ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Myasthenia gravis in the complex scenario of LRBA-related immune dysregulation

Miastenia gravis no cenário clínico complexo das imunodesregulações relacionadas ao gene LRBA

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ABSTRACT

Autoimmune diseases have been progressively recognized as a potential complication of primary immunodeficiency, especially for some genetic subtypes of common variable immunodeficiency. Although often associated with other autoimmune disorders, autoimmune myasthenia gravis is occasionally identified as a neuromuscular complication of primary immunodeficiency. We report the case of a Brazilian woman with common variable immunodeficiency-8 due to an *LRBA* variant, in which myasthenia gravis was identified in association with anti-acetylcholine receptor antibody. Marked clinical improvement occurred after intravenous immunoglobulin therapy.

Keywords: Myasthenia gravis, common variable immunodeficiency, immune system diseases, autoimmune diseases.

RESUMO

Doenças autoimunes foram progressivamente reconhecidas como complicações potenciais das imunodeficiências primárias, especialmente para alguns subtipos genéticos das imunodeficiências comuns variáveis. Embora se associe comumente a outras doenças autoimunes, a Miastenia gravis autoimune adquirida foi raramente associada como complicação neuromuscular de imunodeficiências primárias. É descrito neste artigo o caso de paciente brasileira do sexo feminino com diagnóstico de Imunodeficiência Comum Variável tipo 8 por variante no gene *LRBA*, na qual foi identificada Miastenia gravis em associação a anticorpos antirreceptor de acetilcolina. Ela evoluiu com marcante melhora clínica após a introdução de terapêutica com imunoglobulina endovenosa.

Descritores: Miastenia gravis, imunodeficiência de variável comum, doenças do sistema imunitário, doenças autoimunes.

Introduction

Primary immunodeficiencies have been progressively recognized in association with several autoimmune disorders, representing a complex challenge during the diagnostic work-up and follow-up treatment. Common variable immunodeficiency (CVID) is a complex clinically and genetically heterogenous group of inherited disorders of the immune system, leading to hypogammaglobulinemia, antibody production deficiency, variable reduction of T-cell activation/proliferation, and recurrent infections, generally with childhood onset. CVID is the most common group of primary immunodeficiency diseases.[1,2] Autoimmune disorders are potential life-threatening complications of CVID that may involve compromised hematological, skin, gastrointestinal, neurological, and connective tissue.[3,4] The clinical

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presentation of CVID may vary considerably with age at onset of recurrent infectious complications or autoimmune disorders, ranging from early childhood to late adulthood manifestations.[1] Lipopolysaccharide-responsive beige-like anchor (LRBA) deficiency is a rare primary immunodeficiency associated with CVID with autoimmunity-8 (CVID8), which leads to a difficult clinical scenario involving multiple autoimmunities, immune dysregulation, and high risk of malignancy, especially lymphoproliferation.[5,6]

Myasthenia gravis is the most common acquired disorder of the neuromuscular junction, having an idiopathic or paraneoplastic autoimmune basis. Antibodies directed to the postsynaptic acetylcholine receptor and other epitopes that complement activation play a key role in its pathophysiology.[7,8] Specific genetic markers, such as HLA polymorphisms (ie, HLA-B7, HLA-B8, HLA-DR3, and HLA-DRB115.01) and other concurrent autoimmune comorbidities lead to a higher risk of myasthenia gravis.[9] Myasthenia gravis has been identified as a neuromuscular complication of primary immunodeficiencies, such as selective IgA deficiency.[10-12] Here we describe a rare case of autoimmune acquired myasthenia gravis as a complication of CVID8, which was treated with monthly infusions of intravenous immunoglobulin, resulting in marked clinical improvement in motor symptoms.

Case report

A 31-year-old Brazilian woman presented with a 7-year history of fluctuating weakness and fatigue involving the lower limbs and trunk, which progressed to dysphagia, dysphonia, diplopia, and bilateral eyelid ptosis after 3 years. In the diagnostic work-up, serologic testing was positive for anti-acetylcholine receptor antibodies, and increased thymus size was found in chest CT imaging, which was compatible with thymic hyperplasia. The patient has had 7 myasthenic crises since her diagnosis and was treated with intravenous immunoglobulin several times during acute decompensation. She had no significant response to azathioprine, cyclosporin, or cyclophosphamide. She has been stable since last year, when monthly intravenous immunoglobulin therapy was started. Only minimal manifestations of fatigue and mild lower limb weakness persist.

Her medical history showed: (i) recurrent infections since childhood (urinary tract infection, recurrent sinusitis and pneumonia, including at least 5 lower respiratory tract infections in the last year); (ii) CVID due to abnormal cellular immune response and hypogammaglobulinemia (reduced IgG, IgA and IgM serum levels); (iii) autoimmune polyglandular syndrome type 2 (type 1 diabetes mellitus, anti-GAD antibody-positive, primary adrenal insufficiency, and hypothyroidism) at 25 years of age; (iv) celiac disease at 24 years of age; (v) dermatitis herpetiformis (Duhring-Brocq disease) at 23 years of age; (vi) cerebral venous sinus thrombosis at 29 years of age; (vii) allergies to numerous foods and drugs since childhood, including latex-fruit syndrome at 18 years of age; (viii) asthma since childhood; and (ix) intestinal lymphangiectasia at 27 years of age. In the last three months, she reported subacute diarrhea, flushing, wheezing, and diffuse erythematous plaques lasting 40 days, leading to assessment for carcinoid syndrome. Positron emission tomography revealed a peripancreatic duodenal nodular lesion compatible with neuroendocrine tumor. The family history included 4 paternal aunts with malignant breast cancer, a paternal cousin with early-onset malignant breast cancer at 35 years of age, a paternal cousin with lymphoproliferative disorder at 32 years of age, and a paternal grandmother with multiple allergies. Laboratory examinations revealed variable immunological parameters, including hypogammaglobulinemia (with a mild-to-moderate reduction in serum IgG, IgA, and IgM levels), normal to mildly reduced TCD4+ cells and normal to mildly reduced B cells. Anemia and thrombocytopenia were not observed.

Due to her history of recurrent infection, multiple autoimmunities, and predisposition to malignancy, we performed next-generation sequencing-based multigene testing for autoinflammatory syndromes, primary immunodeficiency, and inborn errors of immunity, which revealed the heterozygous variant c.4367T>C (p.Leu1456Ser) in the *LRBA* gene (NM_001364905.1), fulfilling PM2, PP3 and PP4 criteria according to American College of Medical Genetics and Genomics guidelines (2015). This variant is very rare in the gnomAD database (AF 0.0008% in gnomAD aggregated) and is not included in the ClinVar and ABraOM databases (Online Archive of Brazilian Mutations). Multiple *in silico* prediction tools indicate that this variant has a deleterious impact (MutationTaster, Revel, Varity, SIFT, BayesDel, fitCons, GenoCanyon). Due to the highly suggestive clinical and genomic predictions and previous reports on heterozygous variants[13-16], a diagnosis of CVID8 (MIM #614700) was established.

Discussion

LRBA deficiency (or CVID8) was first described in 2012 as an autosomal recessive immunodeficiency due to biallelic homozygous or compound heterozygous variants in the *LRBA* gene (4q31.3), which codes for the LRBA protein.[17,18] LRBA, a cytoplasmic protein that regulates intracellular vesicle trafficking and the endocytosis and exocytosis of receptors, which prevents the lysosomal degradation of cytotoxic T lymphocyte protein 4, returning it to the cell surface.[19] Thus, LRBA deficiency results in reduced expression of cytotoxic T lymphocyte protein 4, an immune checkpoint protein. Affected individuals present with variable phenotypes, including childhood-onset recurrent infections (particularly sinopulmonary infections), hypogammaglobulinemia, and often multiple autoimmune disorders, in addition to lymphoproliferative and granulomatous diseases.[5,20]

Autoimmune diseases are a common clinical feature in patients with LRBA deficiency (61%), including idiopathic thrombocytopenia purpura, autoimmune hemolytic anemia, autoimmune thyroid disease (hypothyroidism), inflammatory bowel disease, autoimmune enteropathy, type I diabetes mellitus, early-onset chronic polyarthritis, asthma, and interstitial pneumonia.[20-22] Less common manifestations include chronic atrophic gastritis, myasthenia gravis, juvenile idiopathic arthritis, anterior uveitis, autoimmune hepatitis, pancytopenia, neutropenia, allergic dermatitis, alopecia, vitiligo, urticaria and celiac disease.[21-24] Besides autoimmune myasthenia gravis, other neurological complications include cerebral lesions, nervous tissue atrophy, cerebral granulomas (with strabismus, hemiplegia, and seizures as complications), and granuloma-like lesions with demyelination, which result in unilateral optic nerve atrophy, opportunistic neuroinfectious diseases due to baseline immunosuppression (both humoral and cellular immune defects), and longitudinally extensive transverse myelitis.[25]

Burkitt lymphoma, marginal zone lymphoma, lymphoproliferative diseases, and malignant gastrointestinal neoplasms have been associated with LRBA deficiency.[26] Patients with autoimmune myasthenia gravis are at high risk of developing thymic and extrathymic neoplasms.[27,28] Myasthenia gravis has also been associated with carcinoid syndrome in a paraneoplastic context.[29,30] On rare occasions, pathogenic LRBA variants have been associated with autoimmune myasthenia gravis, especially in LRBA deficiency with autoantibodies, regulatory T cell defects, autoimmune infiltration, and enteropathy syndrome.[23] This case emphasizes the complex scenario of a monogenic mechanism leading to multiple autoimmune disorders, malignancies, and the risk of paraneoplasia.

Different medications have been used to treat LRBA deficiency, including intravenous immunoglobulin, corticosteroids, sirolimus, infliximab, rituximab, and azathioprine.[31] More recent studies have found abatacept effective in controlling the disease, especially in immune dysregulation phenotypes, although no validated consensus exists to guide dosage, frequency, or follow-up.[32] Complete or partial remission has been achieved with hematopoietic stem cell transplantation, including better immune hyperactivity control than abatacept, sirolimus, or conventional immunosuppressive therapy.[19]

A review of the current literature on single heterozygous variants due to possible *de novo* variants or an autosomal dominant pattern of inheritance revealed the case of a 7-year-old boy with autoimmune epilepsy, hypogammaglobulinemia, and recurrent infections.[13] Genetic testing revealed a single heterozygous *LRBA* variant (c.6695T>C, p.Ile2232Thr), which has been previously associated with compound heterozygous variants in LRBA deficiency.[13] Other confirmed cases of heterozygosity have been described in at least 3 clinical contexts: an adult with CVID complicated by hemophagocytic lymphohistiocytosis;[14] a girl with monogenic inflammatory bowel disease who had childhood-onset chronic active colitis without granulomas;[15] and an older man with juvenile-onset recurrent infections due to CVID and autoimmune thyroiditis.[16]

CVID with autoimmunity must be included in the differential diagnosis of patients with several associated multiple autoimmunities,[33,34] even without a well-established family history. Autoimmune myasthenia gravis may be a neuromuscular complication in autoimmunities associated with primary immunodeficiencies, as well as in paraneoplastic syndromes. Recognizing the monogenic basis of immune dysregulation in these clinical scenarios is essential for more specific, effective, and safe therapy in neuromuscular junction disorders.

References

1. Yazdani R, Habibi S, Sharifi L, Azizi G, Abolhassani H, Olbrich P, et al. Common variable immunodeficiency: epidemiology, pathogenesis, clinical manifestations, diagnosis, classification, and management. J Investig Allergol Clin Immunol. 2020;30(1):14-34.

2. Ameratunga R, Allan C, Woon ST. Defining Common Variable Immunodeficiency Disorders in 2020. Immunol Allergy Clin North Am. 2020;40(3):403-20. doi: 10.1016/j.iac.2020.03.001.
3. Agarwal S, Cunningham-Rundles C. Autoimmunity in common variable immunodeficiency. Ann Allergy Asthma Immunol. 2019;123(5):454-60. doi: 10.1016/j.anai.2019.07.014.
4. ereige JD, Maglione PJ. Current understanding and recent developments in Common variable immunodeficiency associated autoimmunity. Front Immunol. 2019;10:2753. doi: 10.3389/fimmu.2019.02753.
5. Lopez-Herrera G, Tampella G, Pan-Hammarström Q, Herholz P, Trujillo-Vargas CM, Phadwal K, et al. Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. Am J Hum Genet. 2012;90(6):986-1001. doi: 10.1016/j.ajhg.2012.04.015.
6. Bogaert DJA, Dullaers M, Lambrecht BN, Vermaelen KY, De Baere E, Haerynck F. Genes associated with common variable immunodeficiency: one diagnosis to rule them all? J Med Genet. 2016;53(9):575-90. doi: 10.1136/jmedgenet-2015-103690.
7. Mantegazza R, Bernasconi P, Cavalcante P. Myasthenia gravis: from autoantibodies to therapy. Curr Opin Neurol. 2018;31(5):517-25. doi: 10.1097/WCO.0000000000000596.
8. Melzer N, Ruck T, Fuhr P, Gold R, Hohlfeld R, Marx A, et al. Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the Guidelines of the German Neurological Society. J Neurol. 2016;263(8):1473-94. doi: 10.1007/s00415-016-8045-z.
9. Nacu A, Andersen JB, Lisnic V, Owe JF, Gilhus NE. Complicating autoimmune diseases in myasthenia gravis: a review. Autoimmunity. 2015;48(6):362-8. doi: 10.3109/08916934.2015.1030614.
10. Liblau R, Fischer AM, Shapiro DE, Morel E, Bach JF. The frequency of selective IgA deficiency in myasthenia gravis. Neurology. 1992;42(3):516-8. doi: 10.1212/wnl.42.3.516.
11. Odineal DD, Gershwin ME. The epidemiology and clinical manifestations of autoimmunity in selective IgA deficiency. Clin Rev Allergy Immunol. 2020;58(1):107-33. doi: 10.1007/s12016-019-08756-7.
12. Ramanujam R, Piehl F, Pirskanen R, Gregersen PK, Hammarström L. Concomitant autoimmunity in myasthenia gravis -- lack of association with IgA deficiency. J Neuroimmunol. 2011;236(1-2):118-22. doi: 10.1016/j.jneuroim.2011.05.008.
13. Sandhu A. Heterozygous mutation in LRBA gene resulting in CVID phenotype and autoimmunity. Ann Allergy Asth Immunol 2019;123(5):S124. doi: 10.1016/j.anai.2019.08.403.
14. Ren Y, Xiao F, Cheng F, Huang X, Li J, Wang X, et al. Whole exome sequencing reveals a novel LRBA mutation and clonal hematopoiesis in a common variable immunodeficiency patient presented with hemophagocytic lymphohistiocytosis. Exp Hematol Oncol 2021;10(1):38. doi: 10.1186/s40164-021-00229-y.
15. He M, Wong A, Sutton K, Gondim MJB, Samson C. Very-early onset chronic active colitis with heterozygous variants in LRBA1 and CARD11, a case of "Immune TOR-Opathies". Fetal Pediatr Pathol. 2022;1-10. doi: 10.1080/15513815.2022.2088912.
16. Sewell C, Callahan M, Immaneni N, Saab R, Hostoffer R. Novel heterozygote mutation of LRBA associated with CVID. Ann Allergy Asth Immunol 2022;129(5):S122. doi: 10.1016/j.anai.2022.08.852.
17. Cagdas D, Halaçli SO, Tan C, Lo B, Çetinkaya PG, Esenboga S, et al. A spectrum of clinical findings from ALPS to CVID: several novel LRBA defects. J Clin Immunol. 2019;39(7):726-38. doi: 10.1007/s10875-019-00677-6.
18. Asgardoon MH, Azizi G, Yazdani R, Sohani M, Pashangzadeh S, Kalantari A, et al. Monogenic primary immunodeficiency disorder associated with Common variable immunodeficiency and autoimmunity. Int Arch Allergy Immunol. 2020;181(9):706-14. doi: 10.1159/000508817.
19. Tesch VK, Abolhassani H, Shadur B, Zobel J, Mareika Y, Sharapova S, et al. Long-term outcome of LRBA deficiency in 76 patients after various treatment modalities as evaluated by the immune deficiency and dysregulation activity (IDDA) score. J Allergy Clin Immunol. 2020;145(5):1452-63. doi: 10.1016/j.jaci.2019.12.896.
20. Bal SK, Haskologlu S, Serwas NK, Islamoglu C, Aytekin C, Kendirli T, et al. Multiple presentations of LRBA deficiency: a single-center experience. J Clin Immunol. 2017;37(8):790-800. doi: 10.1007/s10875-017-0446-y.
21. Alkhairy OK, Abolhassani H, Rezaei N, Fang M, Andersen KK, Chavoshzadeh Z, et al. Spectrum of phenotypes associated with mutations in LRBA. J Clin Immunol. 2016;36(1):33-45. doi: 10.1007/s10875-015-0224-7.
22. Azizi G, Abolhassani H, Zaki-Dizaji M, Habibi S, Mohammadi H, Shaghaghi M, et al. Polyautoimmunity in patients with LPS-responsive beige-like anchor (LRBA) deficiency. Immunol Invest. 2018;47(5):457-67. doi: 10.1080/08820139.2018.1446978.
23. Lo B, Fritz JM, Su HC, Uzel G, Jordan MB, Lenardo MJ. CHAI and LATAIE: new genetic diseases of CTLA-4 checkpoint insufficiency. Blood. 2016;128(8):1037-42. doi: 10.1182/blood-2016-04-712612.
24. Lévy E, Stolzenberg MC, Bruneau J, Breton S, Neven B, Sauvion S, et al. LRBA deficiency with autoimmunity and early onset chronic erosive polyarthritis. Clin Immunol. 2016;168:88-93. doi: 10.1016/j.clim.2016.03.006.
25. Chinello M, Mauro M, Cantalupo G, Talenti G, Mariotto S, Balter R, et al. Acute cervical longitudinally extensive transverse myelitis in a child with Lipopolysaccharide-responsive-beige-like-anchor-protein (LRBA) deficiency: a new complication of a rare disease. Front Pediatr. 2020;8:580963. doi: 10.3389/fped.2020.580963.
26. Bratanic N, Kovac J, Pohar K, Podkrajsek KT, Ihan A, Battelino T, et al. Multifocal gastric adenocarcinoma in a patient with LRBA deficiency. Orphanet J Rare Dis. 2017;12:131. doi: 10.1186/s13023-017-0682-5.
27. Levin N, Abramsky O, Lossos A, Karussis D, Siegal T, Argov Z, et al. Extrathymic malignancies in patients with myasthenia gravis. J Neurol Sci. 2005;237(1-2):39-43. doi: 10.1016/j.jns.2005.05.009.
28. Citterio A, Beghi E, Millul A, Evoli A, Mantegazza R, Antozzi C, et al. Risk factors for tumor occurrence in patients with myasthenia gravis. J Neurol. 2009;256(8):1221-7. doi: 10.1007/s00415-009-5091-9.
29. Keens SJ, Desmond MJ, Utting JE. Carcinoid syndrome with myasthenia gravis. An unusual and interesting case. Anaesthesia. 1986;41(4):404-7. doi: 10.1111/j.1365-2044.1986.tb13228.x.
30. Hermans MAW, Stelten BML, Haak HR, de Herder WW, Dercksen MW. Two patients with a neuroendocrine tumour of the small intestine and paraneoplastic myasthenia gravis. Endocrinol Diabetes Metab Case Rep. 2014;2014:140013. doi: 10.1530/EDM-14-0013.
31. Walter JE, Farmer JR, Foldvari Z, Torgerson TR, Cooper MA. Mechanism-based strategies for the management of autoimmunity and immune dysregulation in primary immunodeficiencies. J Allergy Clin Immunol Pract. 2016;4(6):1089-100. doi: 10.1016/j.jaip.2016.08.004.
32. Kiykim A, Ogulur I, Dursun E, Charbonnier LM, Nain E, Cekic S, et al. Abatacept as a long-term targeted therapy for LRBA deficiency. J Allergy Clin Immunol Pract. 2019;7(8):2790-800.e15. doi: 10.1016/j.jaip.2019.06.011.
33. Azizi G, Abolhassani H, Asgardoon MH, Alinia T, Yazdani R, Mohammadi J, et al. Autoimmunity in common variable immunodeficiency: epidemiology, pathophysiology and management. Expert Rev Clin Immunol. 2017;13(2):101-15. doi: 10.1080/1744666X.2016.1224664.
34. Rizvi FS, Zainaldain H, Rafiemanesh H, Jamee M, Hossein-Khannazer N, Hamedifar H, et al. Autoimmunity in common variable immunodeficiency: a systematic review and meta-analysis. Expert Rev Clin Immunol. 2020;16(12):1227-35. doi: 10.1080/1744666X.2021.1850272.

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