Case Report

Severe diabetic ketoacidosis and autoimmune pancreatitis with SIRS in an adolescent with LRBA deficiency – A rare complication of a common primary immunodeficiency disease

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Abstract

Common variable immunodeficiency is the most common primary immunodeficiency disorder. Lipopolysaccharide (LPS)-responsive beige-like anchor protein (LRBA) deficiency is categorized as a common variable immunodeficiency associated with autoimmune manifestations and inflammatory bowel diseases. We report a rare case, an adolescent presenting with severe diabetic ketoacidosis (DKA) and acute pancreatitis with multiorgan dysfunction with common variable immunodeficiency (CVID) with homozygous *LRBA* mutation.

Keywords: Acute pancreatitis, common variable immunodeficiency, diabetic ketoacidosis, LRBA mutation

Introduction

Common variable immunodeficiency (CVID) is characterized by defective antibody production, hypogammaglobulinemia, and increased susceptibility to recurrent and chronic infections.[1,2] The prevalence of CVID is 0.001 to 3.374 per 100,000 population globally.[3] CVID, although rare, is the most common primary immunodeficiency in humans, and awareness of this disease is extremely poor. Awareness about this condition among family physicians may help identify and refer children with recurrent infections early to the specialist so that CVID can be identified early and prevent further complications. They are also at an increased risk for autoimmune disorders such as autoimmune cytopenia, thyroid disorders, gastrointestinal, allergic, or malignant disease. Here we report a rare case of CVID with *LRBA* mutation in an adolescent, who presented with severe diabetic ketoacidosis (DKA) and acute pancreatitis with multiorgan dysfunction.

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Case History

A 16-year-old boy was diagnosed at 14 years of age as CVID in view of recurrent otitis media, persistent diarrhea, and inadequate weight gain starting at 5 years of age, and autoimmune hemolytic anemia. He had low levels of IgA, IgM, and IgE, and B/T cell

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subset, and flow cytometry showed a mild reduction in the number of cells. Genetic studies revealed homozygous *LRBA* mutation, which was pathogenic. He was managed with regular IVIG infusion, cotrimoxazole, and itraconazole prophylaxis.

With non-compliance for a few months due to the pandemic situation, he was brought to the emergency department with abdomen pain, multiple episodes of loose stools for 4 months with acute worsening, and reduced activity for a day. On examination, he was found to have acidotic breathing with hypotensive shock, unresponsiveness (GCS: 10/15). Blood sugar was high (1336 mg/dL), blood gas was suggestive of severe metabolic acidosis (pH: 6.841, HCO_3 5.7 mmol/L), HbA1C: 10.5%, with hyperlactatemia (2.5 mmol/L) and elevated creatinine (2.2 mg/dL); hence, DKA with AKI was considered. In view of hypotensive shock, initial fluid resuscitation was done in ER and DKA treated as per unit protocol and the child was shifted to the pediatric intensive care unit (PICU). With a background of CVID, chronic diarrhea, and DKA, serum amylase (210 U/L) and lipase (1023 U/L) were found to be elevated and a bulky pancreas was identified by ultrasonography. Hence, the possibility of autoimmune pancreatitis was considered. CT abdomen deferred as a child was unstable.

In PICU, the child had a pSOFA score of 12, GCS of 8/15 with bilaterally equal and sluggishly reacting pupils, and hypotensive shock with high blood sugar. Hence, 10 mL/kg crystalloid was given over 1 h. Insulin infusion (0.1 U/kg/h) continued and 3% sodium chloride (5 ml/kg, IV) was given over 1 h in view of suspected cerebral edema, followed by continuous infusion. The child continued to have a persistent shock, and bedside Echocardiography (ECHO) demonstrated myocardial dysfunction (LVEF < 50%). Hence, a low-dose adrenaline infusion was started. Septic shock was considered with a background of CVID, IV antibiotic was given after taking blood cultures, and noradrenaline infusion was added on as diastolic blood pressure (BP) was persistently low and stress dose of IV hydrocortisone was given. Insulin infusion increased to 0.2 U/kg/h as blood sugar was persistently elevated. IABP monitoring was done and inotropes were titrated accordingly. After 2 h of resuscitation in the PICU, sensorium improved to 10/15. Six h later, the child was intubated and ventilated in view of poor respiratory efforts. Child also had severe hypokalemia (1.7 mmol/L), severe hypophosphatemia (0.3 mg/dL), hypomagnesemia (1.2 mg/dL), and spurious hyponatremia (measured [112 mmol/L] corrected [130 mmol/L]). Dyselectrolytemia was managed appropriately. Tissue transglutaminase antibody was negative (<4 AU/mL), celiac disease was ruled out. C-peptide was normal. Free T4 and TSH were normal. Anti-GAD antibody was negative. Hence, chronic diarrhea was attributed to autoimmune pancreatitis.

The child continued to have refractory metabolic acidosis and azotemia, so hemodialysis was initiated, later renal parameters showed a normalizing trend with adequate urine output. The child clinically improved significantly. DKA resolved and blood sugars normalized. Insulin infusion was changed to a basal-bolus regimen of subcutaneous insulin. The length of the PICU stay was 10 days with ventilation days as 5 days. He was discharged home after 23 days of hospital stay. His functional status scale score was 6 at discharge. On follow-up he is well, gaining adequate weight.

Discussion

Lipopolysaccharide (LPS)-responsive beige-like anchor protein (LRBA) deficiency is caused by biallelic mutations in the *LRBA* gene. However, currently, LRBA deficiency is characterized as a clinically variable syndrome with a wide spectrum of manifestations.[4] Numerous studies have proven that immunological and genetic defects are involved in the pathophysiology of CVID, of which LRBA deficiency is associated with autoimmune manifestations and inflammatory bowel diseases.[3,4] LRBA is a cytosolic protein that regulates multiple cellular mechanisms such as vesicular trafficking, signal transduction, cytoskeletal assembly, transcription regulation, autophagy, and apoptosis.[5] Patients with CVID are paradoxically at an increased risk for autoimmune disorders including type 1 diabetes mellitus.[6,7] In a study by Ho HE *et al*. CVID was associated with autoimmunity (33.2%) and gastrointestinal disease (7.3%).[8] According to the new data, type 1 diabetes is substantially more frequent among CVID patients than the estimated incidence in the general population.[9,10] However, autoimmune pancreatitis involving the exocrine pancreas is rare in these patients.

Systemic inflammatory response syndrome (SIRS) is the clinical manifestation of the inflammatory process that may or may not be associated with infection.[11] Our case demonstrates a rare presentation of severe DKA with acute pancreatitis with SIRS in a patient with CVID. Mild elevations in serum amylase and lipase activities are seen in some children with DKA.[12] However, in our case, the diagnosis of acute pancreatitis was made based on a high index of clinical suspicion and was confirmed by imaging. Autoimmune pancreatitis is a potentially fatal disease, the severity ranges from a mild edematous form to a severe necrotizing form.[13]

Type 1 diabetes mellitus is common in patients with CVID associated with *LRBA* mutation. Regular monitoring and early detection can help in preventing life-threatening complications such as DKA. Awareness of this condition is necessary for early recognition by the pediatrician and family physician, which in turn improves the quality of life and well-being of these patients.

Key take-home messages

1. Type 1 diabetes mellitus is common in patients with CVID with homozygous *LRBA* mutation. Early recognition and diagnosis are vital in improving the quality of life and well-being of these patients.
2. Regular monitoring and early detection can help in preventing life-threatening complications such as DKA.

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Conflicts of interest

There are no conflicts of interest.

References

1. Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, Cunningham-Rundles C, de la Morena MT, *et al*. International consensus document (ICON): Common variable immunodeficiency disorders. J Allergy Clin Immunol Pract 2016;4:38-59.
2. Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, *et al*. International union of immunological societies: 2017 Primary immunodeficiency diseases committee report on inborn errors of immunity. J Clin Immunol 2018;38:96-128.
3. Weifenbach N, Schneckenburger AAC, Lötters S. Global distribution of Common variable immunodeficiency (CVID) in the light of the UNDP Human development index (HDI): A preliminary perspective of a rare disease. J Immunol Res 2020;2020:8416124.
4. 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;36:33-45.
5. 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;30:14-34.
6. Seidel MG, Kindle G, Gathmann B, Quinti I, Buckland M, van Montfrans J, *et al*. The European society for immunodeficiencies (ESID) registry working definitions for the clinical diagnosis of inborn errors of immunity. J Allergy Clin Immunol Pract 2019;7:1763-70.
7. Susheela AT, Hale A. Patients with common variable immunodeficiency paradoxically have increased rates of autoimmune disorders. BMJ Case Rep 2017;2017:bcr2017221657.
8. Ho HE, Cunningham-Rundles C. Non-infectious complications of common variable immunodeficiency: Updated clinical spectrum, sequelae, and insights to pathogenesis. Front Immunol 2020;11:149.
9. Bussone G, Mouthon L. Autoimmune manifestations in primary immune deficiencies. Autoimmun Rev 2009;8:332-6.
10. Azizi G, Ahmadi M, Abolhassani H, Yazdani R, Mohammadi H, Mirshafiey A, *et al*. Autoimmunity in primary antibody deficiencies. Int Arch Allergy Immunol 2016;171:180-93.
11. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2-8.
12. Haddad NG, Croffie JM, Eugster EA. Pancreatic enzyme elevations in children with diabetic ketoacidosis. J Pediatr 2004;145:122-4.
13. Hirota M, Sugita H, Maeda K, Ichibara A, Ogawa M. [Concept of SIRS and severe acute pancreatitis]. Nihon Rinsho 2004;62:2128-36.