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Concentration of tumour markers CEA, AFP, alpha and beta subunits of hCG in cerebrospinal fluid in children with inflammatory diseases of the central nervous system

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Carcinoembryonic antigen (CEA), alphafetoprotein (AFP) and alpha-beta subunits of human chorionic gonadotropin (hCG) were determined by radio-immunoassay in CSF of 83 children presenting some central nervous disease and compared to the corresponding values obtained in 88 children without neuroinfection. CEA and alpha hCG were absent in the CSF of children without neuroinfection. CEA and alpha hCG levels in CSF higher than 0.0 ng/ml were regarded as elevated. In patients with inflammatory process of CNS, CEA values were positive in 9% (maximum 8.0 ng/ml) and alpha hCG in 4% (maximum 5.0 ng/ml). AFP in CSF ranged from 15.0 to 49.0 ng/ml in children without neuroinfection, and from 0.0 to 100.0 ng/ml in patients with inflammatory diseases of the CNS. As a normal upper limit of AFP in CSF, 53.2 ng/ml is suggested; in 31% of the patients with inflammatory diseases of CNS the AFP level was elevated. The normal upper limit of beta hCG concentration in CSF was regarded as 0.4 ng/ml; in 12% of the patients with viral meningoencephalitis the beta hCG level in CSF was slightly elevated, it ranged from 0.5 to 3.0 ng/ml.

The usefulness of serum CEA, AFP and hCG as tumour markers and as an indicator of the response to treatment is well established. Subsequently, elevated serum levels of tumour markers were also found in patients with nonmalignant diseases. Several authors observed CEA and AFP activity in body fluids other than plasma [2, 4] and increased CSF levels of CEA in patients with intracranial tumour [7, 8, 9, 12, 13], and preventive and therapeutic properties of AFP were demonstrated in experimentally induced allergic encephalomyelitis.

The present study was designated to determine the concentration of CEA, AFP and alpha and beta subunits of hCG in CSF of children with inflammatory diseases of the CNS.

Material and Methods

CEA, AFP and alpha and beta subunits of hCG were determined in the CSF of 83 children aged from 2 to 14 years, presenting signs of some CNS affection and compared to the corresponding values of 88 healthy children of the same age. Samples were obtained with lumbar puncture from hospitalized patients, without CNS affection. The CSF was not centrifuged. Simultaneously, blood samples were obtained by peripheral venipuncture, centrifuged at 2500/min for 5 minutes and held at −18°C until use (maximum two months). CEA and alpha and beta subunits of hCG were determined by double-antibody radioimmunoassay and AFP level by single-antibody radioimmunoassay with final separation by polyethylene glycol of bound and unbound antigens. All RIA kits were supplied by Isotope Production and Distribution Centre, Swierk, Poland.

Patients were grouped as follows.

Group A. 19 children without inflammatory diseases of the CNS. Their CSF was normal, the indication for its analysis were febrile convulsions during acute respiratory tract infection or severe vomiting suggestive of neuroinfection;

Group B_1. 6 patients with purulent meningitis;

Group B_2. 49 patients with viral meningoencephalitis. In this group the level of tumour markers in CSF was determined several times.

Group C. 26 patients examined after three weeks treatment of viral meningoencephalitis, when the CSF was free of inflammatory signs.

Statistical significance between means was estimated by Student's *t*-test (level of significance, $p = 0.05$).

Results

Plasma concentration of tumour markers in healthy children

In the 88 healthy children the normal value for plasma CEA and AFP was at 2 SD above the mean. The plasma CEA level was less than 4.1 ng/ml (mean 0.83 ± 1.6 ng/ml) and the plasma AFP level less than 12.2 ng/ml (mean 3.18 ± 4.47 ng/ml). The mean alpha hCG was 0.12 ± 0.44 ng/ml, and the beta hCG level 0.80 ± 0.15 ng/ml. The upper normal limit of alpha and beta hCG levels was at two SD above the mean; thus, levels of alpha hCG higher than 1.0 ng/ml and beta hCG higher than 0.4 ng/ml were regarded as elevated. Between 0.0–1.0 ng/ml were 98% of the results for alpha hCG and between 0.0–0.4 ng/ml were 95% of the results for the beta hCG.

Plasma concentration of tumour markers at the time of lumbar puncture for CSF analysis

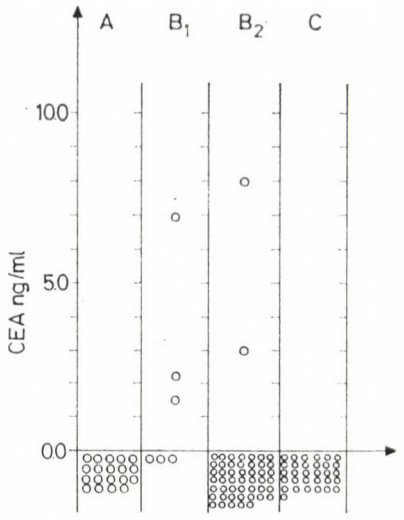
In 3/19 children of the A group plasma CEA levels were higher than 4.10 ng/ml. In 5/55 patients with neuroinfection plasma CEA values were elevated (maximum, 12.5 ng/ml). In 3/26 patients during the recovery period, plasma CEA values were elevated, ranging from 4.2 to 6.0 ng/ml.

Plasma AFP values higher than 12.2 ng/ml were found in 2/19 patients of the A group, and in 7/49 patients with viral meningoencephalitis. In Group C, plasma levels were normal and ranged from 0.0 to 3.2 ng/ml.

In all 83 children, the alpha hCG concentration was not higher than 1.0 ng/ml. Only in 3/49 patients with viral encephalomeningitis was the beta hCG concentration higher than 0.4 ng/ml. Simultaneous elevation of plasma CEA, AFP, alpha and beta hCG levels was not observed in patients with neuroinfection.

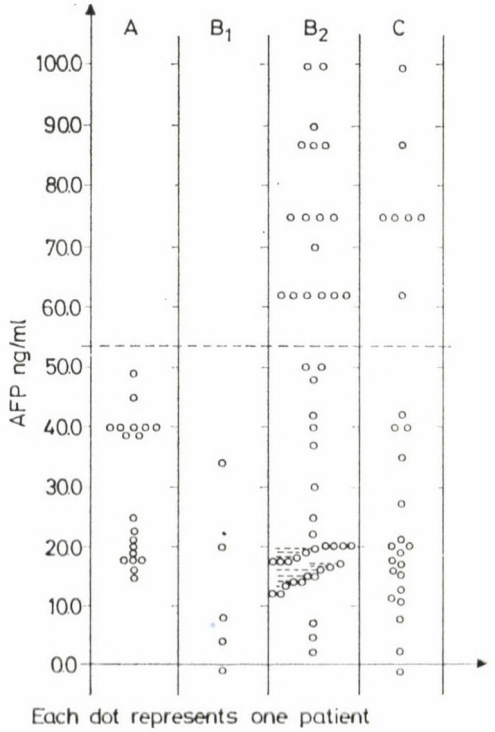
CSF concentration of tumour markers

The results of CEA, AFP, alpha and beta subunits of hCG assay in CSF are shown in Figs 1 to 4. In the results obtained from patients without neuroinfection there was no CEA. Five of 55 patients with inflammatory process had positive CEA values (maximum, 8.0 ng/ml), while during recovery the CEA values were negative. (All CEA levels in CSF higher than 0.0 ng/ml were regarded as elevated.) In patients without neuroinfection AFP values ranged from 15.0 to 49.0



Each dot represents one patient
A. children without symptoms of neuroinfection
B_1. patients with purulent meningitis
B_2. patients with viral meningoencephalitis
C. patients in convalescence after viral meningoencephalitis

FIG. 1



Each dot represents one patient

FIG. 2

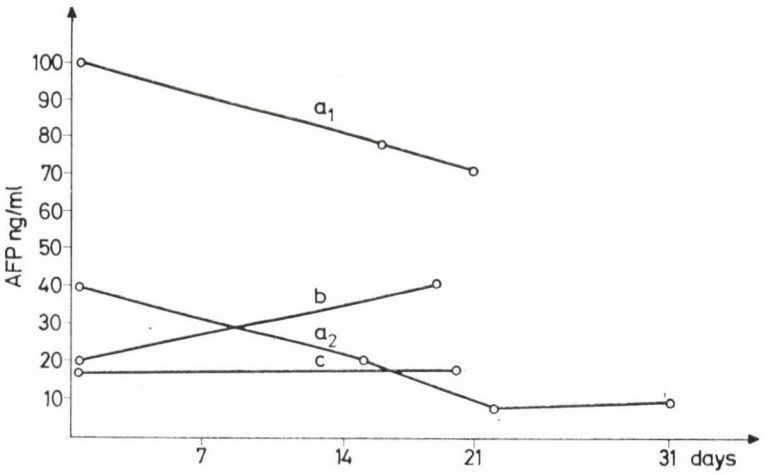


FIG. 3

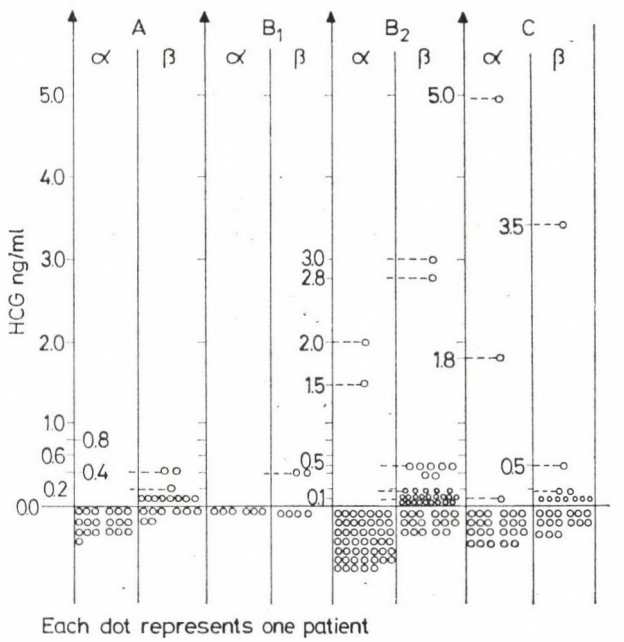


FIG. 4

ng/ml, with a mean of 29.74 ± 11.71 ng/ml. The normal upper limit of AFP in CSF was regarded as 53.20 ng/ml ($\bar{x}$ + 2 SD). In patients with purulent meningitis the AFP level in CSF ranged from 0.0 to 34.0 ng/ml, in patients with viral meningoencephalitis from 2.0 to 100.0 ng/ml. The mean AFP level in the whole B group was 40.5 ± 29.13 ng/ml, by 10.76 ng/ml

higher than that of the normal CSF. In group B, 34.7% of the patients had elevated levels. The mean CSF AFP level during recovery was 35.45 ± 29.11 ng/ml, 5.05 ng/ml lower than with acute inflammatory process but 5.71 ng/ml higher than in the control group A. Statistical differences between the groups were not observed ($p < 0.05$).

In patients without neuroinfection the alpha subunit of hCG was not detectable in the CSF. Two of 49 patients with viral meningoencephalitis and 3/26 patients in the recovery period had positive alpha hCG values ranging from 0.1 to 5.0 ng/ml. The mean beta hCG level in CSF without inflammatory process was 0.095 ± 0.12 ng/ml while its normal upper limit ($\bar{x} + 2$ SD) was set at 0.40 ng/ml, as 100% of the results of group A were between 0.0 and 0.40 ng/ml. In 7/49 patients with viral meningoencephalitis and in 2/26 patients during recovery the beta hCG level in CFS was higher than 0.40 ng/ml, ranging from 0.5 to 3.5 ng/ml.

Serial tumour marker assays in CSF

The level of tumour markers in CSF was determined repeatedly in some patients with viral meningoencephalitis during or after treatment. The initial level in one patient was 3.0 ng/ml and dropped to 0.0 ng/ml during recovery. In the second one with an initial CEA of 8.0 ng/ml we were unable to obtain further values, and in the other patients with meningoencephalitis no CEA was detectable. Figure 3 shows serial CSF AFP levels of patients with neuroinfection; in 15/26 the level decreased during recovery (curves a_1 and a_2 in Fig 3). In 8/26 patients the control AFP levels were higher than at onset of the disease (curve b in Fig 3). There was only a single patient in whom the 18.90 ng/ml AFP level did not change (curve c in Fig 3). All positive alpha and beta hCG levels decreased to 0.0 ng/ml during recovery.

No relationship was found between plasma and CSF levels of CEA and alpha and beta hCG in meningoencephalitis, using correlation analysis and linear regression. Each level seemed to be an independent variable. The same analysis for AFP yielded a positive correlation.

Discussion

Some biological markers have previously been detected in serum and CSF in patients with various intracranial tumours [2, 6, 7, 8, 9, 11, 12, 13, 14, 15]. In some of these, a correlation was observed between the concentration of tumour markers and the clinical data [2] in that in 6 patients with verified intracranial germ-cell tumour the AFP and beta hCG profile for a given tumour correlated with the histological diagnosis [2]. Other authors [6, 8, 12] suggested that the CEA level was of value in the differential diagnosis of primary and metastatic brain tumours, but until now the clinical significance of these biological markers has not sufficiently been proven. It would be useful to

determine CSF fetal-neoplastic antigens both in healthy individuals and in patients with non-neoplastic diseases of the CNS. As there are difficulties in analysing the CSF of healthy subjects we have determined some immunological markers in non-tumorous CSF to receive comparative values for further studies in neoplastic patients.

Suzuki and Tanaka [14] considered 0.5 ng/ml as the upper limit for CEA in normal CSF. In the present study, CEA and alpha hCG were not detectable in CSF obtained from patients without neuroinfection. Our results suggested that the upper normal limit of CEA and alpha hCG in CSF was 0.0 ng/ml. Only in 9% of patients with inflammatory diseases of the CNS was the CEA level elevated, ranging up to 8.0 ng/ml, and the alpha hCG level was elevated only in 4% of them, ranging up to 5.0 ng/ml. The mean beta hCG level in CSF in patients without neuroinfection was 0.95 ± 0.12 ng/ml and in only 12% of the meningoencephalitis patients was it slightly elevated, ranging from 0.5 to 3.0 ng/ml. AFP in CSF obtained from patients without neuroinfection ranged from 15.0 to 49.0 ng/ml, and from 0.0 to 100.0 ng/ml in children with inflammatory disease of the CNS and in 31% of the patients with neuroinfection.

AFP has a non-specific immunosuppressive effect on both the cellular and humoral immune response [3, 5, 9, 10]. Abramsky et al [1] assumed that AFP may prevent experimental allergic encephalomyelitis. In our study we have found elevated AFP levels in CSF that subsequently declined during recovery in patients with neuroinfection. It is possible that AFP is involved in immunoregulative mechanisms during neuroinfection. This hypothesis requires further investigations.

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