Family History in the Aetiology of Gestational Diabetes Mellitus and Type 2 Diabetes

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Abstract

The aetiology of Type 2 diabetes [NIDDM] is assumed to involve a multiplicity of causal factors involving both genetic and environmental, including intrauterine, components.

Aim: To identify the relationship of various aspects of family history and hence the possible role of genetic influence in the development of Type 2 DM in the Maltese population.

Methods: The family history details of a study population undergoing an oGTT during pregnancy was assessed during pregnancy and at follow-up eight years postpartum. The findings were related to previous national epidemiological studies.

Results: The study showed a definite statistical correlation between a maternal and sibling family history of diabetes with the onset of GDM/GIGT and later Type 2 DM. No such correlation was shown with a paternal or grandparent family history.

Conclusions: The findings suggest that genetic factors are poor determinants for adult-onset GDM or Type 2 DM, the major role player being apparently alterations in the intrauterine environment of the fetus.

Introduction

Ethnic susceptibility to diabetes varies tremendously, a variation in liability that must depend both upon the widely differing conditions in which the human species exists and upon the diversity of the genetic endowment. The diabetic state must be considered as the outcome of a multiplicity of causal factors, potentially varying in both the genetic and the environmental components of the mix. The contribution of the intrauterine milieu interior of the fetus to the later development of Type 2 diabetes mellitus (Type 2 DM) and gestational diabetes mellitus (GDM) has been repeatedly demonstrated in both experimental animal models and human epidemiological studies with prenatal hyperglycaemia/hyperinsulinism and prenatal nutritional deprivation both being implicated.

The genetics of Type 2 DM and the genetic influence towards the development of adult-onset diabetes are not well understood. The present study was set up to investigate the family history correlates to the development of gestational diabetes in the Maltese population known to have a high prevalence of Type 2 DM.

Methods

The first and second-degree parental family history data of randomly chosen two hundred and sixty-seven (267) women who had their glucose tolerance assessed during their pregnancy was established. One hundred and sixteen of these subjects were traced and recalled for reassessment eight years later when first degree parental and sibling family history was assessed. The family history characteristics of those women who were identified as having GIGT/GDM (defined as a two-hour blood glucose value >7.8 mmol/l after a 75 g oGTT) or later Type 2 DM/IGT (defined similarly as a two-hour blood glucose value >7.8 mmol/l) was compared to the characteristics of women found to have normal glucose tolerance. These observations were compared to previous national epidemiological studies conducted on female subjects belonging to the same population and using similar diagnostic criteria.

Recruitment of the original study population was carried out by inviting all pregnant women (excluding only non-Maltese or previously known diabetics) seen at the antenatal clinics at St. Luke’s Hospital or the Government Peripheral Health Centres over a period of three months. Statistical analyses were made using a standard statistical package Statcalc (WHO
FAMILY Epidemiological National Study [Phase V] - female data

NGT AbGT P value
Maternal 172 29.2% [n=589] 47 51.6% [n=91] 0.00002 1
Paternal 86 15.3% [n=563] 16 17.9% [n=89] 0.6205 1
Sibling - brother 105 7.3% [n=1434] 49 21.3% [n=230] <0.000001 1
Sibling - sister 89 5.9% [n=1501] 51 23.2% [n=220] <0.000001

Table 2: Family history in Epidemiological studies

(History: 1 = Yates Chi Square test; 2 = Fisher 1-tailed test)

HISTORY

<table>
<thead>
<tr>
<th>FAMILY HISTORY</th>
<th>Pregnant population</th>
<th>Follow-up population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NGT</td>
<td>AbGT</td>
</tr>
<tr>
<td>Maternal</td>
<td>28</td>
<td>1.8%</td>
</tr>
<tr>
<td>Paternal</td>
<td>23</td>
<td>9.7%</td>
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<tr>
<td>Sibling</td>
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<td>N/A</td>
</tr>
<tr>
<td>Grandparent</td>
<td>38</td>
<td>16.0%</td>
</tr>
</tbody>
</table>

Results

Table 1 suggests that a positive maternal family history of diabetes was a statistically significant correlate to the development of GIGT/GDM or later Type 2 DM/IGT in the female population. Similarly a positive sibling family history was a statistically significant correlate to later development of Type 2 DM/IGT. There did not appear to be any significant correlations shown with the development of GIGT/GDM or Type 2 DM/IGT with a family history of diabetes in the father or grandparents. These findings conform to the results of the national epidemiological study conducted on female subjects who similarly confirmed that a statistically significant relationship existed between the development of Type 2 DM and a family history in the mother or siblings. No such relationship was noted with a paternal family history (Table 2).

Discussion

The genetics of Type 2 DM are not well understood since markers such as the HLA system, associated to Type 1 diabetes, are not available. The National Diabetes Programme conducted in Malta showed no significant associations between HLA type and persons suffering from DM and IGT. The reported increased prevalence of Type 2 DM in Mediterranean countries with a high population density - notably Malta, Cyprus, Spain, Israel and Lebanon - may be considered to reflect a genetic predisposition exhibited through increased inbreeding. On the other hand, a high population density increases the degree of urbanisation, a factor that has also been correlated to an increased prevalence of Type 2 DM. Evidence for a genetic susceptibility to developing Type 2 DM has been presented, and defects in both insulin production and action are suspect. Five genes have been associated with the autosomal dominant maturity-onset diabetes of the young [MODY] subtype; glucokinase, and 4 transcription factors that play a key role in the development of the endocrine pancreas or in the expression of glucose metabolism genes. Apart from the monogenic forms of type 2 diabetes, little is known about the nature of the genetic factors involved. Minor contributors include insulin, sulfonylurea receptor and some others. Genome scans of diabetic families have revealed susceptibility loci on chromosomes 1q, 2p, 2q (where the gene calpain 10 was recently cloned), 3q, 12q and 20. Other receptor genes such as the B3-adrenergic receptor gene have been suggested as factors towards the development of weight gain, insulin resistance and the earlier onset of Type 2 DM. This gene polymorphism is predominantly expressed in adipose tissue and regu-
lates lipid metabolism and thermogenesis, so its impairment may lead to obesity through its effect on the energy expenditure of fat tissue. The reported data so far remains conflicting. Recent studies have further suggested that variation within the TH-INS-IGF2 locus, most plausibly at the VNTR, may influence Type 2 DM susceptibility. This locus may be mediated exclusively by the paternally derived allele.

The present study, carried out on the Type 2 DM high-prevalence Maltese population, has shown that a maternal or sibling family history is a significant risk factor. No such statistically significant correlation has been identified with a paternal or grandparent family history. The present cohort compliments earlier family history studies in general diabetes clinics and in the Pima Indian population, which showed a higher maternal than paternal transmission of diabetes. The maternal, but not paternal, association suggests that whereas a familial tendency definitely exists, this is probably not a genetic influence unless it involves transmission through maternal mitochondrial genetic material. Siblings can be assumed to have been influenced in a similar fashion as the subject under study. The familial association is more likely the product of the minor alterations that occur in the intrauterine milieu of the infant of the mother with abnormal carbohydrate metabolism. The role of the altered intrauterine environment in the aetiology of Type 2 DM has been previously suggested by epidemiological studies in other populations. Most convincing are the studies on Pima Indians that have shown that, besides a genetic transmission, the diabetic intrauterine environment can also induce a diabetogenic tendency in the offspring. These studies have shown that impaired glucose tolerance was more frequent in children of mothers who had diabetes during pregnancy than in children of mothers who developed diabetes after pregnancy. In the Pima population today over 70% of persons with prenatal exposure to diabetes have Type 2 DM diabetes by 25-34 years of age, while prenatal exposure to maternal hyperglycaemia is believed to be responsible for 40% of all Type 2 DM in 5-19 year old children. The relationship has also been shown by experimental animal models. These studies showed that adult offspring (second generation) of streptozotocin-injected rats (first generation) developed gestational diabetes, while their fetuses (third generation) showed islet cell hyperplasia and beta cell degranulation to the same degree as second generation fetuses of diabetic mothers. These observations suggest that the main factor in the development of adult-onset GDM or Type 2 DM is probably not purely a genetic one unless determined by maternal mitochondrial genetic transmission. The study supports other previous epidemiological and animal observations that link Type 2 DM with alterations in the intrauterine milieu of the infant of the mother with abnormal carbohydrate metabolism. In the light of this observation and the risk of high antenatal glucose levels to the developing fetus, it may be prudent to advise all pregnant women belonging to an ethnic group known to have a high prevalence of Type 2 DM to avoid taking high doses of refined sugars irrespective of their identified carbohydrate metabolism status. Furthermore, it may be opportune to investigate seriously the role of using oral hypoglycaemic agents during the third trimester in those pregnant women who are shown to suffer from GDM but are not identified as requiring insulin therapy thus ensuring optimum glucose control.

References