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Case Report

Case Report: An Unreported Homozygous Variant within Lipopolysaccharide Responsive Beige-Like Anchor (LRBA) Gene in a Child Exhibiting with Infantile Type 1 Diabetes Mellitus

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Abstract

We report a patient who was born at term as the first son of consanguineous Saudi parents. He developed IDDM at the age of 7 months; the initial symptoms included fever and vomiting. The laboratory findings indicated pronounced ketoacidosis, Initial fluid replacement with normal saline, followed by continuous IV insulin infusion. After a while, the baby was out of DKA. Our endocrinologist advised us to start administering S/C insulin NPH 1 unit BID. Fortunately, a primary immune deficiency was suspected after a few days from the first presentation. The WES revealed A homozygous likely pathogenic variant was identified in the LRBA gene. The result is consistent with a genetic diagnosis of autosomal recessive CVID type 8 with autoimmunity. The LRBA protein regulates the expression of CTLA-4, which is a potent immune checkpoint receptor expressed by activated and regulatory by the T-cells. CTLA-4 blocks the stimulation/proliferation of T-cells and modulates immune responses.

Keywords: LRBA deficiency; Infantile type 1 diabetes mellitus; Immunodeficiency; Whole exome sequencing

Introduction

Lipopolysaccharide (LPS)-Responsive Beige-Like Anchor (LRBA) is a novel gene that is vital to the stander of the immune system's function. [1] In 2012, genetic alterations in LRBA were associated with early-onset Common Variable Immunodeficiency (CVID) type eight, [2] characterized by a wide range of manifestations, including humoral immune deficiency, lymphoproliferation, hematologic and organ autoimmunity [3], for instance, recurrent infections, Inflammatory Bowel Disease (IBD), and Insulin-Dependent Diabetes Mellitus (IDDM). [4] Not to mention, LRBA variations are among the four genetic causes

of early-onset diabetes [4]. As a matter of fact, When IDDM is diagnosed in a patient aged less than 1 year with autoimmune manifestations, mutations in this gene should be suspected. in the present study, we describe a 7 months old patient with early-onset diabetes and further developed recurrent infections. Whole Exome Sequencing (WES) revealed a homozygous frameshift mutation LRBA,c.7863_7864del p.(Arg2621Serfs*27) We focused on blood glucose control and other comorbidities.

Case Presentation

We describe a patient who was born at term as the first son of consanguineous Saudi parents with an unremarkable family history. he developed IDDM at the age of 7 months; the initial symptoms included fever and vomiting with poor oral intake. The laboratory findings indicated pronounced ketoacidosis (pH of 7.013, Hco3 level of 5.5 mEq/l, pCO2 level of 11.8 mmHg, and urine analysis showed glucose +3, ketone +3), a blood glucose level of 590 mg/dL, and a glycated hemoglobin level of 7.73%. The patient was severely ill with dehydration and then she was admitted to the pediatric intensive care unit as a case of neonatal diabetes with severe DKA, kept NPO, we started IV 50 IU regular insulin IN 500 ML normal saline at rate of 6 ml/hour and the IVF was Normal saline at rare of 45 ml/hour + 10 MEQ KCL after 10 hours the baby was having hypoglycemic episodes so we allow breastfeeding and adjust iv fluid to 5% Dextrose and 0.45% Sodium Chloride, after a while the baby was out of diabetic ketoacidosis, so we discontinued IVF and IV insulin then shifted to a regular ward, the patient started on insulin sliding scale, on the next day endocrinologist contacted and advised to stop insulin sliding scale and started on S/C insulin NPH 1 unit BID, Fortunately, we suspected a primary immune deficiency after the few days from the first presentation, and genetic study sent during the next three days baby was having fluctuated readings of asymptomatic hypoglycemia and hyperglycemia. patient discharged with subcutaneous insulin NPH 1 unit BID with follow-up in our diabetic center, 2 months later genetic study came with A homozygous likely pathogenic variant identified in the LRBA gene. The result is consistent with a genetic diagnosis of autosomal recessive Common variable immunodeficiency type 8 with autoimmunity. At this point allowed us to have frequent follow-up visits and referred him to the higher center, for early diagnosis and management of all clinical manifestations.

Discussion

LRBA protein regulates the expression of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which prevents lysosomal degradation of the CTLA-4 receptor. [5,6] CTLA-4 is a potent immune suppressor located in T lymphocytes with the task of blocking the co-stimulation of T cells, downregulating autoimmune processes by binding to CD80 and CD86, and transmitting inhibitory signals. [7,8] Sufficient storage of intracellular CTLA-4 is obligatory in sequence for the protein to mobilize expeditiously to the cell surface and accomplish its function. [9] The LRBA gene comprises 57 exons and encodes 2863 amino acid protein, which is expressed in diverse tissues, involving lymphocytes [10,11]. Low expression of CTLA-4 in patients with LRBA deficiency results in partial loss of the regulatory effects on T-cell activation, leading to increased but inappropriate activation of T- and B-cells with impaired immune surveillance. This increases the risks of cancer and autoimmunity. [5,6] LRBA mutations were first described in 2012` by Lopez Herrera et al. who reported four consanguineous families with childhood-onset humoral immune deficiency and features of autoimmunity [5]. LRBA deficiency is a class within the immune dysregulation disorders family medically categorized as common variable immunodeficiency (CVID) [5]. CVID is described as increased vulnerability to infection or autoimmunity additionally to decreased IgG and IgA and relatively normal T cell levels [12] The patients may present with a wide range of manifestations, including humoral immune deficiency, lymphoproliferation, hematologic and organ autoimmunity [13], for instance, recurrent infections, idiopathic thrombocytopenic purpura, Inflammatory Bowel Disease (IBD), Insulin-Dependent Diabetes Mellitus (IDDM), autoimmune hemolytic anemia, and chronic lung disease [5]. Our patient presented a very early onset, 7 months old, with diabetic ketoacidosis as the first presentation of IDDM. Fortunately, we suspected a primary immune deficiency after the first few weeks of the disease, and thus, a genetic diagnosis was available when he was 8 months old. Our patient exhibited a homozygous likely pathogenic variant that was identified in the LRBA gene. The result is consistent with a genetic diagnosis of autosomal recessive Common variable immunodeficiency type 8 with autoimmunity, The LRBA variant c.7863_7864del p.(Arg2621Serfs*27) creates a shift in the reading frame starting at codon 2621. The new reading frame ends in a stop codon 26 positions downstream, Mode of Inheritance: Autosomal recessive (OMIM®: 614700), This point allowed us to have frequent follow-up visits and early diagnosis of all clinical manifestations, therefore transferred to a higher center for further investigations and management. No etiological treatment is available, but various immunomodulators have been considered, focusing on the several clinical presentations of the disease, including abatacept, cyclosporin, mofetil, glucocorticoids, sirolimus, mycophenolate mofetil, and azathioprine along with symptomatic, antibacterial therapy and immunoglobulin replacement should be given. [3,14,15] Particularly for patients with IDDM, adequate control of inflammatory processes is fundamental to regulating the blood glucose level. [16,17] In the last 20 years, a substantial amount of progressive immunomodulatory treatment variations for T1DM have been delineated by researchers and clinicians, however, the majority of the treatments were not efficacious in achieving insulin independence or were not applicable due to disproportionately

unfavorable effects. [18,19] curiously, auspicious consequences in newly diagnosed T1DM patients were accomplished by autologous nonmyeloablative hematopoietic stem cell transplantation [19,20]. There is a poor correlation between the clinical phenotype and the location of the mutation in the LRBA gene [14]. Members in the same family with the same mutation exhibit variable clinical symptoms [1,20].

Conclusion

This is a report of an infant with early onset diabetes mellitus, The patient carried a new variant of LRBA gene mutation, and the WES revealed a homozygous frameshift mutation LRBA,c.7863_7864del p.(Arg2621Serfs*27), The result is consistent with a genetic diagnosis of autosomal recessive Common variable immunodeficiency type 8 with autoimmunity. kept in mind Primary immune deficiency must be taken into consideration as a differential diagnosis in all patients aged less than 1 year presenting with IDDM.

References

1. Wang, J. (n.d.). Lipopolysaccharide-responsive beige-like anchor (LRBA), a novel regulator of human immune disorders.
2. L Gámez-Díaz, D August, P Stepensky, S Revel-Vilk, MG. Seidel, et al. (2016) The extended phenotype of LPS-responsive beige-like anchor protein (LRBA) deficiency J Allergy Clin Immunol 137: 223-230.
3. Tesch VK, Abolhassani H, Shadur B, Zobel J, Mareika Y, et al. (2020) 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 145: 1452-1463.
4. Barbetti F, Rapini N, Schiaffini R, Bizzarri C, Cianfarani S (2022) The application of precision medicine in monogenic diabetes. Expert Rev. Endocrinol. Metab 2022.
5. Lopez-Herrera G, Tampella G, Pan-Hammarström Q, Herholz P, Trujillo- Vargas CM, et al. (2012) Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. Am J Hum Genet 90: 986-1001.
6. Fischer A, Provot J, Jais JP, Alcais A, Mahlaoui N, et al. (2017) Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. J Allergy Clin Immunol 140: 1388-1393.
7. Valk E, Rudd CE, Schneider H (2008) CTLA-4 trafficking and surface expression. Trends Immunol 29: 272-279.
8. Buchbinder EI, Desai A (2016) CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. Am J Clin Oncol 39: 98-106.
9. Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, et al. (2005) Thompson CB, Riley JL. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 25: 9543-9553.
10. Wang JW, Howson J, Haller E, Kerr WG (2001) Identification of a novel lipopolysaccharide-inducible gene with key features of both A ki- nase anchor proteins and chs1/beige proteins. J Immunol 166: 4586-4595.
11. Dyomin VG, Chaganti SR, Dyomina K, et al. (2002) BCL8 is a novel, evo- lutionarily conserved human gene family encoding proteins with presumptive protein kinase A anchoring function. Genomics 80: 158-165.
12. Ameratunga R, Brewerton M, Slade C, Jordan A, Gillis D, et al. (2014) Comparison of diagnostic criteria for common variable immunodeficiency disorder. Front Immunol 5: 415.
13. Barker JM (2006) Clinical review: type 1 diabetes-associated autoimmunity: natural history, genetic associations, and screening. J Clin Endocrinol Metab 91: 1210-1217.
14. Alkhairy OK, Abolhassani H, Rezaei N, Fang M, Andersen KK, et al. (2016) Spectrum of Phenotypes Associated with Mutations in LRBA. J. Clin. Immunol 36: 33-45.
15. Azizi G, Abolhassani H, Yazdani R, Mohammadikhajehdehi S, Parvaneh N, et al. (2017) New therapeutic approach by sirolimus for enteropathytreatment in patients with LRBA deficiency. Eur. Ann. Allergy Clin. Immunol 49: 235-239.
16. Zhang K, Lu W (2015) Autoimmune Disease. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation re- sponsive to abatacept therapy. Science 349: 436-440.
17. Rossini AA (2004) Autoimmune diabetes and the circle of tolerance. Diabetes 53: 267-275.
18. Robert S, Korf H, Gysemans C, Mathieu C (2013) Antigen-based vs. systemic immunomodulation in type 1 diabetes: the pros and cons. Islets 5: 53-66.
19. Voltarelli JC, Couri CE, Stracieri AB, et al. (2007) Autologous nonmyelo- ablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. JAMA 297: 1568-1576.
20. D'Addio F, Valderrama Vasquez A, Ben Nasr M, et al. (2014) Autologous nonmyeloablative hematopoietic stem cell transplantation in new- onset type 1 diabetes: a multicenter analysis. Diabetes 63: 3041-3046.