OBSERVATIONS

A Case of Insulin-Dependent Diabetes Associated With Enteroviral Infections

Enteroviruses have been reported to be a potential trigger of the development of type 1 diabetes by inducing β-cell autoantibodies and by directly destroying β-cells (1). Although the precise underlying mechanisms for enterovirus-mediated development of diabetes remain unknown, the systematic review and meta-analysis of observational molecular studies demonstrates a clinically significant association between enteroviral infections detected by molecular methods and type 1 diabetes (2). Here we report a case of juvenile-onset insulin-dependent diabetes resulting from various enteroviral infections.

A 20-year-old man was referred and admitted to our hospital because of a penile inflammation, suffering from general fatigue, and body weight loss for 2 weeks in March 2011. He had a high fever (38–39°C) at 2 weeks before the admission. His plasma glucose (430 mg/dL) and HbA_{1c} (10.3%) levels were significantly elevated. Serum ketone bodies were elevated (615 μmol/L; normal, <130 μmol/L); however, blood pH was normal. The intensive insulin therapy promptly ameliorated his blood glucose, and his blood glucose levels were 100–120 mg/dL by using 20 and 15 units of insulin glulisine before breakfast and dinner, respectively, and 11 units of insulin glargine at bedtime. His urinary C-peptide level was significantly reduced (19.4 μg/day; normal, 29.2–167 μg/day). β-Cell autoantibodies, anti-GAD, and anti-IA2 autoantibodies were not detected. He has been consistently treated by insulin after the admission. Plasma glucose and HbA_{1c} levels were 126 mg/dL and 5.8%, respectively, by using 18 and 12 units of insulin glulisine before breakfast and dinner, respectively, and 12 units of insulin glargine at bedtime.

We studied neutralizing antibodies for enteroviruses at the time of admission and at 2 weeks after admission. On admission, serum levels of neutralizing antibodies for coxsackievirus A2 (8×; normal, <4×), A4 (32×; normal, <4×), A5 (64×; normal, <4×), B1 (8×; normal, <4×), B2 (8×; normal, <4×), B4 (64×; normal, <4×), B5 (32×; normal, <4×) and enterovirus 71 (8×; normal, <4×) were significantly elevated, suggesting a history of infections by various enteroviruses. The neutralizing antibody for coxsackievirus A7 was not detected on admission; however, it was significantly elevated (8×; normal, <4×) at 2 weeks after the admission, indicating a recent infection by coxsackievirus A7.

Coxsackievirus B2, B4, B5, and enterovirus 71 have been reported to be associated with the development of diabetes (2). To our knowledge, the association between coxsackievirus A7 infection and diabetes has not been discussed in regard to humans. Coxsackievirus A7 has been reported to impair β-cells by inducing an increase of tumor necrosis factor-α in mice as well as coxsackievirus B4 (3). Further, coxsackievirus A7-infected pancreatic islet cells have been proved to be a suitable model for studies of experimental infection of pancreatic islet cells with coxsackieviruses (4). These findings suggest a significant association of coxsackievirus A7 infection for the development of diabetes in our patient.

In summary, the past history of infections by various enterovuses, which have been reported to induce an impairment of β-cells, and a recent infection by coxsackievirus A7 may be associated with the development of β-cell autoantibody-negative insulin-dependent diabetes in our patient.

HIDETAKA HAMASAKI, MD
HIDEKATSU YANAI, MD, PHD, FACP

From the Department of Internal Medicine, National Center for Global Health and Medicine, Kohnodai Hospital, Chiba, Japan.
Corresponding author: Hidekatsu Yanai, dyanai@hospk.ncgm.go.jp.
DOI: 10.2337/dc11-2051

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

H.H. and H.Y. analyzed data, contributed to discussion, and wrote, reviewed, and edited the manuscript. H.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. van der Werf N, Kroese FG, Rozing J, Hillebrands JL. Viral infections as potential triggers of type 1 diabetes. Diabetes Metab Res Rev 2007;23:169–183
2. Yeung WC, Rawlinson WD, Craig ME. Enterovirus infection and type 1 diabetes mellitus: systematic review and meta-analysis of observational molecular studies. BMJ 2011;342:d35
3. Bopegamage SA, Petrovicová A. Tumour necrosis factor alfa and glucose levels in sera of mice infected with coxsackie B4 and A7 viruses. Acta Virol 1998;42:409–411
4. Bopegamage SA, Petrovicová A. In vitro infection of mouse pancreatic islet cells with coxsackie viruses. Acta Virol 1994;38:251–255