EARLY AGE AT ONSET AND HIGH FREQUENCY OF ASSOCIATED COMPLICATIONS IN MATERNALLY TRANSMITTED TYPE 2 DIABETES MELLITUS

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ABSTRACT

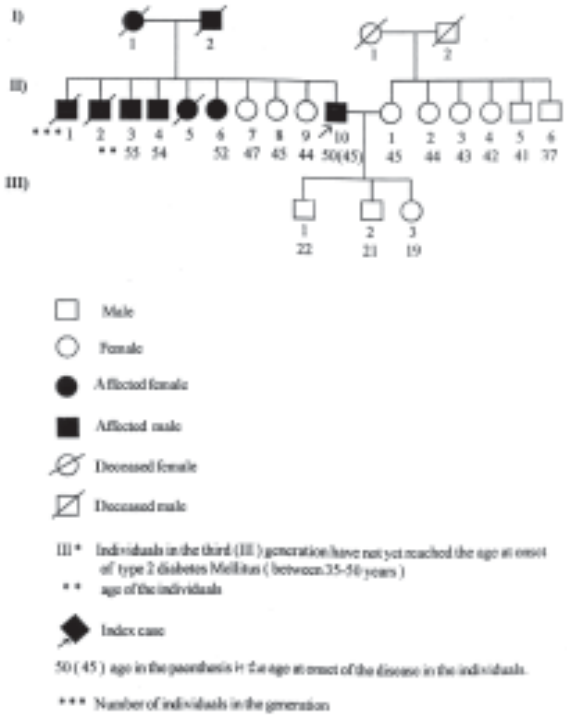
Type 2 diabetes mellitus is a heterogeneous group of conditions characterized by hyperglycemia and shows different modes of inheritance (autosomal dominant, autosomal recessive and maternal inheritance). Inheritance pattern was studied in a total of 223 type 2 diabetic cases through the pedigree data obtained from the index cases. Of the total 223 cases studied, 159 cases showed familial incidence and the remaining cases had no family history of the disorder. The 159 cases, which had family history of diabetes, were analysed for mode of inheritance. 54 had female parent affected and 22 cases had male parent affected with disease thus suggesting that mothers are excessively implicated in the transmission of the disorder. The 54 pedigrees where the female parent was affected were further analysed for the pattern of inheritance. It was observed that 23 (about 10% of the total cases studied) of them showed maternal mode of inheritance, wherein if the mother was affected with the disease, all the offspring's (both male and female) are affected with the disease and only the affected daughters transmitted the condition to their progeny but the sons did not transmit the condition to their progeny. The remaining 31 pedigrees showed Mendelian mode of inheritance. Furthermore, cases showing maternal inheritance have an early age at onset of the disease compared to Mendelian mode of inheritance and are more frequently associated with the complications of the disorder (neuropathy, nephropathy, retinopathy, cardiovascular disorders). This study highlights the clinical importance of maternally inherited type 2 diabetes mellitus.

KEY WORDS: Type 2 diabetes mellitus; Mendelian inheritance; Maternal inheritance; Diabetic complications.

INTRODUCTION

Type 2 diabetes mellitus is a heterogeneous group of disorders characterized by hyperglycemia. This metabolic disorder runs in families showing different patterns of inheritance. Mostly disorders like type 2 diabetes involving genetic susceptibility are due to mutations in the gene(s) located on the chromosome present in the nucleus and follow autosomal dominant, autosomal recessive (due to genes located on autosomes) and sex linked inheritance (due to genes present on sex chromosomes). An affected mother/ father or both can transmit the disease to their progeny (Fig 1). From among the affected progeny either male or female or both can transmit the disease to their children. This type of inheritance is known as Mendelian inheritance (1). Another exceptional pattern

Fig 1 : A Pedigree Showing Mendelian Mode of Inheritance of Type 2 Diabetes Mellitus



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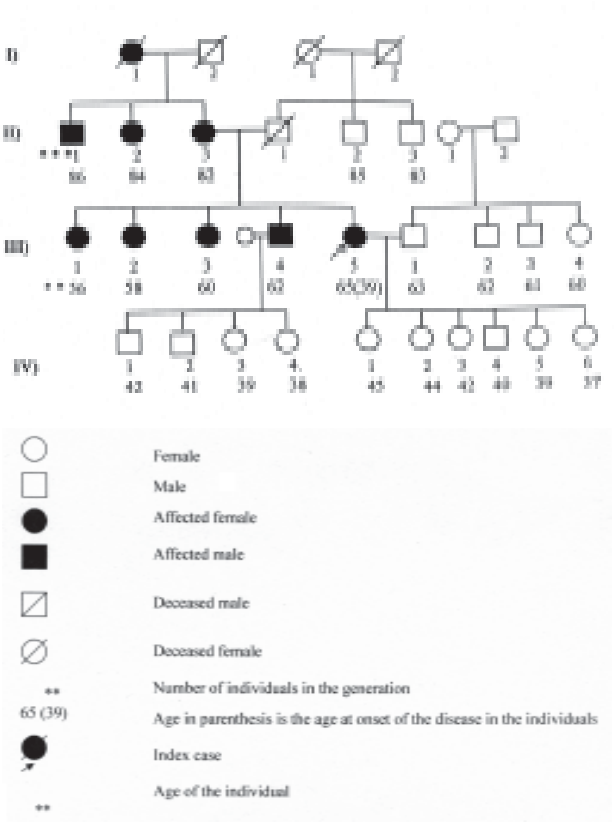
of inheritance referred to as maternal inheritance has been reported in some human diseases including type 2 diabetes mellitus. Studies on maternally inherited type 2 diabetes are of recent origin dating back to mid-nineties and a small proportion of the total cases show maternal inheritance. This type of inheritance is attributed to the mutations in the gene(s) present on mitochondrial (mt) DNA and is transmitted invariably by an affected mother to her progeny (Fig 2). Maternally inherited diabetes is also termed as mitochondrial diabetes by some researchers (2). Mitochondria are cytoplasmic organelles that are the site of oxidative phosphorylation and hence the site of vast majority of energy (ATP) production within the cells (2). The unique feature of mitochondrial DNA is its maternal inheritance. The ovum is well supplied with mitochondria, but the sperm contains a few and even those few do not persist in the offspring, as at fertilization it is only the nucleus of the spermatozoon that enters the ovum and thus all the cytoplasm, mitochondria and mitochondrial DNA are exclusively maternally inherited. This has made mt DNA an important factor in maternal transmission of type 2 diabetes mellitus and in certain other human diseases.

Fig 2 : A Pedigree Showing Maternal Inheritance of Type 2 Diabetes Mellitus



A molecular basis for involvement of mitochondrial gene mutations in susceptibility to maternally transmitted diabetes mellitus is provided by Maehler et al (2000) (3). This research has supported the hypothesis by pointing to the importance of intracellular ATP and mitochondrial function in controlling insulin secretion from pancreatic β cells. Wollheim et al (2000) (4) revealed the importance of mitochondrially derived glutamate in co-ordinating insulin release from the pancreatic β - cell. Any mutation in the gene(s) involved in this coordination process may lead to impaired insulin secretion.

Patients suffering from maternally inherited diabetes have a strong maternal history of the disease, it occurs in adult life and they are generally not overweight. Gebhart et al *(*1996) (5) and Walker M et al (1995) (6) have shown that these patients have a major defect in insulin secretion and the pancreatic beta-cells are stressed with an increasing circulating proinsulin and split products. These patients develop the disease at an early age and since hyperglycemia may be severe in these patients, diabetic complications are more frequently observed (7).

The objective of the present study was to critically analyze the pattern of inheritance of type 2 diabetes from pedigree data obtained from the patients. There is a paucity of information on this aspect in Indian series of patients. Not much is known about what proportion of Indian diabetic patients suffer from maternally inherited type 2 diabetes. Such studies are of clinical importance in view of the observation that there is an early age at onset of the disease with frequently associated complications of diabetes like neuropathy, nephropathy, retinopathy and coronary artery disease (CAD).

MATERIAL AND METHODS

Patients visiting the endocrinology unit of Gandhi General hospital and Osmania General Hospital (Hyderabad) were screened for pedigree information from July 2001 to December 2002. Details regarding the family history of diabetes were recorded in a performa (in order to construct a pedigree) along with other information like age at onset and associated complications like neuropathy, nephropathy, retinopathy and coronary artery disease (CAD).The clinical diagnosis of diabetes mellitus as well as the classification of cases was done according to the criteria laid down by the World Health Organization (8). Blood glucose levels were estimated by glucose oxidase method (glucose oxidase kit, GOD-PAP/end point, Kaizen diagnostics, Hyderabad). Cases were

diagnosed as suffering from type 2 diabetes mellitus as per WHO criteria. The various complications of diabetes like neuropathy, nephropathy, retinopathy and cardiovascular disorders were diagnosed and the respective specialist carried out necessary tests for confirmation. A total of 223 type 2 diabetic cases were included in the present study to understand the mode of inheritance. Of the 223 pedigrees studied, 159 cases showed familial incidence (where the propositii have a first or second degree relative affected with the disease) of which 54 had female parent affected with the disease compared to 22 cases where the male parent was suffering from type 2 diabetes. The 54 pedigrees where the female parent was affected were screened for the mode of inheritance. It was observed that 23 of them showed maternal mode of inheritance where in if the mother is affected with the disease, all the offsprings are affected, and the affected daughters only transmitted the condition to their progeny, but the sons do not transmit the condition to their progeny as depicted in Fig 2**.**

Table 1 : Details of the Different Modes of Inheritance (Mendelian / Maternal) with Respect to Mean Age at Onset and Associated Complications in Type 2 Diabetes Mellitus.

Mode of Inheritance	Parent affected	Total number of Propositi (index case)*	Mean age at onset of index case	Number of Propositi affected with compli-cations	
		n	Mean ± S.E.	n	%
Mendelian	Male	22	45.16 ± 3.62	11	50.0
Mendelian	Female	31	41.27 ± 2.38	20	6.52
Mendelian	Both parents affected	9	38.55 ± 2.92	6	6.66
Mendelian	Both parents normal	74	48.63 ± 4.80	47	3.52
Maternal	Female	23*	36.15* ± 7.23	18	8.26
Non-Familial	None	64	48.56 ± 0.56	18	8.13

** p < 0.05; * Index cases are the cases visiting the endocrinology unit of the hospital through whom the family history was ascertained.*

RESULTS

Results obtained are depicted in table 1**.** A perusal of the table reveals that there are 54 pedigrees (31 Mendelian and 23 maternal) where the mothers of the propositii were affected when compared to 22 pedigrees where the fathers of the propositii were affected. In 9 pedigrees both the parents were affected with diabetes. In the remaining 74 pedigrees both the parents of the propositii were unaffected.

The group of 54 pedigrees where mothers were affected was divided into 31 pedigrees, which showed Mendelian mode of inheritance, and the remaining 23 pedigrees showed maternal mode of inheritance. In these 23 pedigrees, the affected mothers transmitted the disease to all their offsprings and the affected daughters only transmitted the disease to all their offspring; but the sons did not transmit it to their progeny. The mean age at onset of index cases in the non-familial group (index cases where the first or second degree relative were not affected with the disease) was 48.56 ± 0.96 years indicating that they develop the disease at a relatively higher age. A perusal of table 1 also reveals that type 2 diabetic cases with maternal inheritance had more complications (78.26%) when compared to type 2 diabetic cases with Mendelian mode of inheritance. This may be due to severe hyperglycemia in these maternally transmitted type 2 diabetics. In the non-familial cases (where only the index case in the whole family is affected) associated complications were found in only 28.13%.

DISCUSSION

It is a well known fact that almost all the mitochondria in the zygote are contributed by the ovum. In view of this any mutations in mt DNA are referred to as maternally inherited. It is interesting to note that the mean age at onset of type 2 diabetes in maternally inherited group was significantly ($p<0.05$) lower than the mean age at onset of the propositii where the affected male/female parent showed Mendelian mode of inheritance. It was also significantly lower than the mean age at onset where both the parents were normal with Mendelian mode of inheritance.

A pathological basis of maternally transmitted type 2 diabetes mellitus may be explained on the basis that mitochondria are the main source of cell energy and play a critical role in the maintenance of insulin action and insulin secretion (9). Mutations or deletion in mt DNA are reported to cause type 2 diabetes mellitus, mainly causing insulin deficiency (10). These patients have lower levels of mt DNA in their peripheral blood. This reduction precedes the onset of diabetes, and the mt DNA correlates inversely with blood pressure and waist hip ratio. Moreover, these cases have early age at onset of the disease and high frequency of associated complications (78.26%). The various complications in them were neuropathy,

nephropathy, retinopathy and cardiovascular disorders.

This is one of the first few reports on maternally transmitted type 2 diabetes mellitus, in relation to age at onset and complications in a series of Indian patients.

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