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Review

Joint Involvement in Patients with LPS-Responsive and Beige-Like Anchor Protein (LRBA) Deficiency: A Case Report and Literature Review

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Abstract

Background: Lipopolysaccharide-responsive beige-like anchor (LRBA) deficiency is an inborn error of immunity characterized by a heterogeneous spectrum of manifestations, including enteropathy, immune dysregulation, and autoimmune disorder. Joint involvement has been less frequently reported, and limited data regarding its clinical presentation in LRBA deficiency has been published.

Case presentation and review results: We reported an Iranian girl who was initially presented with recurrent respiratory tract infections and otitis media, later complicated by arthritis, growth failure, and organomegaly. The diagnosis of LRBA deficiency was confirmed by the identification of a novel homozygous missense variant in the *LRBA* gene (c.7742T>A, p.M2581K). Along with this report, a literature review focused on joint involvement, on 26 patients with LRBA deficiency was performed.

Conclusion: Non-infectious manifestations such as joint involvement have a broad spectrum in LRBA deficiency. For the timely diagnosis and appropriate clinical management, LRBA deficiency should always be kept in mind as a differential diagnosis in patients with joint involvement and clinically typical immune dysregulation.

Keywords: LRBA Deficiency; Joint Involvement; Rheumatoid Arthritis; Inborn Error of Immunity; Juvenile Idiopathic Arthritis.

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Introduction

LPS-responsive and beige-like anchor protein (*LRBA*) deficiency, is an inborn error of immunity caused by either homozygous or compound heterozygous mutations in the *LRBA* gene, often abrogating the expression of *LRBA* (1, 2). Affected patients, present a variable and wide range of clinical symptoms and immunological manifestations (3), including infectious complications (especially in lungs and gastrointestinal tract), immune dysregulation (mainly organomegaly, lymphoproliferation, and autoimmunity), enteropathy, early-onset hypogammaglobulinemia, and allergic symptoms (4). One of the prevalent symptoms in *LRBA* deficient patients is autoimmune complications mainly involving hematologic, endocrine, and gastrointestinal systems (1, 5). Joint involvement, either autoimmune-mediated or not, is less known in *LRBA* deficiency patients. In the current study, we described an Iranian patient who initially suffered from a prolonged course of coughing and wheezing and then her condition was complicated by arthritis of knee and wrists, growth failure, and organomegaly. Finally, she was diagnosed with a novel homozygous missense mutation at the exon 53 of the *LRBA* gene, c.7742T>A (p.M2581K). Additionally, we reviewed the epidemiological, immunological, and clinical features of the patients with LRBA deficiency affected by variable joint involvements reported in the literature.

Methods

The literature search was carried out on PubMed, Web of Science and Scopus Library databases using the following keyterms: "Lipopolysaccharide-responsive beige-like anchor protein", "LPS-responsive beige-like anchor protein", "LRBA", regulatory T cell defects, autoimmune infiltration, and enteropathy", "LATAIE", "LRBA deficiency", "LRBA immunodeficiency", "LRBA mutation", "JIA"(Juvenile idiopathic arthritis), "RA"(Rheumatoid arthritis), "arthritis", or "joint involvement". Articles with at least one patient with LRBA deficiency and joint involvement, were included in the study and the patients' data were extracted and reviewed.

Results

Case presentation

The patient was a 9-year-old girl, the second child of third degree consanguineous Iranian parents, with unremarkable family history. She was born via cesarean section at term gestational age, and her mother had a history of an spontaneous abortion. She was healthy until 5 years of age when she experienced a prolonged course of coughing and wheezing. At that time, she also suffered from tympanic membrane (TM) perforation due to the complicated otitis media. She had recurrent respiratory tract infections, treated with outpatient broad-spectrum antibiotics several times. When she was 6.5 years old, she was hospitalized for the first time with complaints of coughing, diarrhea and fever. She also presented arthritis of knee and wrist joints and weight loss. The patient's physical examination, showed several symptoms associated with the involvement of joints, ears, and lungs, including right ear purulent discharge, purulent post-nasal drip (PND), right lung crackles, as well as the tenderness, warmth, swelling, and decrease in the range of motion of left wrist, both ankles, and right hip. A mild splenomegaly (133*55mm) was also detected by abdominal ultrasound. Echocardiography was normal, and the bone marrow aspiration did not reveal any abnormalities. In this regard, chest high-resolution computed tomography (HRCT) showed mediastinal and hilar lymphadenopathy dominantly at the right side, with slight left sided tracheal deviation and marked extrinsic compression upon right main bronchus. She was finally discharged with the diagnosis of pneumonia and unclassified rheumatologic disease. The immunological parameters of the patient is described in detail in the supplementary material **(Table 1)**. After 21 months, she was admitted to hospital for the second time, with complaints of productive cough, fever, and chills. The medical examination showed PND, right lung crackle, splenomegaly, and failure to thrive (FTT). She underwent the treatment with vancomycin and meropenem for 14 days. Echocardiography, bone marrow aspiration, and bone marrow flowcytometry were normal. In the spiral chest's CT scan, scattering of some pulmonary nodules (up to 13 mm) in the left

Table 1. Summary of laboratory findings of the patient

Laboratory parameters	The first hospitalization	The second hospitalization	The third hospitalization	Reference value
WBC $\times 10^3$ (cell/uL)	13	7.5	3.7	3.9-10.2
Hemoglobin (g/dL)	12.9	10	9.5	11.5 - 15
Absolute lymphocytes counts (cells /µL)	2470	1575	814	800-4000
Absolute neutrophils counts (cells /µL)	10100	5550	2701	2000-7000
Plt ($\times 10^3$ cells /µL)	160	154	88	150-450
IgG (mg/dL)	1006	<17	-	700-1600
IgM (mg/dL)	86	8	-	40-230
IgA (mg/dL)	10	<3	-	44-395
IgE (IU/mL)	0.6	1	-	Up to 160
ANA	<0.5	<1.0	-	<1.0: Negative ≥1.0 : Positive
Anti-D IgG (IU/mL)	-	0.03	-	<0.1: No response 0.1-1: Poor response >1: Normal response
Anti-T IgG (IU/mL)	0.04	0.23	-	<0.1: No response 0.1-1: Poor response >1: Normal response
CD3+ T cells (% of lymphocytes)	32%	75.5%	-	50-80
CD4+ T cells (% of lymphocytes)	13%	64.8%	-	20-65
CD8+ T cells (% of lymphocytes)	10%	7.54%	-	10-40
CD19+ B cells (% of lymphocytes)	2%	5.89%	-	4-25
CD16+ NK cells (% of lymphocytes)	2%	-	-	3-15
CD56+ NK cells (% of lymphocytes)	0.6%	-	-	3-15
LTT PHA	3.8	-	-	≥3
LTT BCG	1.0	-	-	>2.5
LTT Candida	1.0	-	-	>2.5

WBC, white blood cell; Anti-T, anti-tetanus; Plt, platelet; NK, natural killer; LTT, lymphocyte transformation test; PHA, phytohemagglutinin; BCG, Bacillus Calmette-Guérin; ANA, Antinuclear Antibody.

lung, and complete opacification of the right lower lobe, and the lateral segment of the right middle lobe were observed, in favor of lobar pneumonia and mediastinal reactive lymph nodes. These findings were further supported by the report of multiple bilateral pulmonary nodules (innumerous) with a maximum diameter of 25 mm in both lungs in the outpatient HRCT. The laboratory findings related to the second hospitalization, are summarized in **Table 1**. Nine months later, she was hospitalized again due to fever and productive cough for 2 weeks, and she was admitted in COVID19 pediatric invasive care unit (PICU), following the positive result of COVID19 Polymerase Chain Reaction (PCR). In this regard, Physical examinations, presented illness, splenomegaly, clubbing, tachypnea, and a decrease in the O_2 saturation. She received vancomycin, meropenem, interferon β-1a (ReciGen), remdesivir, dexamethasone, teicoplanin, immune globulin intravenous (IVIG), gancyclovir, aspirin, cotrimoxazole, and voriconazole. The echocardiography was normal, but the chest HRCT showed bilateral patchy ground-glass opacities, suggestive of COVID19 bronchopneumonia. Eventually, her condotion improved, and she was discharged after 14 days. Available data of laboratory findings related to the third hospitalization are listed in **Table 1.** In summary, the symptoms of this patient have started at the age of 5 years, gradually progressed, and included a wide range of manifestations, especially joint and respiratory disorders. Finally, she was a nine-years-old symptomatic girl with arthritis, pulmonary consolidation with pleural effusion, immunodeficiency, recurrent infections, low level of hemoglobin, and abnormal CD markers. Based on the clinical and paraclinical investigations, the common variable immunodeficiency (CVID) was considered as a possible diagnosis. With the impression of CVID, the genetic analysis were performed on whole

blood samples by whole exon sequencing (WES). Analysis of the exome's data showed a variant, at the exon 53 of the *LRBA* gene, c.7742T>A (p.M2581K), as a possible candidate that may explain the clinical history mentioned above. The detected homozygous missense variant in the *LRBA* gene, has not been previously reported for its pathogenicity. This gene has been reported to cause CVID-8 with autoimmunity, among autosomal recessive inheritance. This change has not been previously reported as a pathogenic mutation, and the variant is absent in population databases (ExAC, 1000G, and our local database). Based on american college of medical genetics and genomics)ACMG(guidelines, this variant was classified as a variant of uncertain significance (VUS) (6).

Literature review

The number of twenty six patients with LRBA deficiency affected by variable types of joint involvements (14 females, 11 males, 1 unknown sex), were reported in 15 articles (**Table 2)**. The median age (IQR) at the onset of symptoms, was 1.3 (0.6-2.3) years, and the diagnosis of LRBA deficiency was made at a median age (IQR) of 10.2 (6.8-16.9) years. Consanguinity and positive family history of immunodeficiencies, were reported in 80% (20 of 25) and 33.3% (8 of 24) of the cases, respectively. Four patients (out of 25 with available data) were deceased in a median follow up of 14.0 (10.8-18.0).

Twenty-three patients developed autoimmune complications (88.5%), predominantly in forms of autoimmune entropathy (14 cases), and cytopenia (12 cases). As demonstrated in **Table 2,** 16 out of the 26 patients (61.5%), had organomegaly in different types of splenomegaly (46.2%), hepatomegaly (42.3%), or lymphadenopathy (50%). Infection occurred in 76% (6 of 25) of the patients. Failure to thrive (FTT) (69.2%) and clubbing (50%), were common manifestations among the patients. Hematologic involvement was also a prevalent manifestion, presented in 50% (13 of 26) of the patients, however, malignancy was diagnosed only in two patients (7, 8). Also, among 26 LRBA deficient patients with arthritis, the type of joint involvement was reported as RA in 3, and JIA in 5 patients (**Table 2).**

Decreased CD3+, CD4+, CD8+, CD19+, and NK Tcell counts was detected in 26.1%, 37.5%, 20.8%, 55%, and 64% of the patients, respectively. Decreased serum level of IgG, IgA, IgM, were the most reported abnormalities in immunoglobin level in 65% (16 of 25), 58.3% (14 of 24), and 66.7% (16 of 24) of the patients, respectively.

Sixteen patients were treated with steroids, and 37.5% were responsive. About 15% of the patients (4 out of 26) underwent hematopoietic stem cell transplantation (HSCT), and all responded well to the treatment, and are still alive.

Discussion

LRBA deficiency was first reported in four consanguineous families, who suffered from childhood-onset humoral immune deficiency and features of autoimmunity (2). The *LRBA* gene is located on 4q31.3, contains 57 exons and encodes a protein containing 2851 amino acid residues (9). The LRBA protein is widely expressed in several cell types, with an high expression, especially in lymphocytes (2). LRBA, modulates CTLA-4 (cytotoxic T lymphocyte antigen-4) expression (10), and defects in Treg and CTLA4 have been reported in most cases, highlighting the critical role of LRBA in the CTLA-4 recycling and membrane shuttling process (11, 12). Dysfunction of LRBA results in depletion of the CTLA-4, which causes a functional deficiency of CTLA-4, skewing towards T-cell's hyperactivation (13, 14).

Before the discovery of *LRBA* gene mutations, most of the affected patients were diagnosed with CVID. In the Gámez-Díaz et al. study, 41% of LRBA deficieny patients had a previous tentative diagnosis of CVID (1). Some studies even showed a higher percentage of CVID, as in the study of Azizi et al. 70.6% of the patients were diagnosed with CVID (15). Recent reports of the extended disease's phenotypes, described the clinical characteristics of LRBA deficiency, including chronic diarrhea, pneumonitis, organomegaly, type 1 diabetes mellitus, thyroiditis, hemolytic anemia, and thrombocytopenia (9, 15). Although, some manifestations such as arthritis (as an autoimmune disease), are rare in the LRBA deficiency patients, and little clinical information regarding the pattern of joint involvement has been published so far.

In the current study, we reported a patient who initially presented arthritis, but was eventually

Table 2. Overview of LRBA patients with arthritis

NO.	sex	Cons.	FH	AOO (Y)	Immunologic abnormality	AAb	Autoimmunity-type	Lymphoproliferation	Joint involvement	Infection	Others	mutation	outcome	Ref.
1	ND	ND	ND	1.0	Neutropenia	ND	AIHA,ITP,IBD	+	Arthritis	-	FTT, Renal tubulopathy, GLILD	LRBA	ND	(25)
2	M	+	+	1.8	High CD4+	ANA, Anti-erythrocyte IgG	IDDM, Psoriasis, JIA	-	Arthritis	+	Bilateral medullar nephrocalcinosis, Aortic valve dysplasia	LRBA	Alive	(26)
3*	M	-	-	0.1	Neutropenia, low CD3+,CD4+,CD8+, CD19+,NK	Coombs,	AIHA, ITP, vitilig, CD, Atrophic gastritis	-	Arthritis	-	FTT, Secondary cushing syndrom	LRBA	Alive	(1)
4	F	+	-	2.0	Hypogammaglobulinemia,	ND	-	+	Arthritis	+	FTT,Clubbing,	LRBA	Alive	(15)
5	M	+	-	0.5	-	-	Psoriasis,Vitiligo,AIT,AIE	+	Arthritis	-	FTT, Seizure, Chronic diarrhea	LRBA	Alive	(27)
6	F	+	+	5.0	Hypogammaglobulinemia	Coombs, Anti-platelet	AIHA,AIH,IBD,Vasculitis	+	Arthritis	+	FTT	LRBA	Alive	(1)
7	F	+	-	4.0	Low NK, Low IgG	Anti-neutrophil	AIHA, AIE	+	Arthritis	+	FTT,Abcess, Septicemia, Erythema nodosum, Cellulitis, ILD	LRBA	Alive	(9)
8	M	+	-	0.2	Low IgG,IgM,CD19+,CD8+,CD4+,CD3+,NK	ANA, ANCA	AIE, CD, RA	-	RA	+	FTT, Gastric adenocarcinoma, Melanoma, Cholelithiasis, Cushingoid, HTN, Nephrocalcinosis, Allergy	LRBA	Alive	(7)
9	F	+	+	1.0	Hypogammaglobulinemia, Low NK	ND	ITP	-	Reactive mono-arthritis	+	FTT, Bronchiectasis, Allergy	LRBA	Alive	(2)
10*	F	+	-	1.0	High CD4+	Celiac antibody	AIHA,CD	+	Arthritis	+	FTT, clubbing, Bronchiectasis, Osteomyelitis,Septicemia,Allergy,Renal tubulopathy	LRBA	Alive	(17)
11	M	+	-	2.0	Hypogammaglobulinemia, Low NK,CD19+,CD4+	RF,ANA	JIA,IBD	+	Arthritis	+	Clubbing, Bronchiectasis, Multiple polmunary, hepatic, splenic and adrenal granulomas.	LRBA	Alive	(15)
12	M	+	+	2.0	Hypogammaglobulinemia, Low NK,CD19+	-	-	+	Arthritis	+	FTT, Clubbing, Bronchiectasis	LRBA	Alive	(15)
13	F	+	-	0.5	Hypogammaglobulinemia, Low NK,CD19+,CD4+	ND	JRA	+	Arthritis	+	Clubbing, Bronchiectasis, Septic arthritis	LRBA	Alive	(15)
14	F	+	-	3.0	Hypogammaglobulinemia, Low NK,CD4+	ANA,RF	JRA	+	Arthritis	+	Clubbing, Bronchiectasis, Allergy	LRBA	Dead	(15)
15	F	+	-	2.0	Hypogammaglobulinemia,low NK,CD3+,CD4+,CD8+	ND	Myasthenia Gravis,AIT,CD	-	Arthritis	+	FTT, Clubbing, Bronchiectasis, Allergy	LRBA	Dead	(15)

Continued Table 2. Overview of LRBA patients with arthritis

NO.	sex	Cons.	FH	AOO (Y)	Immunologic abnormality	AAb	Autoimmunity-type	Lymphoproliferation	Joint involvement	Infection	Others	mutation	outcome	Ref.
16	M	+	-	2.0	Hypogammaglobulinemia, Low NK,CD19+	Coombs	ITP,AIHA,IBD,AIE	+	Arthritis	+	FTT, Clubbing, Bronchiectasis, Septicemia, Urticaria, Allergy	LRBA	Dead	(15)
17	F	+	+	4.0	Low CD19+,NK,IgG,IgA	celiac antibody	IBD	-	Arthritis	+	FTT, Clubbing, Bronchiectasis	LRBA	Alive	(18)
18*	F	-	+	0.67	Low NK, IgG	-	JIA	+	Arthritis	-	FTT, Clubbing, GLILD	LRBA	Alive	(28)
19	F	+	+	1.0	ND	ANA, anti-IAA, anti-dsDNA, anti-cardiolipin, thyroglobulin, thyroid peroxidase IgG	AIHA, IDDM, Alopecia	-	Arthritis	+	Malar rash, Pericarditis	LRBA	Dead	(29)
20	F	-	-	3.0	High IgG	-	JIA, AIHA, neutropenia, Autoimmune enteritis	+	Arthritis	-	Brain lesion	LRBA	Alive	(5)
21*	M	+	-	0.25	Low CD3+,CD4+,CD8+,CD19+, NK,Hypogammaglobulinemia	ND	ITP, Arthritis, Hashimoto thyroiditis	+	Arthritis	+	FTT, recurrent folliculitis complicating with skin abscess, renal tubulopathy, Grade I tubular adenocarcinoma	LRBA	Alive	(8)
22	M	+	-	0.58	Low IgA,IgM, CD3+,CD4+, CD19+	ND	ITP, Vitiligo, Arthritis	-	Arthritis	+	Clubbing	LRBA	Alive	(8)
23	M	-	-	1.5	Low CD3+,CD4+,CD8+,CD19+, NK,Hypogammaglobulinemia	Coombs-positive	AIHA, Vitiligo, Arthritis	+	Arthritis	+	FTT, Clubbing, psoriasis like rash,	LRBA	Alive	(8)
24	M	+	-	3.5	High CD3+,CD8+ Low NK, Hypogammaglobulinemia	ND	JIA, Optic neuritis, Transverse myelitis, Multiple sclero, IBD	+	Arthritis	-	FTT, Clubbing, Jaundice	LRBA	Alive	(8)
25	F	+	+	0.75	High CD8+, Low CD19+,IgM	ND	IDDM, Arthritis, Celiac-like disease	-	Arthritis	+	FTT,Bronchiectasis,	LRBA	Alive	(8)
26	F	-	ND	0.75	ND	ND	-	ND	Arthritis	ND	ND	LRBA	Alive	(30)

AOO, Age of onset; Y,year; AAB, Auto-antibody; ITP, Immune thrombocytopenic purpura; AIHA, Autoimmune hemolytic anemia; IBD, Inflammatory bowel disease; ND, No Data; GLILD, Granulomatous-lymphocytic interstitial lung disease; FTT, Failure to thrive; IDDM, Insulin-dependent diabetes mellitus; JIA, Juvenile idiopathic arthritis; CD, Crohn's disease; AIT, Autoimmunthyreoiditis; AIE, Autoimmune enteropathy; RA, Rheumatoid arthritis; ANA, Antinuclear Antibody; ANCA, Antineutrophil Cytoplasmic Antibodies; RF, Rheumatoid factor; JRA, Juvenile rheumatoid arthritis.
*Patients underwent HSCT

diagnosed with LRBA deficiency. We also reviewed the epidemiological, immunological, and clinical features of 26 LRBA deficiency patients with variable joint involvements (**Table 2).**

In the prevoius study, Azizi et al. (15) described the clinical, immunological, molecular analyses and outcomes of 17 Iranian patients with LRBA deficiency, and reported 7 patients (41%) with arthritis; Two of them had positive results for antinuclear antibody (ANA) and rheumatoid factor (RF,) and juvenile rheumatoid arthritis (JRA) were present in three patients. In another study, Mozdarani et al., while evaluating the radiation sensitivity, found arthritis in four out of eleven patients with LRBA deficiency (16). Sinan Sari et al. described LRBA deficiency in a Turkish girl, who presented refractory celiac disease, severe malnutrition, and monoarthritis . Lastly (17), Abdullah Alangari et al. (18) reported a 22-year-old woman who had a history of recurrent arthritis in the large joints, mainly the knees. She was given a diagnosis of combined immunodeficiency (CID), based on low serum IgG and IgA levels, and was started on IVIG replacement, immediately after the diagnosis of hypogammaglobulinemia was made.

Previous studies have reported positive effects of the abatacept and sirolimus in LRBA deficiency patients (8, 19-21). In Meshaal et al. study, sirolimus was added to the treatment plan for five out of 18 Egyptian LRBA Deficiency patients, three of whom improved, while the other two patients did not respond (13). Besides sirolimus which has been reported to improve clinical outcomes (15, 22), abatacept (anti-CTLA-4 antibody) has also been introduced as a targeted therapy for patients with LRBA deficiency (12). In this regard, in a previous study with 15 LRBA-deficient patients, among eleven patients who were given abatacept, just one patient experienced a severe pneumonia with pleural effusion and respiratory distress after the initiation of abatacept, and other patients benefited from the therapy without any complications (23). Currently, there is no established therapeutic consensus for the appropriate dose and frequency of abatcept for LRBA deficiency patients. However, some clinical trials proposed abatacept administration, 125 mg twice every 3 weeks subcutaneously (24), and 10 mg kg– 1 every 2 weeks for 3 months (21).

Conclusion

In virtue of recent advances in genomic sequencing, some patients who were previously classified as CVID, are now considered as LRBA deficiency. Some of these patients have rheumatic manifestations such as joint involvement. Therefore, for timely diagnosis of immunodeficient patients, and prevention of further complications, there should be a multidisciplinary approach between rheumatologists and immunologists.

Conflict of interest

There is no conflict of interest between authors.

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