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Leukocyte adhesion deficiency II syndrome, a generalized defect in fucose metabolism

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Leukocyte adhesion deficiency II has been described in only 2 patients; herein we report extensive investigation of another patient. The physical stigmata were detected during prenatal ultrasonographic investigation. Sialyl-Lewis X (sLe^x) was absent from the surface of polymorphonuclear neutrophils, and cell binding to E- and P-selectin was severely impaired, causing an immunodeficiency. The elevation of peripheral neutrophil counts occurred within several days after birth. A severe hypofucosylation of glycoconjugates bearing fucose in different glycosidic links was present in all cell types investigated, demonstrating that leukocyte adhesion deficiency II is not only a disorder of leukocytes but a generalized inherited metabolic disease affecting the metabolism of fucose. (J Pediatr 1999;134:681-8)

Leukocyte adhesion deficiency II was first described in 2 nonrelated children, each from consanguineous parents by Etzioni et al[1] and Frydman et al[2] in 1992. No other living patient has been identified since, but a recent study described the biochemical investigation of cells derived from an abortus of 1 of the 2 families.[3]

The described children with LAD II had a common spectrum of clinical findings. Physical examination reveals a flat face with a broad and depressed nasal bridge, anteverted nostrils, long eyelashes, short arms and legs, and broad palms.[2] Crowded toes were reported in one patient. In both children there is a severe failure to thrive and considerable psychomotor retardation. Magnetic resonance imaging scans of the brain show frontal cerebral atrophy. Laboratory investigations reveal highly elevated numbers of peripheral neutrophils. Fluorescence-activated cell sorting analysis of neutrophil antigens reveals a characteristic absence of sialyl-Lewis X, a carbohydrate structure that is required for the rolling of neutrophils on endothelial cells before extravasation. Blood group typing of the patients with LAD II shows the absence of the H-antigen at the surface of erythrocytes (Bombay phenotype), and anti-H antibodies are present in the serum.

EDTA	Ethylenediaminetetraacetic acid
FACS	Fluorescence-activated cell sorting
FCS	Fetal calf serum
FITC	Fluorescein isothiocyanate
GDP	Guanosine diphosphate
LAD	Leukocyte adhesion deficiency
sLe^x	Sialyl-Lewis X
UEA	*Ulex europaeus* agglutinin

Sialyl-Lewis X and H-antigen are fucosylated carbohydrates in which fucose is bound in an α1,3- or an α1,2-glycosidic manner to N-acetylglucosamine and galactose, respectively. Furthermore, the α1,4-fucosylated Lewis blood group antigens are missing in patients with LAD II.[2] The absence of fucose in different glycosidic linkages on multiple glycans strongly argues against a specific fucosyl transferase deficiency in LAD II and in favor of a more general defect in the fucose metabolism. Fucose is utilized by fucosyltransferases in the Golgi complex as guanosine diphosphate–fucose, which is synthesized in the cytoplasm and imported into the organelle; 90% of GDP-fucose biosynthesis occurs by conversion of GDP-mannose, which itself originates from mannose uptake into the cell or from fructose 6-phosphate.[4] The remaining 10% is made by a fucose salvage pathway from degraded glycoconjugates or from exogenous fucose.[5] Previous evidence suggests that LAD II is caused by a de-

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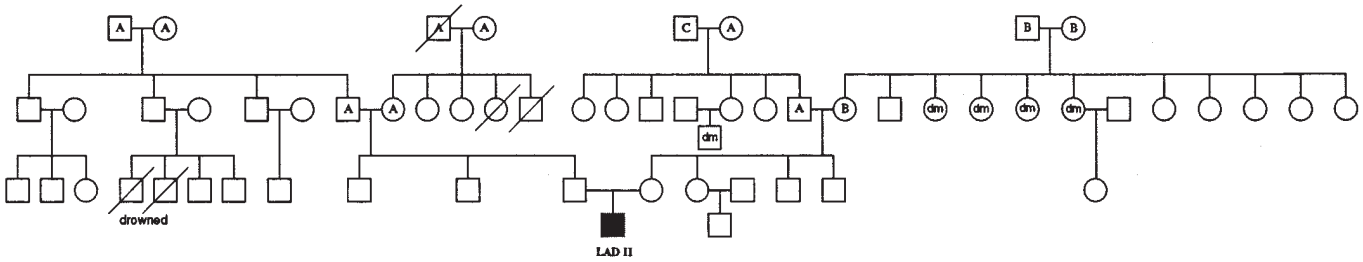


Fig 1. Pedigree of the patient's family. *A*, *B*, and *C* are small villages in a circumscribed area near the Black Sea. *dm*, Deaf.

fect in the conversion of GDP-mannose to GDP-fucose.[3,6] Herein we report clinical and biochemical characteristics of a third child with LAD II.

METHODS

Flow Cytometry

For flow cytometric analysis of cell surface marker expression, peripheral blood cells were incubated for 20 minutes at room temperature with combinations of the following antibodies: anti-CD45-PerCP (anti-HLe-1), anti-CD3-PerCP (SK7), anti-HLA-DR-PerCP (L243), anti-CD56-PE (MY31) (Becton Dickinson, Heidelberg, Germany), anti-CD14-PE (RMO52), anti-CD15-fluorescein isothiocyanate (MOPC.315-43), anti-CD19-PE (J4.119), anti-CD8-FITC (B9.11), and anti-CD4-PE (13B8.2) (Coulter-Immunotech, Hamburg, Germany). In addition, the cells were stained with unspecific isotype control antibodies. Subsequently, the red cells were lysed (FACS Lysing Solution, Becton Dickinson), and the sample was washed twice with phosphate-buffered saline buffer. Data acquisition and analysis were performed on a FACSCalibur by using CellQuest software (Becton Dickinson).

For a more detailed analysis, peripheral blood leukocytes were separated from erythrocytes by centrifugation on a discontinuous Ficoll gradient with a density of 1.119 (Sigma Histopaque-1119) and used in the amount of 5×10^5 cells per analysis. The granulocyte population was defined by forward/sideward scatter. Before incubation with analyzing antibodies, Fc receptors were blocked with the anti-FcγRII antibody IV.3 and the anti-FcγRIII antibody 3G8 (1.2 μg antibody per 10^6 cells), both obtained from Medarex Inc (Annandale, NJ). The cells were incubated, in separate aliquots, with 25 μg/mL purified and biotinylated selectin-IgG[7] or with vascular endothelial–cadherin-IgG[8] fusion proteins in Hank's buffered salt solution containing 3% fetal calf serum and 0.04% azide. The binding specificity was controlled by incubating a second sample in phosphate-buffered saline solution containing 5 mmol/L ethylenediaminetetraacetic acid and 0.04% azide. The incubations with the monoclonal antibody CSLEX-1 (anti-sLe^x mouse IgM, obtained from ATCC) were done in hybridoma supernatant. Cells were washed in the same buffer, and first reagents were detected either with 0.2 μg/mL R-phycoerythrin-conjugated streptavidin or with 0.6 μg/mL FITC-conjugated rabbit anti-mouse IgM antibodies, both obtained from Jackson ImmunoResearch Laboratories, Dianova (Hamburg, Germany). For analysis of the H-antigen, erythrocytes were separated from peripheral blood leukocytes by the same Ficoll gradient. Erythrocytes were incubated with an anti-H antigen monoclonal antibody obtained from Mast Diagnostica (Reinfeld, Germany), which was detected by an FITC-conjugated rabbit anti-mouse IgM antibody as described above. Immunoglobulin fusion proteins were biotinylated by incubating the purified fusion proteins (at 0.4 or 1 mg/mL) with 0.5 mg/mL sulfo-N-hydroxysuccinimide-biotin (Pierce, Rockford, Ill) at 4°C for 30 minutes. The reaction was stopped by addition of Tris (Merck, Darmstadt, Germany) to a final concentration of 0.1 mol/L and by dialysis against phosphate-buffered saline solution.

Lens culinaris *Lectin Affinity Chromatography of Metabolically Labeled Glycopeptides*

Control and patient fibroblasts were plated and grown on 6-cm cell culture plates as described previously.[9] After labeling for 6 hours with 125 μCi mannose labeled with 2-tritium in serum-free minimal essential medium containing 0.5 mmol/L glucose and 0.5% bovine serum albumin, the cells were scraped immediately into methanol/10 mmol/L Tris, 1 mmol/L EDTA, pH 8.0 (1:1) and boiled for 3 minutes in a water bath. Free [2-^{3}H]mannose and labeled metabolites (eg, mannose phosphates, GDP-mannose, dolichol-phosphate mannose, and dolichol-linked oligosaccharides) were removed by sequential extraction with methanol/10 mmol/L Tris, 1 mmol/L EDTA, pH 8.0 (1:1), chloroform/methanol (3:2), and chloroform/methanol/water (10:10:3). The remaining pellet was redissolved in 100 mmol/L Tris, pH 7.5, 0.5% sodium dodecyl sulfate, heated at 95°C for 5 minutes, and treated with 400 μg/mL pronase (Boehringer, Mannheim) at 50°C for 40 hours. The digestion was terminated by heat inactivation at 95°C for 5 minutes. Glycopeptides were desalted with Sephadex G-25 columns and subjected to *Lens culinaris* lectin affinity chromatography as described previously.[10] Bound glycopep-

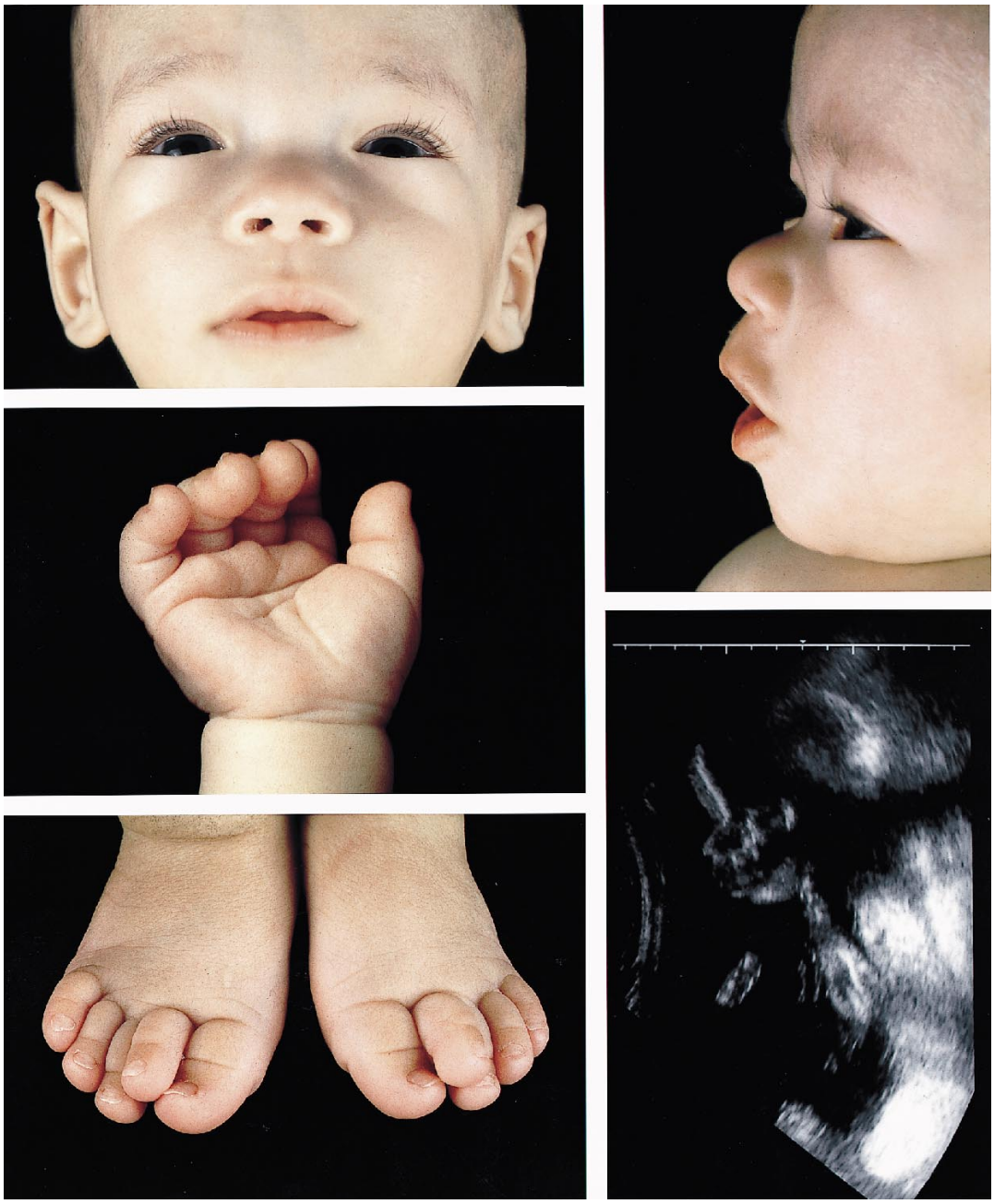


Fig 2. Clinical stigmata. Long eyelashes, a broad and depressed nasal bridge, a simian crease, and dorsally positioned second toes are the clinical stigmata of the patient with LAD II. The depressed nasal bridge was already seen on intrauterine ultrasonographic investigation in the 28th week of gestation **(lower right panel)**.

tides were eluted with 100 mmol/L methyl α-D-mannopyranoside (Sigma) and analyzed by liquid scintillation counting.

Electron Microscopy

Leukocytes were prepared by using Neutrophil Isolation Medium (NIM; Paesel & Lorei, Hanau, Germany). After centrifugation, the cells were fixed with 5% paraformaldehyde in 50 mmol/L N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid and prepared for thin frozen sectioning and immunogold labeling as previously described.[11] The thin frozen sections were incubated with 5% FCS to block unspecific binding sites, followed by an incubation with FITC-conjugated *Ulex europaeus* I lectin (Camon, Wiesbaden, Germany) at a concentration of 50 μg/mL. Lectin binding sites were detected with a rabbit anti-fluorescein IgG (Molecular Probes, Leiden, The Netherlands; dilution 1:150 in 1% FCS) and a goat anti-rabbit IgG conjugated with 12 nm gold particles (Dianova; dilution of 1:50 in 1% FCS). As a control, the labeling procedure was performed without addition of *Ulex*

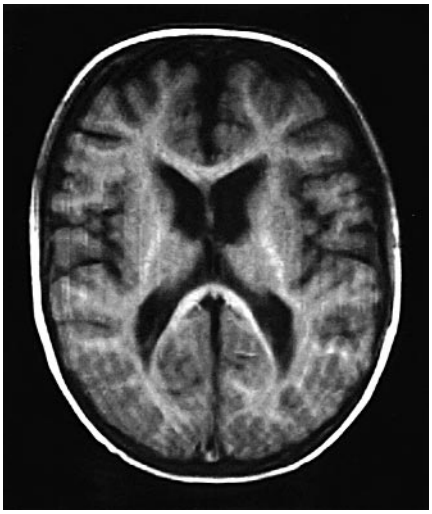


Fig 3. Magnetic resonance imaging scan of the brain. Frontal cerebral atrophy was present at 6 months of age.

europaeus agglutinin and showed no binding sites.

RESULTS

Clinical Presentation

The boy is the first child of non-consanguineous parents. However, the parents may be distantly related, because ancestors of both lived in the same small village in Turkey (Fig 1). The first intrauterine ultrasonographic investigation was done at 28 weeks' gestation and revealed a severely retarded growth of fetal limb bones. The second evaluation, performed just before birth, showed an even more pronounced deviation from the regular growth curves (data not shown; reference values reported by Merz et al[12]).

The child was delivered by cesarean section in the 32nd week of pregnancy, after fetal heart rate monitoring revealed a pathologic pattern. Birth weight was 850 g (<3rd percentile), length at birth was 33.5 cm (<3rd percentile), and head circumference was 26 cm (3rd percentile). A broad and depressed nasal bridge was seen. Short arms and legs were present, and on the broad palms a simian crease was noted. Dorsally positioned second toes overlapped with the first and third toes (Fig 2). No chromosomal abnormalities were found (karyotype 46, XY).

Meconium ileus necessitated surgery on the first day of life. Several severe septic events occurred during the first 3 months of life, requiring intravenous antibiotic therapy. Antibiotic prophylaxis with different drugs has been necessary all his life. Attempts to discontinue the antibiotic prophylaxis resulted in high fever and impaired clinical condition within several days. Even with antibiotic prophylaxis, many episodes of high fever led to hospitalization of the patient. Cultures from blood or cerebrospinal fluid samples obtained during these episodes were always sterile. The only infectious agent, which was repeatedly found, was coronavirus in stool samples.

Postnatal growth was severely impaired. Body length, weight gain, and head circumference remained below the 3rd percentile (data not shown). Several ultrasonographic investigations of the brain in the first month of life revealed no abnormalities. At 6.5 months, magnetic resonance imaging was performed and revealed a slight enlargement of the frontal subarachnoid space (Fig 3). A bulging large anterior fontanelle was observed on several occasions, but lumbar punctures did not reveal increased intracranial pressure, and cerebrospinal fluid cell counts were always within the normal range. Today, at 15 months of age, the boy has a severe neurodevelopmental delay with prominent muscular hypotonia and is unable to sit without support.

Leukocytes

LEUKOCYTE COUNTS AND DIFFERENTIATION. Directly after delivery, peripheral leukocyte counts were 6100/μL with 36% neutrophils. Peripheral leukocyte counts were normal in the first 3 days of life (Fig 4, *inset*), but thereafter, total leukocyte counts were constantly elevated. In the absence of infection, total peripheral leukocyte counts were around 20,000/μL, but during febrile episodes they reached 70,000/μL (Fig 4, *left panel*). Differential counts demonstrated that in addition to neutrophils, total lymphocytes were also elevated (Fig 4, *middle panel*). FACS analysis of the expression of CD3, CD4, CD8, CD56, and HLA-DR revealed a normal distribution of lymphocyte subpopulations (not shown). Peripheral leukocyte counts of the parents were normal.

Increased neutrophil granulocytes often paralleled an increased serum concentration of C-reactive protein, indicating inflammatory activity in the body (Fig 4, *right panel*).

SIALYL-LEWIS X. Because of persistently elevated peripheral leukocyte counts, FACS scan analysis of leukocyte antigens was performed, when the boy was 6 months of age. FACS analysis revealed the absence of CD15 (Fig 5, *A*), indicating the absence of Le^x on the leukocyte surface. When the granulocyte population was tested with a monoclonal antibody that recognizes sLe^x (CSLEX-1), virtually no sLe^x was found on the cell surface (Fig 5, *B*). Sialyl-Lewis X is a carbohydrate structure of neutrophils, which is necessary for the interaction with selectins expressed on endothelial cells. The binding to E- and P-selectin is essential for the rolling of neutrophils on the endothelial cell layer before extravasation. Biotinylated soluble selectin fusion proteins were used to test the selectin binding of the patient's granulocytes.[7] A severely decreased capacity of the patient's granulocytes for the binding to E- and P-selectin was found (Fig 5, *C and D*), indicating the absence of sLe^x-like carbohydrate structures that could serve as selectin ligands. These results indicate the absence of α1,3-fucosylation in the LAD II cells.

Erythrocytes

Directly after birth, the blood group of the patient was determined to be O, RhD-positive (CcDEe), Kell anti-

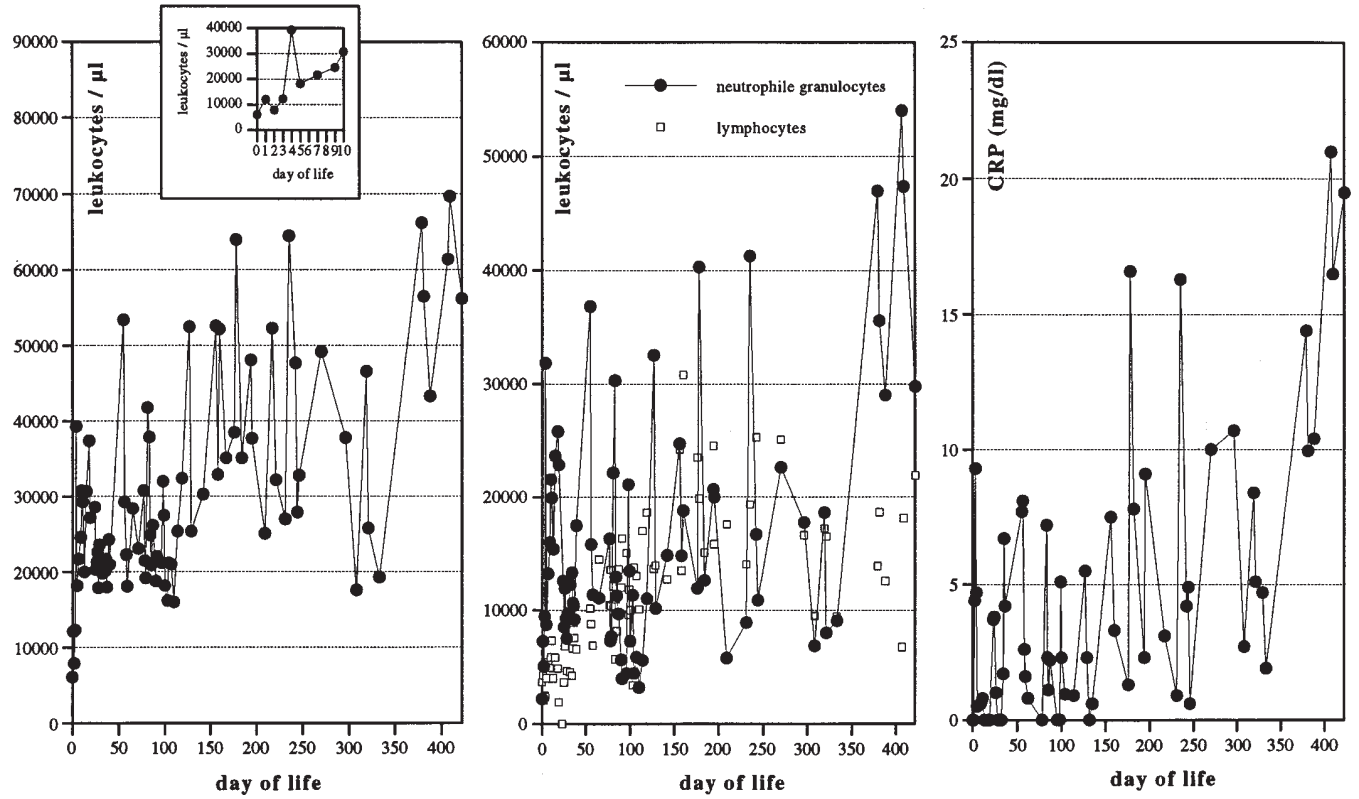


Fig 4. Leukocyte counts and C-reactive protein. Total peripheral leukocyte counts of the patient **(left panel)** and differential counts **(middle panel)**. Concentration of C-reactive protein in the serum **(right panel)**. Normal values: leukocytes, 6000 to 17,000/µL; neutrophils, 1500 to 8500/µL; lymphocytes 4000 to 10,500/µL; C-reactive protein, <1 mg/dL.

gen–negative. The presence of blood group O was concluded, because the patient's erythrocytes did not react with anti-A or anti-B sera. Because the sera of newborns normally do not contain isoagglutinins[13] and because erythrocytes are not routinely checked for the presence of H-antigen (because of the rarity of Bombay blood groups in western Europe), the Bombay phenotype of the patient was missed at this time. At 6 months of age, the O_h Bombay blood group phenotype was detected. Conventional analysis was difficult, because 4 blood transfusions with O RhD-negative erythrocyte concentrates were done at 9, 18, 106, and 107 days of life to treat anemia caused by prematurity and several severe systemic infections. For this reason, a monoclonal antibody for H-antigen was used to search for H-antigen expression on the surface of the patient's erythrocytes and to distinguish the transfused erythrocyte population from that of the patient. The FACS profile of the patient's erythrocytes was identical to genuine Bombay blood. When anti-H antibodies were used, only a small population of transfused erythrocytes with H-antigen expression was detected 2.5 months after the last transfusion (Fig 5, *E*), indicating that α1,2-fucosylation is not occurring either.

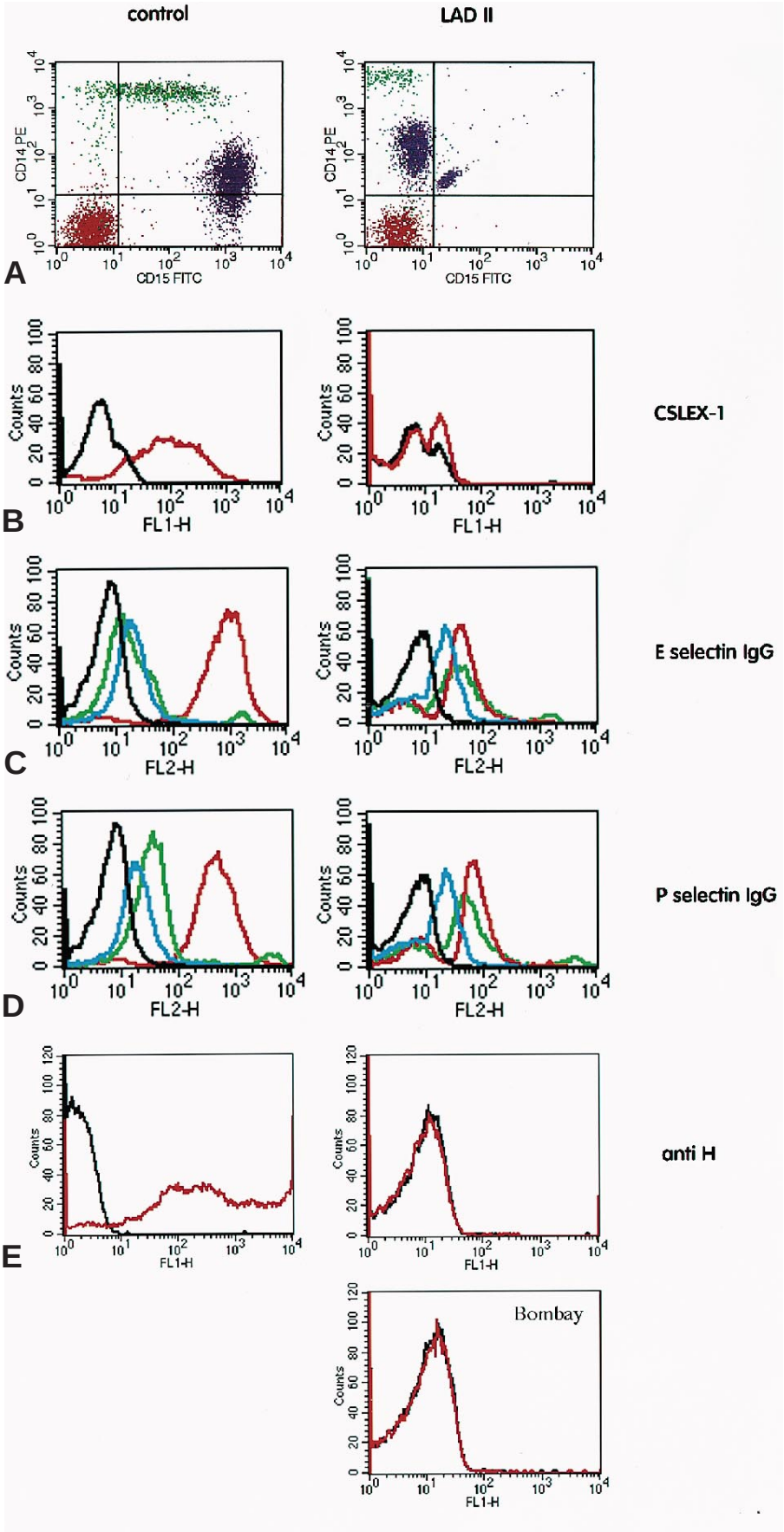
At 6 months of age, no anti-H antibodies were present. However, at 14 months of age, low-titer IgM antibodies were detected, which caused an incomplete lysis of O, RhD-negative erythrocytes at 37°C. Lysis could only be detected when the serum was undiluted. These antibodies most likely represent anti-H antibodies as described in the other patients.[1,2]

Erythrocytes of patients with LAD II do not have the fucosylated Lewis antigens Le^a and Le^b at their surfaces. However, the absence of Le^a and Le^b is not informative in our patient, because it could also be inherited from his parents. The mother's blood group is O, CcDee, Le(a–b+); the father's blood group is O, CcDEe, Le(a+b–). Both parents have the H-antigen. Father and child are non-secretors for the blood group antigens, whereas the mother shows the secretor status (meaning the presence of ABO antigens in the saliva).

Lectin Binding

The absence of sLe^x and H-antigen demonstrates that neither α1,3- nor α1,2-glycosidic linked fucose is present in the patient. Fucose-specific lectins were used to study the level of fucosylation and, in particular, the presence of α1,6-fucosylation of glycoconjugates in different cell types.

ULTRATHIN FROZEN SECTIONS. UEA is a fucose-specific lectin that recognizes fucose in different glycosidic bonds.[10,14] Frozen sections of leuko-



cytes, thrombocytes, and fibroblasts were incubated with this lectin; and lectin binding was visualized by using immunogold labeling. In leukocytes and thrombocytes a marked decrease of the lectin binding was found in the LAD II cells. Most of granules of the control leukocytes were strongly labeled with UEA, whereas the granules of the patient's leukocytes were only weakly labeled. The neutrophil preparations contained a few platelets in which granules and plasma membrane revealed many UEA binding sites. In contrast, the platelets of the patient were free of UEA labeling (Fig 6). UEA binding was modestly reduced in the patient's fibroblasts. The results confirm the hypofucosylation of different cell types in LAD II.

LECTIN AFFINITY CHROMATOGRAPHY. Fibroblast extracts were analyzed by lectin affinity chromatography with *Lens culinaris* agglutinin, a lectin that recognizes high-mannose carbohy-

Fig 5. FACS analysis. **A,** FACS analysis of CD14 and CD15 antigens. *Red,* lymphocytes; *blue,* granulocytes; *green,* monocytes. Granulocytes and lymphocytes of the patient with LAD II do not express the CD15 antigen. **B,** Analysis of granulocytes with monoclonal CSLEX-1 antibody. Background fluorescence with secondary antibody is shown in *black*. The fluorescent signal obtained with CSLEX-1 antibody (shown in *red*) is absent in LAD II cells. **C,** E-selectin binding to granulocytes. Background fluorescence with the streptavidin detection reagent is shown in *black*. A soluble fusion protein of E-selectin and the Fc part of IgG was used for incubations.[7] To control for unspecific binding to unblocked Fc receptors on the cell surface, a VE-cadherin-IgG fusion protein was used *(blue)*. VE-cadherin does not have a specific binding to neutrophil surface antigens.[8] Because binding of selectins to their ligands is Ca^{2+}-dependent, selectin binding was investigated both in the presence *(red)* and absence *(green)* of calcium. In control cells, selectin binding, which can be completely suppressed in the absence of calcium, occurs. In LAD II cells, very little selectin binding is observed, which does not change in the absence of divalent cations. **D,** P-selectin binding. In contrast to control cells, only a small decrease of P-selectin binding was observed in the absence of calcium. **E,** H-antigen expression on erythrocytes.

drate structures but shows high-affinity binding only in the presence of α1,6-linked core fucose residues.[15] The fibroblasts were labeled with [2-^{3}H]mannose, and glycopeptides were prepared. The lectin was coupled to a gel matrix, and the glycopeptides were passed over the column. The bound glycopeptides were eluted with methyl α-D-mannopyranoside. In contrast to controls, very little material was specifically bound to the column in the LAD II samples (Fig *7*). A defect in mannose metabolism leads to carbohydrate-deficient glycoprotein syndromes[4] and was ruled out in the patient with LAD II (T. Marquardt, unpublished results). Therefore the experiments demonstrate that core α1,6 fucosylation is defective in LAD II and that fibroblasts from LAD II cells express the disease phenotype.

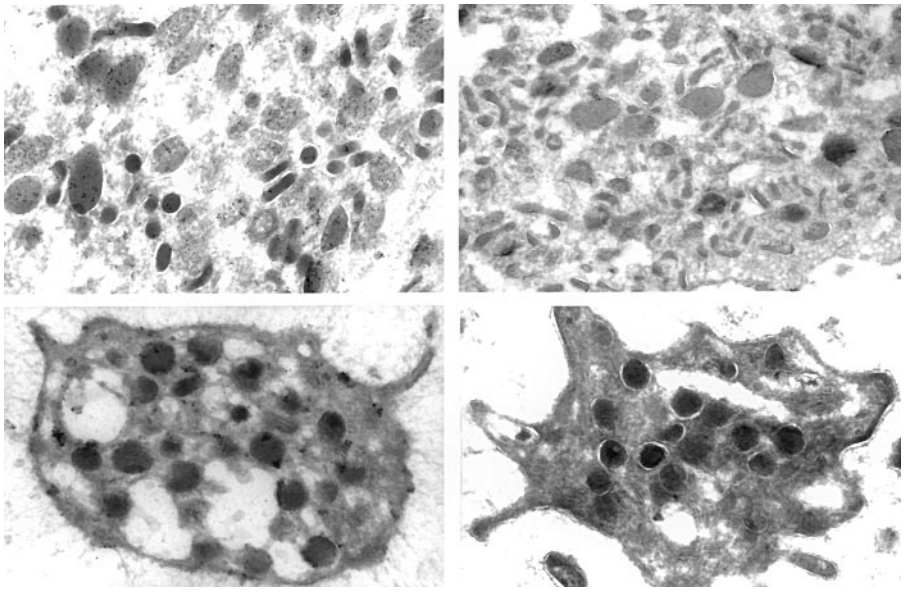


Fig 6. Electron microscopy. UEA binding sites visualized by immunogold in neutrophil granulocytes *(upper 2 panels)* and thrombocytes *(lower 2 panels)*. Photographs at left are from a healthy control subject; those at right are from the patient with LAD II, showing a considerably reduced number of lectin binding sites.

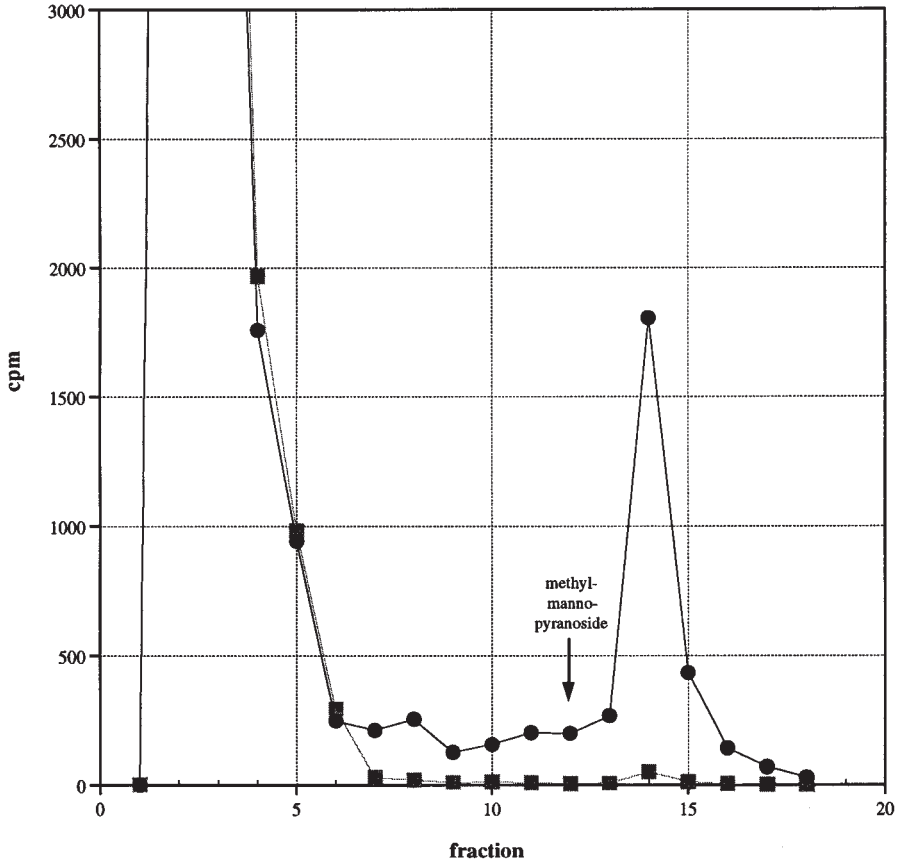


Fig 7. *Lens culinaris* binding of glycopeptides from fibroblasts after mannose labeling. After sample application, the column was washed to remove labeled material that was not specifically bound to the column. Maximal counts were present in the first 2 fractions of the void volume (with 12,000 cpm in second fraction from controls and 13,000 cpm in second fraction from LAD II cells; peaks are cut off in the diagram). On addition of methyl mannopyranoside, labeled glycopeptides were eluted in controls, whereas very few counts were eluted from LAD II cells. *Circles,* Controls; *squares,* LAD II cells.

DISCUSSION

In this article we report a third patient with LAD II and the first born to non-consanguineous parents. He strongly resembles the 2 other patients in morphologic stigmata, lacks sLe^x and H-antigen on leukocytes and erythrocytes, respectively, and shows an inability of neutrophils to bind to endothelial selectins. Peripheral leukocyte counts were constantly elevated after the third day of life and eventually led to the diagnosis of the disorder. Coming from a sterile intrauterine environment, surgery necessitated by the meconium ileus on the first day of life might have triggered the release of neutrophil granulocytes from the bone marrow, leukocytes, which then were unable to extravasate from the blood stream because of sLe^x deficiency. Impaired extravasation led to many infectious complications, which were the predominant clinical problem during the first year of life.

In our patient α1,2-, α1,3-, and α1,6-linked fucoses are missing. The broad spectrum of symptoms—ranging from

morphologic abnormalities, retarded growth, and psychomotor retardation to an immunodeficiency—indicates the importance of fucosylation, which requires GDP-fucose. This sugar nucleotide is generated in the cytoplasm predominantly from GDP-mannose and then imported into the Golgi complex, where it is transferred to glycoconjugates by different fucosyltransferases. The generalized hypofucosylation found in LAD II suggests a decreased availability of GDP-fucose for the different fucosylation processes. The exact molecular defect of LAD II has not been identified yet. In contrast to other reports, the conversion of GDP-mannose to GDP-fucose is not affected in our patient with LAD II.[16] Fucose supplementation can correct the defect in the fibroblasts of our patient and is currently elucidated in vivo in our patient. The nature of the molecular defect and the benefit of fucose therapy are currently under investigation.

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