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ON THE PATHOGENESIS OF MUSCLE-MINDNESS DURING PHENYLKETONURIA

Translation No. 1758

May 1966

U. S. NAVY

FORT SISSETON, FALCONER, MONTANA
ON THE PATHOGENESIS OF FEEBLE-MINDEDNESS DURING PHENYLKETONUREA

(Following is the translation of an article by F. Lenneweh and L. Eurlich, Marburg, published in the German language periodical (Klinische Wochenschrift) Clinical Weekly, 40th year, book 5, March 1, 1962, pages 16-17. Translation performed by Constance L. Lust.)

Among the types of feeble-mindedness caused by metabolic alterations phenylketonurea has obtained a special importance. It has been studied very extensively and is one of the hereditary diseases of metabolism which has been explained best in chemical terms. In 50 million inhabitants in a country one has to figure on 1500 cases of phenylketonurea. To this number one must add about 50 newborns each year.

A decrease in activity of phenylalanine oxidase system during this illness results in an increase of from 20-30 times the concentration of phenylalanine in plasma compared to normals. Feeble-mindedness is developed already in infancy and in most cases an intelligence quotient of less than 20 is found. However, there is as yet no uniform concept about the question, whether phenylalanine itself or other phenoderivatives such as phenylacetic acid or similar products of intermediary metabolism, represent the noxious agent. At the same time feeble-mindedness can be diminished therapeutically, or even prophylactically prevented, by substituting an amino acid mixture without phenylalanine for dietary protein. This procedure is being carried out successfully in several places. The dietary results fully substantiate the pathogenetic presentations.

We have obtained results in 14 cases of untreated phenylketonurea, which lead one to suspect, that the reasons for the pathogenic observations about the genesis of feeble-mindedness must be extended (expanded). Utilizing column chromatography according to Stein and Moore, we have analysed the plasma before institution of dietary therapy. The results we obtained are summarized in tables 1 and 2. If one focuses on the essential amino acids -histidine included- and relates the values found with the normal, average-values (table 1), then the surprising fact becomes apparent that the essential amino acids in part are reduced 50% below normal. We recently reported similar results in two cases of phenylketonurea (5). Only Knox (4) reported that in a column chromatogram of Moore and Stein such a variation occurred.

Our results lead to the question; what mechanism is responsible for the decrease in the essential amino acids. Our knowledge about amino acid transport is inadequate to be able to answer this question at this time. Tubular reabsorption does not decrease, as we demonstrated in clearance studies (5). It can be assumed that the high concentration of phenylalanine in the plasma competitively inhibits the transport of other amino acids and in this way causes metabolic conditions which are presently inexplicable. This has been demonstrated in brain sections in vitro (6).
It is easier to explain the tyrosine decrease which has been known
longer. This is presumably because of the blocked defective enzyme which
is responsible for converting phenylalanine to tyrosine. Tyrosine is not
responsible as a cause of intractability. This was demonstrated in many
experiments where tyrosine was substituted. In this case one of the es-
ential amino acids is not involved.

The decrease of the essential amino acids in plasma on the other hand
offered an opportunity to attempt to explain intractability during phenyl-
ketonuria. It is possible that the functional differentiation of brain
cells in particularly dependent on an optimum concentration of essential
building blocks.

The observations (3) that mothers with phenylketonuria can have mentally
normal children and that dietary therapy appears to have no effect after
the third year of life leads one to believe that a sensible period exists
for cerebral damage occurs (1). This concept is derived from development
physiology and may be applicable for pathologic processes. In this area
of pathology it would seem that the sensitivity against toxic is limited
to a definite time. This time-period for phenylketonuria lies between 4
months of age to the end of the third year. This coincides with the period
of myelination of the brain. On the other hand it may be assumed that
other disturbances are occurring simultaneously in protein synthesis of
brain cells, especially when one remembers that myelination is dependent
on the intact glial cells.

The various forms of metabolic intractability point to the fact that dif-
ferent disturbances in metabolism lead to the complex phenomenon of intractability.
The defective intelligence represents a uniform reaction to heterogeneous
damage.

Summary: During phenylketonuria a 20-35 fold elevation of phenylalanine
is balanced by a compensative decrease of the other essential amino acids
in the plasma. Values of 50% of normal were representative. A possible
meaning of this deficit for the pathogenesis of intractability is discussed.

Literature

[References and citations follow]
Table 1

Concentration of plasma amino acids in 11 untreated cases of phenylketonuria and feeble-mindedness

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<thead>
<tr>
<th>Nr.</th>
<th>Name, Alter</th>
<th>Val</th>
<th>Hya</th>
<th>Leu</th>
<th>Ileu</th>
<th>Lys</th>
<th>Met</th>
<th>Thr</th>
<th>Trp</th>
<th>Tyr</th>
<th>Glu</th>
<th>Gln</th>
<th>Asp</th>
<th>Ser</th>
<th>Gly</th>
<th>Ala</th>
<th>Pro</th>
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<td>R. Sch. 1884, 4 Jahre</td>
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<td>7.</td>
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</table>

Table 2

Average values and standard deviations of amino acid concentrations in plasma of the cases of table 1

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<tr>
<th>Aminosaure</th>
<th>Val</th>
<th>Hya</th>
<th>Leu</th>
<th>Ileu</th>
<th>Lys</th>
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</table>
Figure 1

Average values of essential amino acids in plasma of 14 untreated cases of phenylketonuria—feeble mindedness compared to the average values of healthy individuals (=100%).

Figure 2

Average values of the non-essential amino acids in plasma of 14 untreated cases of phenylketonuria—feeble mindedness compared to average values for healthy individuals (=100%).