The acetylator phenotypes of Saudi Arabian diabetics

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SUMMARY There is a significant association between the rapid acetylator phenotype and diabetes in European populations. Diabetes is a common problem in Saudi Arabsians with some clinical features differentiating it from the disorder in Europeans. A series of 100 Saudi diabetics and 100 Saudi controls has been acetylator phenotyped. The controls showed 33 rapid acetylators (R) and 67 slow acetylators (S), a result closely similar to that previously published for the Saudi population. Overall the diabetics showed 27 R and 73 S which is not significantly different from the controls. The type I diabetics, however, showed two R and 22 S which is not only significantly different from the controls and the type II diabetics, but also the reverse of the association found in European populations.

The idea that one phenotype within a polymorphism might be more prone than the other phenotypes to develop a given disorder was proposed by Alexander (though at the time the biological significance of genetic polymorphism had not been realised). About 30 years ago this idea was put to the test, and particularly extensive investigations were made of the frequencies of the different ABO blood group types in duodenal ulcer by Clarke et al. At the same time some difficulties in the interpretation of the statistical associations became apparent.

Since that time many statistical associations of genetic phenotypes with various disorders have been described. The most striking is the association of HLA-B27 with ankylosing spondylitis and related arthropathies. Even here there is a mystery in that the immunochemical basis remains obscure.

Relatively little work has been published concerning associations between pharmacogenetic polymorphisms and spontaneous disorders. The available knowledge about the acetylator polymorphism in this regard has recently been surveyed.

An early paper pointed out that in a series of 28 Finnish diabetics there was an unexpectedly high frequency of rapid acetylators. Omitting this index series an analysis of the six series subsequently published has been made in table 1. For the UK population three series of diabetics have been

Received for publication 6 June 1985.
Accepted for publication 19 June 1985.

Table 1 A test of the association between diabetes and the rapid acetylator phenotype. (Modification by Haldane of the method of Woolf.)

<table>
<thead>
<tr>
<th>Source of data</th>
<th>No of subjects</th>
<th>Relative incidence x</th>
<th>log10 x = y</th>
<th>Sampling variance V</th>
<th>Weight 1/s2</th>
<th>Significance of difference from zero wy2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diabetics</td>
<td>Controls</td>
<td>Slow Rapid</td>
<td>Slow Rapid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled UK data</td>
<td>126</td>
<td>144</td>
<td>556</td>
<td>375</td>
<td>1-6029</td>
<td>0-5264</td>
</tr>
<tr>
<td>Australian data</td>
<td>39</td>
<td>77</td>
<td>58</td>
<td>54</td>
<td>2-1060</td>
<td>0-7448</td>
</tr>
<tr>
<td>Spanish data</td>
<td>67</td>
<td>52</td>
<td>90</td>
<td>67</td>
<td>1-0428</td>
<td>0-0419</td>
</tr>
<tr>
<td>Italian data</td>
<td>87</td>
<td>69</td>
<td>39</td>
<td>16</td>
<td>0-9015</td>
<td>0-6426</td>
</tr>
</tbody>
</table>

**Weighted mean value of y = y = (Σwy)/(Σw) = 44-1696/91-7291 = 0-4815.**

**SD of y = (Σw)-1/2 = 0-1044.**

**95% fiducial limits of y = ±0-01838 and 0-01493.**

**Antilog y = x = 1-6185.**

The equivalent x values to the 95% fiducial limits of y are 2-2564 and 1-1610.

**Significance of difference of X from unity = b = (Σwy)/(Σw) = 21-27.**

**Homogeneity estimate = b = (Σwy)/(Σw) = 4-55.**

479
pooled, and a large control population has been assembled from various publications as previously described. There was no heterogeneity between the series (all of which were European in origin) in that they all showed some increase in frequency of rapid acetylators among diabetics as compared with their own control groups. The mean relative incidence is about 1-6.

Diabetes is a common disorder among Saudi Arabsians. One notable differentiating clinical feature is the ability of many diabetics to tolerate a grossly raised plasma glucose concentration without symptoms.14

The present study was undertaken to see if there was an association between either acetylator phenotype and diabetes in Saudi Arabsians, and to see how the result compared with the association known in Europeans.

Methods

Diabetics studied were inpatients and outpatients of the Riyadh Armed Forces Hospital. All gave informed consent for the acetylator phenotyping test to be carried out on them. Their diabetic treatment, including diet, was withheld on the morning of the test. Patients were categorised as type I or type II diabetics according to the standard published criteria.15 It is sometimes difficult to categorise an individual patient, and in this series the errors, if any, are in one direction, that is, a type I patient may be called type II but not vice versa.

Healthy control subjects were recruited from the Saudi Arabian staff of the hospital, visitors to the hospital, and ‘watchers’ (a watcher is a healthy person who stays with a seriously ill patient in hospital and tends to his or her needs). It was ensured that the patients and controls were all unrelated.

The phenotyping procedure was carried out as described in method II of Evans 1969.16 A urine sample was obtained from each subject immediately before he or she swallowed the test dose of sulphadimidine. This is referred to below as the ‘pre-test’ urine. The six hour blood and five to six hour urine following drug ingestion were obtained from all subjects.

\[ \text{Diabetics} \]

\[ \text{Controls} \]

\[ \text{FIG 1 The results of the acetylator phenotyping test in healthy Saudi Arabian controls.} \]

\[ \text{FIG 2 The results of the acetylator phenotyping test in Saudi Arabian diabetic patients.} \]
The acetylator phenotypes of Saudi Arabian diabetics

<table>
<thead>
<tr>
<th>Acetylator phenotype</th>
<th>Controls</th>
<th>Type I diabetics</th>
<th>Type II diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid</td>
<td>33</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Slow</td>
<td>67</td>
<td>22</td>
<td>51</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>24</td>
<td>76</td>
</tr>
</tbody>
</table>

The analyses were carried out by an adaptation of the Bratton-Marshall procedure.17

Results

Several pre-test urines showed the presence of chemicals reacting in the Bratton-Marshall reaction. Presumably these were traces of previously ingested drugs. In no instance was the amount sufficient to interfere with the phenotyping procedure. The results of the phenotyping tests are shown in figs 1 and 2.

The dividing line between the phenotypes for both diabetics and controls has been taken to be 45% sulphadimidine acetylated in the plasma. The distribution of phenotypes is shown in table 2, and the distribution of ages, weights, and heights in tables 3, 4, and 5. In these tables it will be seen that the type I diabetics were younger than the type II diabetics.

The frequency of the allele controlling slow acetylation in the healthy control subjects is 0.8185.

The ‘relative incidence’ has been calculated for all the diabetics versus the controls in the same way as in table 1 so that an association between diabetes and rapid acetylation would give a value > 1. The value obtained was 0.7539 (log e = −0.2825) which is 7.3 SD below the mean of the series in table 1.

There was no significant difference in the frequencies of the phenotypes when all the diabetics were compared with all the controls ($\chi^2 = 0.857$). There was, however, a significant difference in phenotype frequencies when type I and type II diabetics were compared ($\chi^2 = 5.58, p < 0.02$). The phenotype frequencies in type II diabetics were closely similar to those in the controls.

Discussion

Figs 1 and 2 show that there is no interference by diabetes in the phenotyping test procedure.
The allele frequency in the controls is similar to that previously described in surveys of Saudi Arabians and other adjacent Middle Eastern populations. This is of interest because the present subjects were Saudi nationals mainly from the central and southern regions, whereas the previous surveys had been conducted from the more heterogeneous populations in the western region.

In the population of Saudi diabetics there is a significant association between slow acetylation and type I diabetes.

It might be postulated that the phenotyping results in type I diabetics might have been affected in some way by the fact that they were on insulin treatment. This idea has been disproved by comparing the phenotype frequencies in type II diabetics who were and who were not receiving insulin.

In 34 in the former category there were 10 rapid acetylators, and in 42 in the latter category there were 15 rapid acetylators ($\chi_1^2=0.34$).

The analysis of diabetics in table 1 pooled both types of diabetes together. This was done because it is not possible consistently to disentangle the two types from the published series. An attempt to show the breakdown is shown in table 6, where it is clear that there is a very high frequency of rapid acetylators in European type I diabetics.

The present preliminary series suggests that as far as the association with the acetylator polymorphism is concerned, type I Saudi diabetics are quite different from type I European diabetics. Further series will be required to confirm or refute the present finding.

There is one appealing feature in studying associations of pharmacogenetic polymorphisms with spontaneous disorders. This is because the biochemical bases of the polymorphisms are known. To acetylate the test drug in the acetylator polymorphism, acetyl groups are transferred from acetyl CoA by the action of the polymorphic N-acetyl transferase.

It is implicit in the phenotyping test that there is an abundant supply of acetyl CoA available.

Disturbances related to this area of metabolism are known in experimental diabetes, for example, the liver concentration and production of acetate is known to be increased in alloxan treated rats and sheep.

The interpretation of the associations of the acetylator phenotypes with diabetes is speculative because the natural substrates for the polymorphic N-acetyl transferase are unknown. A clue to a possibly relevant class of natural substrates is provided by the recent finding that the amino methyl uracil which is an important metabolite of caffeine is polymorphically acetylated. There is evidence that this compound is found in the urines of caffeine-free subjects.

Provided that the present finding about type I diabetes is confirmed, then an hypothesis could be entertained as follows: that a toxic natural substrate which is a factor in precipitating type I diabetes is relatively ineffectively detoxicated by slow acetylators. This hypothesis would not however fit the facts as far as European diabetics are concerned, and so in them some other mechanism would have to be invoked to explain their association with the rapid acetylator phenotype.

We thank the Research and Ethical Committee of the Riyadh Armed Forces Hospital (Chairman Dr Mohamed Al Faghih) and the Special Development Fund of the Riyadh Armed Forces Hospital (Chairman Dr Mohamed Abomelha) for funding the project. Dr R A Bacchus, Director of the Central Laboratory, Riyadh Armed Forces Hospital for analytical facilities, and Miss Margaret A Johnston for preparing the manuscript.

### Table 6: Details of the acetylator phenotypes in different categories of diabetics.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Details of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>28 diabetics, 25 on insulin Overall 13 R 15 S 7 out of 9 patients aged less than 16 years were rapid acetylators</td>
</tr>
<tr>
<td>8</td>
<td>Type I 27 R 28 S Juvenile onset 27 R 22 S Maturity onset 42 R 39 S</td>
</tr>
<tr>
<td>9</td>
<td>Many juvenile onset 19 R 19 S Maturity onset 29 R 18 S</td>
</tr>
<tr>
<td>10</td>
<td>Type I 35 R 12 S Type II 42 R 27 S</td>
</tr>
<tr>
<td>12</td>
<td>Juvenile onset 15 R 17 S Adult onset 37 R 50 S</td>
</tr>
<tr>
<td>13</td>
<td>Type I 32 R 29 S Type II 37 R 58 S</td>
</tr>
</tbody>
</table>

R = rapid acetylator. S = slow acetylator.

### References

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