

Diabetes mellitus type 1, type 2 or type 1.5 — dilemmas in making proper diagnosis



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Abstract

Until recently the diagnostic criteria and division into the two main types of diabetes seemed clear enough. It was thought that just as islet autoantibodies and tendency to ketosis was a feature of type 1 diabetes, the insulin

resistance and slow progress of the disease was typical of diabetes type 2. However, the latest study results and case reports supply evidence, which question that present order. Is there a type 1.5 diabetes? The growing diagnostic abilities in the field of genetics and immunology give new measures to broaden the studies of diabetes pathogenesis and pathophysiology. Formerly described characteristics of types of diabetes become blurred and tend to permeate through one another. All those data contribute to a great need to verify the old and establish the new diagnostic criteria for type 1 and type 2 diabetes.

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The diagnostic criteria, needed to differentiate between types of diabetes, seemed clear not so long ago. However, there is an increasing body of evidence describing cases of diabetes that can not be unambiguously classified [1]. The reports analyzing difficulties in distinguishing between type 1 and type 2 diabetes came lately into view. The opinion about the revision of present classification of diabetes is now being put forward [2–7]. It has been previously considered that the insulin deficiency as a result of islet destruction in type 1 and insulin resistance in type 2 diabetes are essential. Nowadays it is well known that hyperglycemia in both types of diabetes originates from these both disorders [8–11]. The ENDIT study (European Nicotinamide Diabetes Intervention Trial) showed insulin resistance in the groups with high risk of type 1 diabetes development [8]. It has been revealed in numerous studies that the insulin resistance is an accelerating factor for type 1 diabetes development in subjects with detectable antibodies and decreased insulin secretion [8, 12–14]. The differences are rather quantitative than qualitative. The mechanism and the increase rate of both these disorders can be different, which gives specific clinical picture. This results in difficulties in determining the type of diabetes according to present criteria.

The Japanese authors have suggested for example, the introduction of a new subtype of type 1 diabetes i.e. „slowly progressing insulin-dependent diabetes mellitus” (SPIDDM or IDDMS) [15]. They stated that the genetic background including lower prevalence of HLA-A24 in SPIDDM is similar to the one in LADA (latent autoimmune diabetes in adults), however, the clinical picture is quite different [16–20].

Reinehr et al. [18] conducted a study verifying the diagnosis of certain type of diabetes in a group of 7050 adolescents. In 128 of them type 2 diabetes was recognized. Of the latter, 36% had antibodies. Those children were not significantly different from other type 2 diabetes subjects regarding other parameters. Gilliam et al. [21] performed an assessment of HLA-associated genetic and immunological markers in the group of children with newly diagnosed diabetes. Eighty-four percent of the patients from this group were then followed through several years (47.9 ± 8.7 months). In the patients classified as type 1.5 or type 2 diabetes a high prevalence of autoantibodies and type 1 diabetes-specific HLA alleles were revealed. The course of diabetes was more aggressive in patients with autoantibodies compared to similar cases in adults.

The authors had proposed the term LADY (latent autoimmune diabetes in youth) for the patients with autoantibodies present, but with clinical features of type 2 diabetes. Hybrid, mixed or double diabetes are the alternative names that are used [22, 23]. This is because

the types of the disease that meet both type 1 as well as type 2 diabetes criteria, are more and more frequent in adolescents. It is related to overweight epidemic or obesity. The insulin resistance — typical for type 2 diabetes, and anti- β -cell antibodies — essential in type 1 diabetes are concomitant in these patients. The clinical picture also combines these two elements and the pharmacotherapy consists of methods used in both types of diabetes i.e. the insulin injections and oral drugs lowering insulin resistance. The physical activity and diet are important as well as they increase insulin sensitivity.

Up till now one believed that distinguishing between type 1 and type 2 diabetes is usually simple. The differentiation was based upon the case history data, the progress of the disease and phenotype. It was recognized that type 1 diabetes is characterized by the rapidity of symptoms increase, usually considerable hyperglycemia, ketoacidosis, loss of weight, and frequently no family history of diabetes. These features are likely to point at type 1 diabetes. Obesity and slow progression of symptoms are typical of type 2 diabetes. However, this characteristic is only partially true. Nowadays more advanced diagnostic tests are used, like genetic and immunological tests, endogenous insulin secretion and insulin resistance assessment or adipokine secretion assessment [24–27]. Katz et al. [28] for example, in a group of 175 children with newly diagnosed diabetes, during 12 months of follow-up identified a group of 26 children, in whom C-peptide and insulin-like growth factor binding protein-1 (IGFBP-1) assessments contributed to type 2 diabetes diagnosis.

It becomes apparent, that there is an increasing incidence of types of diabetes, that can not be unequivocally classified as either type 1 or type 2 diabetes [22, 23]; maybe type 1.5 then [29, 30]? In these cases the dynamics of symptoms increase can imply type 1 diabetes but it is not crucial, as hyperglycemia increase in type 2 diabetes can also be relatively fast. The ketoacidosis is also possible, particularly during infection or perioperative stress. On the other hand cases of type 1 diabetes with relatively slow symptoms progression and only little tendency to ketosis occur as well. Furthermore obesity is not an essential factor regarding diabetes type diagnosis [31, 32]. Purushothaman et al. [30] conducted a retrospective analysis in a group of 120 children with diabetes. In 64% of the subjects primarily classified as type 2 diabetes, after a verification of tests results and course of treatment, a change of diagnosis to diabetes type 1.5 was made. This type of diabetes is characterized by more dynamic course and higher insulin requirement than type 2.

Cases of early onset of type 2 diabetes without accompanying obesity can cause some difficulties, which is worth remembering. If the obesity is absent one

should consider first of all the monogenic types of diabetes, which are known to date. The immunological tests can be helpful in differential diagnosis, however even those can not give the definitive answer. A group of patients with type 1 diabetes and no immunological markers of β -cell destruction exists. On the other hand auto-antibodies occur in healthy subjects and in some cases of early onset, multigenic type 2 diabetes [24]. Endogenous insulin and C-peptide secretion are another indicators used for diabetes type classification. The former can be normal, increased or decreased in type 2 diabetes. A very high fasting insulin concentration can help in differential diagnosis of type 1 and early-onset type 2 diabetes however, the low concentration can not exclude type 2 diabetes. Moreover, endogenous insulin concentration, although possibly decreased in type 2 diabetes, does not reach as low levels as in type 1 diabetes. The insulin sensitivity assessment was thought to be a quite accurate differentiating marker, as it is generally normal in type 1 and decreased in type 2 diabetes. At present it is known however, that insulin resistance occurs also in type 1 diabetes. The fact, that revealing insulin resistance is not always connected with diagnosing diabetes should be considered as well [33].

In a nutshell, in many cases a very specific clinical picture facilitates with a high degree of probability, the establishment of certain type of diabetes. However, there is a group of patients that need a longer follow-up period regarding the course of the disease, treatment outcomes and frequently a thorough diagnosis using laboratory tests, in order to find the definite type of the disease.

Tuomi [34] presented an analysis of the familial co-existence of type 1 and type 2 diabetes. The cases of mixed genetic and phenotypic features occur in those families.

The assessment of insulin resistance is mainly used to make therapeutic decisions. That kind of test is useful regarding the attempts of prevention in metabolic disorders leading to type 2 diabetes, but also as Xu et al. [14] state, in the prevention and treatment of type 1 diabetes.

Weintrop et al. [35] presented a very interesting case of diagnostic difficulties. A 13.5-year-old boy, with a 5-year history of glucose intolerance without clinical symptoms of diabetes. Since his 6 year of age the boy was overweight. His father was obese, hypertensive and suffered from diabetes diagnosed as type 2. An additional family history of diabetes was noted with his mother having gestational diabetes, his grandmother and great grandmother having diabetes treated with diet. Because of significant hyperglycemia, high level of HbA_{1c}, a little increased C-peptide level, elevated blood pressure, and no symptoms of ketosis as well as negative

antibodies testing (ICA, GAD, IAA), type 2 diabetes was diagnosed. Treatment consisted of diet, physical activity increase and metformin. It resulted after 3 months in body mass as well as blood pressure and HbA_{1c} decrease. Since a very aggravating family history from mother's side genetic tests for MODY were performed. As the results were positive, a MODY 3 diagnosis was established. A sulfonylurea agent was introduced into the former treatment. A similar genetic background was found in patient's younger sister, who were obese but did not show glucose tolerance disorders — preventive measures were undertaken.

The results of these latest studies and the growing diagnostic abilities point at an urgent need of verification of currently existing diabetes classification and the necessity of establishing new diagnostic criteria. This applies especially to cases classified till now, mainly on the basis of genotypic features, as type 2 diabetes. These form a very heterogenic group regarding the clinical picture as well as the laboratory tests results, particularly concerning the endogenous insulin secretion and insulin sensitivity [6, 7]. The diversity also involves the occurrence of autoimmune markers of islet β -cell destruction and mixed genetic configuration [33]. Such heterogeneity, although in lesser extent, concerns the cases classified as type 1 diabetes as well [4, 15, 22, 30, 36].

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