Letters

Observation

Encephalomyocarditis-virus-induced diabetes model resembles “fulminant” Type 1 diabetes in humans

Keywords Aetiology · Diabetic ketoacidosis · EMC virus · HbA_{1c} · Type 1 diabetes.

To the Editor: “Fulminant” Type 1 diabetes, characterised by diabetic ketoacidosis, low HbA_{1c} level at onset, insulin deficiency and elevated serum pancreatic enzymes, has been reported in the Japanese population of Type 1 diabetes patients [1]. The study reported that islet-associated autoantibody was not detected, and insulinitis was not found on pancreatic biopsy within 5 months of the onset of disease. Therefore, this type of diabetes was described as a subtype of Type 1B diabetes [1]. However, others reported clear T cell insulinitis at autopsy in a patient who died 40 minutes after arrival at hospital [2], and a nationwide survey of fulminant Type 1 diabetes revealed that approximately 5% of patients had anti-GAD antibody in their serum [3], suggesting that autoimmunity may be involved in this type of Type 1 diabetes. Following the first report on fulminant Type 1 diabetes [1], many others tried to find a similar phenotype of Type 1 diabetes in the Caucasian population, but they reported that very few cases were found [4]. Therefore, although establishment of the diagnosis and treatment of this subtype of Type 1 diabetes is required at a nationwide level in Japan due to its aggressive disease course, it seems that very few Caucasian researchers are interested in fulminant Type 1 diabetes.

Previously, by several researchers including our group, an encephalomyocarditis (EMC)-virus-induced diabetes model was used as a tool to investigate Type 1 diabetes [5]. Intraperitoneal injection of male DBA/2 mice with 500 plaque-forming units of EMC virus diabetic strain can induce very rapid onset of diabetes (in approximately a few days) (Fig. 1). As indicated by the arrow in Figure 1, just before the onset of hyperglycaemia, the blood glucose level in EMC-virus-injected mice drops into the hypoglycaemic range. This is probably because the destruction of beta cells is extremely acute so that insulin in the destroyed beta cells may flow into the blood stream within a short period of time. Interestingly, a similar phenomenon was also observed in fulminant Type 1 diabetes in humans. Fasting hypoglycaemia, reaching to 3.2 mmol/l, was observed 2 days before the onset of fulminant Type 1 diabetes in a 48-year-old Japanese woman (I. Mineo, Otemae Hospital, Osaka, Japan; personal communication). Not only the very rapid onset

pattern but also the involvement of exocrine tissue damage, as indicated by histological findings and the high serum amylase level (Fig. 1), in the EMC-virus-induced diabetes model resembles fulminant Type 1 diabetes (Table 1). Although it has been recognised that the EMC virus diabetic strain does not infect exocrine acinar cells, this virus does infect exocrine glands in Mongolian gerbils [6] and Syrian hamsters, suggesting that it may also cause exocrine damage in mice as we presented here. Moreover, approximately 70% of fulminant Type 1 diabetic patients have a history of flu-like symptoms such as fever, headache, sore throat, coughing, rhinorrhoea and joint pain, suggesting the involvement of viral infection in this type of Type 1 diabetes [3]. The aetiology of fulminant Type 1 diabetes is still controversial and there is discussion regarding the involvement of autoimmunity other than in relation to viral infection [7]. However, islet-associated autoantibody was also detected in the EMC-virus-induced diabetes model, suggesting that even if viral infection induces diabetes, autoantibody can be detected [5]. Finally, because the RIP-LCMV [8] and Ins-HA models are characterised by slow onset of diabetes (usually a matter of months), they are obviously different from models of fulminant Type 1 diabetes. Based upon this evidence, we propose that the EMC-virus-induced diabetes model can be used as a model of fulminant Type 1 diabetes, and we encourage non-Japanese researchers to take an interest in this phenotype of Type 1 diabetes.

Fig. 1. Changes in serum amylase (individual values, closed triangles; mean values, solid line with open triangles) and mean blood glucose (dotted line with open circles) levels after intraperitoneal injection of EMC virus diabetic strain (500 plaque-forming units). The arrow (↓) indicates the transient fall of blood glucose after injection. * $p < 0.01$ vs day 0 (serum amylase level)

Table 1. Comparison between fulminant Type 1 diabetes and diabetes induced by EMC virus diabetic strain

	Fulminant	EMC virus diabetic strain
1. Very rapid onset	Yes	Yes
2. Complete destruction of islet beta cells at onset	Yes	Yes
3. High serum amylase levels	Yes	Yes
4. Insulinitis	None at biopsy ^a Present at autopsy ^b	None at 27 days Present at 2–7 days
5. Autoantibodies	None ^c	Very low titre (transitory)

^a Biopsy was performed 5 months after diagnosis of diabetes [1]; ^b in an autopsy case, just after the onset of diabetes, the presence of insulinitis was reported [2]; ^c in 5% of patients with

fulminant Type 1 diabetes, a low-titre diabetes-related autoantibody was transiently found [3]

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