lesson of the month (2)

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Latent autoimmune diabetes in the young

This case represents latent autoimmune diabetes in the young (LADY), and demonstrates that autoimmune diabetes can be slowly progressive even in younger patients with insulin independency period lasting for more than two years.

Type 1 diabetes results from β cell destruction which can be immune mediated or idiopathic. Immune-mediated diabetes accounts for only 5–10% of those with diabetes. It results from a cell-mediated autoimmune destruction of the β cells.[1,2] Markers of immune destruction include presence of autoantibodies to glutamate decarboxylase 2 (GAD_{65}), islet cell (ICA) and autoantibodies to the tyrosine phosphatase IA2.[3,4] Usually more than one of these autoantibodies is present in 85–90% of individuals when hyperglycaemia is detected initially. The disease has strong HLA associations, with linkage to the DQA and DQB genes, and it is influenced by the DRB genes. These *HLA-DR/DQ* alleles can be either predisposing or protective. [5]

Immune-mediated diabetes commonly occurs in childhood and adolescence. The rate of β cell destruction is quite variable. In childhood, it is usually seen as a rapidly progressive disease presenting with insulin deficiency at the time of diagnosis. Insulin independence for more than one year after initial diagnosis of diabetes is rather a rare event in Caucasian children with type 1 diabetes.[6] The slowly progressive form generally occurs in adults and is sometimes referred to as latent autoimmune diabetes in adults (LADA).[7] Patterns of susceptibility at the HLA-DRB1 and HLA-DQB1 loci in LADA are similar to those reported for type 1 diabetes, supporting the hypothesis that autoimmune diabetes occurring in adults is an age-related extension of the pathophysiological process presenting as childhood-onset type 1 diabetes. Slowly progressive β cell destruction leading to diabetes has also been described in children and is referred to as latent autoimmune diabetes in the young (LADY).[8]

Lesson

A 15-year-old asymptomatic Caucasian girl was found to have elevated random blood glucose on routine testing. Urine testing revealed moderate ketonuria in addition to glycosuria. She had a body mass index (BMI) of 21.4 kg/m^2, blood pressure of 118/90 mmHg, random capillary blood glucose (CBG) 16.8 mmol/l (confirmed with venous sample) with no evidence of diabetic complications. Her sister had type 1 diabetes and she had presented with diabetic ketoacidosis at the age of 18 years. She was on basal bolus insulin regimen and had never been off insulin.

Investigations on our patient showed positive GAD antibodies 10.0 U/ml (0–1), positive islet cell antibodies and negative insulin antibodies. Antibodies for coeliac disease were negative. Fasting C-peptide was 451 pmol/l and insulin 49 pmol/l. Measurable C-peptide level suggested residual β cell function. The patient was not investigated for maturity onset diabetes of the young (MODY) because of no other family history of diabetes. She was treated with sulfonylurea. In three years' follow up there were two increments in dose of sulfonylurea with HbA1c between 5–6.6% and no ketonuria. Four years after the onset of her diabetes, she became symptomatic and her diabetic control deteriorated. She was started on insulin with a marked improvement in her symptoms and HbA1c. She also developed autoimmune hypothyroidism during this period and has been on thyroxin replacement.

This case demonstrates slowly progressive destruction of β cells in an adolescent patient with diabetes and a period of insulin independency of four years from the time of diagnosis of diabetes, suggesting a diagnosis of LADY.

Comment

Type 1 diabetes is an autoimmune diabetes, whereas, in contrast, type 2 diabetes is non-autoimmune. However, there is a group of phenotypic adult patients with type 2 diabetes (10%) who have islet auto antibodies similar to type 1 diabetes. These patients are said to have LADA. These antibody-positive phenotypic patients with type 2 diabetes also commonly have T cells reactive with islet antigens and share many genetic similarities with type 1 diabetes. These genetic and immunological similarities between

LADA and type 1 diabetes strongly suggest that LADA, like type 1 diabetes, is an autoimmune disease.

The diagnosis of LADA is currently based on three clinical criteria:

- adult age at onset of diabetes
- the presence of circulating islet autoantibodies
- lack of requirement of insulin for at least six months after diagnosis.[9]

Islet autoantibodies distinguish LADA from type 2 diabetes and a period of insulin independence after diagnosis helps to distinguish LADA from classic type 1 diabetes. Among patients with phenotypic type 2 diabetes, LADA occurs in 10% of individuals older than 35 years and in 25% below that age.[10] LADA patients with multiple islet antibodies develop β cell failure within five years, whereas those with only GAD antibodies or only ICAs mostly develop β cell failure after five years.[11] Even though it may take up to 12 years until β cell failure occurs in some patients, impairments in the cell response to intravenous glucose and glucagon can be detected at the diagnosis of diabetes. Consequently as LADA is not a latent disease, autoimmune diabetes in adults with slowly progressive β cell failure might be a more appropriate concept.

These patients may also have other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, and Addison's disease.[12] The prevalence of thyroid antibodies in adult patients with type 1 diabetes has been reported to be between 20–30%. A recent study showed the presence of thyroid peroxidase antibodies in LADA (22.1%) differed significantly to type 2 diabetes (9.4%), whereas no significant difference was found in the presence of thyroglobulin antibodies.[12] The association of autoimmune disease is explained by the spreading of T cell response to new determinants during the course of autoimmunity development. The phenomenon of recruitment of additional T cell epitopes has been reported.[12]

The presence of obesity is not incompatible with diagnosis of immune mediated diabetes. Studies report a mean BMI in the overweight category (BMI >25.0 kg/m^2) in a LADA population of European extraction.[13] Increase in weight may add some kind of insulin resistance to the pathogenesis. This problem will be seen more often because of increase in childhood obesity. Assigning a type of diabetes to an individual often depends on the circumstances present at the time of diagnosis, and some diabetic individuals do not easily fit into a single class. Weight gain could therefore be a risk factor for the early manifestation of type 1 diabetes in these patients.[14]

Immune-mediated diabetes in children is normally a classic disease with insulin deficiency at diagnosis. In a series of 747 children with newly diagnosed type 1 diabetes, remission of up to 18 months after diagnosis has been reported in only a small percentage (3.4%) of children with positive autoantibodies.[6]

Our patient was only 15 years of age and asymptomatic at the time of diagnosis of diabetes. She had positive GAD and islet cell autoantibodies and remained insulin independent for four years from the time of diagnosis, although the requirement of sulfonylurea gradually increased. A diagnosis of LADY was favoured though it is possible that given the duration of insulin independence it is possible that she was diagnosed early in the course of type 1 diabetes.

This case represents latent autoimmune diabetes in the young (LADY). It also demonstrates that immune mediated diabetes can be slowly progressive even in younger patients and that the insulin independency period may last for more than two years. It also shows its association with other autoimmune disorders, like hypothyroidism in our patient.

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