Family history of patients with NIDDM: evidence for aggregation on maternal side

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Non-insulin dependent diabetes mellitus (NIDDM) has a strong genetic component with evidence of significant familial aggregation. Recently, the role of maternal effect has been suggested in its inheritance through generations. In our study, family histories of 358 NIDDM patients, aged between 28 and 80, were evaluated to investigate the maternal effect and familial aggregation over two generations. From all group, 45.8% reported to have at least one, and among them, 40.8% at least two diabetic first degree relatives. These results were in agreement with familial aggregation. Maternal effect, evaluated as frequency of diabetic mothers, was insignificantly greater than paternal effect (p=0.12). When considered as maternal side (mothers, maternal aunts/uncles) and paternal side (fathers, paternal aunts/uncles), there was significantly more aggregation of diabetes in the former compared with the latter (p<0.05). Diabetes on the maternal side was significantly more reported when age of disease onset is between 40-58 (p<0.05). In contrast, when disease onset is between 20-39 and 59-75, maternal side predominance was lacking (p>0.05 for both). These results support the hypothesis emphasizing the dominance cf maternally passed diabetogenic genetic components over paternally passed ones in the inheritance of NIDDM. Moreover, it can be argued that, environmental factors override genetic factors when the disease onset is delayed. [Turk J Med Res 1995; 13(1): 25-27]

Key Words: Diabetes mellitus, Family history, Maternal effect

It is widely accepted that non-insulin dependent diabetes mellitus (NIDDM) has a multifactorial origin in which environmental factors seem to hasten disease progression in genetically predisposed individuals (1). So far, exact mode of NIDDM inheritance have not been eludicated (2,3). However, family studies have confirmed that, NIDDM patients have excess cases of diabetes among their first degree relatives in comparison with normal subjects (4-6). Significant maternal effect has been observed in studies which have been conducted to investigate the mode of NIDDM transmission through generations (7). Moreover, the role of intrauterine environment in the pathogenesis of NIDDM has been suggested (8). Thus, the aim of the present study was to assess whether such a familial aggregation and significant maternal effect exists in analysis of 358 Turkish NIDDM patients' family histories.

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MATERIALS AND METHODS

Family histories of 358 NIDDM patients (129 men and 229 women) attending Endocrinology department of Hacettepe University were investigated. Age range was between 28-80 years (mean: 57.4±9.7 years). They were treated by either diet and/or by oral hypoglycemic drugs or needed insulin at least one year after the diagnosis. Diabetes duration ranged between 1-300 months (mean: 101.5±84.6 months). All patients were asked to answer the following questions during the visit:

1. Is there any diabetic member among your first degree relatives? (i.e. parents, siblings, paternal and maternal aunts/uncles)

2. If the answer is "Yes", what kind of treatment does he/she take?

Statistical analysis: The statistical difference between the groups was assessed by chi-square test. A p value less than 0.05 was considered to be significant.

RESULTS

The percentages of diabetic relatives of the patients (mothers, fathers, siblings, maternal/paternal aunts and

Table 1. Diabetes 'n the family of NIDDM patients

Family relationship (n-358)	Percentage with diabetes	Insulin treated (%)	Non-insulin treated (%)	Treatment not known (%)
Mothers'	17.9(n=64)	12.5	75.0	12.5
Fathers	13.7 (n-49)	8.2	73.4	18.4
Siblings	23.2 (n-81)	11.8	72.4	15.8
Maternal Side*	22.3 (n=80)	10.0	72.5	17.5
Paternal Side**	14.0 (n=50)	10.0	72.0	18.0
At least one	45.8 (n=164)	9.8	67.5	22.7

* Mothers plus maternal aunts/uncles
** Fathers plus paternal aunts/uncles -
' p-0.12 (mothers vs. fathers)

uncles) and their treatment are given in Table 1. As to whole group, 45.8% had at least one diabetic relative whereas, among them, 40.8% reported at least two.

Maternal and paternal effect. Although percentage of diabetic mothers (17.9%; n=64) was greater than that of diabetic fathers (13.7%; n-49), the difference did not reach to statistically significance (p-0.12). On the other hand, 22.3% (n=80) of the patients had at least one diabetic relative from maternal side (mothers, maternal aunts/uncles) and 14% (n-50) from paternal side (fathers, paternal aunts/uncles) ($p<0.05$).

While determining the maternal effect according to age of diabetes onset, patients were stratified into 3 groups. The age of onset of diabetes was between 20-75 (mean: 48.9+10.1). Group I, II and III consisted of patients with disease-onset ages between 20-39, 40-58 and 59-75, respectively. Reported frequencies of diabetic relatives from maternal and paternal sides are presented in Table 2.

As seen from the table, diabetic relatives reported on the maternal side were significantly more than those on the paternal side only in Group II (maternal side: 20.5%, paternal side: 12.2%; $p<0.05$). The difference was not significant in Groups I and III ($p>0.05$). Between the frequencies of diabetic mothers and diabetic fathers, there was no significant difference in any group ($p>0.05$).

Table 2. Percentage of diabetic family members according to age groups of disease onset

	Groupl(%)	Group II (%)	Group III (%)"
Maternal Side	35.5	20.5^	16.7^
	p>0.05	p<0.05	p>0.05
Paternal Side	27.4/	12.2 y	7.6/
Mothers	29.0^	16.2^	13.6^
	p>0.05	p>0.05	p>0.05
Fathers	19.4 /	11.8 /	11.1/

DISCUSSION

Family studies suggest a strong genetic component in the etiology of NIDDM with evidence of dominant or co-dominant effect (1). Monozygotic twin studies have revealed concordance rates approaching 100% when the follow-up is extensively prolonged (9). Significant maternal effect in comparison with paternal effect has been suggested by Alcolado et al (7) and Thomas et al (10). When considered as maternal and paternal sides (i.e. including aunts and uncles to mothers and fathers), our results agree with tneirs. Besides, it can be hypothesized that, mothers of our young diabetics, who may not have developed diabetes yet, might have influenced our results. Moreover, although .insignificant, our data showed more diabetic mothers than diabetic fathers. Approximately half of our patients reported to having at least one first degree diabetic relative. This finding is in agreement with the results obtained from other studies which suggested familial aggregation in NIDDM (7,10).

It has been suggested that, genetic factors as well as intrauterine environment play important role in the development of NIDDM in humans (8) and rats (11). Evidence exists about overexpression of the diabetogenic genes in a metabolically deranged pregnant (8,12). We found significantly more diabetic member from maternal side than paternal side which support the mitochondrial heredity hypothesis (transmission of diabetes to the offsprings by deletion of 10.4 kilobase mitochondrial DNA) (13) emphasizing preferential penetrance of diabetogenic genes coming from the maternal side.

We found that, genetic component and maternal effect is lowest in group III (diabetes onset after age 59). This finding is in agreement with the observations of Simpson et al (4), who have expressed the dominant influence of the environmental factors when disease onset is delayed. According to our results, maternal side diabetic relatives predominate significantly to paternal side ones when disease onset ranges between 40-58 years (i.e.middle aged group). Mothers of our young patiei.ts (Group I), who are possibly

younger than fathers and have not developed diabetes yet, might have contributed to insignificant maternal effect in this group.

In conclusion, our results support the hypothesis emphasizing dominance of maternally passed diabetogenic genes and familial aggregation in the inheritance of NIDDM. Maternal effect and role of genetic factors seem to be least when disease onset is delayed, possibly due to enhanced contribution of environmental factors to disease development. Further studies with larger patients groups are required to assess the mode of inheritance and contribution of genetic and environmental factors in NIDDM.

Tip II diyabetli hastaların aile öyküsü: diyabetik akrabaların anne tarafında yoğunlaştığına dair bulgular

İnsüline bağımlı olmayan (Tip II) diyabette aile öyküsü ve genetik yatkınlık öteden beri bilinmektedir. Son zamanlarda, nesiller boyunca bu hastalığın iletiminde maternal etkinin önemli olduğu vurgulanmaktadır. Bizim çalışmamızda, yaşları 28-30 arasında olan 358 Tip II diyabetik olgunun aile öyküleri, maternal etki ve aile bireylerinde hastalık frekansını belirleme açısından incelenmiştir. Tüm grubun %45.8'i en az bir, bunların da %40.8'i en az iki adet birinci derece diyabetik akraba bildirmişlerdir. Bu veriler, diyabette aile öyküsünün önemli olduğu savını desteklemektedir. Maternal etki (diyabetik anne sıklığı), paternal etkiye (diyabetik baba sıklığı) göre fazla olup, aradaki fark istatistiksel olarak anlamsız bulunmuştur (p>0.05). Anne tarafı (anne, dayı, teyze) ve baba tarafı (baba, amca, hala) olarak değerlendirildiğinde ise, ilk grupta diğerine göre anlamlı olarak daha fazla sayıda diyabetli olduğu gözlenmiştir (p<0.05). Hastalık başlangıç yaşının 40-58 yaş olduğu grupta, anne tarafında, baba tarafına göre anlamlı olarak daha fazla diyabetik akraba olduğu belirlenmiştir (p<0.05). Aksine, hastalık başlangıç yaşı 20-39 ve 59-75 arasında olan gruplarda bu etki ortadan kalkmaktadır (p>0.05). Bu bulgular, Tip II diyabet kalıtımında anne tarafından gelen diyabetojenik genetik yapının hakim olduğunu ve diyabete yakalanma yaşı geç olanlarda bu etkinin muhtemelen, çevresel faktörlerin öne geçmesiyle silikleştiği savını desteklemektedir.
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