Cerebrospinal Fluid Biochemical Markers in Central Nervous System Tumors: A Review

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ABSTRACT

Despite numerous studies over the past three decades, the role of these markers in the diagnosis of central nervous system (CNS) tumors is not yet established. In this report, the literature is reviewed and an attempt is made to define the usefulness of CSF biochemical markers for detecting primary and metastatic CNS neoplasms, with emphasis on the potential of these markers for the early identification of CNS tumors, particularly metastases to the leptomeninges.

Introduction

Circulating tumor markers are polypeptides, glycoproteins or enzymes made and released by neoplastic tissue in excess of that produced by normal parent non-neoplastic tissue. The measurement of tumor markers in blood has proved useful in defining certain systemic cancers. Biochemical tumor markers have been searched for in the cerebrospinal fluid (CSF) for three decades, but their role in the diagnosis of central nervous system (CNS) neoplasms is still not clear. The presence of tumor markers in the CSF may potentially help the physician in several ways. Firstly, they may help differentiate the site of central nervous system metastases (beta-glucuronidase, carcino-embryonic antigen [CEA], and lactic dehydrogenase [LDH] isoenzymes are elevated by leptomeningeal metastases, but not by intraparenchymal brain metastases or epidural spinal metastases). Secondly, they may aid in the early detection of asymptomatic CNS metastases (e.g., beta-subunit human chorionic gonado-
tropin [β-HCG] in metastases from uterine choriocarcinoma and testicular germ cell carcinomas).6,8,66,68 Thirdly, they may help define histologic subtypes of surgically inaccessible tumors (e.g., β-HCG and alpha-fetoprotein [AFP] in the differential diagnosis of intracranial germ cell tumors).1 Fourthly, they may assist in the evaluation of the efficacy of treatment (by changing levels in serial samples of beta-glucuronidase, LDH isoenzymes and CEA in meningeal metastases).20,69,95 Fifthly, they may be of value in differentiating benign from malignant primary tumors (e.g., desmosterol and polyamines in gliomas).22,46,47,48,49,62,91,92 Finally, they help distinguish neoplastic meningitides from subacute or chronic infectious meningitides (beta-glucuronidase, CEA and LDH isoenzymes).20,69,73 This report reviews the literature on the use of biochemical tumor markers in the CSF and speculates on their role in the diagnosis and management of patients with primary and metastatic CNS neoplasms.

Beta-glucuronidase

Beta-glucuronidase, a widely distributed enzyme which hydrolyzes the beta-glycosidic bond between glucuronic acid and a variety of other substances (including steroids, aromatic compounds, and sugar derivatives), has particularly high activity in epithelial tissue, reproductive organs, and leukocytes.3,4,18 It exists primarily in a latent form distributed with lysosomes and microsomes. In the course of malignant transformation in many body tissues, such as breast, the activity of beta-glucuronidase increases.18,53 Elevated levels of beta-glucuronidase are recoverable in effusions caused by neoplastic tissue but not from non-neoplastic effusions.51 In the nervous system, beta-glucuronidase is normally present in both white and gray matter with particularly high levels in the pia arachnoid and the choroid plexus. In some malignant tumors of the nervous system, particularly if they contact the subarachnoid or ventricular surfaces, the activity of beta-glucuronidase in the CSF increases.3,4,5,42,69,72,73 Beta-glucuronidase is usually found in the CSF of individuals without disease of the nervous system (normals) in a concentration below 45 mU per L. In the presence of metastases to the leptomeninges from a systemic carcinoma (lung carcinoma, breast carcinoma, and malignant melanoma), the activity of beta-glucuronidase increases. Eight of nine patients with unequivocal clinical and cytological evidence of leptomeningeal carcinoma secondary to breast carcinoma had beta-glucuronidase levels above 80 mU per L and as high as 220 mU per L. Seven of 12 patients with verified leptomeningeal metastases from lung carcinoma had similar elevations of beta-glucuronidase with a range from 90 mU per L to 260 mU per L. Three of six patients with malignant melanoma also had similar increases, and the three other patients had levels between 45 and 60 mU per L. In the case of meningeal metastases from systemic lymphoma, only two of eight patients had beta-glucuronidase activities above 45 mU per L, but these patients were diagnosed early in their course, before major signs of neurological dysfunction were present. Only one of 20 patients with intraparenchymal brain metastases had beta-glucuronidase activity above 80 mU per L; in this patient, there was a clinical suspicion of concomitant leptomeningeal metastases, never cytologically or pathologically confirmed. None of nine patients with purely epidural metastases from a systemic carcinoma had beta-glucuronidase above 80 mU per L. Only one of 12 patients with a primary CNS tumor had beta-glucuronidase above 80 mU per L; in this patient, there was dissemination of the primary tumor through the subarachnoid space. Gross elevations
(>400 mU per L) of beta-glucuronidase activity in CSF are also caused by bacterial meningitis, and moderate elevations (45 to 100 mU per L) by tuberculous and fungal meningitides. Viral meningitis does not appear to elevate beta-glucuronidase activity in the CSF.\(^4\)

The concentration of the enzyme in lumbar CSF is approximately twice that of ventricular CSF. Its concentration approaches control levels in both lumbar and ventricular CSF with successful treatment of meningeal metastases, and subsequent rises may predict relapse.\(^69\)

In summary, CSF beta-glucuronidase activity is commonly elevated in patients suffering from metastases to the leptomeninges from breast carcinoma, lung carcinoma and malignant melanoma. It is less commonly elevated in meningeal metastases from lymphomas or leukemias, although when present is diagnostically helpful. It is infrequently detected in intraparenchymal or epidural metastases and not consistently elevated in the few primary brain tumors studied. It is grossly elevated in acute and moderately elevated in subacute and chronic infections of the meninges.

**Carcinoembryonic Antigen**

Carcinoembryonic antigen (CEA) is a glycoprotein of high molecular weight believed to be produced by malignantly transformed cells by the process of derepressed dedifferentiation. Originally described in 1965, it was believed at first to be an antigen specific for cancer of the colon. Subsequently, the antigen has been found in serum in association with other malignancies of both endodermal and non-endodermal origin, e.g., breast, bladder, ovarian, and lung carcinomas. CEA is also present in association with inflammatory diseases of the pancreas, liver, and colon as well as benign pulmonary diseases and chronic cigarette smoking. As a serum marker, then, it has had limited value in the early diagnosis of cancer. However, if elevated prior to treatment, serial monitoring of serum CEA levels helps judge the efficacy of treatment and predicts the presence of occult residual tumor.

In the diagnosis of CNS tumors, measurement of CEA has limited value, but in several reports a small percentage of patients with primary or metastatic brain tumors have elevations of serum CEA.\(^10,76\) CEA is also elevated in the serum of patients with neuroblastoma.\(^34\) In the CSF, CEA is usually non-detectable. In about 10 percent of patients without nervous system disease, small amounts of CEA (up to about 1.5 ng per ml) are found, even when serum CEA is normal. When the serum CEA is grossly elevated (above 100 ng per ml), CSF CEA may be one to two percent of the serum value in patients without CNS disease.\(^69\) CNS metastases, particularly to the leptomeninges, elevate CSF CEA.\(^69,95\) In eight of nine patients with metastases to the leptomeninges from lung carcinoma, CEA above one ng per ml was found. Elevations as high as 2400 ng per ml were found in CSF without concomitant elevation in the serum.

CEA was less strikingly elevated in eight of 12 patients with leptomeningeal metastases from breast carcinoma. In two of six patients with leptomeningeal metastases from malignant melanoma, elevations were also found even though melanoma has not been reported to produce CEA. In only two of 20 patients with purely intraparenchymal brain metastases were values of CEA in the CSF above one ng per ml; one of these patients had a parenchymal metastasis which was juxtaposed to the subarachnoid space, and the other clinically was suspected of concomitant leptomeningeal metastases, although this was never proved. Only three of nine patients with epidural metastases had values of CEA in the CSF above one ng per ml, and in these three patients concomitant serum CEA values were not ob-
tained to exclude the possibility of elevated serum CEA. Only one of 10 patients with a primary brain tumor had a mild elevation of CEA in the CSF. Only one of 11 patients with infectious meningitis had CEA values above one ng per ml, and this value was only 1.3 ng per ml in a patient with tuberculous meningitis. CEA in ventricular CSF is approximately 1/2 to 1/5 of simultaneously obtained CEA in lumbar CSF. In those patients who appeared to respond to treatment directed at their leptomeningeal metastases, CEA in the CSF in certain instances appeared to parallel the patients’ clinical response.

Carcinoembryonic antigen in the CSF, then, appears to be a useful marker in the diagnosis of leptomeningeal metastases, particularly from lung carcinoma, less so reliably from breast carcinoma and melanoma. Consistent elevations are not seen in meningeal lymphoma. Intraparenchymal brain metastases, epidural metastases, primary brain tumors, and infectious meningitides also do not usually elevate CEA in the CSF. When the plasma level is high, CEA in the CSF does spill into the cerebrospinal fluid in small amounts.69

Lactic Dehydrogenase

Lactic dehydrogenase (LDH), the enzyme at the end of the metabolic chain of anaerobic glycolysis, can be fractionated into five isoenzymes, each with a distinct chemical structure. In the course of malignant transformation, elevated levels of lactic dehydrogenase can be recovered in the fluid medium that bathes neoplastic tissues. In the brain, lactic dehydrogenase is omnipresent and has an isoenzyme pattern with a predominance of the electrophoretically fast-moving isoenzyme fractions 1 and 2. Studies on brain tissue homogenates have indicated that neoplastic change in brain results in a shift in the isoenzyme pattern from a predominance of fractions 4 and 5 31,61,81 This has been ascribed to a shift to anaerobic metabolism resulting from the malignant change. The aerobic/anaerobic theory is controversial.84

There is conflicting information in the literature about the activity of LDH in the CSF in patients with CNS tumors.15,14,15,19,26,27,37,88,93 In the CSF of patients without CNS disease, the percentage of LDH isoenzyme 5 as a proportion of total LDH is less than 15 percent.20 In patients with metastases to the leptomeninges from breast carcinoma, lung carcinoma, and malignant melanoma, activity above 15 percent is consistently observed. This pattern was observed in spite of normal serum LDH isoenzyme patterns. Patients with purely intraparenchymal metastases or epidural metastases do not have LDH isoenzyme 5/1 ratios which differ from control patients. In a few patients whose primary brain tumors did not disseminate in the subarachnoid space, LDH-5 levels were similar to control values. In patients who had meningeal infections with granulocytes were present, there was a similar change in the LDH isoenzyme pattern with a predominance of LDH-4 and 5, reflecting the LDH pattern of granulocytes.10,85 The LDH pattern seen in the patients with meningeal carcinoma is probably caused by the leptomeningeal tumor itself and not from a granulocytic reaction, as several of the patients with such isoenzyme patterns did not have CSF pleocytosis. Lumbar CSF contains about twice the concentration of LDH-5 as simultaneously obtained ventricular CSF. In some patients, CSF LDH isoenzyme patterns change as the patient responds to treatment.20

Human Chorionic Gonadotropin

Human chorionic gonadotropin (HCG) is a glycoprotein normally produced by
the placenta. It has two subunits, alpha and beta, which can be detected by radio-immunoassay methods. Elevated levels of \( \beta \)-HCG in plasma and urine identify trophoblastic tumors; the higher the level, the more extensive and active the tumor.\(^7\) Beta-human chorionic gonadotropin is detectable in the CSF of patients with hydatidiform mole, choriocarcinoma, and normal pregnancy, indicating that \( \beta \)-HCG only enters the CSF when a threshold value equivalent to a urinary excretion of approximately 200,000 IU's of HCG per day are excreted. In the absence of metastasis to the central nervous system, the spinal fluid concentration of HCG is roughly proportional to that of plasma, with the serum CSF ratio consistently above 60 and on occasions as high as 286. When there is extensive non-CNS disease with extremely high plasma HCG levels, plasma to CSF ratios can be unreliable and ratios must be used with caution.\(^8^4\) In patients with brain metastases from either uterine or testicular tumors, the plasma to CSF ratio is usually below 60.\(^6^,^6^8\)

Abnormal plasma to CSF ratios of \( \beta \)-HCG can occasionally be detected prior to clinical or radiographic evidence of CNS metastasis.\(^8^8\) In some patients, the CSF \( \beta \)-HCG concentration exceeds the plasma concentration, indicating that the tumor locally elaborated \( \beta \)-HCG and the altered ratio cannot be attributed solely to an impairment of the blood-brain barrier.\(^6^,^8^,^6^6^,^7^9\) Normal \( \beta \)-HCG values occur when metastases of gonadotropin-producing tumors apparently fail to produce HCG. Monitoring of the plasma to CSF ratio of \( \beta \)-HCG provides a means of observing the response of the cerebral metastases to therapy in both the uterine choriocarcinomas and germ cell tumors of the testis.\(^6^,^8^,^6^6^,^6^9\)

Cerebrospinal fluid \( \beta \)-HCG has also been used in the diagnosis of primary central nervous system neoplasms of germ cell origin. These highly radio-sensitive midline childhood tumors are usually located in the suprasellar and posterior third ventricular regions in areas relatively inaccessible to surgery. Those of choriocarcinoma and embryonal carcinoma histology may produce HCG,\(^4^1,^5^7\) and their detection in the spinal fluid may obviate the need for surgical biopsy. The response of the tumor to the therapy is reflected by changes in CSF HCG levels. Other histological subtypes of germ cell tumor, such as dysgerminoma or teratoma, produce no HCG and therefore CSF HCG is negative. Endodermal sinus tumors may produce other markers (i.e., alpha-fetoprotein).\(^1\)

**Alpha-fetoprotein**

Alpha-fetoprotein (AFP) is an oncofetal antigen found in fetal serum as early as one month of human embryonic life. It is composed of a polypeptide chain of protein and carbohydrate and is synthesized by the yolk sac, liver, and gastrointestinal tract of the fetus. Its physiological function is unknown. It may reappear in the serum of adults in association with normal restorative processes (i.e., liver regeneration) or with primary hepatic carcinomas and teratocarcinomas of the ovary and testis.\(^8^2\) In the CSF, alpha-fetoprotein may be secreted by certain germ cell tumors, particularly primary intracranial yolk sac tumors, endodermal sinus tumors, and occasionally by embryonal carcinoma.\(^5^7,^9^6\) In the presence of such tumors, levels in the CSF are elevated when serum levels are normal. Since these tumors are relatively inaccessible by surgical approaches, the finding of an elevated CSF alpha-fetoprotein may confirm a clinical impression and obviate the need for craniotomy.\(^1\) An elevated alpha-fetoprotein is more reliable than CSF cytology in identifying these tumors. Occasionally, metastases from testicular carcinomas are associated with elevated CSF AFP.\(^7^8\)
Creatine Phosphokinase

Creatine phosphokinase (CK) is an enzyme that catalyzes the reversible transfer of phosphate between adenosine diphosphate (ADP) and creatine phosphate. It plays an important role in cerebral metabolism by maintaining adenosine triphosphate (ATP) concentrations under different physiological conditions. Creatine phosphokinase is found in high concentrations in human brain and is distributed fairly uniformly throughout the central nervous system tissue. It is normally found in trace amounts in the CSF of patients without nervous system disease and is independent of CSF cell count, protein or serum CK level. Creatine phosphokinase is elevated in a variety of neurological disorders including about 60 percent of brain tumors (chromophobe adenomas, some gliomas). Those tumors which are infiltrative and destructive of surrounding brain tissue are more likely to be associated with elevated CK levels than those that are merely compressive, because destruction of brain tissue is necessary for CK CSF elevations. Destructive lesions of the cerebellum are less likely to be associated with CSF CK elevations than are destructive lesions of the cerebral hemisphere. Recently, CK isoenzymes have been examined in the CSF using radioimmunoassay techniques. Although brain tumors have not specifically been investigated, other neurological disorders in which there is acute destruction of brain tissue have been associated with elevations of CK BB. Meningeal infections have not been associated with such CK BB elevations.11

Acid Phosphatase

Acid phosphatase, a hydrolytic enzyme involved in catabolic phosphorylation, is found in brain tissue and in trace amounts in the CSF (0 to 0.2 units) of normal persons. Acid phosphatase has been little studied in CSF but appears to be increased in cerebral tumors undergoing regressive degenerative changes. In the CSF, acid phosphatase is elevated in some patients with metastatic prostate carcinoma to the cauda equina and to the cerebral hemispheres. It is also elevated in infectious meningitis, the levels correlating with the CSF lymphocyte count. No correlation has been made between serum and CSF acid phosphatase values.12,30

Aspartate Transaminase

Aspartate transaminase (GOT) is an intracellular enzyme present in relatively high concentrations in brain, particularly the cerebral and cerebellar cortices and, to a lesser extent, the white matter. It is normally present in the CSF (up to 20 units). Its level in CSF appears to be independent of serum levels and also of other CSF contents such as cells and protein. Lumbar CSF levels are generally higher than ventricular CSF levels. Although reports vary, GOT levels appear to be normal or only modestly elevated with benign intracranial tumors and somewhat more frequently elevated with malignant primary and metastatic neoplasms. Aspartate transaminase has been elevated in some patients with metastatic epidural spinal cord compression. In other CNS disease processes such as infarction, GOT varies directly with the extent of cerebral necrosis. Glucose Phosphate Isomerase

Glucose phosphate isomerase (phosphohexose isomerase) is a glycolytic enzyme whose highest brain activity is found in the cerebral and cerebellar cortices. It is normally found in small amounts in CSF (1.85 ± 1.15 units). Elevated levels in CSF have been described in about 60 percent of patients with a variety of malignant primary and metastatic
CNS tumors, while only one of seven patients with benign primary CNS tumors had CSF elevations. No correlation was observed between CSF levels and other CSF variables or with serum levels. Cerebrospinal fluid enzyme elevations have also been observed in other CNS processes such as infarction and acute infection. Cerebrospinal fluid phosphohexose isomerase from the cerebral ventricles of patients with gliomas is consistently higher than that in the CSF of patients with metastatic cerebral tumors.

Leucine Aminopeptidase

Leucine aminopeptidase is normally present in brain and CSF (0.4 to 2.3 g per ml). Its concentration increases (3.2 to 6.3 g per ml) in a variety of primary and secondary brain and spinal cord neoplasms. Similar elevations have been described in other CNS processes (such as vascular and degenerative diseases). The level of CSF leucine aminopeptidase follows the level of CSF protein and its measurement in CSF appears to be no more specific than an increase of CSF protein.

Isocitric Dehydrogenase

Isocitric dehydrogenase is the enzyme that catalyzes the conversion of isocitrate to alpha-ketoglutarate. It is normally found in CSF in low activity (0 to 12.2 units). It increases in a variety of primary and metastatic tumors (including leukemic infiltration of the leptomeninges) and is independent of cell counts or protein concentrations. It is also elevated in CSF infections and is proportional to the number of leukocytes. It is transiently elevated after cerebral infarction.

Adenylate Kinase

Adenylate kinase, an enzyme necessary for the maintenance of adenylate, is widely distributed in tissues including brain. It is normally absent from CSF. It is transiently unrecoverable in the CSF of patients after acute cerebral infarction. It was present in CSF of 9/9 patients with malignant brain tumors (astrocytomas) but absent in 2/2 patients with benign tumors (meningioma and cerebellar cyst).

Lysozyme

Lysozyme is a small molecular weight bacteriolytic protein distributed widely in a variety of human tissue but particularly in the monocyte-macrophage system and in precursors of neutrophilic granulocytes. It is sometimes detectable in small quantities in the normal CSF (0.9 ± 0.5 mg per ml). It has been reported to be abnormally elevated in some primary and metastatic neoplasms of the brain and leptomeninges, although similar elevations have been observed in CNS infections, granulomatous diseases, multiple sclerosis, or any process that allows for increased neutrophilic granulocytes and monocytes in the meninges or increased CSF protein.

Cyclic Nucleotides

Cyclic nucleotides (cyclic adenosine 3'5'-monophosphate [AMP] and cyclic guanosine 3'5'-monophosphate [GMP]) are present in the brain and in the CSF. Their functions have not been fully specified, but they appear to be involved in mediating central effects of certain neurotransmitters and modulators. In the CSF of patients with cerebral tumors, if there is no increased intracranial pressure, cyclic AMP and cyclic GMP levels in CSF are normal. When intracranial pressure is elevated by tumor (or by any other process) cyclic GMP appears to be elevated in ventricular CSF in direct proportion to the elevation of intracranial pressure, while cyclic AMP remains normal. If there is long standing hy-
drocephalus in children with thinning of the cerebral mantle, then cyclic AMP concentrations are decreased.65

Adenohypophyseal Hormones

Adenohypophyseal hormone concentrations (corticotropin, growth hormone, thyrotropin, prolactin, leutinizing hormone, and follicle stimulating hormone) are detectable in low levels in the CSF of patients without nervous system or pituitary disease.2,38,58,71

Serum levels appear not to influence CSF levels except in the case of hyperprolactinemia where elevated serum levels from any cause (such as pregnancy) are associated with elevated CSF levels.44 In patients with nonpituitary tumors (primary and metastatic brain tumors), CSF adenohypophyseal hormone levels are unchanged from controls. In patients with pituitary tumors without suprasellar extension, hormone levels are also normal with the exception of some patients with prolactin-secreting tumors or acromegaly.38 In the majority of patients with pituitary tumors with suprasellar extension, elevations of one or more of the hormones being produced can be measured.28,43 There is no correlation of these hormone elevations with CSF protein. Cerebrospinal fluid prolactin concentrations are normal in patients with the empty sella syndrome. Hormone elevations are present in a small percentage of craniopharyngiomas. Effective treatment of tumors results in a fall from previously elevated levels, and serial determinations are useful in determining efficacy of treatment.59

Somatostatin

Somatostatin, a polypeptide hormone that inhibits growth hormone and thyrotropin release, has been found to be elevated in the CSF in diverse CNS diseases (such as infection and degenerative disease). It is also elevated in some tumors, such as medulloblastoma and dysgerminoma, for reasons that remain unclear.59

Desmosterol

Desmosterol, the immediate precursor of cholesterol in the pathway of brain sterol synthesis, is a major constituent of the developing brain when cholesterol biosynthesis is most rapid. In the mature brain it is found only in trace amounts and is normally not detected in the CSF. In human brain tumors, however, sterol synthesis is increased, and increased amounts of desmosterol and cholesterol appear.22,24,91 This phenomenon has been reflected in elevated CSF desmosterol levels and forms the basis of the “sterol test” for the presence of primary brain tumors.23,60 In this diagnostic test, triparanol, a drug which enzymatically inhibits cholesterol synthesis and leads to desmosterol accumulation, is given orally for several days. Patients without brain tumors have either no detectable desmosterol or low concentrations (less than 0.1 g per ml). In patients with primary brain tumors, concentrations of desmosterol above 0.1 g per ml were found in a significant percentage of cases (60 to 80 percent) and the more malignant the tumor the more likely the chance of an abnormal response.60,80 The sterol test has been proposed as a diagnostic test and also as a means of following patients to judge efficacy of treatment and early recurrence of tumor.62,92 In one study, the sterol test predicted tumor regrowth in nine of 11 cases of glioblastoma, all three cases of ependymoma, both cases of medulloblastoma, both cases of meningioma, and both cases of pituitary adenoma. It failed in three of seven cases of grade II astrocytoma and in one case each of craniopharyngioma and choroid plexus papilloma.74 The sterol test has not been of value in the diagnosis of metastatic brain disease.
Polyamines

Polyamines (spermine, spermidine, and their precursor, putrescine) are substances whose precise function has not yet been determined. There is evidence, however, that they are related to metabolism, structure, and function of the nucleic acids. Their metabolism appears to be related to cellular growth and proliferation, and therefore they have been the subject of numerous investigations of urine and sera of patients with malignancies. In the CSF, Marton et al have studied a group of neurologic patients without neoplasms and have found relatively low levels of CSF putrescine (184 ± 54 pmoles per ml), spermidine (150 ± 48 pmoles per ml), and no permene. By contrast, a group of patients with malignant brain tumors had increased levels (putrescine 546 ± 89 and spermidine 285 ± 40 pmoles per ml in glioblastomas and 561 ± 164 and 331 ± 101 pmoles per ml, respectively, in medulloblastomas). The substances appear to be released from dead or dying tumor cells. Less malignant and benign tumors had either “control” levels or mild elevations. Systematic study of metastatic brain tumors or metastases to the leptomeninges has not been reported. Cerebrospinal fluid polyamine levels appear to have no relationship to CSF protein and, therefore, do not merely reflect alteration of the blood-brain barrier. Preliminary data from Marton indicate that levels may also be raised in CNS infections and vascular diseases although to a lesser extent than malignant neoplasms. Significant improvement in CSF polyamine levels correlated with successful treatment of malignant brain tumors in these studies.

Conclusion

Biochemical substances made by malignant neoplasms may appear in CSF in increased concentrations in one of several ways. Increased levels may reflect elevated serum levels and diffusion across an intact blood-brain barrier. Even if the serum level is normal, increased amounts of the substance may appear in the CSF if the blood-brain barrier is “broken down” either by a neoplastic or non-neoplastic process (e.g., cerebral infarction, meningitis, etc.). Finally, the biochemical substance may be produced by neoplastic cells within the CNS; however, in this instance, in order for the substance to appear in the CSF, either the tumor must be in contact with the subarachnoid or ventricular surface of the CNS or the substance must have the ability to diffuse from a tumor deep within the parenchyma to that ventricular or subarachnoid surface. These considerations imply that tumor markers are most likely to be elevated in the CSF of patients with leptomeningeal neoplasms, which directly communicate with the subarachnoid space, and intraparenchymal metastases or primary tumors which are strategically juxtaposed to the CSF pathway.

Beta-glucuronidase, CEA and LDH isoenzymes appear to have greatest value in the diagnosis of leptomeningeal metastases, particularly from carcinomas; less value in lymphomas and leukemias; and of limited value in most intraparenchymal or epidural spinal metastases or primary brain tumors. Their measurement in CSF complements the cytological CSF examination. The potential advantages of tumor marker measurements over exfoliated cytology are the following. Firstly, tumor markers may prove to be more accurate, especially in those patients with meningeal carcinomatosis in whom CSF cytology is persistently negative in spite of repeated lumbar punctures (about 10 percent of patients). Secondly, tumor markers offer a more quantitative measure of assessing the course of the patient and the response to treatment than does cytology. Thirdly, although this has not been proved, tumor markers may potentially prove to be early indicators of
metastases to the leptomeninges prior to the finding of positive cytology or major neurologic symptoms and signs. A previous prospective study has shown equivocal results using LDH and GOT in brain metastases.35

The potential for separating neoplastic meningitis from subacute and chronic infectious meningitis also exists. Although beta-glucuronidase and LDH isoenzymes may be elevated in either instance, CEA and CK BB isoenzymes potentially may assist in this differentiation.

Tumor markers may also be produced by primary brain tumors, as in the case of peri-third ventricular germ cell tumors in children. The measurement of 6-HCG or alpha-fetoprotein (AFP) obviates the need for surgical biopsy in areas of the brain that are not easily accessible. Serial samples, both before and after non-surgical treatment, indicate response of the neoplasm to treatment. Occasionally a solid intraparenchymal metastasis, if strategically located, may also produce markers which are detectable in the CSF. Moreover, there is a suggestion in the literature that these markers may precede, in some instances, both neurologic symptoms and signs and neuroradiologic discovery. With the advent of refined computerized tomography (CT) brain scanning, however, these markers will probably play a more adjunctive role in patient management.

In regard to the reported values of the CSF markers desmosterol and polyamines in the diagnosis of primary brain tumor, these CSF studies must be viewed with caution. Computerized tomography scanning now allows for improved assessment of tumor recurrence and response of tumor to treatment. Lumbar puncture in patients with brain tumors and increased intracranial pressure has significant risk. These measurements will probably also assume adjunctive roles in managing patients with primary brain tumors.

At the present time then, the measurement of biochemical tumor markers in CSF has limited value. However, the potential of these markers in assessing early metastatic disease and in helping to define the role of the blood-brain barrier vis-a-vis effective systemic chemotherapy for brain tumors remains a fertile area for continued investigation.

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