Concentrations of Ag, Al, Au, Bi, Cd, Cu, Pb, Sb, and Se in Cerebrospinal Fluid of Patients with Cerebral Neoplasms

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We measured the concentrations of nine trace elements in cerebrospinal fluid of 11 patients with malignant brain tumors, 11 with benign brain tumors, and 10 control patients, using flameless atomic absorption spectrophotometry. The mean and standard deviation for these concentrations (µg/L) in the control group were 5.1 ± 2.9 (silver), 326.6 ± 171.2 (aluminum), 38.5 ± 32.2 (gold), 36.6 ± 23.7 (bismuth), 1.5 ± 1.3 (cadmium), 39.8 ± 24.7 (copper), 15.7 ± 11.5 (lead), 20.9 ± 3.8 (antimony), and 19.1 ± 13.3 (selenium). Concentrations of silver and lead were markedly increased in patients with malignant cerebral neoplasms. The malignant-tumor/control patient concentration ratios were 2.31 for silver and 2.11 for lead. We observed no significant differences between the results for the benign tumor patients and the control group.

Additional Keyphrases: atomic absorption spectrophotometry · cancer · trace elements · brain tumors

Trace elements in blood and urine have been amply studied, but reports dealing with these elements in cerebrospinal fluid (CSF) are few. We found none on the concentrations of trace elements in the CSF of patients with cerebral neoplasms. Many neurological and other diseases are associated with changes in the chemical composition of the CSF. Trace elements play an important role in the metabolic, biosynthetic, and biochemical activities in the living cells. Malignancy-induced imbalances in these activities often produce abnormal values for these elements in the tumor cells or the surrounding biological fluids. Indeed, the concentrations of copper (1–4), zinc (5, 6), and selenium (7) in serum have been related to different types of malignancies. The iron, antimony, chromium, cobalt, and scandium content of DNA in sarcoma M-1 also varies widely as the disease progresses (8). Schicha et al. (9) found more cobalt and selenium in benign cerebral tumor tissues than in normal brain tissues; other elements (iron, rubidium, and zinc) differed slightly from normal. The concentrations of copper, iron, zinc, manganese, calcium, magnesium, cobalt, and nickel in bone of patients with osteogenic sarcoma differ significantly from those in controls (10).

We undertook to measure the concentrations of silver, aluminum, gold, bismuth, cadmium, lead, antimony, copper, and selenium in the CSF of patients with malignant or benign brain tumors, and, for comparison, in a control (reference) group.

Materials and Methods

Patient Selection and Sample Collection

The 32 patients included in this study (Table 1) had fasted for 8 to 12 h before surgery. A CSF specimen (3 to 4 mL) was collected in a plastic specimen container from each patient at the time of operation through a ventricular catheter or a spinal drainage needle inserted in the lumbar sac. No sample containing blood was used in this study. The patients were divided into three groups:

- Malignant brain tumor: Eleven patients with histologically diagnosed astrocytoma, medulloblastoma, pinealblastoma, or chondrosarcoma were operated upon under general anesthesia between 0930 and 1630 hours for removal of the tumors. CSF from two patients was collected through the ventricular catheter and from nine by lumbar puncture.

- Benign brain tumor: Eleven patients with meningioma or craniopharyngioma were operated upon and a CSF sample was collected from each. Again, the sampling sites were two ventricular and nine lumbar.

Reference group: Ten patients with various non-neoplastic diseases (Table 1) were included in this study as a reference group. CSF was withdrawn from each patient with hydrocephalus via a ventricular catheter as part of the treatment and an aliquot used in this study. CSF samples from other patients in the reference group were collected by lumbar puncture for general chemistry diagnostic workup.

Reagents

Standard solutions (1 g/L) of the eight elements (Fisher Scientific Co., Pittsburgh, PA) were used in preparing the standard curves. Doubly distilled water, stored in a plastic container, was used. The nitric acid was AR grade.

Methods

We used a Model 975 atomic absorption spectrophotometer equipped with a Model GTA-85 electrothermal (graphite tube) atomizer (Varian Techtron Pty., Ltd., Mulgrave, Victoria, Australia). The CSF specimens were centrifuged in a...
rerefrigerated centrifuge at 3500 rpm, and 0.5 mL of the supernate was diluted with dilute (5 mL/L) nitric acid so as to yield absorbance values within the linear range for each element analyzed. Furnace operating conditions (temperature, time, and gas flow in the drying, ashing, and atomization stages) were those recommended by the instrument manufacturer (11). The gas used was nitrogen, except in the case of selenium, for which we used an electrodese discharge lamp with a power supply. The samples were held in autosampler plastic tubes, and the autosampler was programmed to inject 10 or 20 µL. The standard curves were prepared by use of standard solutions diluted with the dilute nitric acid under conditions identical to those used for the unknown samples. The analyses were performed in at least quadruplicate.

Results

The data for standard curves obtained for all the elements examined in this study were subjected to linear least-square regression analysis, and the resulting equations were used in calculating the concentrations of these trace elements in the CSF samples. There was good linearity between concentration and instrument reading for all the elements investigated; the correlation coefficients were 0.999 (silver, copper, and lead), 0.996 (antimony and selenium), 0.992 (aluminum), 0.980 (bismuth), and 0.998 (gold and cadmium). Reproducibility was also good, and the CV for no sample exceeded 15%.

Table 2 gives the mean and standard deviation for the concentrations of the nine elements in the CSF samples from both groups of patients. Table 3 gives the corresponding values for the reference group and also previously reported concentrations for these elements.

The concentrations of the trace elements in CSF from the three groups of patients were evaluated by Student's unpaired t-test. There were significant differences in the concentrations of silver (p <0.012) and lead (p <0.047) between the malignant tumor group and the reference group (Table 4). Differences in the concentration of lead (p <0.014) were also significant between the malignant and benign tumor group. All other differences were not significant. Specifically, we saw no significant differences between the benign tumor group and the control group.

Discussion

As demonstrated in Table 3, the values we obtained for most of these elements agree with those found by other investigators (12–22). The values for gold in CSF were higher than those reported by Kjellin (12), perhaps owing to differences in the analytical techniques or to protein binding differences between the two groups of patients involved in the two studies, because high concentrations of this element were found in patients with high protein concentrations (12). Our value reported for bismuth appears to be the only value yet reported.

Significantly increased values for silver and lead in CSF of patients with malignant cerebral tumors (astrocytoma, medulloblastoma, pinealblastoma, and chondrosarcoma) were observed (Table 4). The ratios for tumor/reference-patient mean CSF concentrations were 2.31 for silver and 2.11 for lead. Although age reportedly influences the chemical composition of the CSF, it does not appear to be cause for the differences we observed: the benign-tumor patients, (mean age 38.1 years) had CSF concentrations similar to
those of much younger reference patients (mean age 10.5 years). Also, this increase cannot be attributed to the difference in the sampling site (i.e., ventricular vs lumbar). Although the sampling from both tumor groups was performed identically (i.e., nine ventricular and two lumbar in each group), differences between the two tumor groups were significant, whereas the differences between the benign-tumor and reference group (six ventricular and four lumbar samplings) were not significant.

The mechanism(s) of the observed increased concentrations of silver and lead in CSF of patients with malignant cerebral tumors is unknown. The concentrations of these trace elements in CSF in cases of brain neoplasms have not been previously reported. Schicha et al. (9) reported marked variations (higher or lower) in the cobalt, iron, rubidium, cobalt, and zinc content of human malignant cerebral tumor tissues, as compared with that in benign cerebral tumors, but the influence of such variations on the concentrations of these elements in CSF was not addressed.

The increased concentrations of silver and lead we observed in patients with malignant brain tumors may reflect disturbed metabolic and biochemical activities in the malignant cells. They may be also related to malignancy-induced alterations in the distribution of these elements between the cerebral cells and the CSF. Alternatively, these changes may be due to a change in the integrity of the blood–brain barrier and subsequent selective leakage of these elements into the CSF.

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References