISCUSSION

The data from seven patients suggests that LAD-I should be suspected in any infant with serious infections accompanied by striking neutrophilia in the peripheral blood. Absence of neutrophilia in a newborn infant who has delayed cord separation but is otherwise well generally rules out the diagnosis. Infections vary from

TABLE I CLINICAL DETAILS OF PATIENTS

Clinical presentation	*Patient 1*	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*	*Patient 6*	*Patient 7*
Age/Sex	3 m/ M	6 days/M	4 m/F	9 m /M	4 m /F	2.5m/F	2y/F
First symptoms	Omphalitis	Omphalitis	Omphalitis, otitis media	Perianal abscess	Omphalitis otitis	Omphalitis	Omphalitis
Average no. of infections/ y	7	6	8	5	4	7	3
Bacterial infections	*S. aureus*	NA	*S.aureus, Pseudomonas*	*Streptococcus*	*Pseudomonas*	*E. Coli*	*S. aureus*
Viral infections	No	No	No	No	No	NA	NA
Fungal infections	No	No	No	No	NA	Oral Candidiasis	NA
Necrotic skin lesions	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Late detachment of cord	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Transfusion	Yes	No	Yes	No	No	Yes	No
Birthweight (g)	3000	NA	2500	1700	2700	3700	NA
Consanguineous marriage	No	No	Yes	No	No	Yes	No
Growth*	NA	NA	25	25	50	NA	NA

*All patients had poor wound healing and dysmorphic features; NA: No information available, *Percentiles according to local growth charts.*

TABLE II HEMATOLOGICAL PARAMETERS AND EXPRESSION OF CD18/CD11 IN THE SEVEN PATIENTS

Parameters	*Family 1*		*Family 2*	*Family 3*	*Family 4*	*Family 5*	*Family 6*
	Patient 1	*Patient 2*					
Hb level (g/dL)	11.5	12.2	6.8	9.8	8.5	7.3	9.2
Platelet count ($\times 10^3$/mL)	300	312	424	416	355	562	532
% Neutrophils	63	56	45	61	50	60	73
WBC count ($\times 10^3$/mL)	58	34	64.2	24	29.7	23.5	50
% Lymphocytes	25	40	15	31	40	35	23
CD11/CD18 expression (%)	0.5	0.5	0.3	1.8	0.5	0.3	0.3

severe bacterial infections to fungal disease. The white blood cell count ranges between 15 - 160 × 10^9/litre and 50–90% of these are neutrophils [7]. The diagnosis can be easily established by studying the expression of CD11 and CD18 on leukocytes by flowcytometry. However, this facility is not available widely in India and hence majority of these cases remain undiagnosed. Leukocyte activation before flow cytometry can greatly enhance the expression of these glycoproteins and magnify the differences between healthy subjects and patients [10]. Other LAD disorders like LAD-II, and LAD-III should be kept in mind while evaluating patients with suspected leukocyte adhesion defects. LAD type II syndrome results from a general defect in fucose metabolism, causing the absence of SLeX and other fucosylated ligands for the selectins [11]. Affected patients present early in life, have recurrent bacterial infections with persistent leukocytosis, but do not have delayed separation of the umbilical cord. The infections are generally not life threatening. These patients also have severe mental retardation, short stature, a distinctive facial appearance and the rare Bombay (hh) blood phenotype. The diagnosis can be done by studying SLeX expression on leukocytes. Recently, a rare autosomal recessive LAD-III syndrome has been described presenting with recurrent severe bacterial infections, leukocytosis and severe bleeding tendencies. CD18 molecule is structurally intact in these patients and they show significant abnormalities in leukocyte and platelet integrin activation. Defects both in Kindlin 3 and CAL-DAG-GEF1 were found to cause LAD III [1,12].

There are very few therapeutic options available for patients with LAD-I. Supportive care is usually not sufficient in the severe form of disease and majority of the children die before the age of 5 years. The only curative option available for these patients is hematopoietic stem cell transplantation. Facilities for hematopoietic stem cell transplantation are not widely available and the cost is prohibitive for majority of the patients in India. Thus, preventing birth of a second child with LAD-I in affected family becomes extremely important. Leucocytes express CD18 and CD11 at 20 weeks gestation and at this time blood can be obtained by cordocentesis for prenatal diagnosis [19]. We have established normal ranges for expression of CD18 and CD11 at 18 weeks of gestation and have started the facility for prenatal diagnosis of LAD-I. Mutational analysis on chorionic villous biopsy or cells obtained by amniocentesis may also be possible when the precise familial mutation is known. However, this facility is not available in India.

Contributors: MM and ZC conceived and designed the study and revised the manuscript for important intellectual content. They will act as guarantor of the study. GM, ZC, MD and RM collected data and drafted the paper. GM and RM also conducted the laboratory tests, and interpreted them. ZC, MD and MM analyzed the data and helped in manuscript writing. The final manuscript was approved by all authors.
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