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Identifying Novel Mutations in Iranian Patients with LPS-responsive Beige-like Anchor Protein (LRBA) Deficiency

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ABSTRACT

LPS-responsive beige-like anchor protein (LRBA) deficiency is a monogenic primary immunodeficiency characterized by a heterogeneous spectrum of clinical manifestations associated with immune dysregulation. In this study, we reported clinical, immunologic, and genetic evaluation of two Iranian patients from unrelated families, both suffering from recurrent respiratory tract infections, failure to thrive, interstitial lung disease, autoimmune cytopenia, and hypogammaglobulinemia. Pulmonary abscess in one patient and persistent enteropathy in another were also observed. Further investigations revealed causative mutations in the exon (c.2166_2766del) and intron (c.4730–3 T > G) of the *LRBA* gene. These results may provide further elucidation of the clinical phenotypes and responsible genetic factors of LRBA deficiency.

KEYWORDS

LPS-responsive beige-like anchor protein deficiency; LRBA; immune dysregulation; autoimmunity; enteropathy

Introduction

LPS-responsive and beige-like anchor protein (LRBA) deficiency is a primary immunodeficiency caused by biallelic mutations in the *LRBA* gene leading to regulatory T cell defects and immune dysregulation (Azizi et al. 2018c). LRBA deficiency is characterized by a broad spectrum of clinical manifestations, predominantly including recurrent respiratory or gastrointestinal tract infections, autoimmunity, lymphoproliferative disorders, enteropathy, and allergic symptoms (Alkhairy et al. 2015; Gamez-Diaz et al. 2016).

The most frequent laboratory findings include hypogammaglobulinemia, normal T cell counts, diminished numbers of regulatory T cells (Tregs) and natural killer cells, and B-cell

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Supplemental data for this article can be accessed here.

abnormalities (increased CD21low B cell count, and decreased number of class-switched memory B cells, marginal-zone B cells, and plasmablasts) (Cepika et al. 2018; Habibi et al. 2019).

Here, we report on the novel clinical, immunological and genetic findings in two patients with LRBA deficiency, thereby extending the phenotypic description of this probably under-diagnosed disorder.

Case presentation

Patient 1

Patient 1 (P1) is a currently 19 years old boy born at term to non-consanguineous Iranian parents. The family history was unremarkable for primary immunodeficiencies. He had two episodes of febrile seizures at 6 and 8 months. The recurrent episodes of respiratory tract infections started at 3 years of age.

At age 7, his growth became stunted, and he developed splenomegaly and thrombocytopenia. Evans syndrome was diagnosed and four years later he underwent splenectomy.

He had no further complications until the age of 15, when he presented with productive cough, nausea and body itching. Based on the galactomannan antigen which was positive in serum and bronchial alveolar lavage (BAL), the pulmonary aspergillosis was suspected and successfully treated with amphotericin B and voriconazole. Primary immunodeficiency was suspected due to recurrent episodes of opportunistic infections, but initial basic immunologic screening yielded normal results with IgG = 520 mg/dL, IgM = 110 mg/dL, and IgA = 32 mg/dL.

At 18 years old, he presented with fever, cough, and hemoptysis. Patchy alveolar opacity and pleural effusion were observed in CXR (chest X-ray) and evidence of porta hepatis and para-aortic lymphadenopathies were identified in chest CT scan. Smear testing and microscopy for the mycobacterium were negative. BAL culture was positive for gram-positive cocci and BAL fluid was positive for Epstein–Barr virus (EBV) and Cytomegalovirus (CMV). Finally, the diagnosis of a lung abscess was made, resulting in a right lung lobectomy (right lower lobe). He recovered but was subsequently re-admitted with productive cough, fever and chills, myalgia, and dyspnea. Upon physical examination, patchy hypopigmented lesions in the lumbar region and limbs, suggestive of vitiligo, were detected. He suffered from recurrent episodes of respiratory tract infections and started to develop interstitial lung disease.

The laboratory evaluation identified leukocytosis associated with hypogammaglobulinemia and low IgG and IgA levels assessed by nephelometry. The lymphocyte subsets were within the normal range except for the low blood levels of B cells. He had poor specific antibody response to diphtheria and tetanus vaccines (Table S1).

Finally, the diagnosis of hyper IgM (HIgM) syndrome was established. The initial management of P1 included intravenous immunoglobulin (IVIg) substitution and rituximab, which resulted in the improvement of lung disease and coombs positive hemolytic anemia and also the normalization of immunoglobulins.

Whole exome sequencing and subsequent computational analysis of patient 1 (P1) revealed a homozygous c4730-3 T > G mutation in intron 29 of the *LRBA* gene, which was considered as a variant of uncertain significance (VUS) according to the American College of Medical Genetics and Genomics (ACMG) guidelines for variant interpretation (Richards et al. 2015). His parents and sibling were also heterozygous for the same mutation, validated by PCR-sanger sequencing (Figure S1).

After obtaining this molecular diagnosis, the treatment with IVIg was continued at a dose of 600 mg/kg which led to remarkable improvement in his clinical manifestations.

Patient 2

Patient 2 (P2) [P72 in (Tesch et al. 2019)] is a now 5 years old girl, born to consanguineous healthy parents. Her female sibling was dead at the age of 2 years old following ascites, hepatosplenomegaly, and thrombocytopenia. There was also a history of sensorineural hearing loss in her relatives.

She presented at 6 months of age with generalized edema involving the face, eyelid and lower limbs, thrombocytopenia, splenomegaly and macular rash in lower limbs following the use of a multivitamin drug. This condition was assumed to be a drug allergy and she was treated with prednisolone; however, thrombocytopenia persisted.

At the age of 2, she was diagnosed with immune thrombocytopenic purpura (ITP) and intravenous immunoglobulin was started. Meanwhile, she experienced multiple episodes of pneumonia.

Four months later, she was re-admitted with diarrhea and suspected protein-losing enteropathy. In the endoscopy, esophagitis, varioliform pan erosive gastritis and atrophic duodenitis were detected. In the histopathology, the lamina propria of the gastric mucosa was severely infiltrated with inflammatory cells, mainly eosinophils, neutrophils, and lymphoid aggregates. Lymphoid follicles were increased and glandular cells in the gastric mucosa showed large eosinophilic intranuclear inclusions, suggestive of CMV but not confirmed. Human leukocyte antigen (HLA) typing was performed which revealed negative HLA DQ2 and DQ8 and celiac disease was ruled out. She was admitted several times due to hypoalbuminemia and received albumin transfusion.

At the age of 3, she presented with respiratory distress requiring airway intubation. On admission, she had growth failure, tachypnea, bilateral rhonchi, and fine crackles. In CXR, evidence of bilateral pleural effusion, cardiomegaly, pulmonary artery dilation, interlobular septal thickening, and patchy consolidation were observed and she was diagnosed to have interstitial lung disease (ILD). She also had generalized osteopenia and flexion deformity in her fingers.

Immunological investigations showed leukocytosis, thrombocytopenia, with normal immunoglobulin phenotype and lymphocyte subsets found through flow cytometry. Lymphocyte transformation tests (LTT) for phytohemagglutinin (PHA), Bacillus Calmette-Guérin (BCG) and candida were normal and specific antibody response to diphtheria and tetanus vaccines were both insufficient (Table S1).

The whole-exome sequencing showed a novel homozygous deletion of 5 exons (exons 18–22, c.2166_2766del) in the *LRBA* gene, leading to a frameshift mutation and premature stop codon (p. V723SfsX25). The homozygous status of this variant was also confirmed by quantitative PCR (Q-PCR) (Figure S2). Her parents were heterozygous for the deletion. The patient received IVIG and Rituximab and was a candidate for hematopoietic stem cell transplantation (HSCT). Now, she is in relatively good and stable health condition; however, her protein-losing enteropathy persists.

Discussion

LPS-responsive beige-like anchor protein (LRBA) deficiency is a monogenic primary immunodeficiency now categorized as a disease of immune dysregulation with autoimmunity (Bousfiha et al. 2017). LRBA interacts with the cytoplasmic tail of CTLA-4 (Cytotoxic T-Lymphocyte Antigen 4), regulates the recycling of CTLA-4 from endosomes to the cell membrane and protects it from lysosomal degradation (Lo et al. 2015; Martinez Jaramillo and Trujillo-Vargas 2018). CTLA-4 outcompetes the costimulatory molecule CD28 for the specific ligation of CD80 and CD86 and inhibits self-reactive T cell activation after antigen recognition (Lo and Abdel-Motal 2017). Therefore, bi-allelic *LRBA* mutations that lead to an insufficient amount of CTLA-4 are accompanied by disruption of immune homeostasis and autoimmunity (Azizi et al. 2018c).

LRBA deficiency presents with a heterogeneous spectrum of clinical manifestations including recurrent infections, autoimmunity, lymphoproliferation, chronic diarrhea, and hypogammaglobulinemia (Azizi et al. 2018b; Gamez-Diaz et al. 2016). Autoimmunity (42%) and chronic diarrhea (27%) have been observed as the first presentations of the disease in most of the LRBA deficient patients (Habibi et al. 2019); however, in a longitudinal study of 17 Iranian patients, respiratory tract infections were the most common presentations in 41.2% of affected individuals (Azizi et al., 2017a). Non-infectious, immune-mediated pulmonary manifestations including interstitial lung disease (ILD), ground glass opacities and lung nodules have been reported with various degrees of frequency, ranging from 6% to 38% of LRBA deficient patients (Azizi et al., 2017a; Alkhairy et al. 2015; Gamez-Diaz et al. 2016; Shamriz et al. 2018). Both of our patients were also found to have evidence of ILD including septal thickening, heterogeneous attenuation pattern, and patchy opacities.

Predisposition to opportunistic infections is a common finding in immunodeficient individuals (Cunha et al. 2011). Invasive pulmonary aspergillosis often presents with non-specific symptoms including fever, cough, dyspnea, chest pain and hemoptysis (Chotirmall et al. 2013) In this study, P1 suffered from pulmonary aspergillosis and Massaad et al. reported two LRBA deficient patients suffering from aspergillus pneumonia (Massaad et al. 2016). The prevalence of invasive aspergillosis is particularly high in patients with chronic granulomatous disease (CGD), autosomal dominant (AD) hyper IgE syndrome (HIES), AD GATA2 deficiency, AD or autosomal recessive (AR) severe congenital neutropenia (SCN), and AR type I leukocyte adhesion deficiency (CD18 deficiency) (Lanternier et al. 2013). However, it is not a common finding in LRBA deficiency.

As described earlier, P1 was complicated with pulmonary abscess and underwent right lung lobectomy. Although abscess formation is not a common complication in LRBA deficient individuals, there are some reports of brain (Azizi et al., 2017a), jaw (Eren Akarcan et al. 2018; Lopez-Herrera et al. 2012), dental (Alkhairy et al. 2015), and psoas muscle (Alkhairy et al. 2015) abscesses in these patients.

Allergic disorders are uncommon findings in LRBA deficiency (Habibi et al. 2019) and mostly include atopic dermatitis (Azizi et al., 2017a; Alkhairy et al. 2015; Gamez-Diaz et al. 2016; Kostel Bal et al. 2017), urticaria (Azizi et al., 2017a; Kostel Bal et al. 2017), allergic enteropathy (Eren Akarcan et al. 2018), food allergy, and insect sting allergy (Azizi et al., 2017a). In this study, drug allergy was the initial presentation in P2, which was associated with edema, organomegaly, thrombocytopenia and macular rash, and was responsive to corticosteroids. However, the prevalence of allergic conditions in LRBA deficiency does not seem to exceed the rate in the normal population.

Previous studies have shown that LRBA deficiency can be associated with hearing loss (Gamez-Diaz et al. 2016). In some patients, this can be attributed to the complication of otitis media (Alkhairy et al. 2015), but in others, no definite etiology has been proposed (Bakhtiar et al. 2016; Li et al. 2018; Lo et al. 2015; Vogl et al. 2017). Recently, Vogl et al. showed that LRBA knockout mice develop progressive sensorineural hearing loss following the instability of hair cell stereociliary bundles and reduced hair cell receptor potential (Vogl et al. 2017). Our patient, P2, was not complicated with hearing abnormalities, but several members of her family had a history of deafness. Although molecular studies were not performed on her relatives, we speculate that LRBA deficiency may predispose affected patients to progressive sensorineural hearing impairment. However, further studies are required to evaluate this genotype-phenotype relationship.

In the current study, both patients suffered from poor specific antibody response. Low vaccine titers in patients with LRBA deficiency have been reported in the literature (Azizi et al., 2017a; Azizi et al. 2018a; Eren Akarcan et al. 2018; Gamez-Diaz et al. 2016; Lo et al. 2015; Soler-Palacin et al. 2018), which can be attributed to the hypogammaglobulinemic state and class switch defect. One study has suggested this to be due to plasma cell dysfunction rather than plasma cell deficiency, as normal formation of germinal center and plasma cells have been observed despite agammaglobulinemia (Al Sukaiti et al. 2017).

High serum levels of IgM, as in P1, have been observed in other reported LRBA deficient individuals (Azizi et al., 2017a; Al Sukaiti et al. 2017; Eren Akarcan et al. 2018; Gamez-Diaz et al. 2016). Therefore, it is recommended to consider immune dysregulative PIDs such as LRBA deficiency as a differential diagnosis for patients with hyper IgM phenotype.

Overall, intravenous immunoglobulins, systemic corticosteroid, and immunosuppressive and biological agents can result in the improvement of clinical manifestations (Azizi et al. 2018c). However, the protein losing enteropathy in P2 persisted despite using intravenous immunoglobulins. The most effective therapy for inflammatory enteropathy in LRBA deficient individuals has not been defined yet. Recently, the use of Sirolimus as an alternative agent for the treatment of intractable enteropathies has been introduced (Azizi et al. 2017b).

In another study, abatacept (CTLA-4-Ig) has been proposed as an effective targeted therapy for autoimmune manifestations, with more favorable outcomes when received at weekly intervals (Kiykim et al. 2019; Lo et al. 2015). However, the effect of long term use of abatacept alone or in combination with other biologics on inflammatory bowel disorders and associated unfavorable outcomes, such as intestinal norovirus infections, should be further investigated (Shouval et al. 2018).

However, for patients who do not respond to conventional therapies, HSCT provides a promising treatment (Bakhtiar et al. 2016; Habibi et al. 2019; Tesch et al. 2019).

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Disclosure statement

The authors declare that they have no conflict of interest.

Ethics statement

Informed consent was obtained from the parents of the patients prior to being included in the study.

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