INTRODUCTION

Leukocyte adhesion deficiency type I (LAD-1) is a rare primary immunodeficiency with a prevalence of 1/100 000 [1]. LAD-1 is an autosomal recessively inherited disorder caused by mutations in ITGB2 gene encoding the β-chain (CD18) of β2 integrins, located at chromosome 21 [2,3]. CD18 expression is essential for integrin dimerization, adhesion between leukocytes and endothelial cells and processes such as extravasation and...
anti-microbial activity [4,5]. Defective or deficient CD18 impairs leukocyte mobilization into inflammation sites, causing tissues to become susceptible to long-lasting bacterial infections. The interleukin (IL)-23/IL-17 axis also becomes dysregulated and wound-healing is diminished [6].

Clinical manifestations of LAD-1 are delayed separation of the umbilical cord (UC), omphalitis and recurrent infections. Besides recurrent bacterial infections of skin and mucosal surfaces, gingivitis, periodontitis, other symptoms are otitis media and anemia secondary to severe infections [7,8]. Laboratory findings of LAD-1 patients are excessive neutrophilic leukocytosis in the circulation and reduced expression or absence of CD18, CD11a and CD11b expression on leukocytes. Hematopoietic stem cell transplantation (HSCT) is the only curative treatment option for patients with LAD-1 [7,9].

Here, we report clinical manifestations, immunological findings, medical approach and outcome of 15 patients diagnosed with leukocyte adhesion deficiency type 1 at three different medical centers in Turkey. Moreover, we highlight the importance of molecular testing with a next-generation sequencing (NGS) targeted primary immunodeficiency panel and/or Sanger sequencing for establishing the genetic diagnosis, which is essential for family studies and genetic counseling.

METHODS

Patients

Fifteen patients were diagnosed with LAD-1 after referral to three Turkish clinical centers: Section of Pediatric Immunology, İhsan Doğramaci Children’s Hospital, Hacettepe University, Ankara; Department of Pediatric Allergy and Immunology, Gaziantep University, Gaziantep; and Department of Pediatrics, Uludag University, Bursa. Demographic characteristics, clinical and laboratory findings of patients were recorded. Written informed consent was obtained from all participants.

Flow cytometry analysis of peripheral blood samples

To measure the expression level of integrins on the leukocyte surface, flow cytometry analysis was performed with the following antibodies at optimal concentrations: anti-CD18-fluorescein isothiocyanate (FITC) and anti-CD11b-PE. For the measurement of lymphocyte subgroups, peripheral blood mononuclear cells were stained with a mixture of the following antibodies at optimal concentrations: anti-CD3-FITC, anti-CD16-phycocerythrin (PE), anti-CD56-PE, anti-CD45-peridinin chlorophyll cyanin (PerCP-Cy) 5.5, anti-CD4-FITC-Cy, anti-CD19-allophycocyanin (APC) and anti-CD8-APC-Cy7. Finally, data were analyzed by fluorescence activated cell sorter (FACS) Canto II flow cytometer and FACS Diva software (BD Biosciences, Franklin Lakes, New Jersey, USA).

Genetic analysis

Genetic analysis was performed at Hacettepe University and at Sanquin Research Institute in Amsterdam, the Netherlands.

Targeted next-generation sequencing was performed with either a primary immunodeficiency gene panel comprising 266 genes consisting of 5242 amplicons or a small LAD-panel consisting of five genes and 74 amplicons on the Ion Torrent PGM platform. Disease-related mutations were determined following the filtration steps [combined annotation dependent depletion (CADD), genome aggregation database (gnomAD), MutationTaster, etc.] . Ion Reporter version 5.16 Bioinformatics software was used for characterization and filtering of variants. Variants with a coverage less than ×5 for single nucleotide polymorphisms (SNPs) and ×10 for small insertions and deletions (INDELs) were excluded. Common polymorphisms were discarded [minor allele frequency (MAF) > 0.05] and exonic and non-synonymous substitutions were selected. We also eliminated variants present in our in-house variant database (n = 600). We filtered rare variants (MAF < 0.01) for presence in a comprehensive list of genes known to be involved in leukocyte adhesion deficiency pathogenesis (ITGB2, FERMT3, SLC35C1) or relevant pathways. Variants present in the gnomAD as homozygous were ruled out. The remaining candidate variants were classified with three different variant function prediction tools [MutationTaster, PolyPhen2 and sorting intolerant from tolerant (SIFT)], following a manual checking step in IGV (integrative genomics viewer). The alterations predicted as ‘disease causing’ and ‘damaging’ with all three prediction tools were selected. Among these, variants with a CADD score higher than 20 were chosen. The final candidates ensured that all the filtering criteria were defined as probable or definite disease-causing variants. All causative and candidate variants detected with primary immunodeficiency gene panel filtering steps were validated through Sanger sequencing.

Exons of the ITGB2 gene were amplified under the following conditions: initial denaturation at 95°C for 5 min, 35 cycles at 95°C for 1 min, 58°C for 1 min, 72°C for 1 min and a final elongation step at 72°C for 10 min. The obtained polymerase chain reaction (PCR) products...
were purified with Exo-SAP (Thermo Scientific, Waltham, Massachusetts, USA). PCR products were sequenced with the appropriate primers and BigDye® Terminator version 3.1 cycle sequencing kits (Applied Biosystems/Thermo Scientific, Waltham, Massachusetts, USA). The products were loaded on the Applied Biosystems version 3130 Genetic Analyzer and the results were analyzed with Sequencing Analysis version 5.2 software.

**Statistical analysis**

Mean, median, minimum and maximum values were calculated on IBM SPSS Statistics version 23.

**RESULTS**

The study included a total of 15 patients [10 males (67%) and five females (33%)] from 15 unrelated families. Ten (67%) patients were Turkish and the other five were refugees of Syrian (n = 4, 27%) and Iraqi (n = 1, 7%) origin. The median age at onset of symptoms of the patients was 21 (6–180) days (mean 41 days). The median age of the patients at diagnosis was 3 (1–48) months (mean 10 months). Eleven (73%) patients had a LAD-1 diagnosis during their first 6 months. Fourteen (93%) patients had consanguineous parents. Demographic characteristics of patients with LAD-1 are shown in Table 1.

**Infections**

Clinical findings observed in our patients at follow-up are shown in Figure 1. Delayed separation of the umbilical cord was present in 12 (80%) patients in our cohort. Eight (53%) patients presented with skin (n = 4, 27%), soft tissue (n = 3, 20%), perianal (n = 2, 13.3%) or abdominal abscess (n = 1, 7%). Viral infections such as Epstein–Barr virus (EBV), cytomegalovirus (CMV), parainfluenza and/or adenovirus were detected in three (20%) patients. Only two (13%) patients showed signs of periodontal diseases such as gingivitis (n = 1, 7%) and periodontitis (n = 1, 7%). Diarrhea was present in six (40%) patients. Gram-positive bacteria (*Staphylococcus aureus, S. epidermidis, Enterococcus faecium, Listeria monocytogenes*) and Gram-negative bacteria (*Escherichia coli, Klebsiella pneumoniae*) were isolated from cultures. Fungal infections (*Aspergillus fumigatus, Candida albicans*) were detected in 20% (n = 3) of the patients.

**Complete blood count analysis**

Leukocytosis was observed in 14 (93%) patients at diagnosis and leukocytosis with neutrophil predominance was observed in 11 (73%) patients. The median leucocyte and neutrophil counts of the patients were 44.7 (13.2–97.1) × 10³/µl (mean 45.2 × 10³/µl) and 29.3 (5.4–82.1) × 10³/µl (mean 30.7 × 10³/µl), respectively. Detailed laboratory results of the patient without

| TABLE 1 Demographic characteristics of patients with LAD-1 |
|-------------------------------------------------------------|
| **Gender** | **Origin** | **Symptomatic age (days)** | **Age at diagnosis (months)** | **Parental consanguinity** |
| P1 | M | Turkish | 180 | 14 | + |
| P2 | M | Turkish | 60 | 2 | + |
| P3 | F | Turkish | 30 | 3 | + |
| P4 | F | Turkish | 60 | 3 | + |
| P5* | F | Turkish | 12 | 3 | + |
| P6* | M | Turkish | 45 | 5 | + |
| P7 | M | Turkish | 21 | 5 | + |
| P8 | F | Syrian | 7 | 1 | + |
| P9 | M | Syrian | 20 | 1 | + |
| P10 | M | Syrian | 18 | 12 | + |
| P11 | M | Iraqi | 30 | 4 | + |
| P12 | F | Syrian | 105 | 48 | + |
| P13 | M | Turkish | 10 | 48 | – |
| P14* | M | Turkish | 6 | 1 | + |
| P15* | M | Turkish | 16 | 2 | + |

Abbreviations: F, female; LAD-1, leukocyte adhesion deficiency type I; M, male.
*Deceased.
leukocytosis and three patients with leukocytosis but no neutrophil predominance are shown in Table 2. Hemoglobin levels were lower than age-related reference values in nine (60%) patients. Platelet counts of 10 (67%) patients were higher than reference values. C-reactive protein levels were higher than reference values in 12 (80%) patients.

**CD18 expression levels and lymphocyte subgroup analysis**

CD18 expression level was undetectable in seven (47%) patients, and ranged from 1 to 8% in eight (53%) patients in our cohort. CD11b expression was evaluated in 14 patients; it was undetectable in five patients (33%) and varied between 1 and 45% in eight (53%) patients. However, one patient showed 99% CD11b expression on the cell surface, but CD18 expression in this patient was only 2%. The percentage of patients according to absolute numbers of lymphocyte subgroups compared to age-related reference values in patients is shown in Figure 2.

**Genetic analysis**

Genetic analysis of the ITGB2 gene revealed nine distinct mutations in 13 of the 15 patients with LAD-1 (two
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patients had died before analysis). The same novel homozygous mutation, c.305_306delAA, was identified in all patients (n = 4) of Syrian origin from unrelated families. c.779_786dup is a novel homozygous mutation identified in a patient. Homozygous c.382G>A, c.382G>T, c.533C>T, c.562C>T, c.817G>A, c.1413_2080del and compound heterozygous c.533C>T and c.1777C>T mutations were identified in eight patients. A homozygous c.533C>T mutation was identified in the patient showing 99% CD11b expression and 2% CD18 expression. All mutations identified in the patients are shown in Table 3 and Figure 3, and the affected domains of CD18 are shown in Figure 4.

**FIGURE 2** Percentage of patients according to absolute numbers of lymphocyte subgroups compared to age-related reference values

**TABLE 3** Mutations in ITGB2 and CD18 expression in patients

| Patients | Zygosity | Exon | cDNA | Amino acid | Novelty | CD18 Expression |
|----------|----------|------|------|------------|---------|-----------------|
| P1       | Compound heterozygous | 6 and 13 | c.533C>T and c.1777C>T | Pro178Leu and Arg593Cys | Both reported | 8% |
| P2       | Homozygous | 12_14 | c.1413_2080del | – | Reported | 0% |
| P3       | Homozygous | 6 | c.562C>T | Arg188* | Reported | 0% |
| P4       | Homozygous | 7 | c.779_786dup | Thr263Cysfs*20 | Novel | 1% |
| P5       | Homozygous | 7 | c.817G>A | Gly273Arg | Reported | 0% |
| P6       | Homozygous | 6 | c.533C>T | Pro178Leu | Reported | 2% |
| P7       | Homozygous | 6 | c.533C>T | Pro178Leu | Reported | 0% |
| P8       | Homozygous | 4 | c.305_306delAA | Lys102Serfs*39 | Novel | 1% |
| P9       | Homozygous | 4 | c.305_306delAA | Lys102Serfs*39 | Novel | 1% |
| P10      | Homozygous | 4 | c.305_306delAA | Lys102Serfs*39 | Novel | 1% |
| P11      | Homozygous | 4 | c.382G>T | Asp128Tyr | Reported | 3% |
| P12      | Homozygous | 4 | c.305_306delAA | Lys102Serfs*39 | Novel | 0% |
| P13      | Homozygous | 4 | c.382G>A | Asp128Asn | Reported | 2% |
| P14      | NA | NA | NA | NA | NA | 0% |
| P15      | NA | NA | NA | NA | NA | 0% |

*NA = not available.*
Treatment and outcome

Two (13%) of the patients died because of infections. Four (27%) patients underwent HSCT from a related donor. Two of these patients died because of HSCT complications, and the other two are alive and well. Human leukocyte antigen (HLA) typing was performed for nine patients. HSCT is planned for three (20%) patients who have matched related donors. Six (40%) of the patients have no matched related donor, and these patients have been carefully followed at our centers since their first admission.

DISCUSSION

Leukocyte adhesion deficiency type 1 is a rare primary immunodeficiency that presents with typical clinical symptoms such as delayed umbilical cord separation and recurrent severe infections. The present report describes one of the largest comprehensive studies on clinical, immunological and molecular findings and outcome of LAD-1 patients from Turkey. Defects in CD18 expression in LAD-1 lead to defective adhesion of leukocytes. Two forms of LAD-1 have been described based on the level of CD18 expression on neutrophils: in severe form, CD18 expression is <2% of normal and in moderate form CD18 expression ranges from 2 to 30% [10]. Our patient cohort consisted of 11 patients with severe LAD-1 and four patients with moderate LAD-1. The median ages at diagnosis of severe and moderate LAD-1 cases were 3 (0.1–48) and 5 (1–78) months, respectively, in a study from India [11]. The median age of our patients at diagnosis was 3 (1–48) months, and 73% (n = 11) of patients had an LAD-1 diagnosis during their first 6 months. Parental consanguinity ratio was reported to be as frequent as 51% (in severe LAD-1) in studies from Israel [7] and India [11]. According to the Turkish Statistical Institute, the ratio of consanguineous marriages in Turkey was 23% in 2012. In our cohort, the consanguinity ratio was 93%, indicating that autosomal recessive inheritance plays an important role, and consanguineous marriages contribute to the occurrence of LAD-1.

In a study with 13 patients with LAD-1 from Iran, all patients presented with leukocytosis and neutrophilia [12]. In our study, leukocytosis was observed in 14 (93%) patients and leukocytosis with neutrophil predominance was observed in 11 (73%) patients. In another study with 15 LAD-1 patients from Iran, leukocyte counts showed persistent leukocytosis of between 12.2 and 91 × 10^3/μl (median = ~29.1 × 10^3/μl), with a neutrophil ratio of 31-90% [13]. In our cohort, the median leukocyte and neutrophil counts of the patients were 44.7 (13.2–97.1) × 10^3/μl (mean = 45.2 × 10^3/μl) and 29.3 (5.4–82.1) × 10^3/μl (mean = 30.7 × 10^3/μl), respectively. These data indicate that persistent leukocytosis is a significant feature of LAD-1.

Delayed umbilical cord detachment was found in eight (62%) of 13 patients with LAD-1 and omphalitis was observed in 67% of the patients in a study from Israel [7]. Additionally, delayed separation of umbilical cord was observed in five (~63%) of eight patients with LAD-1 and omphalitis was observed in only one patient in a study from Italy [14]. In the present study signs of omphalitis were observed in approximately half the patients, and delayed umbilical cord separation ratio was higher than in studies from Israel and Italy. This indicates that delayed umbilical cord detachment is one of the requisite components of LAD-1. De Rose et al. reported that patients with LAD-1 present with numerous
infections and autoimmune phenomena [14]. We did not observe autoimmune findings in our cohort, except in a patient with alopecia areata. Periodontal manifestations such as oral ulcers, gingivitis and periodontitis have also been associated with LAD-1 [2]. In the present study, periodontal destruction of the permanent dentition was observed in a 21-year-old male patient and gingivitis in a 4-year-old male patient. The reason for the low frequency of periodontal findings in our cohort might be that most of the patients were in the infantile age group. In a study with 15 LAD-1 patients from Iran, diarrhea was present in five patients and hepatosplenomegaly was present in four patients [13]. Consistent with this study, diarrhea and hepatosplenomegaly were present in six and three patients, respectively, in our cohort.

In the study by De Rose et al., fungal infections were detected (A. fumigatus and C. parapsilosis) in two of eight patients with LAD-1 [14]. Also, Wolach et al. reported that fungal infections of varying frequency and severity were recorded in approximately three (17%) of 18 patients with LAD-1 [7]. In our LAD-1 cohort, 20% (n = 3) of the patients had fungal infections. IL-17-mediated immunity has a significant role in protection from fungal infections, and IL-17 is abnormally up-regulated in patients with LAD-1 [15,16]. Severe periodontal disease and gingiva inflammation in the patients has also been associated with elevated IL-17 levels [17]. IL-17 induction modulates protection against fungal infections via proinflammatory cytokines, secretion of anti-microbial proteins with candidacidal activities and neutrophil production and migration [15]. As β2 integrin-dependent neutrophil migration is impaired in patients with LAD-1 and anti-microbial proteins alone are not sufficient for fungal clearance, patients with LAD-1 may present with fungal infections.

Wolach et al. reported that 11 of 18 patients (61%) with LAD-1 had chronic anemia [7]. In our cohort, 60% (n = 9) of the patients had anemia, possibly related to chronic infections. Most of our patients (n = 10, 67%) had thrombocytosis, which may have occurred secondarily to an underlying inflammatory condition.

We have characterized nine distinct variants in the ITGB2 gene in 13 patients with LAD-1, two of which have not been reported previously. Interestingly, four unrelated patients from Syria had a novel c.305_306delAA mutation that might be a founder effect for LAD-1 patients of Syrian origin. A homozygous novel c.779_786dup mutation was identified in one patient; the CD18 expression in this patient was 1%. Homozygous c.382G>A, c.382G>T, c.533C>T, c.562C>T, c.817G>A and compound heterozygous c.1777C>T and c.533C>T mutations identified in seven patients in our cohort have been reported previously [18–23]. Large chromosomal deletions, including a whole ITGB2 gene deletion and exonic deletions, were reported in several studies [3,23–26]. In our cohort, one patient harbored a large deletion (exon 12_14), which is probably the same as one reported previously [3]. The patient homozygous for the large exon 12_14 deletion had no detectable CD18 expression.

Cabanillas et al. reported a case of LAD-1 in a 4-year-old girl with CD18 expression levels exceeding 30%, but with a completely non-functional protein [27]. In our cohort, CD18 expression on the cell surface of a patient homozygous for the novel c.305_306delAA variant was absent (clone: L130; BD Biosciences). Interestingly, in repeated testing of the same patient, CD18 expression was found at higher expression levels (clone: 7E4; Beckman Coulter, Brea, California, USA). This variability is related to characteristics of monoclonal antibody binding and incomplete protein expression. However, the clinical features and genetic findings of the disease were consistent with LAD-1. In any case, CD11a, CD11b and CD11c expression on the cell surface of the patient was 0, 1 and 7%, respectively. Conversely, in the other three homozygous patients with the novel c.305_306delAA variant, CD18 expression was only 1%. It must be considered that the results of flow cytometry analysis of CD18 expression in different laboratories may vary. CD18 expression level should be analyzed repeatedly using different antibody clones in patients with clinical findings compatible with LAD-1 and considering the genetic cause and the truncated protein structure.

Gene therapy trials for patients with LAD-1 are ongoing [28], but HSCT is the only curative treatment option of LAD-1 currently available. HSCT was successful for two of four patients in our study. It is planned for three (20%) patients who have matched related donors. Six (40%) of the patients have no matched related donor, and these patients have been followed carefully at our centers since their first admission.

We must consider leukocyte and neutrophil counts of patients presenting with delayed detachment of the umbilical cord, omphalitis and severe infections. Additionally, characterization of CD18 levels by flow cytometry analysis is essential for diagnosis, but molecular characterization of LAD-1 is also important in terms of disease confirmation, therapeutic approach, prognosis and patient follow-up. Early diagnosis of the patients is critical in the management of the disease, and genetic evaluation is essential for family studies and genetic counseling.

In conclusion, we report the clinical manifestations, immunological findings, treatment and outcome of 15 patients diagnosed with LAD-1. Parental consanguinity was extremely high in the current study. Also, delayed umbilical cord detachment was observed more frequently than in
previous reports. Additionally, two novel mutations were reported, extending the molecular spectrum of LAD-1.

ACKNOWLEDGEMENTS
The authors thank the patients and their families for their collaboration and participation. This project was supported by Scientific and Technological Research Council of Turkey (Project Number: 315S125).

CONFLICTS OF INTEREST
The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS
All authors were involved in drafting the manuscript or revising it critically for intellectual content; all authors approved the final version to be published. I.Y. performed experiments, collected the data and wrote the paper. B.O. performed experiments and contributed to data collection. C.T. and S.O.H. contributed to data or analysis tools. H.N.B., E.S.A. and S.E. contributed to follow-up of the patients. S.C., S.S.K. and O.K. contributed to data collection and follow-up of the patients. K.v.L. performed genetic analysis. D.R. supervised the study and corrected the manuscript. D.C. contributed to data collection and follow-up of the patients and supervised the study. I.T. conceived, designed and supervised the study.

ETHICAL APPROVAL
The study complied with the Declaration of Helsinki and was approved by the ethics committee of Hacettepe University.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding authors, I.Y. and I.T.

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How to cite this article: Yaz I, Ozbek B, Bildik HN, Tan C, Oskay Halaci S, Aytekin ES, et al. Clinical and laboratory findings in patients with leukocyte adhesion deficiency type I: A multicenter study in Turkey. Clin Exp Immunol. 2021;206:47–55. https://doi.org/10.1111/cei.13645