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Clinical And İmmunological Features of Three Lrba Deficiency Patients

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LPS-responsive beige-like anchor (LRBA) deficiency is a primary immunodeficiency characterized by; recurrent sinopulmonary infections with hypogammaglobulinemia, lymphoproliferation, immunodysregulation, which presents by enteropathy, cytopenias, and autoimmune endocrinopathy.

The LRBA protein is a cytosolic protein that is expressed in several cell types including hematopoietic, neural, gastrointestinal and endocrine cells. LRBA regulates cytotoxic T lymphocyte antigen-4 (CTLA-4) turnover in endosomes. CTLA-4 is a critical and potent inhibitor of T-cell proliferation that serves as a "checkpoint" of immune responses. CTLA-4 is a crucial T-cell inhibitory receptor. CD28 is principal T-cell costimulatory molecule and critical for inducing T-cell proliferation CD28 and CTLA-4 compete for the same ligands, on the surface of antigen-presenting cells (CD80 and CD86). Moreover, CTLA-4 binds CD80 and CD86 with significantly higher affinity and avidity than CD28. CTLA4 inhibits T cell proliferation by binding to these ligands. Most CTLA-4 is stored in recycling endosomes, which cycle to the cell surface following T-cell activation. LRBA regulates intracellular CTLA-4 traffic. It prevents lysosomal degradation of CTLA4. Therefore, the inflammatory response cannot be limited in LRBA deficiency.

The clinical features are heterogeneous. Age of presentation ranging from two months to 12 years. The majority (71 %) presented at or before 5 years of age. The disease phenotype can be divided into an enteropathy phenotype, an autoimmunity phenotype and an immunodeficiency phenotype. The enteropathy phenotype includes autoimmune enteropathy, IBD/IBD-like disease and non-infectious diarrhea; the immunodeficiency phenotype includes combined immunodeficiency (CID), CVID and a CVID-like disease and the autoimmunity phenotype includes mainly AIHA and/or ITP were the most common, followed by autoimmune thyroid disease, type 1 diabetes mellitus, JIA and celiac like disease.

Case 1.

NG, 14 years 6 months old, female patient

She was diagnosed with Type 1 DM at 9 months of age (Anti-GAD Antibody positive). Her complaints of diarrhea began at the age of 5 (6-7 times / day, watery). She had been brought to an outer center for chronic diarrhea. In the histopathological examination obtained by upper GIS endoscopy, villus atrophy, crypt hiperplasia, and intraepithelial lymphocytosis were detected. Anti-tissue transglutaminase IgA and Anti-endomisium IgA were negative. Other tests for the etiology of chronic diarrhea were normal. She started a gluten-free diet at the age of 5. Since there was no response to the gluten-free diet. HLA DQ2, and DQ8 tests were negative, the gluten-free diet was discontinued when she was 7years old. During this two-year period of gluten-free diet, steroid treatment had also been tried for refractory celiac, for 6 months. A partial response to steroid treatment was achieved and diarrhea increased after discontinuation. At the age of 8, she had swelling, redness and limitation of movement in one knee and then in both knees, which repeated intermittently. She was thought to have JIA and a NSAID was used.

Family history:
There was no consanguineous marriage between her parents, but they were from the same village. There was no family history of a similar disease.
Physical examination: Her weight was at 50-75 percentile and height was at 10-15 percentile. There was no growth and development retardation. System examination was natural.
Laboratory: Complete blood count parameters were normal. Immunoglobulin levels were normal for age and specific antibody responses were poor. Flow cytometric analysis of peripheral blood lymphocytes was normal. ANA and Anti-ds-DNA were positive for the etiology of arthritis. Antibody screening was performed for other autoimmune diseases; thyroid auto antibodies were negative and direct coombs were negative.
The pathological findings (early onset Type 1 DM, autoimmune enteropathy, rheumatologic findings) were thought to be accompanied by immune dysregulation. The LRBA expression of the patient was lower than the simultaneous control, and there was no increase with activation. In the genetic analysis, homozygous frame shift mutation was detected in the 23rd exon of the LRBA gene.
Allogenic Stem Cell Transplantation preparations were performed and abatacept, steroid and IVIG treatment were used. Allogenic stem cell transplantation was performed at the age of 12 years. Diarrhea improved after transplantation.
Case 2.
BG, 5 years 2 months old male patient (sibling case)
Case 2 is brother of case 1. He was asymptomatic, and physical examination, growth and development were normal. The same mutation was homozygous, at the age of 3. The patient had been followed up.
Laboratory:
Complete blood count parameters were normal. Immunoglobulin A and M levels were low for age, while the other immunoglobulin levels were normal. Specific antibody responses were normal. Flow cytometric analysis of peripheral blood lymphocytes was normal. The LRBA expression of the patient was lower than the simultaneous control, and there was no increase with activation. Antibody screening for other autoimmune diseases was performed; Anti-glutamic acid decarboxylase antibody and thyroid auto antibodies were negative and direct coombs assay was negative.
During the follow-up, he frequently had respiratory infection which clinically required antibiotics treatment, 4 times in a 3 months period. Therefore, intravenous immunoglobulin treatment was started. IVIG treatment was administered for 1 year. The frequent infections were controlled under IVIG treatment. IVIG treatment was been discontinued 6 months ago but was started again because of recurrent infections.
Case 3
BU, 5 years old, female patient
At 8 months of age, she was admitted to the clinic with protein losing enteropathy. She had chronic watery diarrhea at that time. In the examinations for protein-losing enteropathietyology, anti-endomisium IgA was positive, tissue transglutaminase IgA was 166 U / mL (tissue transglutaminase antibody was positive but not above 200 U/mL.) Upper GIS endoscopy was normal but histopathological examination revealed villus atrophy, crypt hyperplasis and intraepithelial lymphocytosis, which suggest autoimmune enteropathy. Other intestinal and extra intestinal causes of protein losing enteropathy were ruled out. Gluten-free diet was started. However, there was no clinical response to the gluten-free diet.
At 9 months of age, bloody mucus defecation began. Colonoscopy examination revealed aphthous ulcers in the cecum and recto sigmoid region. Histopathological examination revealed diffuse eosinophilic infiltration.

Family history:
Consanguineous marriage was prsent but there was no family history of a similar disease.

Physical examination:
Her weight and height were below 3 percentile. There was growth and development retardation. Systemic examination was normal.

Laboratory:
Complete blood count parameters were normal. Immunoglobulin G and M levels were found to be low for age, whereas, other immunoglobulin levels were normal. Of specific antibody responses, isohemagglutinin titration was low. Flow cytometric analysis of peripheral blood lymphocytes was normal. Antibody screening was performed for other autoimmune diseases; thyroid autoantibodies were negative and direct coombs assay was negative.

The patient, with autoimmune enteropathy not responding to gluten free diet and early onset inflammatory bowel disease, was evaluated for immune dysregulation. Immunological assays was performed. The LRBA expression of the patient was lower than the simultaneous control, and there was no increase with activation. Genetic analysis revealed homozygous mutation in exon 12 of LRBA gene.

CTLA4-IgG1 (Abatacept) treatment was initiated while preparations for allogenic Stem Cell Transplantation were started. The patient has been waiting for a stem cell transplantation.

Conclusion

Immune dysregulation should be kept in mind especially in patients with IBD and autoimmunity and immunodeficient patients with different autoimmune diseases in the family.