

Two Cases with Nonautoimmune Type 1 Diabetes Resembling to Fulminant Diabetes

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Type 1 diabetes is divided into two subtypes: autoimmune and idiopathic diabetes (1). Recently, a novel subtype of idiopathic type 1 diabetes, called fulminant diabetes has been proposed. These patients are characterized with negative islet related auto antibodies, relatively low glycosylated hemoglobin values, and high serum exocrine pancreatic enzyme concentration at the time of diagnosis. The etiology remains to be uncertain. Most of the reported patients were from Japan. These findings suggest that fulminant type1 diabetes may be specific for Japanese patients. We presented two cases; the first case presented with ketoacidosis with slightly high amylase level after steroid withdrawal. The other case who presented with ketoacidosis had one month history of diabetic symptoms. Both of the patients had family history of diabetes in the first relatives and both of them have negative insulin, islet-cell, glutamic acid decarboxylase (GAD) autoantibodies and low c-peptide levels. We suggest that genetic susceptibility and environmental factors may have influenced the clinical presentation of this form of diabetes. Even though both of the patients have a acute clinical onset of non autoimmune type 1 diabetes the clinical and biochemical signs of the patients did not full fit diagnostic criteria of the fulminant diabetes. Our understanding of the pathogenesis of the disease may improve with more cases reported in the white population.

Key Words: Fulminant diabetes, white population

Introduction

Recently, a novel subtype of type 1 diabetes, called fulminant type 1 diabetes has been proposed (2). These patients characterized with negative islet related auto antibodies at the time of diagnosis. Most of the patients had been reported from Japan. Imagawa et al have suggested that these cases are "non-autoimmune mediated type 1 diabetes" (2). The clinical characteristics of this subtype of the diabetes are rapid onset of the disease with very short duration of the symptoms with negative status of autoantibodies, no C-peptide secretion and elevated serum exocrine pancreatic enzymes.

The pathogenesis of fulminant type 1 diabetes is still not clear. Imagawa et al. reported that fulminant diabetes is not caused by insulinitis. (2). But some

case reports suggested there was an autoimmune process which is presented by GAD-reactive peripheral T cell and elevated serum interferon γ inducible protein levels (3). Viral infections are another candidate for the pathogenesis of the fulminant type 1 diabetes. Two fulminant diabetes type 1 diabetes cases which are presented during the pregnancy have been reported recently (4,5). Although, fulminant diabetes consists of 20% of ketosis-onset type 1 diabetes cases in Japan (6), a few cases have been reported from the other countries. It was postulated that this form of diabetes is rarely seen in white population (7). We reported two cases of type1 diabetes with negative islet cell auto antibodies.

Case I: A 49 year-old woman presented to emergency department with vomiting, epigastralgia and a weight loss of 15 kg during the last 6 months. She was 167 cm in height and weighed 50 kg. Laboratory examination showed glucose level of 425 mg/dl, +++urinary ketones, arterial PH = 7.42, PO₂=87mmHg, HCO₃= 19,8mmol/L. A slightly increased amylasemia was detected (255 IU/L; upper limit =128 IU/L). She was first treated

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with intravenous insulin. The serum C-peptide level was $<0,5$ ng/ml, indicating severe impairment of insulin secretion. Her HbA1c level was 8,6%. No sign of acute infections were detected. Islet cell antibody was negative (measured by IFA), anti-GAD antibody was 0,1U/mL (measured by IRMA, normal range is <1 U/mL) and anti-insulin antibody was 4,6% (measured by RIA, normal range is 4-10%). Anti-TPO Ab was 18,9IU/ml (0-35) and anti-Tg Ab was <20 IU/L (0-40). According to her medical history she has had psoriasis for 30 years, and bronchial asthma for 4 years. During the last 2 years she had used low dose oral corticosteroids for her bronchial asthma which was discontinued 1 month prior to admission. She reported that her symptoms aggravated when the steroid therapy was stopped. The ultrasonographic evaluation of the patients in emergency clinic demonstrated an elevated echogenicity of the pancreas. After one month of the clinical symptoms initiated computerized tomographic evaluation of the pancreas was normal. Her father was also diagnosed with type 2 diabetes. 3 months later on the intensive insulin therapy she has gained 10 kg and has been doing well. After one year with intensive insulin therapy her HbA1c level was 6% but the C-peptide level was $<0,01$ ng/ml, lower than the initial level.

Case II: A 19 year old girl presented to our clinic with fatigue, nausea. She reported that she has lost 6 kgs over a month despite her good appetite. The physical examination was normal except diffuse enlargement of the thyroid gland. The laboratory examination showed fasting blood glucose of 465 mg/dl, ++ ketone bodies and +++ positive glucose in the urine and arterial PH =7.307, PO₂ =104 mmHg, HCO₃⁻ = 13,1mmol/L. The serum amylase level was above the upper limit of normal (134 IU/L; upper limit =128 IU/L). The serum C-peptide level was $<0,1$ ng/ml and insulin was $<2\mu$ U/L, indicating severe impairment of insulin secretion. Her HbA1c level was 8,3%. Islet cell antibody was % 5 (%4-10), anti-GAD was 0,1U/ml (0-1 U/ml) and anti-insulin antibody was negative. Anti TPO ab and anti-Tg ab were 52,9 IU/mL and <20 IU/mL respectively. Her medical history revealed that her mother had gestational diabetes and remained diabetic after delivery. She also reported that she has been stressed out for the last 5 months. After 8 months of the diagnosis when the glucotoxicity resolved with intensive insulin therapy the serum c-peptide levels was $<0,1$ ng/ml.

Discussion

In year 2000 Imagawa et al. reported that there are three distinct subtypes of type 1 diabetes mellitus: autoimmune, nonautoimmune fulminant and nonautoimmune nonfulminant (2). A novel subtype of type 1 diabetes which is called fulminant type 1 diabetes is well defined with reported cases and is characterized by a rapid onset of symptoms and the absence of diabetes-related antibodies and elevated exocrine pancreatic enzymes such as hyperamylasemia (8). This association suggests a common etiopathogenesis in both exocrine and endocrine dysfunction. Most of the cases were reported from Japan. The diabetes related antibodies are more oftenly detected in white patients. Therefore one may speculate that nonautoimmune, fulminant type 1 diabetes may be rare in whites.

The risk of diabetes increases with the number of islet cell antibodies but prospective studies showed that diabetes does not develop in most antibody-positive relatives (9,10). On the other hand the main issue for the diagnosis of fulminant diabetes is the absence of auto antibodies against islet cells. But islet cell antibodies cannot be measured in all laboratories. However, Tanaka et al. established new diagnostic criteria for fulminant type 1 diabetes. They reported that C peptide of <0.033 nmol/L and HbA1c of $<8\%$ are discriminative diagnostic markers (11).

Although the mechanism and etiology remains to be elucidated reported cases may give some clues about the etiologies. Four of the eleven patients who were reported by Imagawa et al. (6) had a family history of diabetes and also had features of genetic susceptibility to diabetes and might have accelerated beta-cell destruction due to some environmental factors such as viral infections. Inagaki et al. reported two cases of type 1 diabetes mellitus developed as diabetic ketoacidosis at 19 weeks of gestation and immediately after delivery (4). All the reported patients were adults from Japan and in the other ethnic groups the feature of the fulminant form diabetes may not be the same as the feature of Japanese adults.

Our two patients not exactly met of the diagnostic criteria which were described by Imagawa et al (2). The first patients presented with severe abdominal pain and vomiting with slightly elevated amylase level. Although in the some report the high serum amylase levels were reported as a primary

characteristic of the patients with fulminant type 1 diabetes, the suggested hypothesis is not generally accepted. There are reported cases with normal levels of serum amylase and increased rheumatoid factors and thyroid stimulating hormone receptor antibody levels (12). In the first patients the mild elevated serum amylase level can be seen also in diabetic ketoacidosis. In the second patient the serum amylase levels were not as high as in the first patient and she did not have any clinical signs of acute pancreatitis. In the first patient the duration of hyperglycemic symptoms were only 7 days before her diabetes was diagnosed. But the second patient reported that her symptoms have started four months ago. The first patient was older than the second patient. Our patients had a family history of diabetes in the first relatives which suggests a genetic susceptibility. In the both of the patients when the glucotoxicity of the pancreas resolved with intensive insulin therapy the serum C-peptide levels remained to be lower than normal limits.

In conclusion the reported two patients from Turkey is not fit full diagnostic criteria of fulminant type 1 diabetes described from Imagawa et al (2). Two reported cases had different clinical presentations. Both of them presented fulminantly. They both had a family history of diabetes, low C-peptide and negative islet cell antibodies. We suggest that a genetic susceptibility, immune suppression and acute stress may accelerate diffuse beta cell necrosis. We concluded that a different form of non-autoimmune type 1 diabetes can be seen in white population. Even though the clinical and diagnostic criteria are not as the same as reported from Japan the patients have a future of acute presented form of type 1 diabetes with negative autoantibodies. We proposed a great national survey for type 1 diabetes with different clinical presentation. This may give novel information about the new subtypes of type 1 diabetes and would increase our understanding of the pathogenesis.

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