Case report

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A case of immune-mediated type 1 diabetes mellitus due to congenital rubella ınfection

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Congenital rubella infection is a transplacental infection that can cause intrauterine growth retardation, cataracts, patent ductus arteriosus, hearing loss, microcephaly, thrombocytopenia, and severe fetal injury. It has been shown that type 1 diabetes mellitus develops in 12%–20% of patients with congenital rubella infection, and disorders in the oral glucose tolerance test is observed in 40% of patients. No biochemical or serological markers exist which could indicate that type 1 diabetes was caused by a congenital rubella infection. We report a 13-year-old male patient who was admitted to our hospital with complaints of new-onset polyuria, polydipsia, urination, and weight loss. In addition, he was found to have neurosensory hearing loss, patent ductus arteriosus, and microcephaly. Immune-mediated type 1 diabetes mellitus was considered due to the fact that the autoantibodies of diabetes mellitus were positive.

Keywords: Rubella, Diabetes, Hearing loss

Introduction

While rubella can lead to a mild clinical picture in children and adults, it can affect all organs and systems of the fetus in pregnancy. If women have rubella infection in the first 3-4 months of pregnancy, the virus is usually transmitted to the fetus and results in spontaneous abortion, stillbirth, or congenital rubella syndrome.[1-3] Congenital rubella infection is a transplacental infection that can cause intrauterine growth retardation, cataracts, patent ductus arteriosus, hearing loss, microcephaly, thrombocytopenia, and severe fetal injury.[1,2] Although the rubella virus is known to infect pancreatic beta cells, the etiological role of this viral infection in the development of type 1 diabetes mellitus (DM) in humans is still unknown.[4] It has been shown that type 1 DM develops in 12%–20% of patients with congenital rubella infection, and disorders in the oral glucose tolerance test is observed in 40% of patients with congenital rubella infection.[5,6] This article describes a case of immune-mediated type 1 DM in a male patient with congenital neurosensory hearing loss, microcephaly, and patent ductus arteriosus that was thought to be associated with congenital rubella infection.

Case report

A 13-year-old male patient presented with complaints of new-onset polydipsia, excessive urination, and weight loss. The patient stated he had lost 7 kg over a period of 2 months. His past medical history included neurosensory hearing loss from birth and patent ductus arteriosus that was discovered at three months of age in the Pediatric Cardiology Department. He had no response to voice warnings at 3 months of age, and his neurosensory hearing loss was diagnosed with an auditory brainstem evoked responses test. In addition, the patient was followed by the Child and Adolescent Psychiatry Department due to behavioral problems and learning disabilities; he had been diagnosed with autistic spectrum disorder. There was

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no kinship between his parents. The patient's mother had a fever and a red rash on her face during the second trimester of pregnancy, although she was not diagnosed with rubella infection at that time.

On physical examination, the patient's weight was 42.7 kg (25th–50th percentile), height was 153.2 cm (25th–50th percentile), and his head circumference was 46 cm (<3rd percentile). A 2/6 cardiac murmur and hearing aid were noted. Laboratory examinations revealed blood glucose was 619 mg/dL, urine ketone was +3, blood gas showed metabolic acidosis (pH, 6.92; HCO_3, 4 mEq/L; $PaCO_2$, 24 mmHg), insulin was 4.1 IU/mL (range, 2–18 IU/mL), and serum C-peptide level was 1.23 ng/mL (range, 1.1–4.4 ng/mL). The patient's glycosylated hemoglobin value was 15.9%, anti-insulin antibody was 0.78 U/mL (range, 0–0.5U), anti-GAD was 22.8 U/mL (<1U/mL), and the islet cell antibody was positive. Orbital magnetic resonance imaging demonstrated no optic atrophy and normal optic nerve thickness, so Wolfram syndrome was excluded. In addition, genetic analysis for Wolfram's syndrome was normal.

The patient was diagnosed with immune-mediated type I DM, and intravenous fluid and insulin therapy were started according to the degree of dehydration. After the patient's metabolic acidity was corrected and blood glucose regulation was achieved, his medication was switched to subcutaneous insulin therapy 1.2 units/kg/day. Considering the patient's patent ductus arteriosus, microcephaly, and neurosensory hearing loss, his immune-mediated type 1 diabetes was thought to be associated with a congenital rubella infection following his mother's febrile rash illness during pregnancy.

Discussion

In this article, we present the case of a 13-year-old male with congenital neurosensory hearing loss, patent ductus arteriosus, and type 1 diabetes that was thought to be associated with a congenital rubella infection following his mother's prenatal fever and red rash disease. Wolfram syndrome has been described as a clinical condition in which DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness) coexist.[7,8] There is a significant difference between DM associated with Wolfram syndrome and autoimmune type 1 diabetes: DM associated with Wolfram syndrome is accompanied by a decrease in the number and function of pancreatic β-cells, and Wolfram patients have no autoimmune diabetes autoantibodies (which are associated with an autoimmune process).[9] In the present case, the immunodiagnostic autoantibodies were found to be positive during the period when diabetes was diagnosed. Although the patient's hearing loss and diabetes suggested Wolfram syndrome, he had was no optic atrophy in either eye on the retinal examination and the optic nerve thickness was normal bilaterally on orbital MR. Finally, Wolfram syndrome was ruled out by a normal genetic analysis that was submitted for Wolfram syndrome. DM related to mitochondrial diseases was excluded for the following reasons: detection of diabetes autoantibodies, lack of family history suggesting hereditary mitochondrial diabetes, normal retinal examination, and absence of clinical findings suggestive of endocrine dysfunction, neuromuscular disease or central nervous system disease, all of which are associated with a mitochondrial disease. Recently, *GATA6* mutations have been associated with severe congenital heart disease and neonatal/childhood-onset diabetes.[10] Our patient had decreased exocrine pancreas function, and there were no hepatobiliary abnormalities that occur with *GATA6* mutations. The presence of diabetes autoantibodies excluded type 2 DM in our patient, although positive antibodies are frequently found in cases of type 2 DM.[11] Because the patient in this case presented with diabetic ketoacidosis, low insulin, and a low C-peptide level according to the blood glucose level, type 1 DM was considered.

Congenital cytomegalovirus (CMV) infection can be indicated by findings such as preterm delivery, intrauterine growth retardation, microcephaly, chorioretinitis, hepatosplenomegaly, sensorineural hearing loss, hyperbilirubinemia, impaired liver function tests, and thrombocytopenia (characterized by petechiae and purpura through direct suppression of bone marrow megakaryocytes).[12] Congenital rubella infection can be associated with similar findings, including intrauterine growth retardation, cataracts, patent ductus arteriosus, hearing loss, microcephaly, thrombocytopenia, and severe fetal injury. Therefore, congenital CMV infection should be included in the differential diagnosis of patients with suspected congenital rubella infection.

In the present case, the patient's mother had a fever and a red rash on her face during pregnancy. From 3 months of age, the patient was followed by the Pediatric Cardiology Department for patent ductus arteriosus, and the case was finally diagnosed as type 1 diabetes due to congenital rubella infection, especially considering the finding that autoimmune type 1 DM develops in 12%–20% of cases with congenital rubella infection.

There are no immunoserological parameters that show a definite association between clinical findings and congenital rubella infection. Likewise, there is no biochemical or serological indication for this viral infection that is associated with immunodeficient type 1 diabetes, although it is known that the rubella virus infects pancreatic beta cells. A literature search revealed a 14-month-old patient who died of diabetic ketoacidosis and was diagnosed with congenital rubella infection. Insulinitis was discovered in the pathological examination of this patient's pancreas.[13] Rubella virus was isolated from the pancreatic tissue of 5 fetuses aborted at the 19th and 21st week of gestation, but morphological abnormalities were not detected.[14] Postmortem pathologic examinations of 45 children diagnosed with DM secondary to congenital rubella infection revealed a normal pancreatic appearance in 43 patients, one case of the insulitis and one case of long-term type 1 diabetes-related pathological changes.[15] We can not perform a pancreatic histological examination in the present case because the procedure is considered too invasive. However, it would be valuable to show insulitis appearance for our case.

Patients with congenital rubella infection usually present with cardiac involvement, hearing loss, eye manifestations, intrauterine growth restriction, microcephaly, behavioral problems and immunologic features, including islet cell surface antibodies with type 1 DM. Congenital rubella infection should be considered in diabetic patients who present with hearing loss, cardiac anomalies, and microcephaly.

Ethical statement

Written informed consent by our patient was obtained for publication of this case report.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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