Development of Type 1 diabetes in a child with inherited CD59 deficiency treated with eculizumab

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BACKGROUND

CD59 is a complement regulatory protein which inhibits membrane attack complex protecting self-cells from complement-mediated damage. Recent evidence suggests that CD59 may also suppress T cell activation via a complement-independent mechanism. Other than an immune regulator, CD59 is involved in the exocytotic machinery of insulin secretion. Herein we report a patient with inherited CD59 deficiency who developed type 1 diabetes.

CASE REPORT

Case

11-year-old girl was admitted for polyuria and polydipsia for the past 4 days. She had hyperglycemia and ketonemia on admission.
She was born after an uneventful pregnancy to consanguineous parents who are first cousins. As a neonate she had indirect hyperbilirubinemia and underwent exhange transfusion.
She had a focal afebrile seizure at the age of 6 months, had hypotonia, nystagmus and titubation on admission. Cranial MRI revealed a swollen, nonenhancing, hemorrhagic lesion in the left middle cerebellar peduncle, and T2-weighted MR and MR angiography failed to visualize blood flow in the ipsilateral posterior inferior cerebellar artery. Left cerebellar hemisphere was shrunken with a chronic hemorrhagic lesion on the left middle cerebellar peduncle on follow-up MRI 5 months later. At age 18 months she developed lower extremity weakness in an ascending, symmetrical, rapidly progressive course involving axial muscles within a day. ENMG showed acute motor axonal neuropathy and lumbar spinal MRI revealed enhancement of nerve roots. She received IVIg for four years which was switched to eculizumab in the last 2 years. At the age of 9 years she had distal atrophy of the lower extremities, had mild learning problems with an IQ of 68, and was shown to have mild Coombs negative hemolysis. Genome-wide linkage analysis combined with WES suggested a homozygous missense mutation (c.A146T) in exon 3 of CD59 gene, confirmed with Sanger analysis, replacing an aspartate with valine on the 49th position (Ref 6). It led to decreased expression of CD59 on RBCs. The parents were heterozygous for the mutation.
The patient was on aripiprazole in the last 2 years for aggressive behavior.

Family history

One male sibling died at the age of 3 weeks during an exchange transfusion for indirect hyperbilirubinemia. An elder female sibling presented with weakness of the lower extremities at the age of 11-months, followed a relapsing-remitting course and died at 16 years after a lung infection while on ventilatory support. A nephew homozygous for the seme mutation presented at 6 months. He has global developmental delay, wekness of lower extremities and hemolytic anemia at the age of 6 years, currently on eculizumab. Both parents, maternal grandmother, one aunt and two paternal uncles had diabetes.

Physical examination

On admission with hyperglycemia she had normal height (141.4 cm 25-50p) and weight (45,9 kg 75-90p) with an increased body mass index (22.5 kg/m2 90-95p). Skin turgor was normal. Puberty was Tanner 1. Neurological examination revealed asymmetrical weakness and rigidity with distal atrophy in lower extremities, a wide-based gait, and strabismus on right eye.

Laboratory

Blood glucose was 326 mg/dL (simultanous serum insulin 2.4 uIU/mL and c-peptide 1.38 ng/mL), urinary ketone was 3+ on dipstick. HbA1c on admission was 9.1%, and antiGAD antibody was positive (14.3 U/L N<1), anti insulin and IA-2 antibodies were negative.

Course

She is on basal-bolus insulin (for 8 months) with a TDD of 0,7 U/kg/d, latest HbA1c is 4,8 %.

DISCUSSION

CD59 is a glycosylphosphatidylinositol (GPI)-anchored cell surface protein broadly expressed on cells from all tissues involved in complement related cell lysis (1,2). It binds to C9 restricting its association with C5b-8, thus inhibits polymerization of the membrane attack complex (MAC)(3). CD59 is also shown to participate in signal transduction during T cell activation with an inhibitory role shown in vitro after infection with recombinant vaccinia virus which is complement-independent (4). Recently CD59 is shown to be co-expressed with insulin inside the pancreatic beta cells, and silencing of CD59 decreases glucose and K+ induced insulin secretion in vitro, suggesting an action directed at the molecular machinery of islet cell exocytosis (5). Primary CD59 deficiency due to molecular defects of the CD59 gene is rare and patients develop recurrent episodes of strokes, chronic immune-mediated polyneuropathy and hemolysis as described in our patient previously (6). Our patient is the first case in the literature who developed T1DM in the course of her disease that could be attributed to a number of defects caused by CD59 deficiency. It could be attributed to facilitation of autoimmune damage to islet cells in an individual genetically predisposed to T1DM due to immunoregulatory defect caused by CD59 deficiency. It could also be attributed to decreased insulin secretion caused by an impaired exocytotic machinery in the remaining islets in an individual with decreased islet cell reserve due to T1DM. Moreover, functional defect in CD59 caused by glycosylation of the protein is shown to be the molecular link between complement and complications of diabetes previously (7). Thus, primary deficiency in CD59 in the current patient, even before glycosylation of CD59 leading to impaired function, may make her more susceptible to develop microvascular complications requiring a close follow-up.

CONCLUSIONS

The development of T1DM in the current patient may be attributed to an enhancement of autoimmune destruction of pancreatic islet cells due to CD59 deficiency in an individual with propensity to T1DM or it could be facilitated by a derangement of insulin secretion in the remaining islets, or both. Moreover, CD59 defect may also increase the likelihood for development of microvascular complications since functional impairment of CD59 in uncontrolled diabetes is the link between complement and vascular complications, thus she requires close follow-up.

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