Tetrahydrobiopterin metabolism in senile dementia of Alzheimer type

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SUMMARY Tetrahydrobiopterin metabolism was shown to be disturbed in 18 patients with senile dementia of Alzheimer type. This may have a bearing on the pathogenesis of the disease.

Tetrahydrobiopterin is the rate-limiting factor in catecholamine synthesis. Defective tetrahydrobiopterin metabolism may cause reduced neurotransmitter production and hence disease of the central nervous system. In children suffering from malignant hyperphenylalaninaemia, a specific deficiency of intracellular tetrahydrobiopterin has been shown to be the direct cause of their degenerative brain disease. In malignant hyperphenylalaninaemia due to reduced tetrahydrobiopterin synthesis serum biopterin concentration is lowered and in malignant hyperphenylalaninaemia caused by dihydropteridine reductase deficiency, serum biopterin levels are elevated. We now report serum biopterin levels in a group of patients with senile dementia of Alzheimer type.

Methods and subjects

Patients The patients were from the acute psychiatric assessment unit at All Saints Hospital, Birmingham. There were 7 males and 11 females, with a mean age of 79 ± 6.8 years (mean ± SD). The diagnosis of senile dementia had been established by experienced psychiatrists for more than a year. All patients had biochemical, haematological and serological tests to exclude such causes of senile dementia as hypothyroidism, vitamin B12 deficiency, chronic renal failure, hepatic failure and syphilis. Two patients had CT scan and one had had air encephalography and in all three global cerebral atrophy had been shown. None had a brain biopsy. The diagnosis Alzheimer's disease was presumed for the whole group on clinical grounds. At the time of study, all patients were completely disoriented to time, place and personality and their recent and past memory faculties were severely defective. In the light of the severe cognitive defects, formal scoring tests were meaningless. The patients did not have any concomitant medical illnesses. Fourteen patients were on thioridazine, four were on dichloralphenazone, one on promazine, one on haloperidol, two on perphenazine, two on ibuprofen, one on triamterene and one on hydrochlorothiazide.

Control subjects Control subjects were obtained from among patients of acute medical wards, schizophrenic long stay patients of All Saints Hospital in Birmingham and from among healthy hospital staff and university staff and students. The patients from the acute medical wards had been admitted on account of one or more of the following illnesses: acute cerebrovascular disease, severe congestive cardiac failure, septicaemia, Huntington's disease, myocardial infarction, severe herpetic zoster ophthalmica and severe Crohn's disease; these patients were divided into two groups: In Group 1 where patients were suffering from chronic mental confusion as the result of their general ill health. They were seven males and eight females, with a mean age of 77 ± 1.3 years (mean ± SD). They were on one or more of the following drugs: prednisolone, α-phenoxyazine, triamterene, α-benzoxyazine, trimipramine, digoxine, frusemide, phenobarbitone, on antibiotic and a β-blocker.

In Group 2 were patients free of any mental symptoms. They were nine males and 11 females with a mean age of 75 ± 0.6 years (mean ± SD). Nine of these patients were not on any drugs and the rest were on one or more of the following drugs: digoxine, dipyridamole, α-phenoxyazine, clormethiazole, frusemide, sulphinpyrazine, lorzepam and cimetine.

The healthy hospital staff and university staff and students were volunteers in a survey to establish biopterin levels in different body fluids of normal population. None of these subjects were on any drugs. They were 231 volunteers. The results of the survey have already been published. In this study we have only used results from 13 subjects, whose ages ranged from 51 to 66 years. Our reason for this selection was that they were the nearest age group to the Senile dementia of Alzheimer type patients. They were five males and eight females. These subjects...
were used as a separate group to compare to Senile dementia of Alzheimer type patients.

The schizophrenic patients were long stay patients who had been diagnosed as chronic schizophrenics by experienced psychiatrists. They were all on fluphenazine decanoate. They were five females and 12 males with a mean age of 59 ± 11 years (mean ± SD). These subjects were also used as a separate group, mainly to observe the effect of a representative antipsychotic drug on our results.

Serum samples from Senile dementia of Alzheimer type patients and the control groups of hospital patients were obtained in the course of their medical management. In the case of Senile dementia of Alzheimer type patients and the control groups from the acute medical wards, serum samples were obtained within a week from their admission. The subjects in this study did not undergo any special preparation prior to blood letting. The samples were frozen at −20°C and assayed within one month.

Chlorpromazine trial
This trial was performed on five volunteers. Each was given a single oral dose of 50 mg of chlorpromazine. Serum samples were obtained just before, 2 hours, 8 hours and 24 hours after the intake of the chlorpromazine dose. The samples were again frozen at −20°C and assayed within one month.

Biopterin assay
The standard bioassay technique as described previously was used to measure the concentrations of serum biopterin. The mean and standard error of serum biopterin concentration were calculated for each group of subjects under study as a whole group and according to sex. Students t test was used to compare results of relevant groups.

Results
The serum biopterin concentrations of Senile Dementia of Alzheimer Type patients were compared to the two groups of controls derived from the patients of acute medical wards (tables 1 and 2). The serum biopterin concentrations in the whole group of Senile Dementia of Alzheimer Type patients (1.11 ± 0.08 μg/l) was lower than the mean concentration in Control Group 1 (2.50 ± 0.27 μg/l); p = <0.001) and in Control Group 2 (1.53 ± 0.10 μg/l; <0.01). Serum biopterin concentrations in female (1.18 ± 0.09 μg/l) and male (0.99 ± 0.09 μg/l) Senile Dementia of Alzheimer Type patients were lower than the mean value of control females in Group 1 (2.70 ± 0.46 μg/l; p < 0.01) and Group 2 (1.50 ± 0.14 μg/l; p < 0.05) and males in Group 1 (2.30 ± 0.28 μg/l; p < 0.001) and Group 2 (1.57 ± 0.17 μg/l; p < 0.02). The mean serum biopterin level of Senile Dementia of Alzheimer Type patients also was lower than that of the healthy control group (p < 0.001) for the whole group, male and female subgroups (table 3).

When comparing Senile Dementia of Alzheimer Type patients to the schizophrenics, it is clear that the serum biopterin mean concentration for the Senile Dementia of Alzheimer Type former patients as a whole group was lower than the mean value in the schizophrenic patients (1.51 ± 0.07 μg/l; p < 0.01)(Table 4). The male Senile Dementia of Alzheimer Type patients had serum biopterin levels lower than those of the male schizophrenic patients (1.60 ± 0.08 μg/l; p < 0.05). The female Senile Dementia of Alzheimer Type patients also had their mean serum biopterin concentrations (1.18 ± 0.09) lower than those of female schizophrenics (1.30 ± 0.06 μg/l) though the difference did not reach statistical significance.

The results from the chlorpromazine trial (table 5) showed that a single dose of 50 mg of chlorpromazine did not change the serum biopterin concentration.

Table 1 Serum biopterin concentration in SDAT* patients and Control Group I patients

<table>
<thead>
<tr>
<th>Group</th>
<th>*SDAT Patients Mean ± SE (No)</th>
<th>Control Group Mean ± SE μg/l (No)</th>
<th>Significance by Student’s t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0.99 ± 0.09 (7)</td>
<td>2.30 ± 0.28 (7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>1.18 ± 0.09 (11)</td>
<td>2.70 ± 0.46 (8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total</td>
<td>1.11 ± 0.08 (18)</td>
<td>2.50 ± 0.27 (15)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Senile Dementia of Alzheimer type

Table 2 Serum biopterin concentration in SDAT* patients and Control Group II of Patients

<table>
<thead>
<tr>
<th>SDAT* Patients Mean ± SE μg/l (No)</th>
<th>Control Group with no mental disturbance Mean ± SE μg/l (No)</th>
<th>Significance by Student’s t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0.99 ± 0.09 (7)</td>
<td>1.57 ± 0.17 (9)</td>
</tr>
<tr>
<td>Female</td>
<td>1.18 ± 0.09 (11)</td>
<td>1.50 ± 0.14 (11)</td>
</tr>
<tr>
<td>Total</td>
<td>1.11 ± 0.08 (18)</td>
<td>1.53 ± 0.1 (20)</td>
</tr>
</tbody>
</table>

*Senile Dementia of Alzheimer type
Table 3  Serum biopterin concentration in SDAT* patients compared to healthy control subjects

<table>
<thead>
<tr>
<th></th>
<th>SDAT patients Mean ± SE μg/l (No)</th>
<th>Healthy control Mean ± SE μg/l (No)</th>
<th>Significance by Student's t test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0.99 ± 0.09 (7)</td>
<td>2.54 ± 0.30 (5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female</td>
<td>1.18 ± 0.09 (11)</td>
<td>1.84 ± 0.15 (8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total</td>
<td>1.11 ± 0.08 (18)</td>
<td>2.11 ± 0.30 (13)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Senile Dementia of Alzheimer type

Table 4  Serum biopterin concentration in SDAT* patients compared to schizophrenic patients

<table>
<thead>
<tr>
<th></th>
<th>SDAT patients Mean ± SE μg/l (No)</th>
<th>Schizophrenic patients Mean ± SE μg/l (No)</th>
<th>Significance by Student's t test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0.99 ± 0.09 (7)</td>
<td>1.60 ± 0.08 (12)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Female</td>
<td>1.18 ± 0.09 (11)</td>
<td>1.30 ± 0.06 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>1.11 ± 0.08 (18)</td>
<td>1.51 ± 0.07 (17)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

*Senile dementia of Alzheimer type

Table 5  Serum biopterin concentration before and 2, 6, 24 hours after oral dose of 50 mg chlorpromazine

<table>
<thead>
<tr>
<th>Patients</th>
<th>Serum biopterin concentration (μg/l)</th>
<th>Significance by Student's t test comparing 2nd, 6th, 24th hour values to zero hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ohr 1.7 ± 0.08</td>
<td>NS</td>
</tr>
<tr>
<td>2</td>
<td>1-70 1.70 1.90 1.70 2.00 1.80</td>
<td>NS</td>
</tr>
<tr>
<td>3</td>
<td>1-70 1.70 1.90 1.70 2.00 1.80</td>
<td>NS</td>
</tr>
<tr>
<td>4</td>
<td>1-70 1.70 1.90 1.70 2.00 1.80</td>
<td>NS</td>
</tr>
<tr>
<td>5</td>
<td>1-70 1.70 1.90 1.70 2.00 1.80</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>Mean ± SE 1.62 ± 0.12 1.64 ± 0.24 1.5 ± 0.15</td>
<td>NS</td>
</tr>
</tbody>
</table>

Discussion

Serum biopterin is normally maintained within a very narrow range. Our results showed a significant decrease in serum biopterin concentration compared with our control groups, confirming an earlier observation and in line with a more recent finding by some other workers in this field. By analogy with malignant hyperphenylalaninaemia these low levels could be due to a low level of intracellular tetrahydrobiopterin caused by a reduction of its synthesis. However the possible effect of antipsychotic drug therapy, especially phenothiazines, in producing these results has to be considered. An in vitro study of the effect of phenothiazines, tricyclics and benzodiazepines on the synthesis of tetrahydrobiopterin has shown that these drugs do not inhibit tetrahydrobiopterin synthesis. A single dose of chlorpromazine did not alter serum biopterin in the present study. Senile Dementia of Alzheimer Type patients had a lower level of serum biopterin than the chronic schizophrenics on similar drug therapy. Thus it seems unlikely that the lowered serum biopterin levels in Senile Dementia of Alzheimer Type are the result of drug therapy. Still, it could be said that the low levels of serum biopterin in this study may be due to loss of brain tissue. However neopterin concentrations in urine and in serum of Senile Dementia of Alzheimer Type patients have been shown to be similar to normal healthy controls. The significance of these findings is in the fact that neopterins exist in the body for the sole aim of producing tetrahydrobiopterin. Therefore a reduced level of serum biopterin because of loss of brain tissue should be accompanied by a proportionate decrease of neopterin levels.

We at present believe that there is a reasonable ground to suppose that our results are related to the pathophysiology of Senile Dementia of Alzheimer Type and not due to non specific effects of drug therapy or cerebral atrophy. Most of the recent work in the field of Senile Dementia of Alzheimer Type studies, has been dominated by attempts to unravel the role of specific loss of cholinergic neurons or failure of catecholamine neurotransmitters of the CNS in the pathogenesis of Senile
Dementia of Alzheimer Type. The bulk of evidence appears to be leaning towards specific cholinergic neuron loss as being the outstanding pathological finding. The analogy of such finding to the dopamine deficiency of Parkinsonism with its therapeutic implications, perhaps explains the enthusiasm with which the evidence for specific cholinergic neuron loss has been accepted. The evidence of possible tetrahydrobiopterin deficiency brings to the field of work on Senile Dementia of Alzheimer Type a new dimension to consider and contend with. It raises two major questions. Could failure of tetrahydrobiopterin metabolism lead or predispose to degenerative brain diseases such as Senile Dementia of Alzheimer Type? Would it be possible by correcting such deficiency to improve clinical symptoms or halt at earlier stages degenerative process of Senile Dementia of Alzheimer Type? There is now a small number of patients with malignant hyperphenylalaninaemia on levodopa and 5HTP treatment who are still living. There are also healthy children with minor defects of tetrahydrobiopterin metabolism. Perhaps the follow up of these subjects may shed light on those questions.

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References

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