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 Arabians 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

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>Diabetics</th>
<th>Controls</th>
<th>Relative incidence x</th>
<th>log x = y</th>
<th>Sampling variance V</th>
<th>Weight ( v^2 = w )</th>
<th>Significance of difference from zero ( w^2 )</th>
</tr>
</thead>
</table>
| Pooled UK data
| 10             | 126           | 144       | 556      | 375                  | 1-6929   | 0-5264              | 0-0192        | 52-0143          | 14-4155         |
| Australian data
| 11             | 39            | 77        | 58       | 54                   | 2-1060   | 0-7448              | 0-0730        | 13-7077          | 7-6041          |
| Spanish data
| 12             | 67            | 52        | 90       | 67                   | 1-0428   | 0-0419              | 0-0593        | 16-8723          | 0-0296          |
| Italian data
| 13             | 87            | 69        | 39       | 16                   | 1-9015   | 0-6426              | 0-1905        | 9-1347           | 3-7724          |

Weighted mean value of \( y = x = \frac{\Sigma wy}{\Sigma w} = 44-1696 \)

\( SD \) of \( y = (\Sigma w^2)^{1/2} = 0-1044 \).

95% fiducial limits of \( y = 2x_{0.025}(\Sigma w)^{1/2} + 0-8138 \) and \( 0-1493 \).

Antilog \( Y = X = 3-6185 \).

The equivalent \( X \) values to the 95% fiducial limits of \( y \) are 2-2564 and 1-1610.

Significance of difference of \( X \) from unity = \( \chi^2 = (\Sigma wy)^2 - \Sigma w = 21-27 \).

Homogeneity estimate = \( \chi^2_{0.01} = \Sigma wy^2 - (\Sigma wy)^2/\Sigma w = 4-55 \).
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 Arabians. One notable differentiating clinical feature is the ability of many diabetics to tolerate a grossly raised plasma glucose concentration without symptoms.

The present study was undertaken to see if there was an association between either acetylator phenotype and diabetics in Saudi Arabians, 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. 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. 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.
The acetylator phenotypes of Saudi Arabian diabetics

TABLE 2 The distribution of acetylator phenotypes in Saudi diabetics and controls.

<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 (log10 = -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 (χ²=0.857). There was, however, a significant difference in phenotype frequencies when type I and type II diabetics were compared (χ²=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.

TABLE 3 The distribution of ages (years) in Saudi diabetic and control subjects.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Acetylator phenotype</th>
<th>Parameter</th>
<th>Category of subject</th>
<th>Control</th>
<th>Type I diabetic</th>
<th>Type II diabetic</th>
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<tr>
<td>Male</td>
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<td></td>
<td>37</td>
<td>8</td>
<td>20</td>
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<tr>
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<td>9-260</td>
<td>22-208</td>
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</tr>
</tbody>
</table>

N=number.<br>M=mean.<br>SD=standard deviation.

TABLE 4 The distribution of body weights (kg) in Saudi diabetic and control subjects.

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<tr>
<th>Sex</th>
<th>Acetylator phenotype</th>
<th>Parameter</th>
<th>Category of subject</th>
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<th>Type II diabetic</th>
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</tbody>
</table>

Persons aged 21 years and less have been omitted.<br>N=number.<br>M=mean.<br>SD=standard deviation.

TABLE 5 The distribution of heights (cm) in Saudi diabetic and control subjects.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Acetylator phenotype</th>
<th>Parameter</th>
<th>Category of subject</th>
<th>Control</th>
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<tr>
<td>Female</td>
<td>Slow</td>
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<td>37</td>
<td>8</td>
<td>20</td>
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<tr>
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<td>M</td>
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<td></td>
<td>33-757</td>
<td>32-200</td>
<td>50-450</td>
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<tr>
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<td>9-731</td>
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<td>10-575</td>
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<td>11</td>
<td>1</td>
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<tr>
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<td>M</td>
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<td>N</td>
<td></td>
<td></td>
<td>31</td>
<td>7</td>
<td>31</td>
</tr>
</tbody>
</table>

Persons aged 21 years and less have been omitted.<br>N=number.<br>M=mean.<br>SD=standard deviation.
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 heter-
egeneous populations in the western region.

In the population of Saudi diabetics there is a
significant association between slow acetylation and
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 compar-
ing 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 ($\chi^2 = 0.34$).

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 associa-
tions of pharmacogenetic polymorphisms with sponta-
neous 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
Saudi diabetics 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
cconcerned, and so in them some other mechanism
would have to be invoked to explain their associa-
tion with the rapid acetylator phenotype.

We thank the Research and Ethical Committee of
the Riyadh Armed Forces Hospital (Chairman Dr
Mohamed Al Fagih) and the Special Development
Fund of the Riyadh Armed Forces Hospital (Chair-
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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.

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groups in patients suffering from malignant disease. Br J Exp

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