# BIOCHEMISTRY OF MENINGIOMAS

## COPPER, CERULOPLASMIN, MAGNESIUM AND SULFUR CONTENTS IN THE BLOOD SERUM, AND CALCIUM, PHOSPHORUS, COPPER, MAGNESIUM, SODIUM AND POTASSIUM CONTENTS IN THE TUMORAL TISSUE

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A series of investigations has evidenced, in the blood serum of patients with several types of neoplasms, an increase of the concentrations of sulfur [15, 16, 17] and copper [22, 25, 28, 29, 30], this latter being most likely related to the non-ceruloplasmin fraction [15, 16, 17]. Data on the magnesemia in such cases are variable [15, 16, 19, 31].

In tumors grown in non-nervous tissues an increase of Cu has also been found [15, 16, 17, 21, 26, 33]. In the rat hepatoma a rise of Mg, K and Na was observed [27]. Regarding the neoplasms of the central nervous system, Grashchenkov and Hekht [20] found an increase of Cu contents. Alexander and Myerson [1], comparing the composition of a spongioblastoma with the normal grey matter, found higher values of K, lower values of Mg and P, and similar levels of Na. Higher concentrations of Ca were found in two-thirds of 25 gliomas studied by Wender and Hierowski [32]; in 60 per cent of the cases Na was increased, while K was lowered; in a third of cases, however, K levels were higher than in normal brain tissue. Studying the biochemistry of 9 astrocytomas, 10 glioblastomas and 10 medulloblastomas as compared to the normal brain tissue, Canelas et al. [6] found higher contents of Ca, Cu and Mg, irrespective of the histological pattern; the levels of Na were higher in astrocytomas and glioblastomas, K showed a trend to higher levels in astrocytomas, and the values of P were higher in glioblastomas and medulloblastomas.

In a survey of the literature on meningiomas we have only found studies on some organic components of the tumors, such as fatty acids, phospholipides, lipides in general, and mucopolysaccharides.

A study has been made of Cu, ceruloplasmin, Mg and S contents in the blood serum of patients with meningiomas, as well as of Cu, Mg, Ca, P, K and Na concentrations in the tumor itself. The results were compared with the normal values in the serum and in the dura mater (it is well

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known that meningiomas arise in the arachnoid membrane; however, owing to the difficulties for the isolated removal of the arachnoid, the concentrations in the normal dura mater of human brain [5] were used as control in the comparative studies, a method already adopted by Cain et al. [4] in a similar investigation).

## MATERIAL AND METHODS

Specimens of 9 meningiomas were studied. Seven tumors were in the supratentorial region and two were intraspinal in location (Table 1). These latter and one intracranial neoplasm were of the psammomatous type; from the remaining 6 cases, 4 were of the meningotheliomatous type and 2 of the fibroblastic type, according to Bailey and Bucy [2] classification.

Eight patients were female; 8 were white and 1 was negro. Ages varied from 23 to 60 years. Symptoms had lasted from 1 to 10 years. The largest diameter of the intracranial tumors varied between 5 and 8 cm.; in the intraspinal meningiomas it was of 2 cm. Calcifications were seen at the X-ray examination in 4 cases of intracranial tumor (Table 1).

In the blood serum of 8 patients the concentrations of Cu, ceruloplasmin, Mg and S were determined. In the tumoral tissue of the same patients plus one Cu, Mg, Ca, P, Na and K contents were determined. The results were submitted to conventional statistical analysis [3].

Immediately after remotion the tumoral samples were placed in a glass container with a plastic cover and put in a freezer. Afterwards each sample was collected in a porcelain crucible and heated at 100°C for approximately hr. until a constant weight was reached. The samples were ashed in a furnace overnight at 550°C. The ashes were dissolved in a known volume of 2N-HCl. In this solution Na and K were determined by flame spectroscopy in a Coleman model 20; Ca by the Clark and Collip [7] method; P by that of Fiske and Subbarow [18]; Mg by the yellow titan method [13]; S by the turbidimetric method described elsewhere [14]. Copper was determined by the diethyldithiocarbamate method [8]; all reagents were tested for copper contamination; the water used in all operations was redistilled

| Case No. | File No. | Age-Sex-Race | Duration of symptoms (years) | Location | Largest diameter (cm.) | Calcif. (X-rays) | Histologic type |
|---|---|---|---|---|---|---|---|
| 1 | 4675 | 60-F-W | 10 | Frontal | 08 | + | Meningoth. |
| 2 | 6236 | 45-F-W | 15 | Temporal | 07 | 0 | Meningoth. |
| 3 | 6264 | 45-F-W | 01 | Spinal | 02 | − | Psammomat. |
| 4 | 6273 | 55-F-W | 02 | Temporal | 07 | + | Meningoth. |
| 5 | 6287 | 59-F-W | Unknown | Parietal | 06 | 0 | Meningoth. |
| 6 | 6366 | 27-F-N | 08 | Parietal | 06 | + | Psammomat. |
| 7 | 6685 | 63-F-W | 01 | Spinal | 02 | − | Psammomat. |
| 8 | 6773 | 41-F-W | 05 | Temporal | 05 | + | Fibroblast. |
| 9 | 7247 | 23-M-W | 02 | Parieto-occipital | 08 | 0 | Fibroblast. |

*Table 1 — Material: F = female; M = male; W = white; N = negro; + = present; 0 = absent; − = not searched for.*

in an all-glass distiller; the glassware used for analytical determinations was soaked overnight in chromic acid and washed thoroughly with redistilled water; the material was boiled in a 20 per cent HCl solution for 2 hr., washed with redistilled water, and put in an oven to dry within a glass container.

The results are expressed in mequiv./100 ml. (blood serum) or mequiv./100 g. dry weight (tumoral tissue) for Mg, Na, K; mg/100 ml. or mg/100 g. for Ca, P, S; μg/100 ml. or μg/100 g. for Cu; and mg/100 ml. for ceruloplasmin. The results were compared with the normal values in the blood serum [8,10,11,12] and in the human dura mater [5].

## RESULTS

The blood serum values of Cu, ceruloplasmin, Mg and S were significantly higher than the normal levels (Table 2). Although the correlation between Cu and copper-oxidase was highly significant ($r = 0.9$) the difference of means of Cu is more significant than that of ceruloplasmin.

| | Case No. | Copper (μg/100 ml) | Ceruloplasmin (mg/100 ml) | Magnesium (mequiv/100 ml) | Sulphur (mg/100 ml) |
|---|---|---|---|---|---|
| Meningiomas | 01 | 164 | 38.4 | 2.659 | — |
| | 02 | 315 | 36.5 | 2.272 | 2.528 |
| | 03 | 310 | 35.0 | 2.500 | 2.349 |
| | 04 | 266 | 40.0 | 2.950 | 1.953 |
| | 05 | 226 | 58.0 | 2.272 | 1.569 |
| | 06 | 171 | 30.2 | 2.500 | 1.957 |
| | 07 | 229 | 35.8 | 1.986 | 2.454 |
| | 09 | 180 | 32.6 | 3.267 | 2.066 |
| | Mean | 233±60 | 38.3±8.5 | 2.551±0.408 | 2.124±0.340 |
| Normal values | Mean | 108.1±9.7(11) | 33.4±3.1(9) | 2.087±0.067(12) | 1.222±0.193(13) |
| | n | 80 | 65 | 130 | 40 |
| | Method | Diethyldithiocarbamate(10) | Houchin(23) | Yellow titan(16) | Turbidimetric(17) |
| | Difference | 124.9 | 4.9 | 0.464 | 0.902 |
| | t | 9.234 | 3.286 | 11.252 | 10.084 |
| | P | <0.001 | <0.001 | <0.001 | <0.001 |

*Table 2 — Concentrations of chemical constituents in the blood serum, and comparison with the normal values. Normal mean values: into parentheses, the reference numbers.*

In the tumoral tissue, the average concentrations of all the elements studied were significantly higher than those of the normal dura mater of human brain (Table 3). If this comparison was made considering apart the 3 psammomatous and the 6 meningotheliomatous or fibroblastic meningiomas, the same result was found, except for Ca content in the latter group, which did not differ statistically from the levels of normal meninx.

| | Case No. | Calcium (mg/100 g) | Phosphorus (mg/100 g) | Copper (μg/100 g) | Magnesium (mequiv/100 g) | Sodium (mequiv/100 g) | Potassium (mequiv/100 g) |
|---|---|---|---|---|---|---|---|
| Meningiomas | 1 | 88 | 734 | 1,095 | 4.61 | 23.51 | 18.66 |
| | 2 | 280 | 875 | 1,541 | 7.05 | 46.81 | 24.87 |
| | 3 | 13,100 | 10,028 | 4,823 | 43.38 | 40.39 | 14.50 |
| | 4 | 87 | 4.485 | 702 | 3.09 | — | — |
| | 5 | 73 | 715 | 877 | 5.21 | 48.89 | 37.63 |
| | 6 | 6,603 | 2.578 | 1,469 | 48.48 | 41.62 | 17.22 |
| | 7 | 511 | 1,818 | 4,407 | 21.02 | 23.25 | 26.43 |
| | 8 | 17 | 473 | 538 | 3.84 | 27.02 | 17.61 |
| | 9 | 52 | 164 | 206 | 2.28 | 8.44 | 8.49 |
| | Mean | 2,312±4,575 | 2,430±3,153 | 1,740±1,673 | 15.44±18.22 | 32.49±14.07 | 20.68±9.76 |
| Normal dura mater | Mean | 120±107 | 68±34.5 | 250±109 | 0.61±0.37 | 1.63±0.27 | 3.68±0.66 |
| | n | 18 | 18 | 18 | 18 | 18 | 18 |
| | Difference | 2,192 | 2,362 | 1,490 | 14.83 | 30.86 | 17.00 |
| | t | 2.074 | 3.243 | 3.840 | 3.524 | 9.554 | 7.550 |
| | P | $= 0.04$ | $= 0.001$ | $< 0.001$ | $< 0.001$ | $< 0.001$ | $< 0.001$ |

*Table 3 — Concentrations of chemical constituents (dry weight) in tumoral tissue and comparison with the concentrations in normal human dura-mater.*

The average concentrations of the elements in the psammomatous meningiomas were compared to the averages in the other types as a whole (Table 4). The levels of Ca, Cu and Mg were significantly higher in the psammomatous type than in the others.

| Elements | Histologic type | | Difference of means | t | |
|---|---|---|---|---|---|
| | Psammomatous (3 samples) | Meningotheliomatous and fibroblastic (6 samples) | | | |
| Ca (mg/100 g) | 6,738±6,296 | 99±73 | 6,639 | 2.790 | 0.05 > P > 0.02 |
| P (mg/100 g) | 4,808±4,537 | 1,241±1,609 | 3,567 | 1.815 | 0.2 > P > 0.1 |
| Cu (μg/100 mg) | 3,566±1,828 | 826±443 | 2,740 | 3.702 | 0.001 > P > 0.01 |
| Mg (mequiv/100 g) | 37.63±14.61 | 4.35±1.69 | 32.28 | 5.930 | < 0.001 |
| Na (mequiv/100 g) | 35.09±10.27 | 30.93±16.96 * | 4.16 | 0.378 | 0.8 > P > 0.7 |
| K (mequiv/100 g) | 19.38± 6.25 | 21.45±10.77 * | 2.07 | 0.298 | 0.8 > P > 0.7 |

*Table 4 — Mean concentrations of chemical constituents (dry weight) in the group of psammomatous meningiomas and in the other types (meningotheliomatous and fibroblastic) as a whole: * Five samples.*

Significant correlations were found between the contents of Ca and P, Ca and Mg, P and Cu, and Cu and Mg in the tumoral tissue of the whole group, while the correlations of Ca and Cu, and P and Mg showed a trend ($0.1 > P > 0.05$) to significant levels.

No significant correlation was found between the concentration of the elements in the neoplastic tissue and the duration of symptoms or the tumor size, except a negative correlation ($r = -0.98$) between Cu levels and tumor size, and a trend to a negative correlation between tumor size and P levels ($r = -0.5$) and Mg ($r = -0.6$).

The concentrations of Cu and Mg in the blood serum did not evidence correlation with those in the tumoral tissue.

## COMMENTS

Concerning the blood serum levels of Cu and S our results confirm the literature data pointing to an increase of them in patients with neoplastic diseases [15, 16, 17, 22, 25, 28, 29, 30]. The increased magnesemia is in accordance with the findings in fibroleiomyomas and cancer of the breast and larynx [15, 16, 17].

In the tumoral tissue our results also agree with the findings of increased concentrations of Ca [6, 32], Cu [6, 15, 16, 17, 21, 26, 33], Na [6, 27, 32], Mg [6, 27] and K [27] in various kinds of neoplams.

Ca levels in the tumoral tissue showed an extremely wide range of variation. Nevertheless, it must be emphasized that significantly higher

values were found in the three cases of psammomatous tòpe than in the meningotheliomatous and fibroblastic types as a whole (table 5). This findings agrees with the results of Huh [24]: calcification was histologically detected in 100 per cent of 52 psammomatous meningiomas, while in 317 meningotheliomatous or fibroblastic meningiomas the proportion of calcification was 31 per cent (the difference of these percentages is highly significant).

Wender and Hierowski [32], studying the biochemistry of gliomas, did not find a correlation between Ca contents and histological signs of calcification. In our material, likewise, no definitive correlation was found between Ca level and presence of calcifications on the X-ray pictures.

The sole biochemical study comparing meningiomas and normal meninges that we could find in a survey of the literature is the investigation of Cain et al. [4] on the concentration of lipides, particularly the proportion of hydrocarbons. These authors found a greater percentage of lipides in the meningiomas than in the normal meninges. Moreover, the composition of hydrocarbons in the two tissues was different and the neoplasm contained almost five times as much squalene as the membrane; this hydrocarbon is most likely involved in the cholesterol synthesis.

The findings of Cain et al. [4] and our results in the study of the inorganic elements are probably related to a difference in the metabolic activity of the normal pachymeninx and the meningeal neoplasm.

## SUMMARY

The concentrations of Cu, ceruloplasmin, Mg and S in the blood serum of eight patients with meningioma were significantly higher than the normal levels. Ca, P, Cu. Mg, Na and K contents in the tumour itself of the same patients plus one were compared with the concentrations in the normal dura mater of human brain. The contents of all elements were significantly increased, except the mean Ca in six meningotheliomatous or fibroblastic meningiomas when this group was studied apart. The psammomatous tumours had higher concentrations of Ca, Cu and Mg than the other histologic types. No significant correlation was found between the concentrations of the element in the neoplastic tissue and the duration of symptoms or the tumour size, except a negative correlation between Cu levels and tumour size.

## RESUMO

*Bioquímica dos meningiomas: conteúdo de cobre, ceruloplasmina, magnésio e enxôfre no sôro sangüíneo, e conteúdo de cálcio, fósforo, cobre, magnésio, sódio e potássio no tecido tumoral.*

As concentrações de Cu, ceruloplamina, Mg e S no sôro de 8 pacientes com meningioma foram significantemente mais elevadas que os níveis normais. Os teores de Ca, P, Cu, Mg, Na e K no próprio tumor dos mesmos

pacientes e de um outro foram comparados com as concentrações na dura máter normal do cérebro humano. Os valôres de todos os elementos foram significantemente mais altos no tecido tumoral, exceto o conteúdo médio de Ca em 6 meningiomas meningoteliomatosos ou fibroblásticos, quando êste grupo foi estudado à parte. Os tumores psamomatosos mostraram maiores concentrações de Ca, Cu e Mg que os outros tipos histológicos. Não foi verificada correlação significante entre as concentrações dos elementos no tecido neoplásico e a duração dos sintomas ou o volume do tumor, exceto uma correlação negativa entre os níveis de Cu e o volume do tumor.

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