CASE REPORT

Leucocyte adhesion deficiency type 1 with developmental delay secondary to CMV infection and filiation questions

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SUMMARY

Leucocyte adhesion deficiency (LAD) is a group of rare autosomal recessive (<1:1 000 000 births) inherited disorders characterised by immune deficiency and peripheral neutrophilia. Three types of LAD syndrome have been distinguished. LAD type 1 (LAD-I) is the most common. It results from a mutation in the integrin β 2 (ITGB2) gene that codes the ITGB subunit (CD18 antigen). Since 1970, it has been reported in more than 300 children worldwide. It is characterised by delayed separation of the umbilical cord, recurrent bacterial and fungal infections, defective wound healing, blood neutrophilia and a high mortality rate at an early age. We report the second fatal case of an infant with LAD-I diagnosed in Chile, with developmental delay associated with a congenital cytomegalovirus infection. CD18/CD11 expression was normal. Genetic analysis of CD18 revealed a homozygous mutation in ITGB2, viz. c.1835G>T; p.C612F, and led us to suspect a biological parent other than the legal father and, therefore, an unwanted social situation.

and her legal father were 15 and 26 years old, respectively. They lived in extreme poverty. Family history at that moment was unremarkable.

Laboratory tests at the time of admission revealed leucocytosis with neutrophil predominance (51 300/mm³—68%) and high C reactive protein (10.7 mg/dL). Intravenous oxacillin was started and maintained for 14 days, with a good clinical response. The patient was discharged in good clinical condition 2 days after completing antibiotic treatment. Two months later, she was re-admitted with hyperthermia, extensive frontal scalp cellulitis and marked neutrophilia. She was treated again with oxacillin with good clinical results, although she never reached a normal white cell count (table 1).

At that time, she also showed psychomotor delay, failure to thrive, hearing loss, bilateral dislocated hips and multidirectional nystagmus without ocular fixation. Funduscopy examination showed pale retinas and absence of cilio-palpebral reflexion. A clinical diagnosis of LAD with developmental delay was made and an extensive workup was performed.

BACKGROUND

We report the second case of an infant with leucocyte adhesion deficiency (LAD) type 1, with a novel mutation on the integrin β 2 (ITGB2) gene, diagnosed in Chile. The family reported non-consanguinity at first, but genetic testing strongly suggested otherwise. Furthermore, the mother revealed an extreme form of hidden inbreeding that prompted us to adopt legal and sanitary actions to protect and prevent future damage to other members of the family. The patient also presented with developmental delay that in the context of an LAD phenotype would suggest LAD II diagnosis. Interestingly, this later diagnosis was ruled out and her neurological damage was attributed to a congenital CMV infection probably also related to her ITGB2 gene mutation.

CASE PRESENTATION

A 55-day-old female baby from a rural insular area near Puerto Montt (Isla Huar—Cheuquear), Chile, was admitted to the paediatric ward of our hospital with *Staphylococcus aureus* omphalitis. The maternal family was from Mechuque, a small rural island near Quemchi—Chiloé, Chile. She was born at term, showed no obvious dysmorphism and presented no neonatal complications. Birth weight, height and head circumference were 3 kg, 49 cm and 34 cm, respectively. The Apgar score was 9-9. Her umbilical cord detached late, at 1 month of age. Her mother

INVESTIGATIONS

Brain CT scan was normal. Brain MRI showed extensive cerebral sulci. Abdominal, renal and bladder ultrasound scans were normal. Pelvic radiography showed bilateral dislocation of hips. Ophthalmological evaluation revealed hypoplasia of optic nerves. The ENT (ear, nose and throat) evaluation showed normal anatomy of upper airways, vocal cord comitis and an open upper oesophageal sphincter related to gastro-oesophageal reflux disease. Auditory brainstem response audiometry (ABR) revealed hearing loss of over 70 decibels in the right ear and 30 decibels in the left ear. The karyotype was normal. T4, thyroid-stimulating hormone (TSH), creatinine kinase, ammonia and lactic acid were normal. Two-dimensional echocardiography with colour Doppler was normal. Blood mass spectrophotometry screening showed a non-specific increase of alanine and tyrosine. IgG for toxoplasmosis was <6.5 and rubella IgG was <5 (negative). Cytomegalovirus (CMV) IgM was reactive and CMV IgG was 3.09 (normal <1.1). Blood type was O IV Rh (+); the patient tested negative for Bombay phenotype.

Lymphocyte populations by flow cytometry: CD3, CD4, CD8, CD19, CD56 and CD4/CD8, serum immunoglobulin assay, complement titres, basal and stimulated polymorphonuclear neutrophils respiratory burst with phorbol myristate acetate, basal and

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Table 1 Haematological parameters and CRP

	Hct (%)	Hb (g/dL)	WCC ($\times 10^3$ mm ³)	Bands (%)	PMN (%)	Ly (%)	Mo (%)	Platelets ($\times 10^3$ mm ³)	CRP (mg/dL)
04/15/09	27.3	9.8	52	–	68.9	23.9		379	10.7
04/21/09	24.8	8.6	39	6.0	46.0	38.0	8.0	406	1.0
06/26/09	32.8	10.8	53	–	55.5	37.6	7.8	401	–
07/20/09	25.7	7.9	67	10.0	56.0	29.0	5.0	627	13.0
08/13/09	25.2	7.9	64	0.0	69.3	20.9	8.8	481	26.7
08/25/09	22.9	7.1	76	–	74.6	20.3	5.0	548	8.8
09/03/09	36.5	12.0	29	5.0	54.0	39.0	2.0	337	5.3
01/20/10	36.1	11.9	33	2.0	47.0	43.0	6.0	397	0.8
03/08/10	28.2	9.2	93	8.0	63.0	19.0	5.0	485	17.8
07/23/10	28.8	9.4	102	0.1	83.8	11.7	4.1	267	31.7
08/09/10	25.4	8.0	84	1.0	91.0	6.0	2.0	121	27.8
10/09/10	23.5	7.7	109	0.0	86.2	10.1	3.3	242	30.6

CRP, C reactive protein; Hb, haemoglobin; Hct, haematocrit; Ly, lymphocytes; Mo, monocytes; PMN, polymorphonuclear neutrophils; WCC, white cell count.

stimulated MIF, and liver and kidney function were normal. HIV serology was negative.

Flow cytometry was performed on a mononuclear cell population, showing normal results (table 2). The antibodies used for each integrin in the flow cytometry analysis are from Becton Dickinson. Only after requested authorisation for genetic testing did the parents reveal a history of the biological father not being the same as the legal father. The mother identified her older brother as being the biological father; the brother refused the test, so the DNA was extracted only from the patient and her mother. The pedigree provided by the mother revealed inbreeding with her brother. The mother stated that her parents are first cousins, although this could not be corroborated in the pedigree. Furthermore, the genogram showed unrecognised paternity in some generations (figure 1). We requested legal protection for the mother and daughter consisting of living in a foster home for ambulatory follow-up, and they received financial aid to build a small paediatric furnished bedroom in the house of the parents of the legal parent, diapers, and other items.

DNA samples were sent for genetic testing to the National Institutes of Health, Maryland (USA). They performed sequencing of the exons and flanking splice sites of ITGB2. A homozygous mutation was identified, c.1835-G>-T, resulting from the substitution of a phenylalanine for cysteine at amino acid 612 (p.C612F).

DIFFERENTIAL DIAGNOSIS

- ▶ Sepsis
- ▶ IRAK-4 deficiency
- ▶ Job syndrome
- ▶ Chronic granulomatous disease
- ▶ Myeloperoxidase deficiency
- ▶ Congenital disorders of glycosylation

- ▶ Leukemoid reaction in infants
- ▶ Other congenital coagulation disorders (particularly in LAD-III due to bleeding tendency)

OUTCOME AND FOLLOW-UP

Further clinical course was marked by successive and progressive infections by Gram-positive and Gram-negative bacteria: otitis, urinary, respiratory, skin infections and septicaemia despite prophylactic treatment with cotrimoxazole. Furthermore, the patient presented cutaneous candidiasis characterised by slow-healing lesions in the anterior cervical region and perianal area. The infections responded to therapy initially but relapsed 24 h after stopping therapy. She evolved with progressive failure to thrive up to cachexia. We considered the possibility of bone marrow transplantation, which is restricted by the limited availability of this treatment. At 18 months of age she presented severe acute obstructive type A influenza laryngitis, remaining with severe respiratory stridor. Nasofibrolaryngoscopy showed total paralysis of vocal cords with glottic lumen limitation, so a tracheostomy was performed. Flexible bronchoscopy also showed tracheobronchomalasia with persistent atelectasis of the right upper lobe. Three months later, she presented fulminant sepsis due to *Enterococcus faecalis*, *Klebsiella pneumoniae* and *Stenotrophomonas maltophilia* with no response to various second-line and third-line antimicrobials, including imipenem, vancomycin, ceftazidim and others. Her weight was 5 kg. Her case was discussed with the Ethics Committee, which suggested limitation of treatment, comfort measures and family nurturing. The patient finally died at home 7 days after discharge.

DISCUSSION

Genetic mutations that thwart CD18 expression or function can produce profound disruption in host defence.^{1 2} LAD-I (OMIM 116920) is a rare disease that should be suspected in any patient

Table 2 Flow cytometry in mononuclear cell population

Antigen	Case-control (child) Positive cells (%)	Case-control (child) IMF	Case-control (adult) Positive cells (%)	Case-control (adult) IMF	Patient Positive cells (%)	Patient IMF
CD18	100	178	100	124	100	167
CD11 a	100	326	100	275	100	320
CD11 b	100	492	100	813	100	497
CD11 c	100	178	100	156	100	167

Figure 1 Roman numerals correspond to generations, Arabic numerals to the present age and the letter 'M' in red means a single last name was repeated in both branches in all generations. The unknown father could be another family member.

whose umbilical cord presents delay in falling off, and who presents with recurrent severe infections. Infections are usually apparent from birth onward, and a common presenting infection is omphalitis with delayed separation of the umbilical cord (often beyond 21 days),^{3–9} as in our patient, although LAD-I may occur in patients without late detachment of the umbilical cord.^{10–11} Life-threatening infections such as septicaemia, bronchopneumonia and aseptic meningitis can occur. The most frequent microorganisms involved are *S. aureus*, Gram-negative enteric organisms and fungi. The seriousness of infections and complications is related to the severity of CD18 deficiency; cases with <1% expression compared with normal controls are clinically severe, whereas those with 2.5–10% expression are moderate to mild.¹² The diagnosis of LAD-I in our patient was based on typical clinical presentation, including delayed cord separation. Clinically, she presented a severe phenotype, but flow cytometric analysis of blood samples showed normal $\beta 2$ integrin expression, suggesting a severe functional deficiency of the $\beta 2$ integrins. We could not perform functional assays because they are not available in our country. For this reason, we decided to send DNA of the patient and her parents for sequence analysis to the NIH for genetic molecular testing. Only through testing we could get a history of strong inbreeding, because the infant had been legally registered as a biological daughter to the mother's current partner, and they did not give a history of consanguinity. Indeed, the true probable filiation and the potential incest were discovered as a result of performing genetic tests for LAD-I, confirming on the other hand that the primary health system has yet serious deficiencies in rural areas and it is necessary to teach and recognise the risk of consanguinity and its consequences in closed communities. In India, Iran and Arabic countries, with a very high rate of

consanguineous marriages in certain communities (as also seen in rural insular areas in Chiloe-Chile), a relatively higher frequency of this recessive disorder is reported.^{12–19}

Until 2012, 201 gene mutations in ITGB2 have been identified (86 different ones). The publications by van de Vijver *et al* provide the most comprehensive summary of LAD (LAD-I, LAD-II and LAD-III) to date.^{5–6} In the present case, a homozygous mutation (p.C612F) of the ITGB2 gene was detected, confirming diagnosis. While this mutation has not been previously reported, it occurs at one of the conserved cysteines within the cysteine-rich domain. There is a reported case by Fiorini of a different mutation affecting the same amino acid.⁷ That patient, unlike our case, presented with a moderate and consistent flow cytometry phenotype. The first case notified in South America was a 4-month-old male infant, the only child of consanguineous parents from Santiago-Chile. The diagnosis of LAD-I was based on clinical findings, and a flow cytometry analysis detected that the CD11 and CD18 levels were low. The patient died at the age of 4 years because of severe sepsis. As in our case, a bone marrow or stem cell transplant option was not available.^{20–24}

Another remarkable finding was the association with developmental delay and facial anomalies detected during the second hospitalisation. The LAD-II phenotype includes immunological features similar to LAD-I in its mildest form, and LAD-II exhibits somatic features as well as severe mental retardation, short stature and distinctive facies. We ruled out the diagnosis of LAD-II because the patient had no blood group Bombay phenotype and her developmental delay and neurological sequelae, especially hearing loss, were typical manifestations of congenital CMV infection,^{25–33} confirmed with specific serological tests, since we do not have available PCR studies for CMV yet. The prevalence of CMV

infection is high in low-level socioeconomic countries, such as Chile.²⁵ Furthermore, congenital CMV infection is more frequent than rubella or even Down syndrome, but can be frequently missed.^{26–33} In this case, retrospective diagnosis and the update of congenital CMV infection knowledge and its sequelae induced the local board of perinatology to develop new clinical guidelines for prevention and therapy, and the implementation of PCR for CMV in our hospital.

In conclusion, we report a case of LAD-I associated with developmental delay, with normal expression of CD18 antigen. We could not perform functional tests but genetic testing confirmed LAD-I. Developmental delay was consistent with CMV infection, a condition associated with bad hygiene and poor socioeconomic status, frequently under-diagnosed by lack of awareness and understanding of this condition, in the general population and health staff.^{34–36} However, we could not rule out other, undiagnosed genetic alterations. Also, genetic testing revealed the high consanguinity and the possible true filiation, and the risk factors of genetic, infectious and psychological diseases that can be prevented with timely, and efficient, legal and health intervention.

Learning points

- The diagnosis of leucocyte adhesion deficiency (LAD) should raise suspicion of the existence of hidden consanguinity.
- LAD-I may be associated with failure to thrive secondary to other causes, such as a genetic disease or sequelae of congenital infection.
- The normal expression of CD18 associated with severe phenotype of LAD-I suggests a severe functional deficiency.
- Genetic testing can confirm the diagnosis if functional studies are not readily available.

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Contributors AS was the attending physician and wrote the manuscript. SG was the paediatrics resident and collaborated with clinical information. AK assessed the patient's immunology. SDR performed the genetic testing and reviewed the manuscript.

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