Available online at
ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com/en
Diabetes & Metabolism 42 (2016) 33–37

Original article

High-sensitivity C-reactive protein does not improve the differential diagnosis of HNF1A–MODY and familial young-onset type 2 diabetes: A grey zone analysis

C. Bellanné-Chantelot[a,*], J. Coste[b], C. Ciangura[c], M. Fonfrède[d], C. Saint-Martin[a], C. Bouché[e], E. Sonnet[f], R. Valéro[g], D.-J. Lévy[h], D. Dubois-Laforgue[h], J. Timsit[h], the Monogenic Diabetes Study Group of the Société Francophone du Diabète (SFD)[1]

[a] *Department of Genetics, AP–HP, Hôpital Pitié-Salpétrière, Université Pierre-et-Marie-Curie, 47-83, boulevard de l'Hôpital, 75013 Paris, France*
[b] *Unit of Biostatistics and Epidemiology, AP–HP, Hôtel Dieu; Unit Research APEMAC, EA 4360, Université Paris-Descartes, Sorbonne Paris Cité, Lorraine Université, 75004 Paris, France*
[c] *Department of Diabetology, AP–HP, Hôpital Pitié-Salpétrière, Université Pierre-et-Marie-Curie, 75013 Paris, France*
[d] *Department of Medical Biochemistry, AP–HP, Hôpital Pitié-Salpétrière, 75013 Paris, France*
[e] *Department of Diabetology, AP–HP, Hôpital Lariboisière, 75010 Paris, France*
[f] *Department of Endocrinology, CHU de Brest, 29609 Brest, France*
[g] *Department of Nutrition, Metabolic diseases, Endocrinology, AP–HM, Hôpital de la Timone, Aix-Marseille Université, 13385 Marseille, France*
[h] *Department of Diabetology, AP–HP, Hôpital Cochin, Université Paris-Descartes, 75014 Paris, France*

Received 21 November 2014; received in revised form 4 February 2015; accepted 5 February 2015
Available online 6 March 2015

Abstract

Aim. – Low plasma levels of high-sensitivity C-reactive protein (hs-CRP) have been suggested to differentiate hepatocyte nuclear factor 1 alpha–maturity-onset diabetes of the young (HNF1A–MODY) from type 2 diabetes (T2D). Yet, differential diagnosis of HNF1A–MODY and familial young-onset type 2 diabetes (F-YT2D) remains a difficult challenge. Thus, this study assessed the added value of hs-CRP to distinguish between the two conditions.

Methods. – This prospective multicentre study included 143 HNF1A–MODY patients, 310 patients with a clinical history suggestive of HNF1A–MODY, but not confirmed genetically (F-YT2D), and 215 patients with T2D. The ability of models, including clinical characteristics and hs-CRP to predict HNF1A–MODY was analyzed, using the area of the receiver operating characteristic (AUROC) curve, and a grey zone approach was used to evaluate these models in clinical practice.

Results. – Median hs-CRP values were lower in HNF1A–MODY (0.25 mg/L) than in F-YT2D (1.14 mg/L) and T2D (1.70 mg/L) patients. Clinical parameters were sufficient to differentiate HNF1A–MODY from classical T2D (AUROC: 0.99). AUROC analyses to distinguish HNF1A–MODY from F-YT2D were 0.82 for clinical features and 0.87 after including hs-CRP. For the grey zone analysis, the lower boundary was set to miss < 1.5% of true positives in non-tested subjects, while the upper boundary was set to perform 50% of genetic tests in individuals with no *HNF1A* mutation. On comparing HNF1A–MODY with F-YT2D, 65% of patients were classified in between these categories – in the zone of diagnostic uncertainty – even after adding hs-CRP to clinical parameters.

Conclusion. – hs-CRP does not improve the differential diagnosis of HNF1A–MODY and F-YT2D.

Keywords: MODY; HNF1A; C-reactive protein; ROC analysis; Grey zone analysis

* Corresponding author. Tel.: +33 1 42 17 76 52; fax: +33 1 42 17 76 18.
E-mail address: christine.bellanne-chantelot@psl.aphp.fr (C. Bellanné-Chantelot).
[1] Coinvestigators are listed in Table S3 (see supplementary material associated with this article online).

http://dx.doi.org/10.1016/j.diabet.2015.02.001
1262-3636/

1. Introduction

Monogenic diabetes accounts for 1–3% of diabetes cases and has been associated with mutations of at least 30 genes. Recently developed techniques allow screening of many genes in the same assay [1,2]. Thus, one major challenge is to identify those patients in whom genetic screening is warranted.

Hepatocyte nuclear factor 1 alpha–maturity-onset diabetes of the young (HNF1A–MODY, or MODY3) is a frequent monogenic diabetes subtype [3,4]. In a majority of cases, the HNF1A–MODY phenotype suggests young-onset type 2 diabetes (T2D) [5]. Given the current epidemics of obesity and T2D, increasing numbers of individuals now present with a family history of diabetes, and 30% of patients with HNF1A–MODY have excess body weight, making differential diagnosis with familial young-onset T2D (F-YT2D) difficult [5]. Moreover, in half of cases, HNF1A–MODY is diagnosed in patients > 25 years of age [6,7]. Consequently, the classical criteria used for the diagnosis of MODY are neither sensitive nor specific enough to identify HNF1A–MODY patients. Indeed, in patients with a strong clinical suspicion of HNF1A–MODY, the pick-up rate is only 15% [4,5].

Thus, there is a need for algorithms and/or biomarkers to improve identification of patients in whom *HNF1A* screening is worthwhile. These should combine high-sensitivity, permitting no missed diagnoses, and high specificity, as genetic testing is costly and time-consuming. Previously, an algorithm was developed based on refined clinical and biological criteria to discriminate HNF1A–MODY from F-YT2D, but its performance remains inadequate for the above-mentioned goals [5].

Several groups have shown that high-sensitivity C-reactive protein (hs-CRP) levels are lower in HNF1A–MODY patients than in those with other diabetes subtypes, including type 1 diabetes (T1D), T2D, HNF4A–MODY and glucokinase (GCK)–MODY, and that hs-CRP may allow identification of patients with HNF1A–MODY [8–10]. However, to what extent hs-CRP might help to differentiate patients with HNF1A–MODY from those with F-YT2D has not been fully assessed.

Thus, using grey zone analysis, the value of hs-CRP in combination with clinical characteristics to diagnose HNF1A–MODY was assessed in our present study.

2. Patients and methods

2.1. Patients

The present prospective study included 668 unrelated patients. In 453 of them, genetic testing was performed because of a clinical suspicion of HNF1A–MODY, based on a diagnosis of diabetes at age < 40 years, a family history of diabetes in at least two generations and the absence of obesity. At least two of these three criteria were present in 96% of our patients. Excluded were those with other aetiologies of diabetes, such as autoimmune diabetes in the absence of glutamic acid decarboxylase antibodies, and monogenic diabetes in the absence of features consistent with maternally inherited diabetes and deafness, or renal cysts and diabetes syndrome (RCAD, HNF1B–MODY). In those with a family history of mild fasting hyperglycaemia or an HbA_{1c} concentration < 7%, suggesting a clinical history of GCK–MODY, a mutation in *GCK* was excluded. A molecular abnormality of *HNF1A* was found in 143 patients whereas, in 310 patients referred to as F-YT2D, no mutation or large deletion of *HNF1A* was found. In 166 (54%) of these 310 patients, mutations and large deletions of *HNF4A* were excluded. There were 215 patients with classical T2D, diagnosed on the basis of age > 40 years at onset or body mass index (BMI) ≥ 25 kg/m^2 and the presence of arterial hypertension and/or dyslipidaemia [5,11].

Sequencing of *HNF1A*, *HNF4A* and the search for *HNF1A/4A* deletions were sequentially carried out as described elsewhere [12]. All patients gave their written informed consent to participate.

2.2. Methods

Plasma hs-CRP levels were measured using a latex-enhanced immunoturbidometric assay (Roche Diagnostics, Mannheim, Germany) and routine chemistry analysis (Cobas Integra 400 analyzer, Roche). Coefficients of variation were 10.0% at 0.05 mg/L, 3.6% at 0.37 mg/L and < 5.0% at 1–10 mg/L. Subjects with hs-CRP values ≥ 10 mg/L were excluded from the study [8–10].

2.3. Statistical analysis

Data are presented as frequencies and percentages or medians and ranges. Univariate analyses were performed using non-parametric tests. Spearman's rank-order correlation and partial Spearman's rank-order correlation tests were used to check the correlation of hs-CRP with other predictors. For the multivariate analyses, variables associated with HNF1A–MODY on univariate analyses were included in logistic models in three steps: first, constitutional and genetic factors were included (gender, euro-Caucasian origin, number of affected generations); second, age at diabetes diagnosis was added; and third, current BMI, current HbA_{1c} and finally hs-CRP were inserted. The ability of these models to predict HNF1A–MODY was analyzed using the area under the receiver operating characteristic (AUROC) curve or Harrell's C index. The grey zone approach [13] was used to evaluate the diagnostic added value of hs-CRP: three-zone partitions (negative, positive and the grey zone in between) were constructed from cut-off values of the diagnostic (logistic) scores, with or without hs-CRP. Cut-off points delimiting the grey zone were chosen to ensure that post-test probabilities would either confirm or exclude the diagnosis of HNF1A–MODY. These cut-offs were associated with the minimum value of the positive likelihood ratio (LR+) or the maximum value of the negative likelihood ratio (LR–), respectively. Analyses were performed with SAS version 9.3 software (SAS Institute, Cary, NC, USA).