

Non-insulin-dependent Diabetes in the Young

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DEFINITION

Non-insulin-dependent diabetes in the young (NIDDDY) may be defined as diabetes occurring in patients less than 25 (or 30 years) of age, which does not require insulin for adequate metabolic control [1]. A special form of NIDDDY is known as maturity-onset diabetes of the young (MODY) (2). In this entity patients have the clinical features of NIDDDY, but in addition the diabetes is inherited in an autosomal dominant fashion.

A. WESTERN LITERATURE

Prevalence

In the West, the most common form of diabetes occurring in individuals below the age of 30 years is Type 1 (insulin-dependent) diabetes. NIDDDY or Maturity onset Diabetes of the Young (MODY) has also been described in the young population in the West, but occurs rarely. Families with MODY have been described from most of the countries in the West (Europe, United States, Australia) [1,3]. However, their prevalence is low. In a population study conducted in the German Democratic Republic, it was estimated that its prevalence was 0.15% of all diabetic patients [4]. In USA, NIDDDM is diagnosed in less than 0.05% of the population < 25 years of age [5].

A recent report suggests that a similar form of NIDDDM may exist in American Blacks [6]. In this report 12/129 black patients with youth-onset diabetes had an unusual clinical presentation with apparent insulin dependence and ketosis at the time of presentation, followed by absence of dependence months or years later. These patients had a history of atypical diabetes in at least 2 generations in 9/12 families.

Clinical Features

The disease may present in different clinical forms. It is frequently asymptomatic in the younger age groups, though some patients may have symptoms at times of stress [7]. In many families the diagnosis is made on the basis of prospective testing in asymptomatic patients with a family history of diabetes in 1 or more generations [8]. The rate of

progression of glucose intolerance is variable among different families and even among members of the same family. The frequency of obesity in young patients with MODY (25-55%) is probably higher than the general White population, when matched for age [1].

The elevated glucose levels may respond to diet, or diet and sulphonylureas, even when the onset is at a young age [9]. In some patients, however, after a few years or decades of diabetes, insulin may be required for control of fasting hyperglycemia. This is associated with a decrease in C-peptide levels [10].

In contrast to this mild form of diabetes described above, an early onset Type 2 diabetes has been described by O'Rahilly et al (1987) [11,12]. This differs from MODY in that there is a high incidence of diabetes in the parents (92%) and in sibs (69%), suggesting that the inheritance is not autosomal dominant. In contrast to the indolent course of MODY these patients had a more severe clinical presentation, and a high incidence of microvascular complications. An atypical syndrome of severe diabetes at onset, followed by a course consistent with NIDDDM, has been described in young Black Americans [6]. Though the clinical presentation in this group is similar to Type 1 diabetes, it can be differentiated from it on other clinical, immunological, and metabolic characteristics.

Metabolic Studies

There are wide differences in the abnormalities of insulin secretion among different families and populations with MODY. Thus, the insulin response to glucose load have varied from very low to high, in different families with MODY [1,8,13,14].

Many authors have described a delayed and sub-normal insulin secretory response as the predominant abnormality in these patients [11,14-16]. The low insulin response to glucose may be inherited and present in family members prior to the onset of diabetes [15]. In a study on French MODY subjects with a linkage to the glucokinase gene, the first phase insulin response to intravenous glucose was normal, but the insulin secretion in response to prolonged glucose infusion was subnormal [15].

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Insulin resistance has been demonstrated in a few White patients with MODY [1,13]. However, it is only found in a few patients, mostly those with significant fasting hyperglycemia.

In the study on young Blacks with NIDDM, C-peptide responses to a meal were significantly less than in non-obese controls but higher than in Type 1 diabetics [6]. The insulin deficiency did not appear to worsen over time. Insulin-receptor number was significantly increased but the insulin-receptor affinity was decreased, and the maximum percentage binding was not significantly different from controls. Thus, in this population of NIDDM insulin resistance was not a constant feature.

Typical microvascular and macrovascular complications of diabetes are known to occur in patients with MODY [8,18-20]. The fact that the hyperglycemia is mild may be the reason that the prevalence of complications is lower in some families with MODY.

Autoimmunity

Islet cell antibodies have been found to be absent in all patients of MODY investigated thus far [1,6,17,18]. In addition, MODY is not associated with any of the HLA antigens known to be associated with Type 1 diabetes [19].

Genetics

Many studies have supported the view that MODY is inherited as an autosomal dominant trait [1,2,8,16]. In the subtype of NIDDM known to have early-onset Type 2 diabetes, there is a high incidence of diabetes in the parents (92%) and sibs (69%), suggesting that there is a double gene effect [11,12].

No HLA antigen has been shown to be associated with MODY, either among Whites, or among Black American patients. Another marker for diabetes studied is the adenosine deaminase (ADA) locus on chromosome 20q. In a large MODY family studied by Bell et al (1991) there was significant linkage of diabetes with the ADA locus [21].

Recently, a new marker has been found to be linked to MODY in certain families [15,22,23]. This marker is the glucokinase gene. Glucokinase is an enzyme which mediates glucose phosphorylation, the first step in glycolysis. Evidence suggests that glucokinase plays an important role in glucose sensing and in initiating glucose-induced insulin

secretion in the beta cells [24]. Thus, glucokinase gene defects may contribute to NIDDM.

DNA microsatellite polymorphisms have been detected at the human glucokinase locus, 3' to the glucokinase gene and in intron 1 [25]. These polymorphisms represent differences in the number of dinucleotide repeats, with alleles differing in size by 2-15 nucleotides in unrelated individuals. They are detected by using a polymerase chain reaction assay to amplify the required segment and defining the alleles of different sizes by electrophoresis. It has been shown by direct sequencing that these different polymorphisms are associated with nonsense (codon 279 C-T, exon 7) or missense (codon 299 G-C, exon 8) mutations in the nucleotide sequence of different exons of the glucokinase gene, providing strong evidence that the mutations are the cause of diabetes in the affected family members [26]. In a recent report, Froguel et al (1993) studied 32 French families with MODY and 21 families with late-onset NIDDM [27]. 16 mutations were identified in 18 of the 32 families with MODY, but none were found in families with late-onset NIDDM. These included 10 mutations that resulted in an amino acid substitution, 3 that resulted in the synthesis of a truncated protein, and 3 that affected RNA processing.

Genetic studies in families with MODY have shown a high degree of linkage to the glucokinase gene. In a study by Froguel et al (1992), 16 families were studied and highly significant maximum lod score of 11.6 was found [22]. In another study, a positive lod score of 4.6 was found in another large MODY family [23]. In a recent study of 32 families with MODY, the odds in favour of linkage of the glucokinase gene and diabetes were more than $10^{23}:1$ [27]. However, further analysis showed that the disorder was linked to the glucokinase gene in only about 60% of the families. This suggests that MODY is genetically heterogeneous.

Population studies in Black NIDDM patients and in Mauritian-Creole NIDDM patients have also shown a significant association with glucokinase gene polymorphisms [28,29]. However, no linkage could be found between glucokinase gene polymorphisms in families with Type 2 diabetes in White Caucasians [30].

B. INDIAN LITERATURE

Prevalence

In contrast to the situation in the West, the prevalence of unusual variants of diabetes is much

higher in different parts of India. Thus, in addition to Type 1 diabetes, malnutrition-related diabetes (protein deficient pancreatic diabetes and fibrocalcific pancreatic diabetes) is frequent in the young population [20]. Mohan et al (1985) from the Diabetes Research Center, Madras found that the prevalence of non-insulin-dependent diabetes among young subjects (onset 25 years or less) attending their clinic was much higher compared to the West [31]. 4.8% of their patients < 25 years of age had MODY. A high prevalence of this type of diabetes is also present among Indians settled in South Africa. 10% of Indian patients studied had NIDDM with an onset before 35 years of age [32].

The prevalence of NIDDDY among young diabetics in different parts of India (especially North India) is not known thus far.

Clinical Characteristics of Indian NIDDDY

32% of South Indian NIDDDY were obese, while the corresponding figure for South African NIDDDY was 55% [32,34]. However, the distribution of obesity among the diabetic subjects has not been commented upon. Most Indian MODY present with symptomatic hyperglycemia [32-35]. The degree of glucose intolerance appeared to be greater than in Western subjects, with most patients manifesting fasting blood glucose of > 200 mg%. Most patients were treated with diet and/or sulphonylureas. With this treatment fasting euglycemia was obtained in 21% of Indian patients from South Africa [33].

Chronic vascular complications of diabetes were present in a substantial number of South Indian NIDDDY patients [31]. The prevalence of these complications depended upon the inheritance i.e. definite autosomal dominant, probable autosomal dominant, or non-hereditary. Among those with known duration greater than 15 years, background retinopathy was found in 25, 41, and 44% respectively. Proliferative retinopathy was found in 6, 6, and 11% respectively. Nephropathy was found in 6, 23, and 33% respectively. Among the South African NIDDDY subjects, 17% had retinopathy and 7% had nephropathy [36, 37]. Those patients with microvascular complications had significantly higher Haemoglobin A_{1c} compared to those without vascular complications [35]. Among Indians with MODY, diabetic neuropathy was present in 31-55% of patients [31, 32].

Metabolic Studies in Indian MODY

Obese and non-obese patients with NIDDDY in South India had reduced insulin and C-peptide response to

glucose when compared with nondiabetic controls [38]. The reduction in insulin response was more in the obese NIDDDY subjects compared to the non-obese subjects. The insulin and C-peptide response to glucose was also tested in euglycemic offsprings of patients with NIDDDY [39]. Mean IRI response was lower among obese offspring when compared with controls, though non-obese offspring did not differ significantly from their respective control subjects. Mean C-peptide values were lower in both obese and non-obese offspring. These data were interpreted to mean that insulin deficiency is the primary lesion causing glucose intolerance in these patients.

Among South African Indian with NIDDDY, fasting hyperinsulinemia was detected (25.3 vs 14.6 uU/ml), but the response of insulin and C-peptide to glucose was diminished and delayed [33-35, 40, 41].

Immunological Studies

There are no available studies on the frequency of different autoantibodies and on the HLA markers in patients with NIDDDY in India.

Genetic Studies

Among the 219 South Indian patients studied by Mohan et al (1985) only 27% had a definite autosomal dominant inheritance. In 53% the mode of inheritance was probably autosomal dominant, while in 20% the diabetes was not associated with a positive family history [31]. Among the Indians in South Africa with earlyonset NIDDM, a positive family history of diabetes was obtained in 75% of the patients [32]. Both parents were diabetic in 37% of the patients, while a history of diabetes was obtained in nearly 50% of sibs.

Preliminary work done at SGPGI, Lucknow

At the Diabetes Clinic at SGPGI (Sanjay Gandhi Post Graduate Institute) we have found that a substantial number of the young diabetic population have NIDDDY. A preliminary study has been launched in which the clinical characteristics of these subjects, as well as their metabolic response to glucose and their autoantibody profile is being evaluated.

A total of 18 subjects (9 male, 9 female) have been studied thus far. Their mean age of onset of diabetes was 26 years $\pm$ 4 years, and they remained controlled for 9.7 $\pm$ 9.6 years on diet and/or oral hypoglycemic agents. None of the patients had suffered from ketoacidosis. This is in contrast to

patients with Type 1 diabetes, who require insulin from the onset of the illness, and often give a history of ketosis. A family history of diabetes was present in 59% of families, with a history of diabetes in 3 generations in 29% of the families. The mean BMI was 23.9 ± 6.0 , indicating that most of the patients were not obese. Microvascular complications of diabetes retinopathy in 23%, nephropathy in 6%, and neuropathy in 29% - were present in a large proportion of patients. Thus, inspite of a "milder" variety of diabetes these patients were not immune to the chronic complications of diabetes.

From this preliminary data it appears that NIDDDY in the North Indian setting differs from the classical phenotype of MODY seen in the West, in view of the severe hypoglycemia at presentation, history of autosomal dominant inheritance in only 29%, and an increased risk of complications. Further studies will clarify the natural history and pathogenesis of this entity, and if it is a homogenous entity or not. Since the management of patients with NIDDDY differs significantly from that with Type 1 diabetes, it is important for physicians to recognize that this entity exists in young North Indian diabetics.

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