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Diagnostic Sensitivity of Serum and Lumbar CSF bHCG in Newly Diagnosed CNS Germinoma

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Abstract

Background—Marked elevations of AFP and bHCG in serum or CSF may serve as surrogate diagnostic markers in lieu of histology for primary CNS mixed, malignant germ cell tumors. There is less information on the diagnostic sensitivity of bHCG assays in germinoma.

Procedure—We report baseline serum and lumbar CSF bHCG values in 58 newly diagnosed, histologically confirmed germinoma patients gathered from 2 prospective clinical trials which required that patients have a normal AFP and bHCG ≤50 mIU/ml in serum and lumbar CSF.

Results—The location of the primary tumors was: suprasellar(23); pineal(20); suprasellar/pineal(9) and other sites(6). The mean age of the study population was 13.5 (4.3–25.9) years. A total of 23(40%) patients had elevations of bHCG in either serum or CSF, 20(34.5%) of whom had only bHCG elevations in CSF. The patients bHCG profiles were divided into 4 categories: I (normal serum and lumbar CSF bHCG) - 35(60%); II (normal serum and elevated CSF bHCG) - 20(34.5%); III (elevated serum and CSF bHCG) - 2(3.5%) and IV (elevated serum and normal CSF bHCG) - 1(2%). The median CSF bHCG level was 7.7(2.5–16) in the 22 patients with abnormal CSF values and the lumbar value was higher than the serum value in 20 of 23(87%) patients with bHCG elevations.

Conclusions—Lumbar CSF was a more informative screen for bHCG than serum but the majority of patients (60%) had normal bHCG values at diagnosis. Until a more sensitive tumor marker for germinoma is devised, histologic confirmation remains the standard of care.

Keywords

germinoma; bHCG; tumor markers; diagnosis

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Introduction

CNS germ cell tumors may secrete specific proteins in either blood or CSF such as AFP and bHCG which can serve as surrogate diagnostic tumor markers. These tumor markers can provide supportive evidence for the existence of a germ cell tumor prior to biopsy, confirmation of the histology following a limited biopsy or, in some cases, sufficient diagnostic evidence for the presence of a non-germinoma or mixed germ cell tumor.[1, 2]

Germinomas do not secrete AFP but may secrete low levels of bHCG. bHCG is not frequently used as a surrogate diagnostic tool in lieu of a biopsy for germinoma because it is frequently undetectable in serum at diagnosis and low levels have been reported in other conditions.[2, 3] Histologic confirmation currently serves as the standard of care.[4] One exception may be patients with multi-focal (pineal/suprasellar) presentations since the majority harbor a pure germinoma.[5] Knowledge of the range of bHCG values in both serum and lumbar CSF at diagnosis and the relative sensitivity of serum vs. lumbar CSF assays may support the use of these or related screening measures in the future. This report summarizes the pre-treatment serum and lumbar CSF tumor marker profiles of 58 newly diagnosed germinoma patients who participated in 2 prospective clinical trials.

Methods

An exploratory phase II CNS Germinoma trial conducted by the Beth Israel/NYU consortium utilized pre-radiotherapy chemotherapy (carboplatin/etoposide for 2–4 courses) followed by response-dependent radiotherapy. Based on the preliminary results of this pilot study, a phase III Children's Oncology Group(COG) protocol, ACNS0232 (ClinicalTrials.gov Identifier: NCT00085098), was devised to compare a modified version of the multi-modality treatment strategy utilized in the Beth Israel/NYU pilot to standard radiotherapy alone. There were 37 evaluable patients from the Beth Israel/NYU pilot and 21 patients from the COG trial.

The eligibility criteria for the phase II and phase III studies were identical. All patients were required to have histological verification of a germinoma as determined by the institutional neuropathologist, peri-operative MRI's of the brain and spine, lumbar CSF cytology and contemporaneous serum and lumbar CSF AFP and bHCG determinations within 24 hours, either before or after surgery. The majority of the biopsy specimens from both studies was obtained via a neuroendoscopic procedure, often in the context of performing an endoscopic third ventriculostomy and the amount of tissue available for examination was limited. If the diagnosis of a pure germinoma could not be established following the neuroendoscopic procedure, than an open craniotomy was required to establish the diagnosis. There was no central review of the pathology. None of the 58 patients enrolled on these studies had a serious complication from the diagnostic procedure.

All patients had to have normal serum and CSF AFP levels according to the institutional norms and a serum and/or CSF bHCG ≤ 50 mIU/ml. Since the commercial laboratories that performed the CSF bHCG immunoassays used different methodologies, the normative data for CSF varied slightly. In most instances, normal CSF levels were reported as less than the upper limit of normal for the laboratory's methodology, rather than a precise value. IRB approval for these protocols was obtained from each participating institution and written, informed consent was obtained from for all study patients or their guardians.

Results

Patient Demographics

There were a total of 58 newly diagnosed patients with histologically confirmed, completely staged patients with a CNS germinoma (Table I). Combining the data from the 2 studies, the primary tumor arose in the suprasellar region in 23 patients, in the pineal region in 20, in both the suprasellar and pineal regions (multi-focal) in 9 and in other supratentorial sites in 6. The M or metastasis staging criteria differed slightly in the 2 studies. The BI/NYU pilot defined M+ (disseminated) as evidence of intraventricular or spinal metastases, multifocal presentations and an abnormal CSF cytology. All other patients were classified as M0 (localized). The COG protocol, ACNS0232 added several additional categories of M+ including MRI evidence of parenchymal infiltration of the brain around the primary tumor > 1 cm; patients presenting with isolated pineal region tumors and symptomatic diabetes insipidus and occult intraventricular metastases observed by the neurosurgeon at endoscopy. Thus, 11 of 37(30%) patients in the BI/NYU study were M+ and 12 of 21(57%) in ACNS0232 were M+. When the M-stage data are combined, 35(60%) patients were M0 and 23(40%) were M+. The overall mean age was 13.5(4.3–25.9) and the overall M/F sex distribution was 41/17.

Tumor Marker Analysis

The baseline serum and CSF bHCG assessments of the 58 patients were divided into 4 categories (Table I). Category I (normal serum and lumbar CSF bHCG) was the largest - 35(60%) patients; followed by Category II (normal serum and elevated CSF bHCG) - 20(34.5%) patients; followed by Category III (elevated serum and elevated CSF bHCG) - 2(3.5%) patients; and Category IV (elevated serum and normal CSF) - 1(2%) patient.

In the 23 patients with abnormal values of bHCG in serum and/or CSF (Table III), the lumbar CSF value was higher than the serum value in 20(87%) patients, the same in 1 and higher in the serum in 2. The median CSF bHCG in the 20 patients with abnormal CSF values alone in category II was 7.2(2.5–16) mIU/ml and 7.7(2.5–16) mIU/ml in all 22 patients with elevations of CSF bHCG. There was no significant difference in the CSF bHCG levels in the M+ vs. M0 patients (mean M+/M0 = 2.0/1.8 mIU/ml).

Discussion

We present baseline serum and lumbar CSF bHCG data from a relatively large cohort of 58 patients with newly diagnosed, histologically confirmed CNS germinoma enrolled in 2 separate clinical trials. All patients were required to have a serum and/or lumbar CSF bHCG level < 50 mIU/ml and normal AFP assays. We conclude that neither serum nor lumbar CSF bHCG measurements are sensitive screens for germinoma. The majority of patients (60%) in our series had normal bHCG assays in both serum and CSF (Table II). Serum bHCG is the least sensitive screen for only 5% (3/58) of patients had abnormal bHCG values. Lumbar CSF is more sensitive as has been previously documented.[6] Approximately 34.5% (20/58) of patients had elevated lumbar CSF bHCG values with normal serum values. The median value of lumbar CSF bHCG was low [7.7 (2.5–16) mIU/ml] in the 22 patients with abnormal CSF values (Table III). Rarely higher levels can be observed in histologically confirmed germinoma, especially in clinical series reported from Japan.[7, 8] Although a bHCG value ≤ 50 mIU/ml in either serum or CSF has been arbitrarily selected by several cooperative groups, the absolute bHCG ceiling consistent with a pure CNS germinoma has not been established.

There remain certain risks in accepting low elevations of bHCG alone in either serum and/or CSF as a surrogate marker for germinoma. Serum tumor marker assays alone may fail to

exclude mixed germ cell components and elevations of CSF bHCG have been reported in other tumors such as pituitary adenoma, craniopharyngioma and as well as benign conditions such as arachnoidal cysts.[3, 9] Several investigators have argued that the multi-focal midline presentation is so uniquely associated with germinoma that biopsy confirmation is not be necessary.[5] However, there are a growing number of case reports citing an exception to this observation.[10]

In conclusion, we recommend that serum and lumbar CSF tumor marker assays be performed in all patients suspected of harboring a CNS germ cell tumor. Currently there is not sufficient data to rely on ventricular CSF. Lumbar punctures can usually be safely performed after raised intracranial pressure is relieved by either an endoscopic third ventriculostomy, VP shunt or external ventricular drain. Any elevation of AFP alone in serum or lumbar CSF excludes a pure germinoma. In patients with normal tumor marker assays in both serum and CSF, histological confirmation of a germinoma is usually indicated. Although both germinomas and mixed germ cell tumors are curable with multi-modality therapy, mixed tumors require more intensive therapy.[11, 12] S-kit, a soluble product of the c-kit oncogene, appears to be a more sensitive screening tool than bHCG for germinomma in several series from Japan.[13] Prospective testing can be performed when this assay becomes more widely available.

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Table I

Patient demographics (58 patients)

Demographic		BI/NYU (37)	ACNS0232 (21)	Combined (58)
Age	<13 years ≥13 years	20 17	9 12	29 (50%) 29 (50%)
Sex	Male Female	24 13	17 4	41 (71%) 17 (29%)
M stage	M0 M+	26 11	9 12	35 (60%) 23 (40%)
Primary Tumor Site	Suprasellar(SS) Pineal (P) SS/P Other	18 11 6 2	5 9 3 4	23 (40%) 20 (34%) 9 (16%) 6 (10%)

Table II

Patient distribution in tumor marker categories

Categories of CSF and Serum bHCG Values	BI/NYU patients (37)	ACNS0232 patients (21)	Combined patients (58)
I. Normal serum/normal CSF	25	10	35(60%)
II. Normal serum/elevated CSF	10	10	20(34.5%)
III. Elevated serum/elevated CSF	1	1	2(3.5%)
IV. Elevated serum/normal CSF	1	0	1(2%)

Table III

Individual values of 23 patients with elevations of serum and/or CSF bHCG (mIU/ml)

Protocol	Category II[a] (20 Patients)		Category III[b] (2 Patients)		Category IV[c] (1 Patient)	
	Normal serum	Elevated CSF	Elevated serum	Elevated CSF	Elevated serum	Normal CSF
BI/NYU(12)	-	16	12	4.9	6	-
	-	16				
	-	8				
	-	7				
	-	6.9				
	-	6.0				
	-	4.9				
	-	4.8				
	-	3				
	-	2.9				
ACNS0232(11)	-	15.3	13	13		
	-	10				
	-	10				
	-	7				
	-	6.6				
	-	6.0				
	-	5.5				
	-	3.1				
	-	3.0				
	-	2.5				
Median (range)		7.2 (2.5–16)	12.5		6	

[a]Category II - elevated bHCG in CSF alone;

[b]Category III - elevated bHCG in both serum and CSF;

[c] Category IV - elevated bHCG in serum alone