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Elevated Lactate and Total Protein Levels in Stereotactic Brain Biopsy Specimen; Potential Biomarkers of Malignancy and Poor Prognosis

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Abstract

Background: Cancer cells bear various metabolic alterations in order to survive and progress. Neoplastic cells rewire their metabolic pathways for fermentation of glucose and production of more lactate. Microenvironment acidification is a common feature of many neoplastic lesions. In other words, most cancer cells produce energy ineffectively, by aerobic glycolysis, considered as "Warburg effect". Mounting on previous evidence, hypoxia also induces tumor stemness, diminished apoptosis, and more invasive behavior as well as angiogenesis. In this study, we aimed to investigate whether more lactate concentration in stereotactic puncture specimen of various brain lesions can be an alarming sign of malignancy and higher grades. The current study aims at providing a rapid prognostic biomarker of higher grades for cystic brain lesions approached stereotactically before the complete pathologic grading report is prepared.

Methods: We investigated the biochemical cyst content of 44 patients with astrocytomas, 8 craniopharyngiomas, 1 oligodendroglioma and 2 cases with metastatic lesions after stereotactic surgery (47 patients were enrolled in the study). Cyst fluid was analyzed for pH, total protein concentration, cytology, and lactate. The association of these parameters was explored relative to tumor behavior (e.g., tumor grade, type, and cyst progression). The current study was conducted at Firoozgar hospital, Tehran, Iran. Patients were followed for any possible progression from 2014 to 2017.

Results: The analyses revealed a significant and positive correlation between grade and lactate concentration ($P \leq 0.001$); as well as between grade and mean total protein concentration ($P = 0.046$). This suggests that more lactate and total protein concentration in stereotactic specimen can be an alarming sign of higher grades and poor outcome in astrocytoma cysts. However, craniopharyngiomas; as benign lesions; had significantly lower lactate ($P \leq 0.001$) and total protein concentrations ($P = 0.018$) than astrocytomas.

Conclusion: Higher total protein and lactate concentrations in the stereotactic biopsy specimens are alarming signs of poor outcome and higher grades in astrocytomas.

Trial Ethics Registration: IR.IUMS.FMD.REC 1396.88215207.

Keywords: Grade, Lactate, Protein, Stereotactic biopsy

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Introduction

In cases of deep-seated lesions of eloquent areas, magnetic resonance imaging (MRI)-guided stereotactic puncture, as a minimally invasive procedure, could be an efficient initial approach to make histopathological diagnosis and a contemporary treatment by cyst fluid drainage for some cases is used.[1-3] As a general rule, total resection of solid and cystic parts of brain tumors is the best treatment strategy to avoid tumor recurrence. Unfortunately, this approach is not possible for deep-seated tumors (e.g., thalamus gliomas) or for those with structural attachments of capsule to eloquent areas (e.g., some types of craniopharyngiomas). In such cases, stereotactic puncture provides the possibility to target the intact cysts.[4-6] Therefore, some cystic brain lesions in areas where open surgery is not feasible, could be approached stereotactically for diagnostic goals and even symptom management.[1-3] This is thought to be safe and the efficacy is considered adequate.[7,8] Stereotactic puncture can be followed by radiotherapy, chemotherapy or a combination of both depending on the primary neoplasm phenotype, histological subtypes, progression, and possible comorbidities.[1-3] Despite all previous therapeutic advances, long term management of gliomatous lesions is still challenging. Much research has been carried out to guess the underlying pathophysiology and metabolism of brain tumors by focusing on vascular endothelial growth factor, N-acetyl aspartate, pH, and choline; yet, the role of many chemicals are controversial and significant gaps

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exist.[9-16]

Recently, increased serum lactate is considered as a prognostic biomarker correlating with tumor grade and malignancy extent in both non-glial brain tumors and primary adult brain neoplasms.[17,18] Here, we focused on the "Warburg effect" and hypoxia-induced angiogenesis. Tumor hypoxia results in lactate production, increased angiogenesis extent and tumor invasiveness.[19-21] Cysts originated from increased vascular permeability and angiogenesis may benefit from corticosteroid therapy (e.g., dexamethasone) and prescription of anti-angiogenic factors such as bevacizumab (e.g., for recurrent glioblastoma multiform).[1-3,22-24] Consequently, understanding the nature of tumor metabolism results in better treatment. The aim of our study was finding simple parameters related to malignancy and tumor grade, as a rapid indicator of patients' prognosis. The biochemical content of various types of intra-tumoral cysts aspirated by stereotactic puncture was investigated relative to tumor characteristics (e.g., tumor grade, type, and cyst progression).

Patients and Methods

Patients

This paper summarizes our findings in analyzing 47 patients admitted to Firoozgar hospital, Tehran, Iran, with cystic brain lesions of 2 groups, namely craniopharyngiomas, and astrocytomas of different grades in eloquent areas. We received ethics approval from the university ethics board with number IR.IUMS.FMD.REC 1396.88215207. Patients suffering from cystic brain lesions not candidate for open surgery (e.g., lesions adherent to internal capsule, or in eloquent areas) referred to Firoozgar hospital, Tehran, Iran, from 2014 to 2017 were included in the study. Patients with resectable brain lesions were excluded from the study and were treated by open total or subtotal resection surgery. After passing the inclusion criteria, MRI-guided Stereotactic puncture was performed to aspirate the cysts. No additional therapeutic intervention was done before the cyst aspiration. After gaining consent, biopsy was carried out under local anesthesia. After fixation of the frame, Leksell, standard stereotactic approach was performed through MRI guidance. After the aspiration, the patients were discharged and referred to neurooncologists for additional treatment.

In the following paragraphs, a general portrait of patient follow-ups conducted in the current study is provided based on a combination of various international guidelines as well as neurooncologists and neurosurgeons' consults.[1-3]

Craniopharyngiomas (WHO Grade 1)

Microsurgical sub-frontal or pterional approach is a common resection approach for craniopharyngiomas. More recently, resection can be carried out through endoscopic skull base approach from the sphenoid sinus. In cases of incomplete resection, postoperation radiation therapy must be performed. For lesions without a well-defined plane between the tumor bulk and hypothalamus, total aggressive resection is challenging and dangerous and may cause hypopituitarism, included diabetes insipidus, and electrolyte disorders.[25] For cystic craniopharyngiomas, intra-cavitary bleomycin or radioisotopes (^{32}p, and ^{99}y) injection as well as stereotactic cyst aspiration and cyst compression are also another recommended treatment strategies. However, after stereotactic puncture, radiation therapy may be required. More recent evidence proposes that in cases of cystic craniopharyngiomas, stereotactic drainage contributes to less endocrinological deteriorations and is more effective than conventional microsurgery.[26] The patients admitted to the stereotactic biopsy center, were referred to neurooncologists for further additional treatments after the puncture.

Astrocytomas

Gliomas are of heterogeneous nature. Hence, therapy is guided due to the most aggressive grade and pattern diagnosed in the specimen. To achieve this goal, total resection is the most ideal treatment strategy, as it provides more tissue for pathological investigation and also less risk of progression. However, in eloquent areas, resection of the deep-seated cystic brain lesions could be associated with the risk of mortality or morbidity.

- WHO grade 1 (pilocytic astrocytoma, pleomorphic xanthoastrocytomas, and subependymal giant cell astrocytoma); are indolent, non-infiltrative, and well-circumcised neoplasms. For non-symptomatic cases, no treatment is required and watch and wait strategy is the choice. In cases of symptomatic lesions with MRI enhancement, the mainstay therapy, is aggressive, near total resection, if feasible. However, for symptomatic lesions with not enhanced MRI, or for those in eloquent areas, fenestration, stereotactic puncture and nidus resection is the treatment of choice. The follow up strategy was radiotherapy for adults, in cases of cyst progression; excessive residues; or for those in critical locations. For follow up of pediatric lesions, chemotherapy was performed. In cases of pediatric recurrence, the patient underwent radiotherapy.[1-3]
- In non-pilocytic infiltrative astrocytomas (WHO grade 2), surgery is the treatment of choice. Moreover, the surgery is followed by radiotherapy and PCV chemotherapy regimen. Only in cases aged under 40 with successful total resection, chemoradiotherapy is not performed. The cases presented in the study, had cysts in eloquent and critical areas, where open surgery and total resection was not feasible. Therefore, stereotactic puncture was performed on the consult of neurosurgeons and neurooncologists.[1-3]
- For anaplastic astrocytomas (WHO grade 3), the standard treatment is surgery followed by radiotherapy.

In recurrent cases, anti-vascular endothelial growth factor agents, nitrous urea agents, and Temozolomide are choices for treatment. The patients referred to the stereotaxy center, were not candidate for surgery on the basis of neurosurgeons' decision, and were approached stereotactic.[1-3]

- For glioblastoma (WHO grade 4), Vuorinen et al suggested that total resection is associated with a two-fold increase in overall survival.[27] Stummer et al also proposed that presence of contrast-enhancing residues is associated with lower survival rates.[28] The standard therapy is surgery, adjuvant chemoradiotherapy with temozolomide, another course of temozolomide chemotherapy. For recurrent glioblastomas, avastin/irinotecan regimen is considered to be effective. However, in cases of eloquent areas where resection was associated with risk of comorbidities, the patients underwent stereotactic drainage and were referred to neurooncologists for further treatment.[1-3]

Oligodendroglioma

In cases of oligodendrogliomas and oligoastrocytomas, because of their indolent nature and prolonged survival, initial watch and wait strategy can avoid the adverse effects followed by neurosurgery, chemotherapy or radiotherapy. However, in most cases, the patients can benefit from surgery. After the surgery, radiotherapy combined with PCV chemotherapy for 1p19q co-deletion positive cases, is the most common treatment strategy. For 1p19q co-deletion negative cases, only radiotherapy is recommended. The most common chemotherapy regimen for anaplastic oligodendrogliomas is PCV (procarbazine, CCNU and vincristine).[29] Expected symptoms can be controlled by anticonvulsants and steroids. For highly infiltrative oligodendrogliomas, not eligible for safe open resection, patients may benefit from stereotactic surgery. The results of the cyst analysis of the only patient with oligodendroglioma is reported below.[1-3]

Metastases

Metastatic cases were managed with respect to the neurooncologists consult. Furthermore, any possible cyst progression was reported for 3 years of the study period. The sample analysis was performed immediately after the puncture, and the observations were investigated with respect to their pH, total protein concentration, lactate, tumor grade, type, and cyst progression.

Total protein concentration was measured through spectrophotometry methods using the device HITACHI912, and the results were expressed in mg/dL and lactate concentration was examined through enzymatic method and was expressed in mmol/L. Table 1 summarizes sample formation with respect to the above-mentioned factors.

Table 1. Sample Formation

Variable	Variable Subgroups	Frequency	Share (%)
Tumor type	Astrocytoma	36	76.6
	Craniopharyngioma (grade 1)	8	17
	Metastases	2	4.3
	Oligodendroglioma (grade 2)	1	2.1
	Total	**47**	**100**
Tumor grade (not for metastases)	1	15	33.3
	2	18	40
	3	6	13.3
	4	6	13.3
	Total	**45**	**100**
Cyst progression	Positive	30	63.8
	Negative	17	36.2
	Total	**47**	**100**

Note: 47 patients were enrolled; 36 astrocytoma, and 8 craniopharyngioma. Two metastatic cases and one oligodendroglioma were also included.

Statistical Methods

The data were analyzed by Stata SE 15, and SPSS. The analyses conducted are two-fold: descriptive statistics to gain a general understanding, followed by well-known statistical models to draw inferences and test certain hypotheses. Classical linear regression and logit regression are the statistical methods estimated to model continuous and binary outcomes, respectively for parameters fitting normal distribution. Non-parametric analyses were conducted by Mann-Whitney U test to estimate the discrepancy of total protein concentration and lactate between 2 groups, craniopharyngiomas and astrocytomas.

Various methods have been proposed in the literature to analyze discrete and continuous relationships. In this study, we use the widely accepted binary logit and classical linear regression models, respectively, for the case of discrete and continuous relationships. These models are elaborated in the following. Binary logit regression is a well-known statistical model to estimate the relationship between predictors and predicted variable in cases with binary dependent variable.[30,31]

The classical linear regression model, on the other hand, assumes a linear relationship between the independent variable(s) and the dependent variable.

Possible similarities of mean protein and lactate concentration with the blood's orcerebrospinal fluid's were explored using students' *t* test in various cysts. Tables 1 to 4 outline the results. *P* value significance level was set as less than 0.05, and small *P* values are reported as less than <0.001.

Results

The results section is devoted to a detailed discussion on results of the various analyses conducted according to the comparison of astrocytomas and craniopharyngiomas. Additionally, a detailed comparison of low grade and high grade astrocytomas is conducted in this section.

The descriptive results of the metastatic cases and oligodendrogliomas are also provided. Sample formation is summarized in Table 1. Table 2 outlines descriptive statistics regarding tumor types. Based on the histological origin of the 4 different cyst types, the following results were obtained.

Out of 44 patients, 36 were diagnosed with astrocytoma, and 8 were craniopharyngioma. Additionally, 2 cases of secondary metastasis and a patient with oligodendroglioma, referred to the stereotactic biopsy center were also included, as supplementary data for further possible studies (totally, 47 patients enrolled). In the following paragraphs the conducted results are explained and categorized by tumor histological subtype.

Craniopharyngiomas (WHO Grade 1)

Per Table 2, mean protein value of craniopharyngioma cyst samples was considerably low (22.85 mg/dL). Lactate concentration was also the lowest of the 3 cyst subtypes studied (3.7 mmol/L). However, cyst lactate was still higher than the CSF's (1.1–2.8 mmol/L) or the blood's (0.5–1 mmol/L) which may result from the necrotic nature of tumor cells. Moreover, mean pH was reported (7.72) for craniopharyngiomas that was above the normal values for both CSF (7.28–7.32) and blood (7.35–7.45). Six patients out of 8 had cyst progression (75%). The senile average was reported 13. In comparison with normal total protein values of both CSF and blood, mean protein value of craniopharyngiomas bore some similarities to that of CSF ($P = 0.307$); but significant dichotomy was observed to that of blood ($P \leq 0.001$). In addition, no similarities in pH or lactate level of craniopharyngiomas to those of CSF or blood were observed ($P \leq 0.001$). Seven cysts out of 8 had positive cytology (87.5%) in craniopharyngiomas. But no significant correlation was reported ($P = 0.09$), per Table 4.

Astrocytomas

As tabulated in Table 2, mean total protein concentration, mean lactate level, and mean pH were 41.56 mg/dL, 8.28 mmol/L, and 7.65, respectively. Mean pH of astrocytoma cysts (7.65) was above the normal range of blood (7.35–7.45) and CSF (7.28–7.32). Progression was recorded in 61.11% of the cysts (22 out of 36). Patients aged about 30 years old on average. Mean protein value in astrocytomas was significantly far from that of both CSF and blood ($P \leq 0.001$), and no similarities were detected in pH or lactate level to those of blood or CSF ($P \leq 0.001$). Eighteen out of 36 samples of astrocytoma had positive cytology with no significant correlation (50%, $P = 0.077$).

Table 3 depicts a detailed comparison due to tumor grade for astrocytomas. According to Table 3, cysts of higher grades have higher lactate concentrations. Strong evidence for significant positive correlation between tumor grade and mean lactate concentration was found ($P \leq 0.001$), per Table 4. In order to compare the characteristics

Table 2. Descriptive Statistics by Tumor Type

Variable	Tumor Type	Frequency	Mean	Standard Variation	Minimum	Maximum
Protein	Astrocytomas	36	41.56	12.88	8.20	58
	Craniopharyngiomas	8	22.85	18.43	3.90	48
	Metastases	2	48	7.07	43	53
	Oligodendroglioma	1	42	_	42	42
	Total	**47**	**38.65**	**15.25**	**3.90**	**58**
Lactate	Astrocytomas	36	8.28	5.33	3.20	20.90
	Craniopharyngiomas	8	3.70	0.77	2.60	5
	Metastases	2	12.35	0.77	11.80	12.90
	Oligodendroglioma	1	17.60		17.60	17.60
	Total	**47**	**7.87**	**5.28**	**2.60**	**20.90**
pH	Astrocytomas	36	7.65	0.17	7.30	8
	Craniopharyngiomas	8	7.72	0.20	7.39	8
	Metastases	2	7.60	0.06	7.56	7.65
	Oligodendroglioma	1	7.90		7.90	7.90
	Total	**47**	**7.66**	**0.17**	**7.30**	**8**
Cyst progression time	Astrocytomas	36	8.36	4.80	2	12
	Craniopharyngiomas	8	10.57	8.73	2	24
	Metastases	2	14	9.89	14	14
	Oligodendroglioma	1	27		27	27
	Total	**47**	**9.64**	**6.57**	**2**	**27**

Note: Astrocytomas had higher total protein and lactate concentration in comparison with craniopharyngioma.

Table 3. Descriptive Statistics by Tumor Grade for Astrocytoma

Variable	Tumor Grade	Mean for Astrocytoma	Standard Variation	Minimum	Maximum
Protein	Grade 1	40.71	17.76	10	57
	Grade 2	41.76	11.74	16	58
	Grade 3	41.40	13.96	8.20	45
	Grade 4	47.66	7.89	36	57
	Total	**42.51**	**12.88**	**8.20**	**58**
Lactate	Grade 1	3.98	0.39	3.20	4.50
	Grade 2	5.38	3.36	3.90	18.80
	Grade 3	12.40	2.67	9.7	16.70
	Grade 4	17.36	6.12	13	20.90
	Total	**7.98**	**5.33**	**3.20**	**20.90**
pH	Grade 1	7.72	0.18	7.56	8
	Grade 2	7.66	0.16	7.38	7.96
	Grade 3	7.72	0.16	7.54	7.98
	Grade 4	7.56	0.13	7.30	7.70
	Total	**7.64**	**0.17**	**7.30**	**8**

Note: Higher grades associated positively with more lactate and total protein concentration.

of craniopharyngiomas and astrocytomas, the analyses using Mann-Whitney U test revealed that mean protein concentration was significantly higher in astrocytomas ($P \leq 0.001$). Similar results were also obtained in case of lactate ($P = 0.018$). The analyses also revealed a significant positive correlation between the grade and mean protein value as well as grade and lactate ($P = 0.046$, and $P \leq 0.001$; respectively), per Table 4.

Metastases

Two cases aged 67 and 54 years old. Stereotactic biopsy was carried out to make an initial histopathological diagnosis. The first case had progression after 14 months. As tabulated in Table 2, mean total protein concentration was reported 48 mg/dL, and mean lactate level was 12.35 mmol/L. In addition, mean pH was 7.60. Mean total protein concentration in metastatic cysts (48 mg/dL) was above the normal protein value of CSF (20–40 mg/dL) but not as high as that in blood (60–80 mg/dL). Metastases bore some similarities in total protein concentration to that of CSF ($P = 0.126$). No similarities were observed in case of lactate ($P \leq 0.001$). We are aware that our study was restricted due to a small sample size since such cases referred for stereotactic approaches are rare especially for metastasis.

Oligodendroglioma

The only cyst at hand was a low grade oligodendroglioma (grade 2). The patient aged 23 years old. Protein concentration of oligodendroglioma cyst fluid was 42 mg/dL. Lactate and pH were reported the highest of all, 17.6 mmol/L and 7.9, respectively. The cyst progressed after 27 months. Table 2 summarizes the results above. Due to the restricted sample size of oligodendroglioma, only descriptive results are reported.

Discussion

Craniopharyngiomas (WHO Grade 1)

To conclude the obtained results, we can note that craniopharyngiomas, as benign lesions, had considerably low protein and lactate concentrations (22.85 mg/dL, and 3.7 mmol/L, respectively), per Table 2. Moreover, mean pH (7.72) for craniopharyngiomas was above the normal values of both CSF (7.28–7.32) and blood (7.35–7.45), as described in Table 2. This supports the hypothesis that discrepancy of high lactate levels in the cyst with the alkaline surrounding, is responsible for efflux of H^+-ions through a Na^+/H^+ transporter to compensate for the pH.[32]

The similarity of mean protein value of craniopharyngiomas to that of CSF ($P = 0.307$) points to the probability that CSF overproduction is responsible for pathogenesis of craniopharyngioma cysts. This is in agreement with previous literature noting that non-gliomatous cysts overproduce angiogenic factors which speed up capillary formation.[22] The structural abnormalities and increased pinocytic vesicles are observed which can

Table 4. Model Estimation Results

Dependent Variable	Independent Variable	Model		Intercept	Coefficient	95% CI		*P* Value	OR
		Linear Regression	Logit Model			Lower Bound	Upper Bound		
Cytology	Astrocytoma		×	1.50	-1.50	-3.16	0.16	0.077	0.22
Cytology	Craniopharyngioma		×	0.05	1.89	-0.29	4.08	0.090	6.65
Protein	Grade	×		28.802	4.568	0.075	9.061	0.046	-
Lactate	Grade	×		-1.138	4.089	2.835	5.343	≤0.001	-

OR, odds ratio.

cause over-leakage of the plasma and produce more CSF.[33] Also, previous literature suggests extent of angiogenesis as of prognostic value for craniopharyngiomas which plays a critical role in proliferation, spread, and recurrence proven by immunohistochemistry and *in-situ* hybridization.[34]

Astrocytomas

Astrocytomas had higher total protein and lactate concentrations (41.56 mg/dL, 8.28 mmol/L) in comparison with craniopharyngiomas, as tabulated in Table 2. Significant dichotomy of lactate and total protein of astrocytoma to those of blood and CSF, as described in the results section, may suggest a complex pathogenesis to form the glioma cysts. The theorem is in line with the previous literature, describing the proliferated endothelia as a fenestrated lining with insufficient ensheathment of basal membrane; increased pinocytic vesicles[33]; as well as blood-brain-barrier impairment.[35-38] Higher pH of astrocytoma cysts (7.65) compared with the normal range of blood (7.35–7.45) and CSF (7.28–7.32) again suggests that the increased negative charge inside the cysts results in efflux of H^+ ions and increases the pH.[30]

Metastases

Maximal protein concentration was reported in metastases (48 mg/dL). Metastases bore some similarities in the total protein concentration compared to that of CSF (P = 0.126). Hence, it would appear to indicate that CSF overproduction, as discussed for craniopharyngiomas, is the main cause to form cysts within metastatic brain tumors. This supports the theorem that enhanced capillary formation is the main concern in non-gliomatous cysts.[16,19]

In summary, strong correlation of tumor grade and mean lactate concentration lends to support previous findings in the literature that increased lactate concentration of the cyst could be associated with increased risk of malignancy.[39]

The current study reveals that increased intra-tumoral cysts' total protein and lactate concentration can be a sign of malignancy extent and higher grades in stereotactic puncture specimen in astrocytomas but not in craniopharyngioma cysts. Our study was restricted by sample size, especially for oligodendroglioma and metastases, according to the referral frequencies to the stereotactic surgery center. Yet, the current study provides a preliminary portrait of malignancy status of the aspirated cysts before the accurate pathology report. Consequently, in candidate cases for stereotactic puncture, lactate and total protein concentration can be investigated directly from aspirated cyst fluid. Further experimental investigations need to be carried out in order to give predictive hints on the accurate pathogenesis and effective treatment of cystic brain neoplasms.

Authors' Contribution

MN: conducting the surgery, gathering the samples. PS: writing up the paper. ZAN: writing up the paper. SFH: preparing the data sheet.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

This original research has been evaluated and accepted by the ethics committee of Iran University of Medical Sciences by the approval number: IR.IUMS.FMD.REC 139688215207.

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