

Problems in differential diagnosis of diabetes types*

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Abstract: Diabetes mellitus is a group of diseases characterized by chronic increase of glucose level. The last years brought progress in understanding the multiplicity of its forms, as well as, its complex pathogenesis. In 1999, a classification of diabetes based on the etiology of individual types, was proposed by the Experts Committee of the World Health Organization, and is now commonly accepted. Etiologic classification in the last decade was gradually extended with the progress of knowledge, in particular, with successes of researchers in the field of genetics. Monogenic forms of diabetes such as MODY, mitochondrial diabetes, neonatal diabetes and lipotrophic diabetes, discovered over a dozen years ago, are characterized by unique clinical features and possibility of applying a tailored treatment, assuring optimal correction of genetically conditioned metabolic defect. The differential diagnostics of types of the diseases is playing an increasing role in diabetology, as it enables selection of optimal treatment methods, as well as, the assessment of prognosis referring to the diabetes course and complications occurrence. In this article, a review of problems associated with the differential diagnostics of diabetes and its practical clinical application was made.

Key words: diabetes mellitus, differential diagnosis, genes

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INTRODUCTION

Diabetes mellitus is a common name for a group of diseases of a very diversified etiopathogenesis, characterized by chronically increased concentration of blood glucose. Investigators have been aware of existence of different forms of diabetes for a long time, however, only the last decade brought a substantial progress in identification and understanding of etiology of its distinct types. The present classification of diabetes, published by WHO in 1999, is based on the etiology of its individual forms [1]. Progress of knowledge concerning the pathogenesis of different types of diabetes often finds a spectacular application in the clinical practice, enabling the employment of individually selected, effective treatment, determining the prognosis and risk of complications.

The most frequent form of disease is type 2 diabetes mellitus, formerly referred to as noninsulin dependent diabetes mellitus (NIDDM). It develops as a result of interactions of genetic and environmental risk factors, which lead to relative deficiency of insulin with coexisting resistance to its activity [2]. It is typically observed in adulthood, often in elderly and characterized by a possibility, in many instances, to con-

trol glycemia with diet or diet combined with oral hypoglycemic drugs, without need of insulin therapy, at least at the beginning of the disease. Obesity, hypertension and lipid abnormalities usually accompany type 2 diabetes. The is difficult to identify, asymptomatic or oligosymptomatic. The family history for diabetes is often positive.

The second most frequent form of the disease is type 1 diabetes [3]. It is characterized by absolute insulin deficiency. The diagnosis is most often accompanied by acute symptoms resulting from dehydration and accompanying ketoacidosis, sometimes with dramatic course. Type 1 diabetes definitely requires insulin treatment. The cause of the disease is the autoimmune process directed against pancreatic β cells. The diabetes afflicts almost frequently young people, in the first, second and third decade of life. The occurrence of elements of the metabolic syndrome does not fit the standard image of type 1 diabetes, however, it can sometimes accompany the disease.

Differentiation of type 1 and type 2 diabetes is not a difficult task when the image of the disease does not diverge from the above description. Nevertheless, in clinical practice, we can face difficulties resulting from the fact that not all patients present typical features of the most frequent forms, mainly with reference to clinical symptoms, body weight or age recognition.

Diabetes type 2 in children and adolescents, and latent autoimmune diabetes of adults (LADA)

The lowering age of diagnosing type 2 diabetes, particularly in developed countries, is a growing and worrying phenom-

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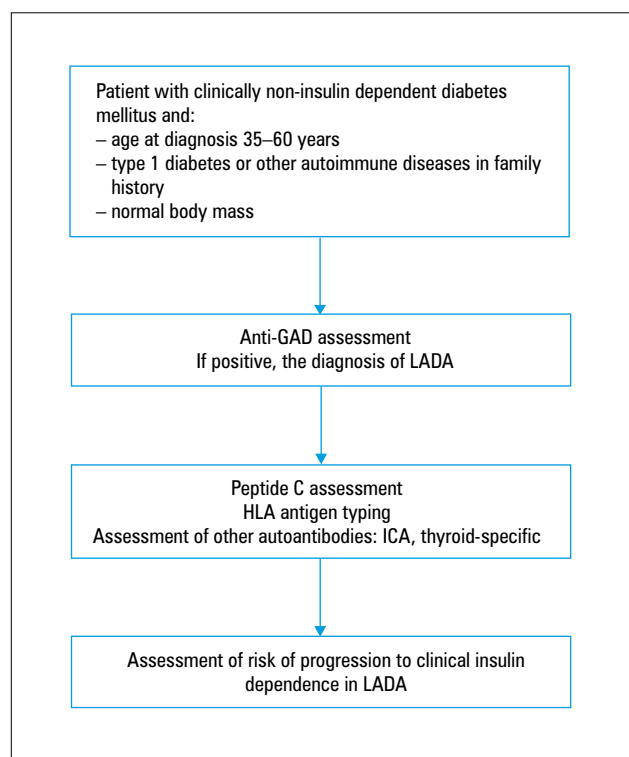


Fig. Proposed diagnostic algorithm in latent autoimmune diabetes of adults (LADA), according to reference [9]. Abbreviations: GAD – glutamic acid decarboxylase, HLA – human lymphocyte antigens, ICA – islet cell antibodies

enon [4]. This disease more and more often affects pediatric populations. The main role is being assigned to environmental factors: high caloric diet and low physical activity. Children, adolescents and young adults with type 2 diabetes present the characteristic clinical picture, which comprise the elements of the metabolic syndrome. The parents of these patients are often affected with type 2 diabetes. In biochemical tests, a high C-peptide is typical and markers of autoimmunity are negative.

Type 1 diabetes can develop in persons in the fourth decade of life or later without any characteristic acute symptoms [5]. The most popular acronym describing this form of diabetes (not included as a separate entity in the WHO classification) is LADA – latent autoimmune diabetes of adults [6]. When type 1 diabetes develops with acute symptoms in a person over 30 years old, then the appropriate diagnosis is most often not difficult [7]. However, LADA diabetes develops secretly, under the mask of insulin independency. Differentiating type 2 diabetes and LADA has important clinical meaning. It is caused by the fact that animal models suggest a protective action of exogenously administered insulin in sustaining function of the β cells in the presence of the autoimmune process. The phenomenon of this protective action of insulin is explained by immunomodulating action of the hormone [8] or by reducing exhaustion of the damaged cells as a re-

sult of the exogenous insulin supplementation [9,10]. Nevertheless, the direct evidence for the beneficial action of early insulin therapy in type 1 diabetes in humans turned out to be difficult. Using insulin in healthy persons with genetic predisposition to type 1 diabetes and the presence of autoantibodies against the β cells did not show any benefit from such intervention [11]. However, a study in Japanese population showed a protective insulin activity in LADA diabetes [12]. Certain indirect evidence for beneficial influence of insulin on preserving activity of insulin secreting cells, measured with C-peptide level, was revealed by the DCCT trial (Diabetes Control and Complications Trial), showing association with treatment regimen [13]. Since preserving the residual pancreatic endocrine function, i.e. secreting insulin, is an important aspect of therapy of type 1 diabetes, an early identification of patients with LADA in order to apply insulin treatment, has a serious clinical importance. The lack of metabolic syndrome features or type 2 diabetes in family and the presence of different diseases from the autoimmunity, both in the patient and his relatives, might be helpful in differential diagnosis in respect to type 2 diabetes. The C-peptide level can be decreased or within the normal range. Assessment of anti-GAD antibodies (glutamic acid decarboxylase – GAD) is a deciding test. It is worth to emphasize its high diagnostic sensitivity, long lasting increased titre and relatively simple methodology of detection [14-16]. The islet cell antibodies (ICA) are equally sensitive, however, soon after diagnosing diabetes, they are not detectable, moreover, they require a complicated detection assay [15]. Other autoimmune markers of β cells are rarely used due to their lower sensitivity [17,18]. Because of similar clinical value of anti-GAD and ICA, their routine combined assessment is not necessary. Patients with LADA are characterized by much faster loss of the endocrine function of islets than patients with type 2 diabetes, therefore, an early ineffectiveness of treatment with oral drugs is an essential clinical symptom [19]. The Figure shows the suggested diagnostic procedure in LADA diabetes. The Tables 1 and 2 present clinical features of MODY, LADA and type 2 diabetes, useful in differential diagnostics.

Other specific forms of diabetes

The problems we can encounter in differentiating type 1 and 2 diabetes were presented above. WHO classification [1] includes, except these two, dozens of different forms of the disease. Numerous forms of secondary diabetes, evoked by medicines or hormonal disorders can clinically resemble type 2 diabetes, rarely type 1, for example diabetes of autoimmune basis, triggered by interferon administration [20]. The differential diagnostics of such secondary diabetes is based on the identification of factor being capable to trigger the disease. We deal with such a situation in case of pancreatic disorders or surgery on this organ, complicated by diabetes. Monogenic forms of diabetes, such as genetic defects of insulin secretion and, rarely appearing, genetic defects of the hormone action are of great clinical importance. The most fre-

Table 1. Comparison of selected clinical features helpful in differential diagnosis of MODY and LADA

	MODY	LADA
Multigeneration family history	Frequent	Rare
Anti-pancreatic antibodies	Absent	Present
C-peptide after several years from diagnosis	Present	Not detectable
Renal and genital tract malformations	May occur	Not typical
Accompanying autoimmune diseases	Not typical	May occur
HLA-DR3 and DR4 haplotypes	Several percent of cases	In over half cases

quent form of genetic defect of β cells is a group of disorders referred to with acronym MODY (maturity onset diabetes of the young) [21].

MODY diabetes

Currently, there are 6 MODY subtypes associated with gene mutations: hepatocyte nuclear factor (HNF)-4 α – MODY1 [22], glucokinase (GCK) – MODY2 [23,24], HNF1 α – MODY3 [25,26], insulin promoter factor (IPF)-1 – MODY4 [27], HNF1 β – MODY5 [28], NEUROD1/ β_2 – MODY6 [29]. MODY is usually diagnosed in the second or third decade of life, the beginning of the disease is asymptomatic, usually there is no ketoacidosis. The diabetes do not require insulin treatment for many years after the diagnosis has been made and it is not accompanied by metabolic syndrome features such as obesity, lipid disorders or hypertension [21]. A positive family history is characteristic, typical for the dominant autosomal inheritance of a diseases with high phenotypic penetrance. The patients with MODY diabetes do not have elevated C-peptide level, they also do not reveal the presence of specific autoantibodies for β cells. The definitive diagnosis can be made on the basis of genetic testing, as in case of other monogenic forms of diabetes. Certain MODY subtypes reveal some characteristic features, facilitating the preliminary diagnosis. A common MODY2 diabetes, which is the mildest form of the disease, is included here. The satisfying metabolic compensation is usually achieved by only diabetic diet. The risk of chronic complications is small [30]. The patients are characterized by increased fasting glucose level, however after a challenge test, the increase in the glucose concentration is relatively small and it is not exceeding 2–3 mmol/l compared to the baseline [31]. The metabolic defect does not reveal a tendency to increase over time. The remaining MODY subtypes are associated with mutations of transcription factors. The most common of the forms is MODY3 linked to the mutations of the HNF1 α gene. The element facilitating

Table 2. Comparison of selected clinical features helpful in differential diagnosis of MODY and type 2 diabetes mellitus

	MODY	Type 2 diabetes
Clinically insulin independent	Yes	Yes
Parents with diabetes	1	1–2
Obesity	Not common	Common
Autoantibodies	No	No
Genetic testing	Helpful	Not useful

differential diagnosis is renal tubulopathy resulting in lowered renal threshold for glucose [32]. Plasma 1,5-anhydroglucitol, a monosaccharide which concentration depends on the renal threshold for the glucose, can be a useful biochemical marker [33]. Moreover, the MODY3 can rarely be accompanied by developmental renal defects in form of hypoplasia or agenesis [33], and adenomas of the liver [34]. Diagnosing MODY3 has a great clinical meaning as a treatment of choice in this disease are the derivatives of sulphonylurea [35]. The other, less common subtype, where clinically extrapancreatic symptoms facilitating differentiating diagnostics appear, is MODY5. Here, the developmental renal disorders often appear in the form of polycystic degeneration and the impairments of filtration function [36].

Mitochondrial diabetes

This monogenic form of diabetes resulting from impairment of insulin secretion is associated with mutations of the mitochondrial genome [37]. As a result of such etiology, the disease reveals so-called maternal inheritance as it is passing in family from generation to generation, transmitted exclusively by women. It is accompanied by the characteristic extrapancreatic symptoms, the most often sensoric hypoacusis, hence the MIDD acronym (maternally inherited diabetes with deafness) [38]. Mutations responsible for MIDD, first of all and most frequent, in position 3243 of mitochondrial genome, are also linked with different syndrome – MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and strokelike episodes) [39]. Even though MIDD and MELAS constitute separate entities, their elements overlap in some instances. The clinical picture of diabetes is diversified from asymptomatic, slowly developing diabetes, to relatively fast progressing defect of β cells requiring insulin therapy [40]. The diagnosis usually takes place between the second and the fifth decade of life. Metformin should be avoided in treatment, due to a potential risk of lactic acidosis. This rare form of diabetes should be expected in case of maternally inherited diabetes combined with deafness. The level of C-peptide is normal or decreased, the autoimmune markers are negative. In differential diagnostics, an audiogram and ophthalmological examination is sometimes helpful, because of a characteristic macu-

lar pattern dystrophy [41]. The history of elements of MELAS syndrome, as well as family history might be helpful in differential diagnosis.

Genetic forms of insulin resistance

This is a diversified group of diabetes of different degree of severity. Lethal pediatric syndromes, such as leprechaunism [42] or Rabson-Mendenhall syndrome [43], associated with mutations of the insulin receptor, are included here. Other mutations are responsible for milder form, type A insulin resistance [44]. The range of different genes is associated with generalized or partial lipodystrophy (lamin gene mutations and PPAR- γ receptor are associated with the latter [45,46]). According to the name, the syndromes are characterized by subcutaneous tissue atrophy and its altered distribution. The common features of diabetes with extreme insulin resistance are: hypertriglyceridemia, hypercholesterolemia, low level of HDL, hepatosplenomegaly, acanthosis nigricans, hyperandrogenism, hirsutism, virilisation and menstruation disorders [47]. Nevertheless, these are not the characteristic symptoms of monogenic defects of insulin action.

Neonatal diabetes

The most important diagnostic criterion of neonatal diabetes is disease onset in the first 6 months of life [48]. Neonatal diabetes can have a transient or permanent form, clinically resembling type 1 diabetes. About 50% of cases of the latter form are linked to mutations in genes of potassium channel subunits expressed in β cells: Kir6.2 and SUR1 [48,49]. Some carriers of these genes mutation (about one third) reveal, apart from diabetes, neurological symptoms such as mental retardation, muscle weakness, epilepsy [48,49]. The derivatives of sulphonylurea, enable not only normoglycemia but also, to certain extent, decrease of neurologic disorders [50]. The treatment was effective in treatment of the majority of cases [51]. Referral of a patient with neonatal diabetes to a health centre, which has genetic testing facility, has a crucial meaning for later prognosis and life quality.

In summary, it should be emphasized that the appropriate differentiating of forms of diabetes has more and more clinical meaning. Most often, the appropriate diagnosis can be made, with great probability, on the basis of interview, physical examination and relatively simple biochemical or immunological tests. Currently, the genetic screening and counseling play an important role in clinical care of patients with monogenic forms of diabetes, and in a smaller degree in the complex forms of the disease. However, the prognostic value of such tests is very limited in type 1 diabetes and particularly type 2 diabetes. Hence, we draw a conclusion that molecular diagnostics of these complex, polygenic types of diabetes still do not have clinical application. Nevertheless, there is a hope that in the future with the improved understanding of a more complete image of the role of genetic factors and their inter-

action with environment, prognostic, diagnostic and therapeutic role of genetic testing will considerably increase. This will create a field for diabetes specialists, clinical geneticists, molecular biologists and pharmacologists for a wide cooperation with a patient complex care which will allow individualization the therapy.

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