Classification of diabetes in young adults: New concepts for an old disease

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SUMMARY
As clinicians, we are faced to difficult situations in young diabetic patients. The prevalence of type 2 diabetes increases in these patients due to a rising incidence of obesity. We present two clinical observations which both illustrate the insufficiencies of the present classifications. Modern tools are now available for diagnosis such as anti-GAD65 and IA-2 antibodies, genetic tools to investigate for specific mutations, but quantitative means of beta cell mass are lacking. Clinical examination is still accurate to identify type 1 or type 2 diabetes, MODY and mitochondrial diabetes. Weight curve, lesions of acanthosis nigricans, criteria of metabolic syndrome, history of diabetes are critical factors. This problematic has important consequences in our daily practice: the right choice for rapid and good metabolic control.

Key-words: Diabetes · Classification · Insulin.

RÉSUMÉ
Nous sommes confrontés en tant que cliniciens à des difficultés diagnostiques chez nos jeunes patients diabétiques. On observe de plus en plus de cas de diabètes de type 2 dans cette population qui suit les courbes d’incidence de l’obésité. Nous présentons deux observations qui permettent de mettre l’accent sur les insuffisances des classifications actuelles. Des outils modernes sont désormais à notre disposition pour étayer le diagnostic nosologique : anticorps anti-GAD et IA2, outils génétiques pour la recherche de mutations ponctuelles. Toutefois, des méthodes précises de quantification de la masse et de la fonction des cellules bêta sont encore à développer. La clinique reste importante dans cette démarche diagnostique, afin de repérer rapidement un diabète de type 1, un diabète de type 2, un diabète de type MODY ou un diabète mitochondrial. L’évolution pondérale, la présence d’un acanthosis nigricans, les critères du syndrome métabolique, le contexte familial sont des éléments essentiels. L’intérêt de cette démarche est importante dans notre activité quotidienne : donner le traitement approprié pour obtenir rapidement les objectifs de bon contrôle glycémique.

Mots-clés : Diabète · Classification · Insuline.

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**Introduction**

Many clinicians are faced to difficult situations in young adults with diabetes regarding the mechanisms underlying hyperglycaemia. For many years, the diabetes community was reassured by using simple terms such as insulin-dependent or non-insulin dependent forms of diabetes mellitus, assimilating the classification of diabetes to insulin needs. The increasing use of insulin treatment in non-insulin dependent diabetic patients which has reached 30% in France, have led to contradictions illustrated by the insulin-requiring non-insulin dependent patients. The recent classification of the American Diabetes Association [1] brought some clarity. Indeed, the type 1/type 2 paradigm has improved our views of the problem by excluding the insulin needs for classification. However, increasing discordance between clinical features and therapy resulted in type 1.5 forms that overlap in many ways the LADA (Latent Autoimmune Diabetes in Adults) type and other atypical forms that cannot enter easily into the established type 1/type 2 frame. Presence of insulin resistance and variable levels of insulin deficiency may have important impacts for treatment strategies. Furthermore, recent individualization of genetic forms of diabetes in the young such as MODY and mitochondrial diabetes has underlined the importance of modern genetic tools for adequate retrospective diagnosis. In the last few years, the diagnosis of autoimmune type 1 diabetes (Type IA) has been also hampered by the growing prevalence of obesity in young children due to modifications in obesity and lifestyle habits and emerging forms of type 2 diabetes in adolescents. Links between autoimmune beta cell loss and beta cell exhaustion due to increase in insulin needs were suggested with the critical role of beta cell mass and function in pathogenesis [2]. All these considerations reinforce the necessity for practical means of classification.

**Case reports of atypical diabetes in young adults**

**Case 1**

A 19 year-old black woman born in Congo was referred to hospital for hyperglycaemia (≥ 3 g/l) and clinical symptoms for one week. She lived in France for 13 years and had never experienced any clinical problem. When she arrived at the emergency ward, plasma glucose was 3.23 g/l without ketoacidosis despite massive glycosuria and slight ketonuria. HbA1c level was 11.4%. This patient was obese (BMI: 37 kg/m²) with typical lesions of acanthosis nigricans in the neck. During the last 4 months, she had an increase in body weight of 30 kg due to overfeeding and depression despite regular physical activity. Euglycaemia was obtained after 48 hours using 150 units of regular insulin administered subcutaneously with an insulin pump. Liver biology, iron blood concentrations and blood lipids were normal. Fasting C-peptide levels were in the normal range at 0.32 nmol/l (normal values:0.22-0.83 nmol/l). GAD and IA2 antibodies were negative. Following a strict dietetic program at 1800 kcal per day and an increased physical activity, metabolic control was rapidly obtained and the patient was given a combination of metformine 3 g daily together with insulin glargine administrated at bed time at a dose of 0.5 units/kg. One month later, insulin dosage was markedly reduced due to weight loss.

**Case 2**

A 20 years old girl was hospitalised to equilibrate a diabetes of 12 years duration with chronic hyperglycaemia and HbA1c level at 12%. While she decided to stop by herself her treatment i.e. a combination of metformin and insulin for 5 months, no ketoacidosis occurred and her body weight increased by 6 kgs during this period. This patient experienced difficult social and personal problems. Her history reveals several family members with diabetes and obesity and she developed pre-pubertal obesity. Her present BMI was 33 with axillary and nucchal acanthosis nigricans cutaneous lesions. She doesn’t have any menstruation but gonadal exploration was normal. Blood pressure was normal but triglyceride levels were increased at 5.80 mmol/l with hepatic steatosis. GAD and IA2 antibodies were negative. Metabolic control was rapidly obtained with a 1600 kcal per day diet, insulin treatment (0.75 units/kg) and 2500 g of metformine daily with better results.

**What can be expected from modern biological tools?**

A large array of biological tools are now available to help the clinicians although it remains important to perform an accurate choice based on the expected pathogenesis.

For many years since the discovery of islet cell antibodies by GF Bottazzo in 1974 [3], identification of peripheral markers of autoimmunity to beta cells has become a routine procedure. Cloning of defined autoantigens has facilitated the procedure allowing mass screening. Presence of antibodies to GAD65 and IA-2 links any clinical form of diabetes to an autoimmune process and type 1A diabetes requiring exogenous insulin. These peripheral markers have good specificity, sensitivity and high predictive values as demonstrated in the DPT-1 trial [4]. No cellular marker of autoimmunity is available in routine practice.

Genetic tools for the rapid detection of known mutations associated with monogenic diabetes are available in centres with the relevant expertise. Hepatocyte nuclear
factor-1a (HNF-1a) maturity onset diabetes of the young (MODY 3) is the commonest cause of monogenic diabetes but is frequently misdiagnosed as type 1 diabetes [5]. The availability of genetic testing of MODY has improved diagnosis. Sulphonylurea sensitivity in HNF-1a patients means that those on insulin from diagnosis can transfer to sulphonylureas and may improve glycaemic control. Genetic analysis may apply as a second step procedure in front of an important family history of diabetes and negativity of peripheral autoantibodies. Additional screening for mutations may be also justified in some occasions such as Glucokinase (MODY2), HNF4 a (MODY 1) or HNF1 b (MODY 5). To investigate the presence of mitochondrial DNA point mutation A3243G, clinical patterns of the patient and his family are highly evocative and can be easily distinguished from the other forms of diabetes in the young. This mutation is associated with the MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes), or with MIDD (Maternally inherited diabetes and deafness)[6, 7].

While in vivo insulin sensitivity can be measured by several techniques including the euglycaemic clamp technique, evaluation of beta cell mass by measuring insulin secretion remains difficult [8]. Beside the problems posed by the variability and specificity of insulin assays due to proinsulin and its split products, circulating insulin concentrations are dependent upon insulin distribution and clearance mostly by hepatic and renal degradation. Beta cell function can be evaluated through first-phase insulin release after intravenous glucose but the most informative tests such as the hyperglycaemic clamp or graded glucose infusions are quite complex with limited applications. Morphometric studies have shown that beta cells harbour different populations of secretory granules, in different stages of maturation and in variable spatial array. Direct quantitative methods of beta cell mass are clearly lacking and development for example of specific PET (Positron Emission Tomography) markers for in vivo imaging would be clearly helpful.

**Practical discussion for the clinicians**

Type 2 diabetes (T2D) among youths is more and more frequent. This phenomenon parallels the increase in prevalence of obesity in children [9]. Some 20 years after the initial report in Pima Indians [10], prevalence of obesity and type 2 diabetes has dramatically increased in adolescents from industrialized countries. A recent study in 520 obese young Germans [11] revealed that 1.5% had already diabetes and 6.7% an impaired glucose tolerance. For classification, weight curves and absence of acute symptoms are interesting factors to identify these non-autoimmune forms of diabetes in adolescents. Due to the presence of insulin resistance, drugs targeting insulin receptors are clearly useful and this is one of the major contributions of adequate classification. In addition, T2D must be quickly detected to prevent subsequent beta cell failure [12, 13] by decreasing insulin resistance through weight loss and oral agents acting at the periphery. Insulin resistance is indeed the most important risk factor for development of impaired glucose tolerance in severe childhood obesity. Family history of T2D is present in 65% of the cases[14] and diagnosis is usually performed after a routine biological test [15, 16] while only 30% of them have mild symptoms. A paradoxical increase in body weight before the discovery of diabetes may also occur as indicated in both patients described above. Only one third of young obese patients present ketonuria at diagnosis. During clinical examination, acanthosis nigricans is present in almost 90% of these children [17] and polycystic ovary syndrome is frequent in females. Criteria of metabolic syndrome are often present including hypertriglyceridemia, low HDL, excessive waist circumference, hypertension in addition to hepatic steatosis [18].

These new forms of diabetes in young adults do not suggest that classical type 1A (autoimmune) diabetes has disappeared. Recent epidemiological studies have revealed an epidemics due to unknown environmental changes. T1D is associated with acute symptoms reflecting beta cell failure. Ketoacidosis may be absent due to the rapid detection of metabolic changes and the organization of emergency units. Among youths, autoimmune T1D is still the most frequent form of diabetes. This form of diabetes is associated with peripheral markers of autoimmunity. T1D must be distinguished from monogenic forms of diabetes (MODY, MIDD). These monogenic forms are rare, but are more likely to appear in childhood [9]. A family tree must be carried out illustrating diabetes in three or more consecutive generations, which is compatible with a dominant autosomal hereditary transmission [5]. Although signs of beta cell failure are uncommon at discovery, some MODY3 patients can present as classical T1D in adults. Misclassification of MODY with T2D can also occur but there is no metabolic syndrome and acanthosis nigricans is never present [17,19]. Mitochondrial diabetes syndrome is strictly transmitted by the mother. The disease results of mutation in mitochondrial DNA and again the clinical situation is highly evocative [6, 7]. Non autoimmune ketosis-prone diabetic syndromes are also increasingly frequent in non-white populations especially from sub-Saharan African origin. Initially classified as type 1B diabetes, these patients have many features in common with type 2 diabetes with a strong male predominance and family history, higher age and BMI and more severe metabolic decompensation than classical type 1A diabetes. In this form of ketosis-prone diabetes, discontinuation of insulin therapy with development of remission of insulin dependence is achieved in 76% of patients whereas only 24% of patients remain insulin dependent [20]. During evolution, specific beta-cell dysfunction features may occur with ketotic relapses suggesting glucotoxicity. This form of diabetes has to be also discussed in our first case report.
In summary, it is sometimes difficult to classify diabetes in the young and to extrapolate on the underlying mechanisms of beta cell failure. Additional tools for the evaluation of beta cell mass are urgently needed. We are faced to new challenges for adequate therapeutic strategies since prevention of beta cell exhaustion has been proven in T2D by controlling diet and physical activity [9, 21-24] and oral agents, including biguanides [22], thiazolidinediones [25], and conversion enzyme inhibitors [26]. Prevention of obesity is also a critical but complex issue in this age group.

References

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