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Atypical course of type 1 diabetes mellitus in a patient with Ollier's disease - a case report

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Abstract

Background

Nowadays, we can distinguish more than two types of diabetes mellitus. Due to blood glucose measurement and genetic tests, different types of diabetes (such as autoimmune, monogenetic,

atypical) can be detected. Despite the constantly updated recommendations and the progress of diagnostic tests, making a diagnosis may be difficult.

Case report

A 23-year old patient was admitted to the Department of Endocrinology due to diagnosed diabetes mellitus to determine its primary cause. Elevated blood glucose level was identified during periodic medical test and was confirmed by OGTT test. In the patient's medical history: Ollier's disease with multiple enchondromas, treated surgically in childhood, no typical symptoms and risk factors of hyperglycaemia.
During hospitalization the laboratory tests showed decreased level of C-peptide, nevertheless the patient represented acceptable levels of glycaemia following only by diet restriction. MODY, LADA and diabetes due to Ollier's disease was speculated. Due to suspicion of autoimmunological cause the diagnostic was extended by testing antibodies: IAA, IA2, GAD, IC, which confirmation allowed to recognise untypical diabetes mellitus type 1.
The patient objected to insulin treatment, limited it only to a diet and maintained normoglycemia for 15months. However, after an increase in glycaemia and in HbA1c, insulin therapy was introduced.

Disscussion with conclusion

Atypical course of diabetes should be considered in patients with a known disorder or with comorbidities associated with diabetes and without typical symptoms of hyperglycaemia. Atypical forms of diabetes are uncommon and require etiology-specific therapies.

Keywords: diabetes mellitus, Ollier's disease, diabetology

Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from impaired insulin secretion or dysfunction or a combination of both. In recent years, there is a constant increase in the incidence and detection of diabetes. It is estimated that 10,5% of the world's population in the 20 – 79 age ranged were suffering from this illness in 2021. [1]

We can distinguish more than two, most common, types of diabetes mellitus. American Diabetes Association differentiates 4 types: type 1 (T1D), type 2 (T2D), specific types of diabetes due to other causes (monogenic diabetes, drug-induced diabetes, diseases of the exocrine pancreas), and gestational diabetes.
Due to blood glucose measurement, antibodies detection, genetic tests and many other evolving diagnostic methods, different types of diabetes can be detected.
Type 1 diabetes has two peaks of occurrence. One in childhood and the other in the 35-50 age range (it is called LADA- latent autoimmune diabetes in adults). This type of disease is usually detected when the patient already has clinical manifestation of hyperglycemia or even when diabetic ketoacidosis is developed.
An example of monogenic diabetes is MODY diabetes. It is caused by a single gene mutation and occurs in people under the age of 25 with a family history of diabetes. [2] Despite the

constantly updated recommendations and the progress of diagnostic tests, sometimes making a diagnosis may be difficult.

Chronic hyperglycemia in diabetes leads to many complications. In particular, dysfunction and failure of various organs, such as eyes, kidneys, nerves, heart and blood vessels. Therefore, there is a great necessity for early identification of this disease, especially in a young population. [3]

This paper describes the case of a male patient aged 23 presented with type 1 diabetes mellitus who had no clinical symptoms, such as polyuria, polydipsia, weight loss or even signs of dehydration, weakness or drowsiness, which could indicate this illness.

Case report

A 23-year old patient was admitted to the Department of Endocrinology due to accidentally diagnosed diabetes mellitus to determine its primary cause. Elevated blood glucose level (126 mg/dl; N: 70 – 99 mg/dl) was identified during periodic medical test and was confirmed by OGTT (oral glucose tolerance test) which was 335mg/dl after 2 hours.

Ollier's disease with multiple enchondromas was reported in the patient's medical history. Numerous surgical procedures was performed in childhood (at the age of 4, 6 and the last one at 16 years old) to correct bones deformities.

Upon questioning, he has not been chronically treated for any systemic diseases.

The patient presented neither typical symptoms such as polyuria, polydipsia or weakness nor risk factors of hyperglycaemia. Patient had healthy and active lifestyle. His physical examination was normal. He weighed 64 kg, had a proper body mass index (BMI) of 21.6 kg/m^2 and blood pressure of 125/79 mmHg.

During hospitalization the laboratory tests showed decreased level of C-peptide (0,48 ng/ml; N: 0,81 – 3,85ng/ml). Glucagon test revealed a decreased endogenous insulin secretory capacity of pancreatic β-cells. Nevertheless the patient represented acceptable levels of glycaemia following only by diet restriction. His glycated hemoglobin A1c (HbA1c) measurement was 6,3% (N: 4-6%).

Considering young age, benign onset of disease and absence of obesity, MODY diabetes was speculated. Lack of family history and low postprandial blood glucose level eliminated this diagnosis. Impaired regeneration of pancreas (due to mutation in PTHrP gene) and the presence of ketone bodies in the urine (which is a consequence of the increased metabolism of fatty acids in enchondromatosis) could suggest connecion with Ollier's disease.

Due to suspicion of autoimmunological cause the diagnostic was extended by testing antibodies: IAA (antibodies against insulin; 4,0 μIU/ml; N: 2 – 25 μIU/ml), IA-2A (islet antigen 2 antibodies; 409,24 IU/ml; N < 10 IU/ml), anti-GAD (glutamic acid decarboxylase antibodies; 10,15 IU/ml; N: < 10 IU/ml), ICA (islet cells antibodies; 1:10), which confirmation allowed to recognise untypical diabetes mellitus type 1.

At discharge, the patient was recommended to follow the diabetic diet and was required to measure blood glucose levels daily. Continued treatment at the diabetes clinic was recommended.

The patient objected to insulin treatment, limited it only to a diet and maintained normoglycemia for 15 months. However, after an increase in glycaemia (up to 160 mg/dl; N: 70 – 99 mg/dl) and in HbA1c (6,7%; N: 4-6%), insulin therapy was introduced.

Discussion

The heterogeneity of diabetes mellitus makes it a disease that demands an accurate and careful diagnosis before an appropriate treatment implementation. Frequently, the cause cannot be identified due to the overlap of many pathogenetic mechanisms. [4,5]

Several genes responsible for monogenic diabetes are known in the literature. These include: HNF1A (the most common genetic variant), HNF4A, GCK, BLK , KLF11 , NEUROD1 , PAX4 and PDX1. However, ongoing studies are isolating more and more genes showing correlations with diabetes. A diagnosis of MODY should be considered in individuals who have atypical features of diabetes based on age <25, negative antibodies, multiple family members with diabetes not characteristic of type 1 or type 2 diabetes. In such cases, it is essential to perform genetic tests to confirm the diagnosis. [6,7]

In addition to genetic testing, other diagnostic tests like C-peptide levels are helpful in diagnosing MODY. The timing of this test to differentiate monogenic diabetes from type 1 diabetes is controversial. Endogenous insulin production outside of the "honeymoon" phase (more than 3-5 years) with a detectable C-peptide (>0.6 ng/mL or >0.2 nmol/L [>200 pmol/L) and a corresponding glucose > 72 mg/dL (> 4 mmol/L) indicate that MODY is the more likely diagnosis. [6]

The clinical presentation of the described patient - young age (23 years) and nonobesity - body weight (64 kg), normal BMI (21,6kg/m^2) indicates that MODY diabetes should be considered. He also had preserved endogenous insulin and C-peptide production and low insulin requirement for treatment. However, with newly diagnosed hyperglycemia, it is difficult to assess whether this may be related to residual pancreatic function in type 1 diabetes or whether it is indicative of MODY diabetes. [7]

Additionally, none of the family members suffered from diabetes. A positive 3-generation (or more) family history of this illness is obtained in patients with MODY, although there were reported some patients without parents affected by monogenetic diabetes. [6,8]

One of the classic exclusion criteria for MODY diabetes is the presence of antibodies to pancreatic islet cells or to insulin (anti-GAD, IA-2A, ZnT8- zinc transporter 8 antibodies, IAA, ICA). Most of them were found in the case presented in this article but a review of the literature states that they may be present in 1% of patients diagnosed with monogenic diabetes. There are monogenic forms of autoimmunity when patients are tested positive for pancreatic autoantibodies. In order to better define genetic testing criteria and treatment plans for patients, there is a necessity for further studies on forms of autoimmunity. [8]

In addition, patient's co-occurrence of Ollier's disease, may suggest a genetic cause of diabetes. The direct effect of genetic mutations on the occurrence of hyperglycemia in this disease has not been studied yet. However, the PTHrP gene mutation, present in enchondromatosis, may impair pancreatic β-cell regeneration and consequently be the cause of diabetes. [9]

Latent Autoimmune Diabetes in Adults (LADA) is also worth considering when diagnosing diabetes. The lack of specific diagnostic criteria for LADA is extremely problematic. In its diagnosis, the following should be taken into account: adult age of its onset, presence of any antibody to pancreatic islets cells or insulin, no need for insulin therapy. [10]

None of these criteria are categorical. LADA is clinically and metabolically a hybrid of T1D and T2D. It is a challenge for medicine to define categorical immunogenetic and phenotypic features.

This type of diabetes is often diagnosed over the age of 30 in people with lower: BMI, HOMA score and blood pressure in comparison with type 2 diabetes but with higher mentioned measures in type 1 diabetes. Studies show that the risk of developing both LADA and T2D increases gradually as BMI increases.

As a form of autoimmune diabetes, LADA has the same autoantibodies as these used to identify T1D. Anti-GAD antibodies are considered the most sensitive markers of latent autoimmune diabetes in adults. Patients with high levels of Anti-GAD and lower BMI have a phenotype more similar to T1D. [11]

The case described in this article did not correspond to the above criteria related to age, weight, and increased anti-GAD levels therefore clinically it was most appropriate for type 1 diabetes.

Patients diagnosed with LADA diabetes typically have higher C-peptide levels that decrease much more slowly in comparison to type 1 diabetes and they do not require insulin therapy for at least 6 months after the diagnosis. These characteristics indicate preserved endogenous insulin production over a long period of time in LADA patients. With new-onset hyperglycemia, it is difficult to indicate whether the underlying cause is T1D or LADA. The diagnostic criteria for LADA are considered to be limited by an arbitrary age limit or pharmacological insulin requirement. [12]

Diagnosis of diabetes can be difficult because of the frequent overlapping between different subtypes of the disease. Current state of knowledge often does not allow to reach the main cause of diabetes. Therefore, there are unclassified forms that present most, but not all, of the characteristics of a particular type of diabetes.

Conclusions

Beyond the presence of classic type 1 and type 2 diabetes mellitus, a number of hybrid forms are found that combine features of each type. The complete genetic structure of type 1, type 2, MODY, or LADA diabetes is not currently known. The influence of particular genetic mutations in the course of other disorders such as Ollier's disease on the development of

diabetes has not been discovered yet. It is important to continue genetic testing in order to make an appropriate diagnosis of the type of diabetes so that suitable treatment can be implemented. The clinical condition of the patient should always be taken into account, even in the absence of unambiguous features or criteria for diagnosis of a particular type of diabetes.

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