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CASE REPORT

Severe ITGB2-Associated Leukocyte Adhesion Deficiency Type 1 in Two Siblings : Early Family-Based Diagnosis and Clinical Variability

Déficit d'adhésion leucocytaire de type 1 sévère associé à ITGB2 chez deux membres d'une même fratrie : diagnostic précoce par dépistage familial et variabilité Clinique

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KEYWORDS

Leukocyte Adhesion
Deficiency type 1 LAD-
I ;
ITGB2 ;
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Abstract

Introduction: Leukocyte Adhesion Deficiency Type 1 (LAD-I) is a rare autosomal recessive inborn error of immunity caused by pathogenic variants in the ITGB2 gene encoding CD18. Severe forms are associated with impaired leukocyte migration, recurrent infections, persistent neutrophilic leukocytosis, and high mortality in the absence of curative treatment.

Case Presentation: We report two siblings from a consanguineous family with severe ITGB2-associated LAD-I. The older sibling was diagnosed at 3 months of age after presenting with a severe necrotic perineal lesion and subsequently developed recurrent gingivostomatitis, bronchiolitis, and osteoarticular involvement. Following identification of the index case, the younger sibling was diagnosed much earlier, at 10 days of life, after developing omphalitis. She later experienced recurrent necrotic perineal lesions and acute gastroenteritis. Both patients exhibited persistent leukocytosis with neutrophilia and markedly reduced CD18 expression (0–2%) on flow cytometry, consistent with severe LAD-I. Whole-exome sequencing identified the same previously reported homozygous pathogenic ITGB2 variant (NM_000211:c.119_128del; p.G40Afs*7) in both siblings. Despite sharing an identical molecular defect and severe

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immunophenotype, the two children displayed distinct clinical manifestations, illustrating intrafamilial phenotypic variability.

Conclusion: This report highlights the importance of family-based screening for early diagnosis of LAD-I and emphasizes that the absence of markedly delayed umbilical cord separation should not exclude the diagnosis. Early immunophenotypic and molecular confirmation remains essential to optimize management and facilitate timely access to curative therapies, including hematopoietic stem cell transplantation (HSCT) and emerging gene therapy approaches.

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Résumé

Introduction: Le déficit d'adhésion leucocytaire de type 1 (Leukocyte Adhesion Deficiency type 1, LAD-I) est une erreur congénitale rare de l'immunité autosomique récessive causée par des variants pathogènes dans le gène ITGB2 codant pour CD18. Les formes sévères sont associées à une altération de la migration leucocytaire, des infections récurrentes, une leucocytose neutrophile persistante et une mortalité élevée en l'absence de traitement curatif.

Observations: Nous rapportons les cas de deux enfants issus d'une famille consanguine atteints d'un LAD-I sévère associé à une anomalie d'ITGB2. Le frère aîné a été diagnostiqué à l'âge de 3 mois à la suite d'une lésion périnéale nécrotique sévère, puis a présenté des épisodes récurrents de gingivostomatite, une bronchiolite et une atteinte ostéoarticulaire. Après identification du cas index, sa sœur cadette a bénéficié d'un diagnostic beaucoup plus précoce, dès l'âge de 10 jours, devant une omphalite. Son évolution a été marquée par des lésions périnéales nécrotiques récidivantes et un épisode de gastroentérite aiguë. Les deux patients présentaient une hyperleucocytose persistante avec neutrophilie ainsi qu'une expression fortement diminuée de CD18 (0-2 %) à la cytométrie en flux, compatible avec une forme sévère de LAD-I. Le séquençage de l'exome a mis en évidence chez les deux enfants le même variant pathogène homozygote ITGB2 précédemment rapporté (NM_000211.119_128del ; p.G40Afs*7). Malgré un défaut moléculaire identique et un immunophénotype sévère comparable, les deux enfants présentaient des manifestations cliniques distinctes, illustrant une variabilité phénotypique intrafamiliale.

Conclusion: Cette observation souligne l'importance du dépistage familial pour un diagnostic précoce du LAD-I et rappelle que l'absence de retard marqué de chute du cordon ombilical ne doit pas faire écarter ce diagnostic. La confirmation immunophénotypique et moléculaire précoce demeure essentielle afin d'optimiser la prise en charge et de faciliter l'accès aux traitements curatifs, notamment la transplantation de cellules souches hématopoïétiques (HSCT) et les nouvelles approches de thérapie génique.

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Introduction

Leukocyte adhesion deficiency (LAD) represents a rare group of inherited errors of

immunity (IEI) that is characterized by the absence of adhesion molecules on leukocytes, preventing them from migrating to the site of

infection/inflammation [1]. Based on the site of defect throughout the activation cascade, four different LAD types have been reported, LAD I- IV [2].

Leukocyte adhesion deficiency type I (LAD-I), first described in 1970 [3], affects approximately 1 in 1 million individuals globally [4,5]. It is a rare autosomal recessive inborn error of immunity caused by damaging variants in ITGB2, which encodes the $\beta 2$ common integrin subunit (CD18) [4]. CD18 deficiency prevents leukocyte surface expression and heterodimerization with α integrin subunits (CD11a, CD11b, CD11c, and CD11d), which are essential for leukocyte (particularly neutrophil) endothelial adhesion and extravasation to sites of inflammation and injury [6,7]. CD18 is a subunit of two heteromeric proteins, lymphocyte function-associated antigen 1 (composed of CD18 and CD11a), a primary regulator of endothelial adhesion, and Macrophage-1 antigen (composed of CD18 and CD11b), which mediates intravascular crawling on endothelial surfaces before extravasation [8].

Based on CD18 expression on neutrophils, LAD-I was sub-classified into severe: $< 2\%$ (LAD-I $^{\circ}$); moderate: $2-30\%$ (LAD-I $-$); and mild: $\geq 30\%$ (LAD-I $+$) [9]. Patients with severe LAD-I, are at high risk of life-threatening infections and early mortality if curative treatment is not performed [10,11].

LAD-I often manifests with umbilical-cord complications (e.g., delayed separation and omphalitis), frequent lifethreatening infections, impaired wound healing, persistent leukocytosis, and hyperinflammatory complications, including cutaneous lesions and periodontitis [4,12–14].

Flow cytometry remains the cornerstone of diagnosis, demonstrating absent or markedly decreased expression of CD18 and associated CD11 molecules on leukocytes [11,15]. Molecular confirmation by ITGB2 sequencing is recommended whenever available, as it allows confirmation of the diagnosis, family counselling, prenatal diagnosis, and better understanding of genotype–phenotype correlations [10,11].

For many years, allogeneic hematopoietic stem cell transplantation (HSCT) has represented the only curative treatment for severe LAD-I [10,11]. However, the therapeutic landscape has recently changed with the development of autologous lentiviral gene therapy. In a recent clinical trial, lentiviral vector-mediated gene therapy for severe LAD-I showed sustained CD18 expression, immune reconstitution, and favorable survival outcomes, opening a new era in the management of this rare but life-threatening disorder [16,17].

Herein, we report two siblings from a consanguineous family with severe ITGB2-associated Leukocyte Adhesion Deficiency Type 1, confirmed by both flow cytometric analysis and molecular characterization. By describing their

clinical course, immunological profile, and shared pathogenic truncating ITGB2 mutation, we aim to illustrate the early warning signs of LAD-I, emphasize the contribution of family screening to prompt diagnosis, and explore the genotype–phenotype relationship underlying the intrafamilial clinical variability observed in these patients.

Case 1

A 3.5-year-old boy, the first child of a second-degree consanguineous couple. He was born at term by cesarean section following a pregnancy complicated by maternal gestational hypertension and a history of primary infertility. His birth weight was 2800 g, and the APGAR score was 8/10. Umbilical cord separation occurred on day 15 of life. Growth and psychomotor development were normal, and routine immunizations were administered according to the national immunization schedule.

The clinical history began at 20 days of age with a prolonged hospitalization for ascites associated with portal hypertension secondary to a portohepatic block. Extensive investigations failed to identify a specific etiology, and the patient improved following antibiotic therapy.

At three months of age, he developed a severe necrotic perineal ulceration requiring hospitalization. Given the unusual severity of the lesion and the marked inflammatory response, an immunological evaluation was performed. Flow cytometric analysis demonstrated complete absence of CD18 expression, establishing the diagnosis of severe Leukocyte Adhesion Deficiency Type 1 (LAD-I). Antimicrobial prophylaxis with trimethoprim-sulfamethoxazole was subsequently initiated.

During follow-up, the patient experienced multiple infectious complications. At six months of age, he was hospitalized for moderate bronchiolitis. Later, he developed recurrent episodes of gingivostomatitis, including a severe herpetic form at the age of 2 years and 8 months requiring prolonged hospitalization and treatment with acyclovir and broad-spectrum antibiotics. Additional episodes were managed on an outpatient basis. At the age of three years, another episode of gingivostomatitis was associated with diarrhea and vomiting. More recently, at 3.5 years of age, he presented with right knee arthritis occurring after minor trauma and requiring antibiotic treatment.

At the most recent evaluation, physical examination showed a child in good general condition with preserved growth parameters. Laboratory investigations revealed persistent leukocytosis ($27.51 \times 10^9/L$) associated with neutrophilia and lymphocytosis. Flow cytometry confirmed severe CD18 deficiency with a residual expression of 1.58%.

Genetic analysis performed by whole-exome sequencing identified a homozygous pathogenic variant in the ITGB2 gene encoding the CD18 β -integrin subunit, namely ITGB2 (CD18) ; NM_000211 ; c.119_128del ; p.G40Afs*7 deletion. This 10-base pair deletion generates a premature translational stop codon, resulting in truncation of the encoded protein and loss of normal CD18 function. The mutation had previously been reported in association with LAD-I and was considered disease-causing. These molecular findings confirmed the diagnosis of severe LAD-I and were fully consistent with the patient's immunophenotypic profile. In view of the severe clinical phenotype and the profound CD18 deficiency, hematopoietic stem cell transplantation was considered as a curative therapeutic option.

Case 2

An 18-month-old girl, the younger sister of Case 1, was born at term by cesarean section following an uneventful pregnancy. Her birth weight was 3700 g, and the APGAR score was 9/10. Umbilical cord separation occurred on day 14 of life. Growth and neurodevelopment were appropriate for age.

Unlike her older brother, the presence of a previously diagnosed sibling with severe CD18 deficiency prompted early clinical suspicion and immunological investigation. At 10 days of age, she developed severe omphalitis requiring prolonged hospitalization. Given the strong family history of primary immunodeficiency, an early immunological work-up was undertaken and demonstrated markedly reduced CD18 expression, consistent with severe LAD-I.

The subsequent clinical course was characterized by recurrent infectious and inflammatory complications, predominantly affecting the skin and soft tissues. At the age of 1 month and 18 days, she developed extensive perineal necrosis requiring hospitalization for approximately one month. Similar episodes recurred at three and four months of age. At one year of age, she was hospitalized for a febrile episode of acute gastroenteritis requiring prolonged inpatient management.

At the latest follow-up evaluation, physical examination revealed a child in good general condition with preserved nutritional status and normal growth parameters. Laboratory investigations demonstrated marked leukocytosis ($32.98 \times 10^9/L$), persistent neutrophilia, thrombocytosis, and mild microcytic anemia. Flow cytometric analysis revealed residual CD18 expression of approximately 2%, confirming a severe form of LAD-I.

Whole-exome sequencing identified the same homozygous pathogenic ITGB2 variant, ITGB2 (CD18) ; NM_000211 ; c.119_128del ; p.G40Afs*7 deletion, as detected in her older brother. This 10-base pair deletion results in a premature stop

codon and predicted truncation of the CD18 protein. The variant has previously been reported and is recognized as pathogenic. The molecular findings therefore confirmed the diagnosis of severe LAD-I and established the genetic basis of the disease within this family.

Despite sharing the same pathogenic ITGB2 mutation and a similarly severe immunological phenotype, the patient exhibited a clinical presentation dominated by neonatal omphalitis and recurrent necrotic skin lesions, contrasting with the more prominent mucosal and osteoarticular manifestations observed in her brother. Owing to the severity of the immunological defect, she was also considered a candidate for hematopoietic stem cell transplantation.

A comparative summary of the clinical presentation, laboratory findings, immunophenotypic profile, and molecular characteristics of both patients is provided in Table 1.

Table 1. Clinical, Hematological, Immunological, and Molecular Characteristics of Two Siblings with Severe Leukocyte Adhesion Deficiency Type 1 (LAD-I)

Characteristics	Case 1	Case 2
Sex	Male	Female
Consanguinity	Yes	Yes
Age at symptom onset	20 days	10 days
Age at diagnosis	3 months	10 days
Omphalitis	No	Yes
Necrotic perineal lesions	Yes	Yes (recurrent)
Recurrent mucocutaneous infections	Severe recurrent gingivostomatitis	No
Respiratory infections	Bronchiolitis	Not reported
Gastrointestinal manifestations	Diarrhea, vomiting, gingivostomatitis	Febrile acute gastroenteritis
Osteoarticular involvement	Right knee arthritis	No
Persistent leukocytosis	Yes ($27.5 \times 10^9/L$)	Yes ($32.9 \times 10^9/L$)
Neutrophilia	Yes	Yes
Anemia	Yes (Hb 9.3 g/dL)	Yes (Hb 8.8 g/dL)

Thrombocytosis	No	Yes (634 × 10 ⁹ /L)
CD18 expression (%)	0% initially, then 1.58%	2%
LAD-I phenotype	Severe LAD-I (LAD-I ⁰)	Severe LAD-I (LAD-I ⁰)
Molecular diagnosis	Homozygous pathogenic ITGB2 variant	Same homozygous pathogenic ITGB2 variant
Genetic variant	NM_000211: c.119_128del; p.G40Afs*7	NM_000211: c.119_128del; p.G40Afs*7
Candidate for HSCT	Yes	Yes

Discussion

Leukocyte Adhesion Deficiency Type 1 (LAD-I) is a rare autosomal recessive inborn error of immunity with only around 300 cases published before 2018 [14]. It results from pathogenic variants in the ITGB2 gene, which encodes CD18, the common β2-integrin subunit expressed on leukocytes. Consequently, severe CD18 deficiency leads to profound impairment of neutrophil extravasation despite marked peripheral neutrophilia, predisposing affected children to recurrent and often life-threatening bacterial and fungal infections [10,15].

Consanguinity and familial occurrence of LAD-I

The two siblings described in our report exhibited several classical hallmarks of severe LAD-I, including early-onset infectious complications, persistent leukocytosis with neutrophilia, severe cutaneous inflammatory lesions, and markedly reduced CD18 expression. Both children were born to a consanguineous couple, a well-recognized risk factor for autosomal recessive inborn errors of immunity (IEIs), particularly in North African and Middle Eastern populations where consanguinity remains highly prevalent [10,14].

Similarly, among the 34 Egyptian patients with LAD-I reported by Saad et al. [18], 88% were born to consanguineous families, underscoring the substantial burden of autosomal recessive IEIs in highly consanguineous populations such as those of Egypt and Pakistan [19,20]. In the Turkish cohort [21] comprising 15 patients with LAD-I, 14 (93%) were born to consanguineous parents, highlighting the prominent role of autosomal recessive inheritance in the disease and emphasizing the contribution of consanguineous marriages to the occurrence of LAD-I.

Notably, a family history of similarly affected siblings was documented in 49% of patients in the Egyptian cohort [18]. However, only two index cases were diagnosed with LAD-I before the death of an affected sibling, a finding that is consistent with observations from other published series [9,20]. In contrast, the diagnosis established in the older sibling in our family enabled prompt immunological investigation and early molecular confirmation in his younger sister shortly after the onset of symptoms. This observation highlights the critical value of family-based screening and genetic counseling in facilitating earlier diagnosis and timely therapeutic intervention in families affected by LAD-I.

Diagnostic delay and the impact of Family-Based Screening

In our series, LAD-I was diagnosed in the older sibling at the age of three months following the occurrence of a severe necrotic perineal lesion. In contrast, the diagnosis in his younger sister was established much earlier, at only 10 days of life, shortly after the onset of omphalitis. This reduction in diagnostic delay was largely attributable to heightened clinical awareness and family-based screening after identification of the index case.

Similarly, Saad et al. [18] reported that 97% of patients presented during the first year of life, with a median diagnostic delay of 2.3 months in recent years, reflecting improved recognition of primary immunodeficiencies. In the Turkish cohort [21], the median age at diagnosis was 3 months, comparable to that observed in our index case. This reflects the improved awareness of many developing countries' pediatricians, as currently witnessed in Egypt and Pakistan [20].

Consistent with previous reports, both of our patients exhibited the severe LAD-I⁰ phenotype, characterized by markedly reduced CD18 expression (<2%) and early-onset infectious manifestations. This severe phenotype was also predominant in the Egyptian cohort [18] and was associated with substantial morbidity and mortality, emphasizing the importance of early recognition and timely referral for curative treatment [1,9,22,23].

Clinical spectrum

Delayed umbilical cord separation is traditionally considered a hallmark feature of LAD-I. Interestingly, neither child demonstrated markedly prolonged cord separation, with cord detachment occurring at approximately two weeks of life. This observation highlights an important clinical message: the absence of delayed cord separation should not exclude the diagnosis of LAD-I when other warning signs are present. Indeed, recent analyses of large LAD-I cohorts have demonstrated substantial phenotypic heterogeneity, and several patients with severe CD18 deficiency may initially present with recurrent skin infections, omphalitis, perineal

ulcerations, or severe periodontal disease without the classical delayed cord separation described in early reports [10,11].

Consistent with these observations, umbilical stump disease and/or skin and soft tissue infections constituted the initial clinical manifestations in all patients included in the Egyptian cohort [18], as well as in several previously published series [9,15,20–22,24–28]. Similarly, delayed umbilical cord separation was observed in five (62.5%) of eight patients in an Italian study, whereas omphalitis was reported in only one patient [29].

In contrast, signs of omphalitis were observed in approximately half of the patients in the Turkish cohort [21], and the frequency of delayed umbilical cord separation was higher than that reported in the Italian series [29].

Taken together, these findings illustrate the marked clinical variability of LAD-I across different populations and emphasize that, although delayed umbilical cord detachment remains an important diagnostic clue, its absence should not preclude the diagnosis when other suggestive clinical features are present, as illustrated by both patients in our report.

Necrotic perineal lesions represented a prominent manifestation in both children. Severe skin ulcerations and pyoderma gangrenosum-like lesions have increasingly been recognized as characteristic inflammatory complications of LAD-I. The pathophysiology extends beyond defective antimicrobial defense and involves dysregulated inflammatory pathways, particularly excessive IL-23/IL-17 signaling resulting from impaired neutrophil trafficking. This mechanism may explain the paradoxical coexistence of immunodeficiency and severe inflammatory tissue destruction observed in affected patients [10,14]. Beyond these early inflammatory skin manifestations, surviving patients may develop a broader spectrum of autoinflammatory complications with advancing age. In the Egyptian cohort [18], autoinflammatory manifestations were predominantly represented by severe periodontitis, premature tooth loss, and enteropathy. Similar findings have been reported in several studies identifying periodontal disease as the most frequent manifestation among older LAD-I patients who had not undergone HSCT [30,31].

Persistent leukocytosis with neutrophilia was a consistent finding in both of our patients, with leukocyte counts of $27.5 \times 10^9/L$ and $32.9 \times 10^9/L$, respectively. This hematological pattern is considered a hallmark laboratory feature of LAD-I and reflects the inability of neutrophils to extravasate and migrate effectively to sites of infection, resulting in their accumulation within the peripheral circulation [10,14].

Consistent with our observations, all patients in an Iranian cohort of 13 individuals with LAD-I presented with leukocytosis and neutrophilia [32]. Similarly, in another Iranian study including 15 patients, persistent leukocytosis ranged from 12.2 to $91 \times 10^3/\mu L$ (median: $29.1 \times 10^3/\mu L$), with neutrophil ratio of 31% - 90% [33].

Comparable findings were reported in the Turkish cohort, where leukocytosis was observed in 14 of 15 patients (93%), while leukocytosis with neutrophil predominance was documented in 11 patients (73%). The median leukocyte and neutrophil counts were $44.7 \times 10^3/\mu L$ and $29.3 \times 10^3/\mu L$, respectively [21].

Taken together, these observations further support persistent neutrophilic leukocytosis as one of the most characteristic laboratory hallmarks of LAD-I and an important diagnostic clue, particularly when associated with recurrent infections and impaired wound healing.

In addition to leukocytosis, both of our patients exhibited mild anemia. This finding has been frequently reported in LAD-I cohorts, with prevalence rates ranging from 67% to 85% in previous studies [18,19,21]. Anemia in LAD-I is generally attributed to chronic inflammation, recurrent infections, prolonged hospitalizations, and reduced nutritional intake, all of which may contribute to impaired erythropoiesis and iron homeostasis.

Interestingly, thrombocytosis was observed in our second patient. Similar findings have been reported in LAD-I cohorts and are generally considered a reactive phenomenon secondary to chronic inflammation and recurrent infectious episodes. In the Turkish cohort, thrombocytosis was documented in 10 patients (67%), further supporting the association between persistent inflammatory activity and elevated platelet counts in LAD-I [21].

Intrafamilial phenotypic variability and Genotype-Phenotype correlation in ITGB2-Associated LAD-I

One of the most remarkable findings in our report is the intrafamilial phenotypic variability observed despite a shared familial background and a similarly severe immunological phenotype. While the older sibling developed a broader spectrum of manifestations, including recurrent gingivostomatitis, respiratory infections, and osteoarticular involvement, the younger sibling predominantly presented with neonatal omphalitis and recurrent necrotic cutaneous lesions. These observations illustrate the complexity of genotype-phenotype relationships in LAD-I and support previous reports describing considerable clinical heterogeneity among patients with the same molecular defect [10].

The molecular findings were fully concordant with the severe immunophenotype observed in both patients, as truncating ITGB2 mutations are

typically associated with absent or markedly reduced CD18 expression and profound impairment of leukocyte adhesion and migration [11,14]. Nevertheless, accumulating evidence suggests that disease severity and clinical expression in LAD-I correlate more closely with residual CD18 expression than with the specific underlying mutation [11,14]. The phenotypic differences observed between our patients may therefore reflect the influence of additional factors, including environmental exposures, infectious burden, epigenetic regulation, microbiome composition, and other genetic modifiers [10,34]. Furthermore, the younger age of the second patient may partly explain her less diversified clinical presentation, as some characteristic manifestations of LAD-I, particularly severe periodontal disease and chronic inflammatory complications, often emerge later during childhood [10,14].

Immunophenotypic and Molecular Confirmation of Disease

Flow cytometric assessment of CD18 remains the cornerstone of LAD-I diagnosis. In our patients, CD18 expression ranged from 0% to 2%, consistent with severe LAD-I. Previous studies have shown that residual CD18 expression below 2% is strongly associated with severe infections, increased hospitalization rates, and poor clinical outcomes [10,11]. The profound CD18 deficiency observed in both siblings was therefore consistent with their severe clinical phenotype and supported consideration of definitive curative therapy.

ITGB2 gene, is located on chromosome 21q22.3 (OMIM *600,065), where a range of mutations have been identified in patients with LAD-I. A few mutations could cause a nonfunctional but normally expressed CD18 molecule. Most ITGB2 mutations lead to reduced/null expression of β 2-integrins on the leukocyte surface [35].

In our family, whole-exome sequencing identified the same previously reported homozygous pathogenic ITGB2 (CD18) variant in both siblings (NM_000211: c.119_128del; p.G40Afs*7). This 10-base pair deletion causes a frameshift and premature stop codon, resulting in truncation of the CD18 protein and severe impairment of β 2-integrin function. The mutation has previously been reported in association with LAD-I and is considered pathogenic according to current molecular diagnostic criteria [10,14].

Prognosis and Curative Treatment Perspectives

Both of our patients are currently alive and remain under regular follow-up while awaiting definitive treatment. Given the severe phenotype associated with profound CD18 deficiency, their long-term prognosis largely depends on timely access to curative hematopoietic stem cell transplantation (HSCT).

This is particularly relevant in light of the high mortality reported in the Egyptian cohort, where

58% of patients died, largely reflecting disease severity and limited access to early curative HSCT [18]. In contrast, Bakhtiar et al. reported a 3-year post-transplant survival rate of 84% among LAD-I patients, with the best outcomes observed following sibling, matched related, or matched unrelated donor transplantation, highlighting the critical role of early HSCT in improving survival [9,14,20,36].

Historically, HSCT has been regarded as the standard curative treatment for severe LAD-I. Early transplantation significantly improves survival and reduces infectious complications. However, HSCT remains limited by donor availability, transplant-related toxicity, graft failure, and graft-versus-host disease [10,14,36].

The therapeutic landscape of LAD-I has recently undergone a major transformation with the emergence of autologous lentiviral gene therapy. In the landmark phase I/II study published by Booth and colleagues in 2025, nine children with severe LAD-I received autologous CD34+ hematopoietic stem cells transduced with a lentiviral vector carrying a functional ITGB2 gene. The investigators reported sustained CD18 expression, resolution of neutrophilia, marked reduction in infection-related hospitalizations, and 100% HSCT-free survival at one year after treatment, supporting gene therapy as a promising curative option for severe LAD-I [16].

Although limited by the small number of patients and the absence of long-term follow-up data, our report provides a comprehensive clinical, immunophenotypic, and molecular characterization of two siblings carrying the same homozygous pathogenic ITGB2 variant. The markedly earlier diagnosis achieved in the younger sibling further highlights the value of family-based screening and genetic counseling in facilitating timely recognition of affected relatives.

Conclusion

In conclusion, this familial case report highlights the diagnostic and clinical challenges posed by severe Leukocyte Adhesion Deficiency Type 1. Despite sharing the same homozygous pathogenic ITGB2 mutation and a similarly profound CD18 deficiency, the two siblings exhibited distinct clinical presentations, underscoring the intrafamilial phenotypic variability that may characterize this disorder.

Our observations demonstrate the value of early family-based screening, which enabled substantially earlier diagnosis in the younger sibling and facilitated timely initiation of appropriate management. They also emphasize that the absence of classical manifestations, such as delayed umbilical cord separation, should not deter clinicians from considering LAD-I in infants presenting with recurrent infections, omphalitis,

severe skin lesions, and persistent neutrophilic leukocytosis.

Finally, in the era of expanding curative options, including HSCT and emerging gene therapy approaches, early recognition and molecular confirmation of LAD-I are essential to improve survival and long-term outcomes. Further studies are needed to better elucidate the factors underlying phenotypic variability among patients carrying identical ITGB2 mutations.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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