Folate Studies in Underprivileged Children with Epilepsy*

Red Cross War Memorial Children's Hospital, Cape Town

SUMMARY

A study has been made of the serum folate levels, vitamin
B₁₂ levels, and red cells of underprivileged Cape Town
children receiving long-term anticonvulsant therapy. A
significantly lower level of serum folate was demonstrated
when comparison was made with other children in the
community. As no evidence of anaemia was found, it is felt
that the addition of extra folate to the therapeutic regimen
of the children studied, cannot be justified.


Folate deficiency after long-term anticonvulsant therapy
was first reported in 1952 and has since been extensively
studied. An investigation by Friedman into latent folate
deficiency in healthy underprivileged infants living in Cape
Town has shown an incidence of 11.6% in those followed
prospectively, and 7.1% in those investigated once only.
In another study Friedman et al. have drawn attention
to the prevalence of folate deficiency in young Cape Town
children suffering from gastro-enteritis. The objective of
the investigation here reported was to assess the effect of
long-term anticonvulsant therapy on the serum folate
levels and red cells of epileptic children drawn from the
same underprivileged community as those studied by
Friedman and her associates.

METHODS

All children in the group receiving anticonvulsant therapy
had attended a special epilepsy outpatient clinic for at
least 1 year. Good control of seizures and regular attend­
ance at the clinic for further supplies of tablets suggested
that these were administered as prescribed. Children in the
control group had attended hospital for the treatment of
minor traumatic lesions. None in this group had received
oral or parenteral drug therapy. All the children studied
were non-White. There were 39 in the epileptic group and
13 in the control group. Ages ranged from 2 to 12 years,
with a mean in the epileptic group of 6.6 years and in the
control group of 7.4 years. There was a male preponder­
ance in each group. In the epileptic group 17 had
histories which suggested that epilepsy might have been
secondary to perinatal or postnatal brain damage. In the
remainder, seizures were regarded as idiopathic. Thirty­
one received phenobarbitone alone, 3 were treated with
primidone, 3 with phenytoin, and 2 with a combination
of phenobarbitone and phenytoin. In every case standard
doses were administered 2 or 3 times a day.

Investigations were carried out on samples of venous
blood. The serum folate activity was assayed micro­biologically
using Lactobacillus casei in the method
described by Walters and Mollin. Serum vitamin B₁₂
concentration was assayed using the Euglena method. Haemoglobin,
packed cell volume, mean corpuscular volumes, mean corpuscular haemoglobin concentration, and
total white blood cells, were read on a Coulter counter
(Coulter Electronics Inc., Hileah, Florida, USA). White
cell differential counts were determined from peripheral
smears. Serum folate and vitamin B₁₂ levels were deter­
mined on all members of each group. The other values
were determined for all members of the epileptic group
and 6 of the control group.

RESULTS

The results (Tables I - IV) of serum folate estimations were
subjected to a U-test of statistical significance.* Levels in
the epileptic group were found to be significantly lower
than those in the control group (P = 0.0005). Serum vitamin B₁₂
levels were found to be significantly lower in
the control group (P = 0.001). The mean of every red
and white cell measurement was normal and few figures
were recorded outside the accepted normal range for each
measurement. In no case did the mean red cell volume
exceed 92 µm³ and hypersegmentation of polymorph
nuclei was not noted.

<table>
<thead>
<tr>
<th>TABLE I. SERUM FOLATE LEVELS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum folate (ng/ml)</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Epileptic group ... ... 39</td>
</tr>
<tr>
<td>Control group ... ... 13</td>
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</table>

<table>
<thead>
<tr>
<th>TABLE II. SERUM VITAMIN B₁₂ CONCENTRATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B₁₂ (pg/ml)</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Epileptic group ... ... 39</td>
</tr>
<tr>
<td>Control group ... ... 13</td>
</tr>
</tbody>
</table>

*Date received: 26 June 1973.
**DISCUSSION**

This study has shown that in Cape Town, as elsewhere, long-term treatment with anticonvulsants results in a significant reduction in serum folate levels. No associated anaemia or macrocytosis has been demonstrated. In other studies of epileptics on anticonvulsants, serum vitamin B₁₂ levels have been found to be normal. The finding in this study that control subjects had significantly lower serum levels of vitamin B₁₂ than epileptics was a surprise and cannot be readily explained.

The manner in which anticonvulsant therapy produces reduced serum folate levels remains uncertain. It is known that folate deficiency can be produced by phenobarbitone, phenytoin, and primidone, whether they are taken singly or in combination. It has been suggested that this may be brought about by interference with the intestinal absorption of folic acid. Recently, Benn et al. have demonstrated an alteration in the jejunal pH of patients on long-term anticonvulsants, which might cause malabsorption of folic acid. Phenyltoin inhibits the activity of small intestine conjugase which breaks down dietary folic polyglutamates into the monoglutamate form in which absorption takes place. However, the return of serum folate levels to normal after the oral administration of folic acid to patients on anticonvulsants makes it unlikely that interference with absorption is responsible to any major degree for the low levels found. The presently favoured hypothesis is that the induction of drug metabolizing enzymes in the liver by anticonvulsants creates an increased demand for folate which is a necessary cofactor in hydroxylation reactions. The administration of additional folic acid will thus facilitate the metabolic degradation of anticonvulsant drugs and this may account for the increased incidence of convulsions recorded in some epileptic patients so treated.

In this study, no anaemia or macrocytosis was found. In a study of epileptic patients on anticonvulsants, Reynolds et al. have shown significant evidence of megaloblastic haemopoiesis in bone marrow despite the presence of normal peripheral blood. Bone marrow examinations were not undertaken in the present study so that proof is lacking that the low folate levels have no adverse effect.

The question arises of the need for patients on anticonvulsants to receive extra folic acid. Haematological response after the administration of folic acid has been demonstrated, but there have also been some reports of an increase in convulsions. These have not been confirmed by more recent studies. In dealing with an ordinary outpatient population, simplicity of the dosage regimen is essential. When more than 2 drugs are prescribed together, regular administration as instructed is seldom achieved, and control of convulsions suffers. The addition of folate, or as has recently been suggested, yeast, in the form of yet another tablet, may create a treatment regimen too complicated for the mother. This practical problem, together with the present lack of evidence that reduced folate levels in the absence of anaemia are in any way detrimental to the child, appears to militate against the routine prescription of additional folate for epileptic children drawn from Cape Town's underprivileged population.

I am indebted to Miss R. Pearl, Mrs D. Maxwell, Mrs P. Lundwall and Miss L. Neville, without whose technical assistance this study would not have been possible. Permission to publish has been granted by the Medical Superintendent of the Hospital.

**REFERENCES**


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**TABLE III. RED CELL MEASUREMENTS**

<table>
<thead>
<tr>
<th></th>
<th>Hb (g/100 ml)</th>
<th>PCV (%)</th>
<th>MCV (µm³)</th>
<th>MCHC (%)</th>
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</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>12.8</td>
<td>37</td>
<td>79.4</td>
<td></td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>11.0 - 14.8</td>
<td>32.9 - 42.5</td>
<td>68 - 92</td>
<td></td>
</tr>
<tr>
<td><strong>Epileptic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>group</strong></td>
<td>13.4</td>
<td>38.1</td>
<td>81.2</td>
<td></td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>12.6 - 14.0</td>
<td>35.8 - 39.5</td>
<td>72 - 86</td>
<td></td>
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</tbody>
</table>

**TABLE IV. WHITE BLOOD CELLS**

<table>
<thead>
<tr>
<th></th>
<th>Cells/mm³</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>9413</td>
<td>5900 - 14 100</td>
<td>6400 - 17 300</td>
<td></td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Epileptic</strong></td>
<td>9900</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>9 900</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>