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Case Report

Baseline serum/cerebrospinal fluid ratio of carcinoembryonic antigen and carbohydrate antigen series biomarkers in non-neoplastic diseases: a cross-sectional study on 224 patients

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ABSTRACT

Background: The measurement of carcinoembryonic antigen, carbohydrate antigen series biomarkers in cerebrospinal fluid (CSF), is useful for the diagnosis of brain metastasis and leptomeningeal metastases to a certain extent. Their serum/CSF ratios may be of benefit to earlier diagnosis and treatment. However, the normal reference values of the ratios were not available. Accordingly, in this study we analyzed the serum/CSF ratios of tumor markers levels in non-neoplastic diseases patients for possible normal values.

Material and methods: We screened our database for paired CSF and serum samples which have been collected by lumbar puncture. 224 pairs of CSF and serum samples were obtained and compared. The 97.5th percentile, maximum value, and their serum/CSF ratios were obtained.

Results: The 97.5th percentile and maximum value of CSF CEA, CA125, CA19–9, CA15–3, CA724, and CYFRA21-1 concentration for overall participants were 0.572 μ/mL, 4.343 μ/mL, 2.872 μ/mL, 2.108 μ/mL, 1.62 μ/mL, and 1.997 μ/mL, respectively. Gender had no significant difference in these CSF biomarkers except CA15–3. The 97.5th percentile serum/CSF ratio of CEA, CA125, CA19–9, CA15–3, CA724, and CYFRA21-1 level were 34.554, 44.772, 51.232, 20.941, 20.737, and 5.389 respectively. The serum/CSF ratios in different age groups were also described.

Conclusions: Here, serum/CSF ratios of six tumor markers were determined in non-neoplastic diseases. The usefulness of this index for diagnosis, management, and prognostic utility of leptomeningeal metastases must be validated in larger cohort studies over the long term.

1. Introduction

Leptomeningeal metastasis (LM) is a complication occurring in oncological patients when tumor cells spread into the subarachnoid space and cerebrospinal fluid (CSF) compartment. According to autopsy studies, LM occurs in 5%–8% of cancer cases and presents in advanced stages of cancer, which has an ominous prognosis with the average untreated survival of from four to six weeks. The incidence of LM increases with the overall improving survival of cancer patients. However, the diagnosis of LM might sometimes be difficult to assess. Identification of neoplastic cells in CSF by cytological analysis is a diagnostic feature of LM. Based on previous research results, the sensitivity of this test is 50%–60% at the initial lumbar puncture, which could be improved up to 80% with the repeated test [1,2].

In addition to microbial culture, cytology, and immunological studies, physicians rely on the clinical chemistry laboratory for biochemical analysis of the cerebrospinal fluid of patients. However, apart from routine glucose and protein determinations, the clinical value of other CSF analytes is often unclear. In physiological conditions within the central nervous system (CNS), no cells can produce a tumor marker. Increased concentrations of carcinoembryonic antigen (CEA) [3], a-fetoprotein and β-human chorionic gonadotropin [4], CA125, CA15–3, and CA19–9 [5,6] have been observed in the CSF of patients with LM.

Based on the previous studies, CSF/serum CEA and CYFRA21-1 [7],CSF/serum CA153 [8], CSF/serum CA19–9 [9] all had diagnostic value for leptomeningeal metastasis. Accordingly, we analyzed serum/CSF ratios of six tumor markers in non-neoplastic diseases, which may be helpful for predicting LM.

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Table 1
The CSF, serum CEA concentration and serum/CSF ratio in overall, male, and female participants.

Cohort	CSF CEA concentration (u/ml)					Serum CEA concentration (u/ml)					Serum/CSF ratio				
	No.	Min.	Med.	97.5th	Max.	No.	Min.	Med.	97.5th	Max.	No.	Min.	Med.	97.5th	Max.
Overall	220	0.200	0.200	0.572	4.740	220	0.200	1.630	7.423	11.950	220	1.000	7.800	34.554	59.750
Gender															
Male	134	0.200	0.200	0.430	0.580	134	0.200	1.750	7.556	11.950	134	1.000	8.290	37.781	59.750
Female	86	0.200	0.200	0.943	4.740	86	0.310	1.545	9.392	11.290	86	1.023	6.975	28.934	50.600
	P value (Mann-Whitney *U* test) 0.277					P value (Mann-Whitney *U* test) 0.008					*P* value (Mann-Whitney *U* test)				0.003

Note. Min. = Minimum, Med. = Median, 97.5th = 97.5th percentile, Max. = Maximum.

Table 2
The CSF, serum CA125 concentrations and serum/CSF ratio in overall, male, and female participants.

Cohort	CSF CA125 concentration (μ/mL)					Serum CA125 concentration (μ/mL)					Serum/CSF ratio				
	No.	Min.	Med.	97.5th	Max.	No.	Min.	Med.	97.5th	Max.	No.	Min.	Med.	97.5th	Max.
Overall	195	0.600	0.795	4.343	6.770	195	1.780	10.990	33.340	46.260	195	1.449	11.613	44.772	55.117
Gender															
Male	117	0.600	0.692	4.342	4.500	117	1.780	10.000	30.568	46.260	117	1.449	11.396	44.494	54.941
Female	78	0.600	1.085	4.645	6.770	78	2.030	15.111	35.953	43.070	78	2.396	11.629	52.419	55.117
	P value (Mann-Whitney U test) 0.248					P value (Mann-Whitney U test) 0.005					*P* value (Mann-Whitney *U* test)				0.443

Note. Min. = Minimum, Med. = Median, 97.5th = 97.5th percentile, Max. = Maximum.

Table 3
The CSF, serum CA19–9 concentrations and serum/CSF ratio in overall, male, and female participants.

Cohort	CSF CA19–9 concentration (μ/mL)					Serum CA CA19–9 concentration (μ/mL)					Serum /CSF ratio				
	No.	Min.	Med.	97.5th	Max.	No.	Min.	Med.	97.5th	Max.	No.	Min.	Med.	97.5th	Max.
Overall	187	0.600	0.688	2.872	27.340	187	0.600	8.580	32.633	35.830	187	0.300	9.867	51.232	59.717
Gender															
Male	115	0.600	0.615	2.740	3.000	115	0.600	7.540	31.343	33.970	115	0.300	9.503	48.278	52.433
Female	72	0.600	0.777	11.475	27.340	72	0.600	11.980	35.286	35.830	72	0.328	11.983	58.809	59.717
	P value (Mann-Whitney U test) 0.648					P value (Mann-Whitney U test) 0.003					*P* value (Mann-Whitney *U* test)				0.202

Note. Min. = Minimum, Med. = Median, 97.5th = 97.5th percentile, Max. = Maximum.

Table 4
The CSF, serum CA15–3 concentrations and serum/CSF ratio in overall, male, and female participants.

Cohort	CSF CA15–3 concentration (μ/mL)					Serum CA15–3 concentration (μ/mL)					Serum /CSF ratio				
	No.	Min.	Med.	97.5th	Max.	No.	Min.	Med.	97.5th	Max.	No.	Min.	Med.	97.5th	Max.
Overall	186	1.000	1.000	2.108	24.770	186	1.120	8.810	23.490	37.520	186	1.120	8.202	20.941	28.542
Gender															
Male	113	1.000	1.000	1.329	2.020	113	1.120	8.970	21.023	26.460	113	1.120	8.640	21.023	26.460
Female	73	1.000	1.000	6.818	24.770	73	3.160	8.790	34.256	37.520	73	1.515	7.900	23.372	28.542
	P value (Mann-Whitney U test) 0.005					P value (Mann-Whitney U test) 0.715					*P* value (Mann-Whitney *U* test)				0.464

Note. Min. = Minimum, Med. = Median, 97.5th = 97.5th percentile, Max. = Maximum.

2. Material and methods

2.1. Subjects

A total of 137 male and 87 female inpatients were included in this study. Their mean age was 47.95 ± 15.84 years, ranging from 11 to 99 years of age. The diagnoses of these non-neoplastic diseases included cerebral venous sinus thrombosis, inflammatory demyelinating disease, and peripheral neuropathy. Lumbar puncture was performed for clinical diagnostic and differential diagnosis purposes. This study has been reviewed and approved by the Ethics Committee of Chinese PLA General Hospital. All participants or their guardians signed the necessary written consent.

2.2. Measurement of CSF and serum biomarkers

Pairs CSF and serum samples were simultaneously obtained and measured on Roche Modular Analytic E170 analyzer (Roche Company, Germany).

Table 5
The CSF, serum CA724 concentration, and serum/CSF ratio in overall, male, and female participants.

Cohort	CSF CA724 concentration (μ/mL)					Serum CA724 concentration (μ/mL)					Serum/CSF ratio				
	No.	Min.	Med.	97.5th	Max.	No.	Min.	Med.	97.5th	Max.	No.	Min.	Med.	97.5th	Max.
Overall	189	0.380	1.120	1.620	1.760	189	0.400	1.440	14.688	29.850	189	0.515	1.344	20.737	30.274
Gender															
Male	116	0.380	1.090	1.611	1.760	116	0.400	1.645	23.834	29.850	116	0.538	1.464	23.852	30.274
Female	73	0.430	1.170	1.633	1.650	73	0.450	1.260	13.585	22.960	73	0.515	1.242	16.897	22.510
	P value (Mann-Whitney U test) 0.815					P value (Mann-Whitney U test) 0.051					*P* value (Mann-Whitney *U* test)				0.112

Note. Min. = Minimum, Med. = Median, 97.5th = 97.5th percentile, Max. = Maximum.

2.3. Statistical analysis

The concentration of CSF biomarkers and serum/CSF ratio were given as minimum, maximum, and percentile. Gender difference that had skewed distributions was tested with Mann-Whitney U rank-sum test. All statistical tests were performed with SPSS 18 (SPSS Inc., Chicago, Illinois). A statistically significant difference was considered as $p < .05$.

3. Results

The minimum and maximum values of CSF CEA, CA125, CA19–9, CA15–3, CA724, and CYFRA21-1 concentration were 0.2 and 4.74 μ/mL, 0.6 and 6.77 μ/mL, 0.6 and 27.34 μ/mL, 1 and 24.77 u/ml, 0.38 and 1.76 u/ml, 0.26 and 2.47 u/ml for overall participants. The 97.5th percentile of CSF CEA, CA125, CA19–9, CA15–3, CA724, and CYFRA21-1 concentration was 0.572 μ/mL, 4.343 μ/mL, 2.872 μ/mL, 2.108 μ/mL, 1.62 μ/mL, and 1.997 μ/mL, respectively (Tables 1-6). The results of the measurement of its serum concentrations were also summarised in Tables 1-6. Gender made no significant difference in these CSF biomarkers except for CA15–3. The 97.5th percentile serum/CSF ratio of CEA, CA125, CA19–9, CA15–3, CA724, and CYFRA21-1 level were 34.554, 44.772, 51.232, 20.941, 20.737, and 5.389, respectively. The serum/CSF ratios in different age groups are described in **Table 7**.

4. Discussion

Although there is no effective treatment for LM, it is better to diagnose the disease at the early stage, and new diagnostic tools to facilitate diagnosis of LM would be a welcome addition. By analyzing CSF tumor markers in non-neoplastic patients, diagnostic clues have been provided and proven to be effective [10–13]. Regardless of serum/CSF ratio or CSF/serum ratio of tumor markers, it has been described in the previous literature and proven to be helpful for the diagnosis of LM [7–9].

In our study, two conclusions can be drawn. First, the 97.5th percentile and even the maximum value of CSF concentration were far lower than its serum concentration. The results of this study suggest the previously used reference value, which usually was serum reference value, might result in many abnormal cerebrospinal fluid tumor markers to be mistaken as normal [7]. Second, we described in detail serum/CSF ratios in different age groups, expanding the clinical application of CSF tumor markers as an indicator for LM.

Alternatively, evaluation of the ratio of serum/CSF ratio may have additional clinical utility. CEA and carbohydrate antigen series biomarkers have limited penetrability with an intact blood-brain barrier [14]. In LM, the blood-brain barrier is usually damaged; elevated tumor markers in CSF may result from trans-blood–brain barrier diffusion from blood rather than intrathecal synthesis [8]. As such, serum/CSF ratio may partly reflect the function of the blood-brain barrier, further suggesting the diagnosis of LM.

There are some limitations in this study. First, the CSF analyzed in this study was lumbar CSF, so our findings might not be applied to ventricular CSF. Secondly, it should also be noted that our findings are method-specific. In a different laboratory, the reference value may change according to different methods [15]. From a clinical perspective, these ratios must be validated in larger cohort studies over the long term because of the above limitations.

In summary, serum/CSF ratios of six tumor markers were determined in non-neoplastic diseases in this study. As a baseline indicator, it may be useful for the diagnosis of leptomeningeal metastases.

Table 6
The CSF, serum CYFRA21-1 concentrations and serum/CSF ratio in overall, male, and female participants.

Cohort	CSF CYFRA21-1 concentration (μ/mL)					Serum CYFRA21-1 concentration (μ/mL)					Serum/CSF ratio				
	No.	Min.	Med.	97.5th	Max.	No.	Min.	Med.	97.5th	Max.	No.	Min.	Med.	97.5th	Max.
Overall	177	0.260	1.110	1.997	2.470	177	0.470	1.590	4.368	5.370	177	0.238	1.610	5.389	7.771
Gender															
Male	109	0.260	1.090	2.293	2.470	109	0.580	1.640	4.525	5.370	109	0.238	1.651	5.507	7.771
Female	68	0.330	1.115	1.988	2.010	68	0.470	1.545	4.523	4.740	68	0.465	1.481	5.882	7.093
	P value (Mann-Whitney U test) 0.636					P value (Mann-Whitney *U* test) 0.328					*P* value (Mann-Whitney U test)				0.219

Note. Min. = Minimum, Med. = Median, 97.5th = 97.5th percentile, Max. = Maximum.

Table 7
The serum/CSF ratios in overall and different age groups. (Median, 25th percentile, and 75th percentile.)

Age (years)	Serum/CSF Ratios											
	No.	CEA	No.	CA125	No.	CA19–9	No.	CA15–3	No.	CA724	No.	CYFRA21-1
Overall	220	7.800(4.840, 11.175)	195	11.613(6.534, 19.546)	187	9.867(4.461, 18.443)	186	8.202(6.263, 11.421)	189	1.344(0.917, 2.626)	177	1.610(1.107, 2.334)
< 21	14	5.570(4.213, 8.450)	8	8.604(6.293, 30.068)	8	12.270(3.593, 27.353)	8	7.090(6.013, 10.568)	8	2.103(1.100, 8.373)	7	1.757(1.077, 2.221)
21–40	46	7.025(4.049, 8.950)	43	14.537(6.350,19.683)	39	7.683(3.213, 15.067)	41	9.020(6.439, 10.865)	41	1.635(0.976, 2.865)	39	1.490(1.021, 2.090)
41–60	115	7.800(4.495, 11.350)	101	10.680(6.693, 18.183)	98	7.833(3.490, 15.684)	95	8.115(6.500, 11.060)	98	1.351(0.853, 2.608)	93	1.556(1.083, 2.377)
61–80	42	9.982(7.488, 14.274)	40	13.625(5.622, 21.098)	40	16.088(8.664, 26.246)	39	9.440(5.740, 13.660)	39	1.115(0.837, 1.492)	35	1.967(1.261, 2.702)
81–99	3	*7.333 ± 1.765	3	*11.784 ± 5.717	2	*13.208 ± 12.208	3	*8.043 ± 3.541	3	*7.038 ± 7.001	3	*2.537 ± 1.917

Note. No. = Number; *mean ± standard deviation.

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Declarations of interest

None.

References

[1] R.J. van Oostenbrugge, A. Twijnstra, Presenting features and value of diagnostic procedures in leptomeningeal metastases, Neurology 53 (2) (1999) 382–385.

[2] J.P. Glass, M. Melamed, N.L. Chernik, J.B. Posner, Malignant cells in cerebrospinal fluid (CSF): the meaning of a positive CSF cytology, Neurology 29 (10) (1979) 1369–1375.

[3] S.K. Batabyal, B. Ghosh, S. Sengupta, S.N. Ghosh, R. Chatterjee, Cerebrospinal fluid and serum carcinoembryonic antigen in brain tumors, Neoplasma 50 (5) (2003) 377–379.

[4] E. Seregni, M. Massimino, S. Nerini Molteni, F. Pallotti, B. van der Hiel, G. Cefalo, et al., Serum and cerebrospinal fluid human chorionic gonadotropin (hCG) and alpha-fetoprotein (AFP) in intracranial germ cell tumors, Int. J. Biol. Markers 17 (2) (2002) 112–118.

[5] Q. Shi, C.Q. Pu, W.P. Wu, X.S. Huang, S.Y. Yu, C.L. Tian, et al., Value of tumor markers in the cerebrospinal fluid in the diagnosis of meningeal carcinomatosis, Nan Fang Yi Ke Da Xue Xue Bao 30 (5) (2010) 1192–1194.

[6] Corsini E, Bernardi G, Gaviani P, Silvani A, de Grazia U, Ciusani E, et al. Intrathecal synthesis of tumor markers is a highly sensitive test in the diagnosis of leptomeningeal metastasis from solid cancers. Clin. Chem. Lab. Med.. 2009;47(7):874–879. doi:https://doi.org/10.1515/cclm.2009.183. doi: https://doi.org/10.1515/CCLM.2009.183.

[7] Z. Zhang, C. Tian, Q. Shi, J. Hao, N. Zhao, Z. Liu, Diagnostic value of CYFRA 21-1 in the cerebrospinal fluid for leptomeningeal metastasis, Dis. Markers 2017 (2017) 2467870, https://doi.org/10.1155/2017/2467870.

[8] E. Le Rhun, A. Kramar, S. Salingue, M. Girot, I. Rodrigues, A. Mailliez, et al., CSF CA 15-3 in breast cancer-related leptomeningeal metastases, J. Neuro-Oncol. 117 (1) (2014) 117–124, https://doi.org/10.1007/s11060-014-1361-1.

[9] Y. Sato, Y. Ohta, T. Ohtsuka, H. Shoji, K. Oizumi, A case of leptomeningeal carcinomatosis: demonstration of CA19-9 and CEA positive malignant cells in the CSF and particular elevation of CA19-9 level in the CSF, Rinsho Shinkeigaku 31 (2) (1991) 175–178.

[10] C. Tian, Q. Shi, G. Xiao, C. Pu, X. Huang, S. Yu, et al., CSF and serum hCG in patients without gestational and neoplastic hCG-secretion, Scand. J. Clin. Lab. Invest. 71 (4) (2011) 264–268, https://doi.org/10.3109/00365513.2011.558911.

[11] Q. Shi, C. Tian, C. Pu, S. Yu, X. Huang, CSF and serum AFP in patients without gestational or neoplastic AFP-secretion, Scand. J. Clin. Lab. Invest. 72 (8) (2012) 619–622, https://doi.org/10.3109/00365513.2012.725865.

[12] Q. Shi, C. Tian, X. Huang, C. Pu, Analysis of Cerebrospinal Fluid Carbohydrate Antigen Series Biomarkers in Non-neoplastic Diseases, Ann. Clin. Lab. Sci. 45 (6) (2015) 623–626.

[13] Q. Shi, C. Tian, X. Huang, C. Pu, Analysis of Cerebrospinal Fluid and Serum CEA Concentration in Non-neoplastic Diseases, Ann. Clin. Lab. Sci. 46 (2) (2016) 180–183.

[14] S. Guepratte, C. Pallud, M.F. Pichon, Dosage des marqueurs tumoraux ACE, CA 15.3, CA 125 et CA 19.9 dans les liquides d?épanchement et le LCR par immunoanalyse en phase homogène. Corrélation avec les résultats cytologiques et les concentrations sériques, Immuno-analyse Biol. Spécial. 17 (1) (2002) 18–25.

[15] E. Yagmur, R. Driesch, A.M. Gressner, P. Kiefer, Technical evaluation of the Beckman Coulter OV-Monitor (CA 125 antigen) immunoassay, Clin. Chem. Lab. Med. 8 (4) (2006) 135–422, https://doi.org/10.1515/CCLM.2006.083.