Disorders of magnesium metabolism in epilepsy

HORACIO M. CANELAS, LUÍS MARQUES DE ASSIS, AND FRANCISCO B. DE JORGE

From the Departments of Neurology and Medicine, University of São Paulo
School of Medicine, São Paulo, Brazil

Clinical observations in man (Griffiths, 1947; Randall, Rossmeisl, and Bleifer, 1959; Hanna, Harrison, MacIntyre, and Fraser, 1960; Vallee, Wacker, and Ulmer, 1960) and experimental investigations in animals (Kruse, Orent, and McClum, 1932) have shown that magnesium (Mg) depletion causes a marked irritability of the nervous system, eventually resulting in epileptic seizures. The possibility that convulsions may occur in Mg deficiency led some investigators to study the metabolism of this metal in the epilepsies, and a trend to low blood concentrations was usually found (Denis and Talbot, 1921; Blumgarten and Rohdenburg, 1927; Hirschfelder and Haury, 1934, 1935; Haury, 1942; Suter and Klingman, 1955). In successive studies, Hirschfelder and Haury (1935, 1938) found a lowering of Mg and a rise of potassium in the blood of epileptic patients, leading to a definite increase in the K/Mg ratio, proportional to the severity of the disease. Concerning the metabolism of magnesium in the cerebrospinal fluid, Cohen (1927), McCance and Watchorn (1931), and Greenberg and Aird (1938) found in epilepsy the same range of magnesium levels as in other nervous diseases. Hirschfelder and Haury (1938) found low concentrations of Mg in the cerebrospinal fluid of epileptic patients, though the levels were higher than in the blood.

These findings, associated with the fact that Mg is a known depressor of the central nervous system and is involved in several enzymatic processes, including the synthesis of acetylcholine, were not appreciated by some authorities in the field of epilepsy, even when the neurochemistry of this disease was analysed (Tower, 1960).

MATERIAL AND METHODS

Two groups of patients, including 83 cases of epilepsy and 34 of mental disease (mostly schizophrenic), were studied.

The neurological examination was normal in all the epileptic patients and no sign of intracranial hypertension was present. They were from 9 to 56 years old; 44 were males, and 39 females; 67 were white, nine were negroes, and seven were mulattoes. Convulsive manifestations were reported by 71 patients; in 14 the seizures had a centroencephalic pattern and, in 57 they resulted from diffusion of focal discharge; among the latter, 11 patients showed concomitant psychomotor fits. Four patients had only petit mal absences; one had myoclonic petit mal; two had only psychomotor fits. In four cases the seizures were not well characterized from the clinical viewpoint. In one case no epileptic manifestations were reported but the electroencephalogram evidenced a temporal focus.

The epileptic patients were divided into two subgroups. In the first set (cases 1 to 80), blood (79 cases) and cerebrospinal fluid (78 cases) were sampled to determine Mg levels in the period between seizures. In the second set of patients, blood (eight cases) and cerebrospinal fluid (four cases) were sampled immediately after the seizure or during status epilepticus.

Electroencephalograms were recorded in 76 cases. In 25 patients the tracings were normal, in 36 focal abnormalities were recorded, and in 15 the changes were diffuse.

In the mental patients, blood (34 cases) and cerebrospinal fluid (nine cases) were sampled just before and after the electroshock (complete crisis) in the post-convulsive coma.

Cerebrospinal fluid was always collected through cisternal puncture. Magnesium was determined according to the method of yellow titan in alkaline solution, slightly modified (De Jorge, Silva, and Cintra, 1964b). The results were compared with the normal concentrations determined by the same method (De Jorge, Canelas, and Zanini, 1964a).

RESULTS

The results, submitted to conventional statistical analysis, are summarized in Tables I, II, and III.

The existence of hypomagnesaemia in epilepsy, at the interseizure period, was confirmed (Table I). The study of the statistical correlations showed that the blood Mg concentration was lower when the time elapsed after the last convulsion was shorter (Table II).

Although no significant correlation was found with the frequency of fits, our results agree, in a general way, with the findings of Hirschfelder and Haury (1935, 1938). The frequency of fits showed a
Disorders of magnesium metabolism in epilepsy

TABLE I
AVERAGE CONCENTRATIONS OF MAGNESIUM (MEq./L) IN THE BLOOD AND CEREBROSPINAL FLUID IN CASES OF EPILEPSY

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of Cases</th>
<th>Mean ± S.D.</th>
<th>Range</th>
<th>Significance of the Difference of Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood/Epilepsy</td>
<td>79</td>
<td>1.868 ± 0.202</td>
<td>1.466 - 2.429</td>
<td>r = 9.34, d.f. 89, P &lt; 0.001</td>
</tr>
<tr>
<td>Normal</td>
<td>130</td>
<td>2.087 ± 0.067</td>
<td>1.916 - 2.185</td>
<td></td>
</tr>
<tr>
<td>Cerebrospinal/Epilepsy</td>
<td>78</td>
<td>2.419 ± 0.270</td>
<td>1.721 - 2.986</td>
<td>r = 4.747, d.f. 90, P &lt; 0.001</td>
</tr>
<tr>
<td>Normal</td>
<td>36</td>
<td>2.266 ± 0.061</td>
<td>2.178 - 2.360</td>
<td></td>
</tr>
</tbody>
</table>

1 t test for independent samples assuming unequal variances (Dixon and Massey, 1957).

The concentrations of Mg in the blood and in the cerebrospinal fluid of patients with normal, diffuse, or focal electroencephalographic patterns did not show significant differences (Table III). Likewise, the concentrations of blood and cerebrospinal fluid magnesium in post-convulsive cases and in status epilepticus were not significantly different from the levels of the same patients at the interseizure period (mean difference in the blood = -0.035 ± 0.297 mEq./l., t = 0.327; 0.8 > P > 0.7; mean difference in the cerebrospinal fluid = -0.071 ± 0.252 mEq./l., t = 0.563; 0.7 > P > 0.6).

In the second group of patients, after electroshock-induced convulsions the Mg contents showed an increase both in the blood and in the cerebrospinal fluid (mean difference in the blood = +0.472 ± 0.201; t = 13.681; P < 0.001; mean difference in the cerebrospinal fluid = +0.307 ± 0.121; t = 7.595; P < 0.001).

TABLE III
AVERAGE CONCENTRATIONS OF MAGNESIUM IN THE BLOOD AND CEREBROSPINAL FLUID IN DIFFERENT ELECTROENCEPHALOGRAPHIC PATTERNS AND SIGNIFICANCE OF THE DIFFERENCES BETWEEN THEM

<table>
<thead>
<tr>
<th>E.E.G.</th>
<th>No.</th>
<th>Mean ± S.D.</th>
<th>Significance of the Differences (t)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse</td>
<td>15</td>
<td>1.895 ± 0.231</td>
<td>Focal = 0.22, Normal = 0.253</td>
</tr>
<tr>
<td>Focal</td>
<td>25</td>
<td>1.879 ± 0.210</td>
<td>Normal = 0.253, Diffuse = 0.85</td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse</td>
<td>14</td>
<td>2.395 ± 0.472</td>
<td>Focal = 0.355</td>
</tr>
<tr>
<td>Focal</td>
<td>25</td>
<td>2.439 ± 0.314</td>
<td>Normal = 0.631, Diffuse = 0.34</td>
</tr>
</tbody>
</table>

1 As the whole level of significance adopted was α = 5%, we worked in the individual independent tests, with the level α = 5/3% (Steel and Torrie, 1960).

DISCUSSION

Notwithstanding the numerous studies on Mg metabolism, their interpretation is still obscure. Magnesium is the fourth most abundant cation of the human body. If only the intracellular component is analysed, Mg is the second most frequent cation, following potassium (MacIntyre, 1959; Clough, 1960). The views on the interpretation of the Mg depletion syndrome are still conflicting, the condition being ascribed either to a fall of the intracellular Mg, with a lowering of the intracellular/extracellular ratio (Clough, 1960), or to a depletion of the extracellular concentration, in a way very similar to the behaviour of sodium (Suter and Klingman, 1955).

If an inhibition of acetylcholine synthesis by Mg was assumed to occur at the cerebral level, as it happens at the periphery (Del Castillo and Engbaek, 1954; Hutter and Kostial, 1954; Maurat, 1958), then it could be understood why, in the Mg depletion syndrome and in epilepsy, acetylcholine is more

negative correlation with the time after the last seizure, as could be expected (Table II). However, the low level of significance (P ≈ 0.04) of this coefficient may explain the absence of a negative correlation between the Mg content and the frequency of fits. Concerning the cerebrospinal fluid, however, our results did not quite agree with those of the literature since a significant increase of the Mg content in this fluid was found (Table I). An unexpected finding was the positive correlation between the Mg concentration in the blood and in the cerebrospinal fluid (Table II). In this fluid the Mg contents were not significantly correlated with either the frequency or with the time interval after the last seizure.
evidently mere leptic crisis, probably opposite convulsions; elicited in animals. Sacco in such Mg already increase. Nevertheless, Wacker convulsions, in found to the compartment.

epilepsy, the Mg concentration of changes metabolic infusion of to the higher concentration in than in the blood. This is of knowledge concerning Mg metabolism in general. Kemény, Boldizsár, and Pethes (1961), studying in dogs the distribution of cations in the blood and cerebrospinal fluid after infusion of saline solutions, found that Mg is unable to cross the blood-cerebrospinal fluid barrier in normal conditions. This fact is of fundamental significance, for it leads to the assumption that the changes of Mg in the cerebrospinal fluid depend on metabolic processes which take place in the nervous tissue. On these grounds, it could be assumed that, in epilepsy, the Mg concentration in the cerebrospinal fluid would rise as a consequence of its transference from the intracellular to the extracellular compartment.

In the mental patients, after electroshock-induced convulsions, apparently paradoxical results were found in the blood, since the Mg content showed an increase. Nevertheless, this is not a new finding. Wacker (see Walker and Walker, 1936) had already found a marked rise of the blood Mg as a result of forceful muscular activity electrically elicited in animals. Sacco (1957) found a fall in the blood potassium content just after electroshock-induced convulsions; as the behaviour of this cation is opposite to Mg, one could actually expect a rise of Mg in such conditions.

The interpretation of our results, however, is evidently mere conjecture, because, during the epileptic crisis, changes in the blood-cerebrospinal fluid barrier probably occur. Moreover, our material comprises two groups of cases evidencing very distinct patho-physiological features, namely, epileptic patients with disorders of Mg metabolism, and schizophrenics with a seemingly normal Mg metabolism. In any event, further studies, including the use of curare during the performance of electroshock, will eventually throw more light on the problem.

SUMMARY

Magnesium metabolism was studied in 83 epileptic patients and in 34 cases of mental disease (mostly schizophrenics) submitted to electroshock. In the first group of patients, the Mg contents of blood and cerebrospinal fluid were compared with the severity of the epilepsy and the electroencephalographic pattern.

The following conclusions were drawn. (1) At the interseizure period the Mg concentration is low in the blood serum and high in the cerebrospinal fluid. (2) The Mg level in the blood is as low as the time elapsed after the last seizure is shorter. (3) There are no significant differences in the Mg levels in the blood and cerebrospinal fluid when patients with normal or abnormal electroencephalographic patterns are compared. (4) In the mental patients the Mg concentrations increase both in the blood and in the cerebrospinal fluid just after the complete crisis elicited through electroshock.

A tentative interpretation of these results is advanced, especially based on the depolarizing effect of hypomagnesaemia and on the possibility of a greater liberation of acetylcholine under such condition.

We are deeply indebted to Dr. Rubens Murillo Marques, from the Department of Statistics of the University of São Paulo School of Hygiene and Public Health, for his advice and technical assistance in the execution of the statistical analysis of our material.

REFERENCES

Disorders of magnesium metabolism in epilepsy


The June 1965 Issue

THE JUNE 1965 ISSUE CONTAINS THE FOLLOWING PAPERS


Studies in man and cat of the significance of the H wave R. F. MAYER and C. MAWDSLEY

Serum cholesterol linoleate levels in multiple sclerosis R. W. R. BAKER, HAZEL SANDERS, R. H. S. THOMPSON, and K. J. ZILKHA

Studies of blood groups, genetic linkage, trait association, and chromosomal pattern in multiple sclerosis DAVID C. POSKANZER, KURT SCHAPIRA, RONALD A. BRACK, and HENRY MILLER

Independence of central controls of vascular and sweat gland responses in the paw of the cat B. J. PROUT, J. H. COOTE, and C. B. B. DOWNMAN

Anatomical pathways related to the clinical findings in aneurysms of the anterior communicating artery JAMES ARTHUR TAREN

Occlusion of the vertebral artery TETSUO TATSUMI and HENRY A. SHENKIN

Studies by fluorescence photography of papilloedema in malignant hypertension C. T. DOLLLERY, C. M. MAILER, and J. V. HODGE

Hydrodynamic mechanism of syringomyelia: its relationship to myelocèle W. JAMES GARDNER

Progressive multifocal leucoencephalopathy S. B. CHANDOR, L. S. FORNO, and N. A. WIVEL

Myoclonus and ataxia occurring in a family HAROLD JACOBS

Squamous cell carcinoma developing in an intracranial epidermoid cyst (cholesteatoma) H. FOX and E. A. SOUTH

Neuropsychiatric manifestations of chronic manganese poisoning S. ABD EL NABY and M. HASSANINE

Book reviews

Copies are still available and may be obtained from the PUBLISHING MANAGER,

BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, W.C.1, price 18s. 6d.
Disorders of magnesium metabolism in epilepsy

Horacio M. Canelas, Luís Marques De Assis and Francisco B. De Jorge

*J Neurol Neurosurg Psychiatry* 1965 28: 378-381
doi: 10.1136/jnnp.28.4.378

Updated information and services can be found at:
http://jnnp.bmj.com/content/28/4/378.citation

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/