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Brief report

Easily obtainable clinical features increase the diagnostic accuracy for latent autoimmune diabetes in adults: An evidence-based report

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ABSTRACT

Background: Latent autoimmune diabetes in adults (LADA) represents a subgroup of diabetes mellitus. LADA is characterised by adult-onset diabetes and circulating autoimmune antibodies. LADA patients may need a different therapeutic approach than the usual type 2 diabetes mellitus. When LADA is inadequately diagnosed as type 2 diabetes mellitus, LADA patients will mistakenly be exposed to a high dose of oral glucose lowering drugs and their possible side effects.

Aim: To assess which clinical features predict the presence or absence of LADA in patients older than 25 years presenting with hyperglycemia.

Methods: A structured Medline and Embase search was conducted. Titles and abstracts were screened using predetermined selection criteria. Critical appraisal was based on standardized validity criteria for diagnostic research.

Results: One-hundred and eighty-four papers were retrieved of which after assessment of relevance and validity 2 studies remained for further analysis. One study reported a probability of LADA of 0.99 with one or two out of the following five clinical features: age at onset <50 years; acute symptoms; BMI < 25 kg/m^2; a history of autoimmune disease; a family history positive for diabetes mellitus. The other study reported a probability of LADA of zero with none of the following clinical features and of 0.32 with one out of three: fasting blood glucose ≥ 15 mmol/l and/or HbA_{1c} ≥ 10%; 10% reduction in body weight in the previous 3 months; BMI < 25 kg/m^2.

Conclusion: Further testing for LADA by measurement of autoimmune antibodies appears to be unnecessary in the absence of a specific set of clinical features. Before initiating therapy applying the above criteria may help to separate LADA from usual type 2 diabetes.

Abbreviations: GP, general practitioner; LADA, latent autoimmune diabetes in adults; GADA, glutamic acid decarboxylase antibodies; UKPDS, United Kingdom Prospective Diabetes Study; BMI, body mass index; PPV, positive predictive value; NPV, negative predictive value; NICE, National Institute for Health and Clinical Excellence; ADA, American Diabetes Association; ICA, Islet cell antibodies.

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1. Introduction

Latent autoimmune diabetes in adults (LADA) is a slowly progressive form of autoimmune β-cell destruction and characterised by adult-onset diabetes and circulating autoimmune antibodies, most commonly glutamic acid decarboxylase antibodies (GADA). These antibodies can be determined by a radioligand assay anti-GAD65-test (sensitivity 80%, specificity 97%) [1]. GADA is recognized as the marker with the highest sensitivity for LADA [2].

LADA is often misdiagnosed as type 2 diabetes mellitus because of late onset and patients are treated initially with oral glucose lowering drugs and in a much later stage with insulin therapy. The U.K. Prospective Diabetes Study (UKPDS) reported that 10% of adult patients with diabetes had LADA [3].

In order to reduce their elevated risk of severe long-term complications, diabetic patients should be treated adequately for their high blood glucose levels [4]. But, mistaking LADA for type 2 diabetes mellitus may lead to unnecessary treatment with high dose oral glucose lowering drugs with possible side-effects. Therefore it is important to diagnose LADA as early as possible. Although LADA is common, no universal recommendations exist regarding testing for autoimmune antibodies in adult-onset diabetes. LADA is not mentioned in the Diabetes guidelines of both the NICE (National Institute for Health and Clinical Excellence) and the ADA (American Diabetes Association).

Many physicians test for GADA only if LADA is suspected, generally on the basis of a BMI < 25 kg/m^2 [5]. There are, however, several studies [6–10] showing that patients with a BMI above 25 kg/m^2 are diagnosed with LADA. With the increasing incidence of overweight and consequently the difficulty of distinguishing between type 2 diabetes mellitus and LADA, screening all type 2 diabetics for GADA will not be feasible and is expected to reduce cost-effectiveness. It may be of help to define a set of clinical features to determine which patients with hyperglycaemia should be tested for GADA.

2. Methods

2.1. Search strategy

A Medline and Embase search was conducted on 23 January 2007 using various search terms within the domain (e.g., hyperglycemia), determinant (e.g., clinical characteristics) and outcome (e.g., LADA) (See appendix Table 1 for details).

2.2. Selection

184 articles (73 in Medline and 111 in Embase) were retrieved initially (See appendix Fig. 1 for an overview of the selection of articles). The first selection was based on title/abstract, using in- and exclusion-criteria and eliminating double publications. The remaining 98 articles were reviewed further applying in and exclusion criteria. Six articles were left, out of which 2 articles were relevant and in line with our domain, determinant and outcome. The reference lists of identified articles were checked for additional studies, but this did not add any publication.

2.3. Critical appraisal

Two relevant articles, Monge et al. [11] and Fourlanos et al. [5], were each appraised independently by two authors using standardized validity criteria for diagnostic research [12]. Several aspects were critically reviewed: whether there was a valid reference test, i.e., GADA test, whether reference test and clinical features were valued independently and blinded from each other, whether all patients received the reference test, whether the patients all had diabetes not requiring insulin at diagnosis, whether the methods of index test and reference test were described, and how comparable the study population was with clinical practice.

3. Results

An overview of the clinical features used in the two remaining articles is given in Table 1. In a population of 460 patients diagnosed with diabetes mellitus, Monge et al. studied the predictive value of three clinical features for LADA being present, that is a positive GADA or Islet cell antibodies (ICA) test, notably fasting blood glucose ≥ 15 mmol/l and/or HbA_{1c} ≥ 10%; 10% reduction in body weight in the previous 3 months; BMI < 25 kg/m^2. They report a probability for LADA of zero (negative predicting value of 1.0) when none of the evaluated clinical features were present and of 0.32 (positive predicting value) when one out of three of these clinical features were present.

In a retrospective study, Fourlanos et al. aimed to develop a clinical screening tool to identify adults at risk of LADA who require GADA-testing. They identified five clinical features that were significantly more frequent in LADA compared to type 2 diabetes mellitus at diagnosis: age at onset < 50 years; acute symptoms; BMI < 25 kg/m^2; a history of autoimmune disease; a family history positive for diabetes mellitus.

Table 1 – Clinical features

Clinical features used by Monge et al.	Clinical features used by Fourlanos et al.
1. Fasting blood glucose ≥ 15 mmol/l and/or HbA1c ≥ 10% in spite of adequate compliance to diet and treatment	1. Age of onset <50 years
2. Decreasing body weight ≥ 10% in the previous 3 months in spite of constant diet	2. Acute symptoms, i.e., polyuria and/or polydipsia and/or unintentional weight loss
3. BMI < 25 kg/m^2	3. BMI < 25 kg/m^2
	4. Personal history of autoimmune disease
	5. Family history of autoimmune disease